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ORIGINAL PAPER

The Trends of Uveal Melanoma Research in the Past Two Decades and Future Perspectives

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Abstract

Evaluation of the research trends in uveal melanoma in the past two decades. Data were extracted from the Web of Science database website. VOSviewer and Citespace software were used to analyze the retrieved data. The leading country in terms of output and international collaboration is the USA. 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, *BAP1* mutation, therapeutic target, and systematic reviews. The keywords with the strongest citation bursts are immunotherapy, outcome, and in situ hybridization. The output of uveal melanoma research increased during the past two decades. Before 2015, the main focus of the research was to facilitate prognostication and metastatic risk stratification. Recently, research has moved to examine the metastatic microenvironment. Future research foci may include exploring the role of different mutations, immunotherapy, molecular alterations, and finding ideal clinical biomarkers.

Keywords Choroidal melanoma · Uveal melanoma · Trends · Bibliometric · Future perspectives · Analysis using software · Ocular oncology · COVID-19

Introduction

The uveal tract 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 associated with short survival [4]. The genetic and molecular alterations have a role in 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 to improve survival [7, 8]. We tried to identify the change in research trends in uveal melanoma in the past two decades and elaborate on future perspectives. Bibliometric indicators help identify 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 explanation of these changes. This study also aimed to determine the countries' collaboration, the top-cited articles, the top journals, institutes, and the keywords with the highest citations bursts in this topic.

Methods and Materials

The data were retrieved from the Web of Science database (Science Citation Index Expanded) on the 3rd of July 2020. We confined documents type to articles and reviews. We confined results to the English language. We searched for topic terms in the title, abstract, and keywords fields within a record. We used the following terms: uveal melanoma or

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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. To identify the most cited articles in uveal melanoma, we limited the query to the title field within a record for the formerly mentioned terms. The selected period was from 2000 to 2019. The full records and cited references were exported for the aim of the 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 having strong citation burst in recent years. We selected the following parameters: term source from all options, the period was from 2000 to 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, and log-likelihood test scoring for cluster labeling. Using the full-counting method, we identified the keywords clusters through the VOSviewer (version 1.6.15) analysis of (keywords plus). 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 period between 2011 and 2019 for the keyword burst detection. The selection criteria were the top 50 levels of most cited items for each slice. We adopted a fractional counting method in the analysis of countries' collaboration and keywords co-occurrence rankings. Ethical approval is not applicable because we used a public database (Web of Science) in our study.

Results

The results indicate 3806 published papers on uveal melanoma during the period from 2000 to 2019. Its h-index was high 116, and the average citations per item were 25. 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.

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 54,007, respectively. The following two countries in productivity are Germany and UK by 387 documents; 11,658 citations, and 336 documents; 10,004 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 the UK, the People's Republic of China (PRC), and Germany, in descending order. According to the overlay map analysis, the average publication year for all countries ranges from 2009 to 2015, and the average is 2012. The average publication year for PRC is 2015, which indicates a notable increase in the productivity of this country in recent years. The network and overlay visualization maps appeared in Fig. 2.

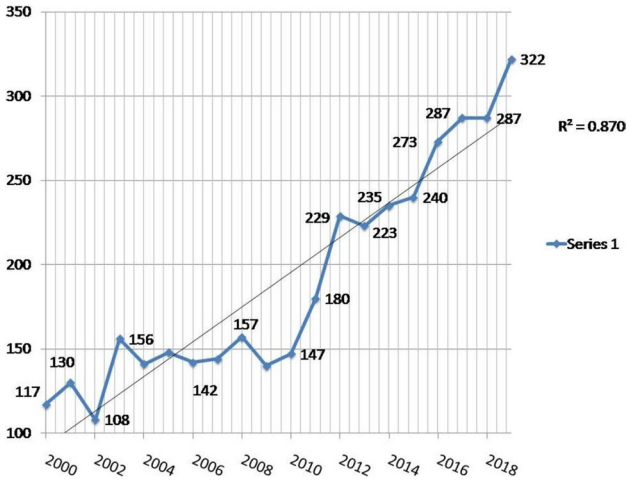


Fig. 1 Publications count per year. Highest number of publication was in 2019 (322 articles). Number of published articles per year increased over time. The value of R^2, the coefficient of determination, is 0.8703. The P-value is < .00001. The result is statistical significant at $p < .05$

Top Journals and Institutes in Uveal Melanoma Research

The number of journals that participated in at least one document in uveal melanoma research was 688. However, only 145 journals have published five or more articles on uveal melanoma. 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 journal with the highest number of published documents 221 and total citations count 7534, followed by the 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 2. The geographical distribution of these institutes

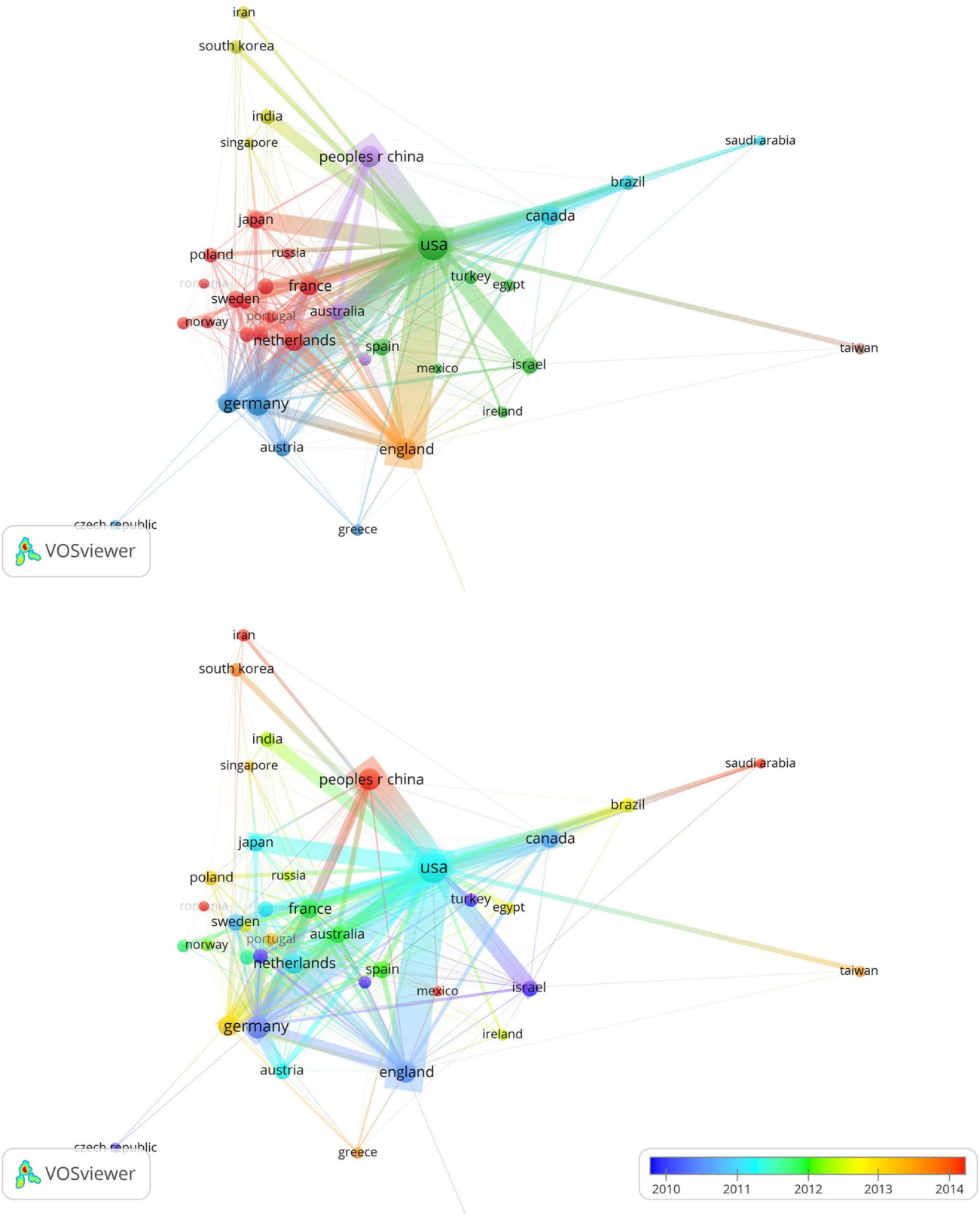


Fig. 2 The network and overlay visualization maps for the countries collaboration in uveal melanoma research. In the network map larger nodes indicate higher total link strength, wider link indicates stronger link between two countries, each cluster of co-authorship coded by a color. In the overlay map the warm color indicates that average publication year is 2014, and the cold color indicates that average publication year is 2010

Table 1 The top 10 journals in the research field of uveal melanoma

Journal	Documents (%)	Impact Factor* (2019)
Investigative Ophthalmology Visual Science	221 (5.8%)	3.47
British Journal Of Ophthalmology	141 (3.7%)	3.61
Melanoma Research	134 (3.5%)	2.75
Ophthalmology	130 (3.4%)	8.47
American Journal Of Ophthalmology	103 (2.7%)	4.01
Archives Of Ophthalmology	96 (2.5%)	4.40
Retina The Journal Of Retinal And Vitreous Diseases	93 (2.4%)	3.65
Graefes Archive For Clinical And Experimental Ophthalmology	80 (2.1%)	2.40
International Journal Of Radiation Oncology Biology Physics	71 (1.9%)	5.86
Ophthalmology	67(1.8%)	2.74

*Data are from the 2019 edition of Journal Citation Reports

Table 2 The top 10 institutes in the research field of uveal melanoma

Institute	Publication Count (%)	Country
Thomas Jefferson University	203 (5.3%)	USA
Leiden University	153 (4.0%)	Netherlands
Royal Liverpool University Hosp	93 (2.4%)	United Kingdom
University of California San Francisco	92 (2.42%)	USA
Memorial Sloan Kettering Cancer Center	89 (2.34%)	USA
University of Liverpool	87 (2.29%)	United Kingdom
Harvard University	80 (2.1%)	USA
Institute Curie	75 (1.97%)	France
University of Texas MD Anderson Cancer Center	71 (1.87%)	USA
Washington University	68 (1.79%)	USA

includes the USA, Netherlands, UK, and France. Half of them are located in the USA.

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 16 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 *BAP1* 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, #7ranges from 2013 to 2017, mean year of clusters designated by orange color #5, #10, #11 ranges from 2010 to 2011, mean year of clusters designated by pink color (the rest of clusters) ranges from 2001 to 2008. The most cited article is about the *GNAQ* mutation in uveal melanoma, published in 2009, and has been cited 875 times [12]. The top-cited articles in uveal melanoma are shown in Table 3.

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 had identified. 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

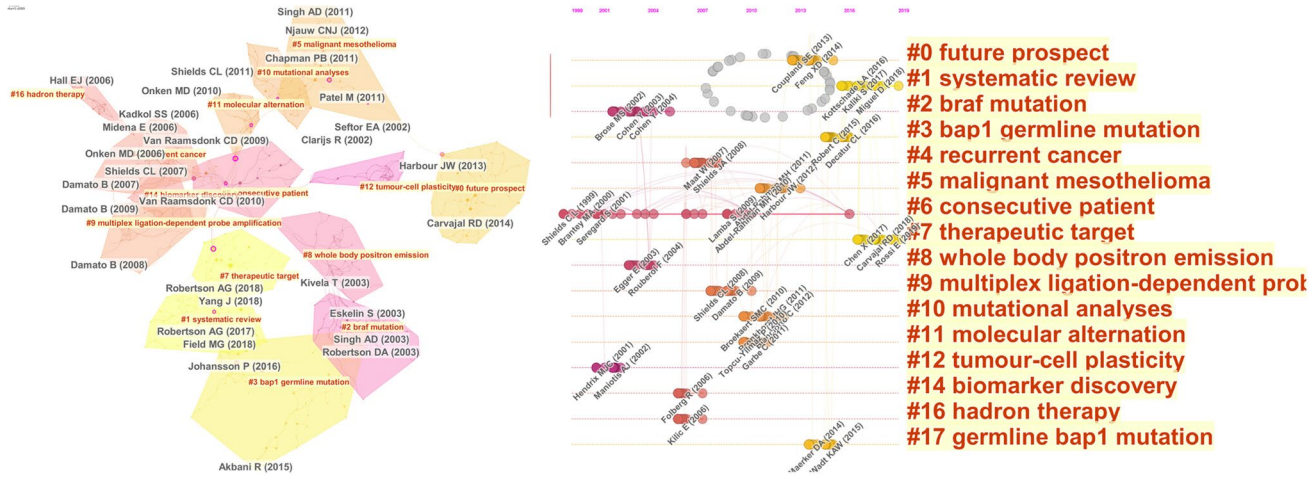


Fig. 3 The top hotspots and co-cited references. The top 16 hotspots in the uveal melanoma research. The mean year of the publication of the articles in the clusters designated by yellow color (#0, #1, #3, #7) ranges from (2013–2017), mean year of clusters designated by orange color (#5, #10, #11) ranges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

alterations. The keywords in order of occurrence frequency are expression, cancer, metastasis, cells, growth, activation, breast cancer, progression, identification, apoptosis, and angiogenesis, respectively. The fourth cluster in orange color is about immunotherapy and 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 the dark blue color is about epidemiology comprises the keywords: tumors, risk factors, risk, USA, sun exposure, prevalence, ciliary body melanoma, iris melanoma, nevus, lesion, oculocutaneous 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.

Discussion

The research output in uveal melanoma has increased in the past twenty years. The USA is the most productive country in uveal melanoma research and participated in nearly half of all publications. The USA is also distinguished by strong international collaboration. While the productivity of the People's Republic of China increased in recent years, it's still less than Germany and England, ranking 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 to decide where to submit articles. Most of the leading journals in this topic specialized in ophthalmology, and only two of them specialized in oncology. Thomas Jefferson University is the most active institute in this regard, as well as most of the top ten, are located in the USA.

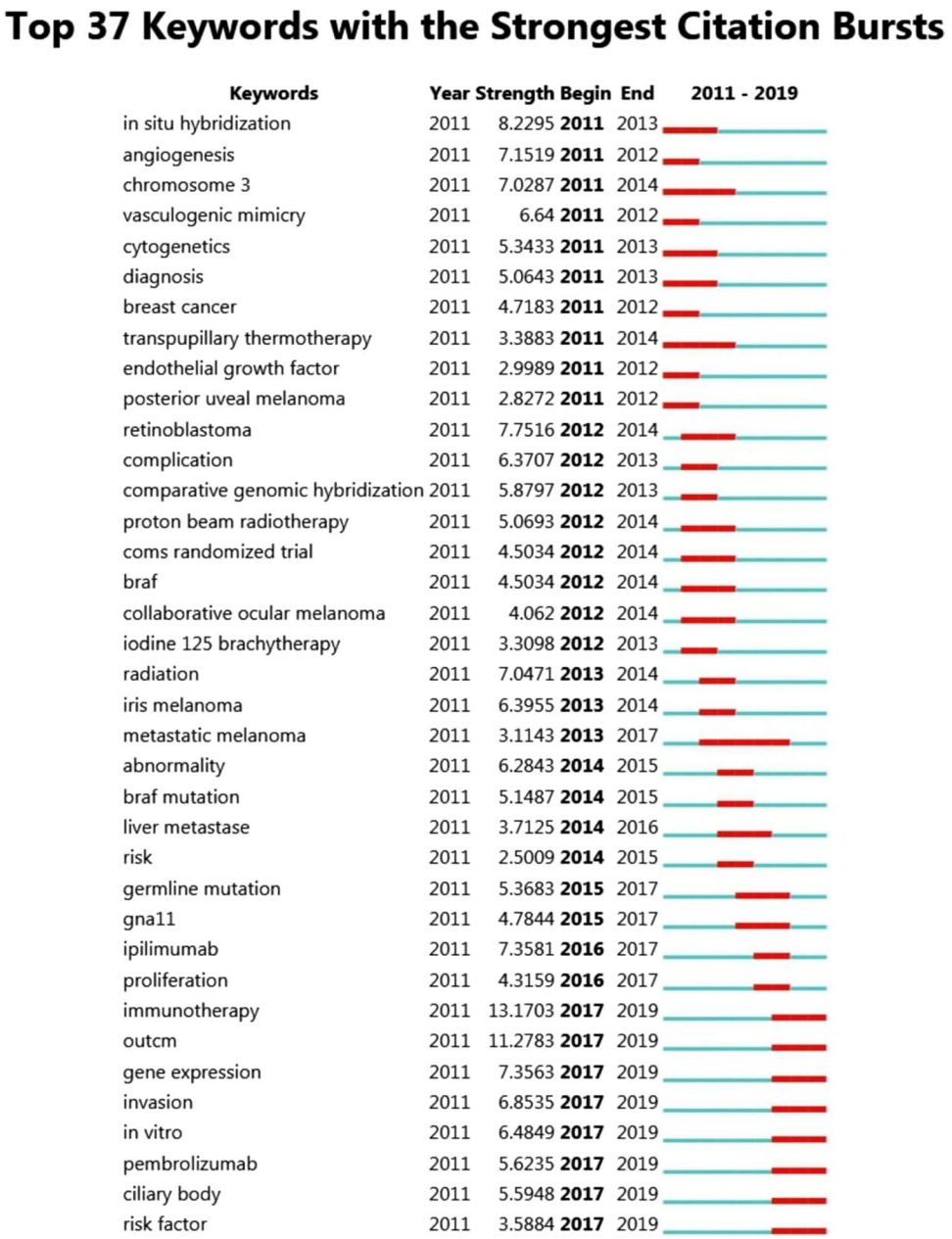
Based on the analysis of co-cited references and keywords citations burst, there is a change of research interest from studying radiation therapy and chromosomes abnormalities in the early years of the past two decades toward the study of genetic mutations and immunotherapy outcomes in recent years. In recent years, the main research themes are about therapeutic targets' efficacy in the uveal melanoma treatment, *BAP1*mutation role, prospects, and systematic reviews. The older themes are 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 recent attention in research to themes of immunotherapy agents like pembrolizumab and ipilimumab and mutations like *GNA11* and *BAP1*. In contrast, before 2015, the keywords with the strongest burst were related mainly to carcinogenesis, therapy, and chromosome 3 status themes. Increased research interest on the metastatic microenvironment was evident. However, comparing to cutaneous melanoma, research in the single-cell examination is less prevalent. Spending more efforts to fulfill some of these research gaps might improve our standing in the metastasis microenvironment of uveal melanoma, thus improving the targeted drugs and immunotherapies. The development of this field

Table 3 The most cited articles in uveal melanoma research

Title	1st Author	Journal title	Publication year	Total citations	Average per year	Type of paper
Frequent somatic mutations of GNAQ in uveal melanoma and blue naevi [12]	Van Raamsdonk, Catherine D	Nature	2009	944	73	Original article
Mutations in GNA11 in Uveal Melanoma [13]	Van Raamsdonk, Catherine D	New England Journal of Medicine	2010	779	72	Original article
Uveal Melanoma: Trends in Incidence, Treatment, and Survival [14]	Singh, Arun D	Ophthalmology	2011	550	50	Review
Very long-term prognosis of patients with malignant uveal melanoma [15]	Kujala, E	Investigative Ophthalmology & Visual Science	2003	521	27	Original article
Gene expression profiling in uveal melanoma reveals two molecular classes and predicts metastatic death [16]	Onken, MD	Cancer Research	2004	456	25	Original article
The COMS randomized trial of iodine 125 brachytherapy for choroidal melanoma, III: Initial mortality findings [17]	Diener-West, M	Archives Of Ophthalmology	2001	423	20	Original article
Development of metastatic disease after enrollment in the COMS trials for treatment of choroidal melanoma—Collaborative ocular melanoma study group report no. 26 [18]	Diener-West, M	Archives Of Ophthalmology	2005	326	19	Original article
The COMS randomized trial of iodine 125 brachytherapy for choroidal melanoma—V. Twelve-year mortality rates and prognostic factors: COMS report no. 28 [19]	Collaborative Ocular Melanoma Grp	Archives Of Ophthalmology	2006	323	20	Original article
Incidence of uveal melanoma in the United States: 1973–1997 [20]	Singh, AD	Ophthalmology	2003	316	17	Review
Hippo-Independent Activation of YAP by the GNAQ Uveal Melanoma Oncogene through a Trio-Regulated Rho GTPase Signaling Circuitry [21]	Feng, Xiaodong	Cancer Cell	2014	299	37	Original article

Fig. 4 The top keywords with the strongest citation burts



may hopefully improve uveal melanoma patients' survival. 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* associated with a high potential of malignancy. Other mutations include *GNAQ*, *GNA11*, *EIF1AX*, and *SF3B1* have received noticeable 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 in association with the risk of metastasis. Nonetheless, the potential risk for metastasis is lower with *SF3B1* mutation than with *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 identified in cutaneous rather than uveal melanomas [25].

In the second cluster, three elements of keywords had identified: (1) chromosome 3, (2) classification, and (3) prognosis. These elements are closely related, as the microsatellite analyses and pathology examinations had used to determine the classification and prognosis in a precise manner [26]. There are several chromosomes in which abnormalities, losses, or gains had associated with an increased risk of metastasis. Chromosome 3 abnormalities could be valuable 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 and cytokines in tumor promotion is well studied. Unfortunately, they are associated with a bad prognosis in uveal melanoma [30]. The 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 its role in tumors pathogenesis was known for a long time, it has recently emerged in uveal melanoma research. 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 might 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 keywords 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 might 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 are represented by large nodes in the network visualization maps because they occurred frequently. The American Association of Physicists in Medicine (AAPM) guidelines emerged in the arena of uveal melanoma management recently and are getting the focus of attention in recent years [37]. Most of the articles on bevacizumab and the outcome of agents got published in the past decade. The previously mentioned observation is obtainable from the overlay visualization map and keywords burst detection.

Some keywords represented by large nodes in the epidemiology cluster are risk factors, sun exposure, and the USA. 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 USA and Europe may attribute 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 and cisplatin. However, none were approved to improve the survival rate, which has been stable for decades [41].

Our study’s limitations include reliance on a single database *Web of Science* for data extraction. However, it 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. It is noteworthy to mention that the COVID-19 pandemic has had a considerable impact on ocular oncology services [45]. Wang H et al. reported a reduction in referral and confirmed cases during 2020 comparing to the preceding two years across all UK ocular oncology services. They observed changes in treatment modalities during COVID -19 pandemic. For instance, they found a significant increase in enucleations surgeries and a reduction in globe salvage operations [46]. Therefore, that may have an impact on research trends in uveal melanoma. The future bibliometric analysis could rely on this study and highlight the changes in uveal melanoma research trends during the COVID-19 pandemic comparing to previous years.

Conclusion

Given the above, the research trends are changing with time. Before 2015, the main focus of the research was to facilitate prognostication and metastatic risk stratification. We expect research on immunotherapy, biomarkers, and genetic alterations of uveal melanoma will continue to expand in the coming years. Future analysis can rely on this study to explore the change in research hotspots and output.

Author Contributions Khaled Ali Elubous: conceptualization, data acquisition, formal analysis, methodology, supervision, review and editing; Ali D Alebous: methodology, formal analysis, visualization, writing—original draft preparation; Hebah A Abous: methodology, resources, writing—original draft preparation; Rawan A Elubous:

methodology, resources, visualization, writing—original draft preparation. All the authors approve the final version to be published and agree to be 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.

Data Availability The data that support the findings of this study are available from the corresponding author, K.E, upon reasonable request.

Declarations

Ethics Approval Not applicable.

Consent to Participate Not applicable.

Consent for Publication Not applicable.

Competing Interests The authors declare no competing interests.

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