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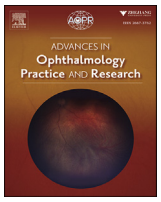

Full Length Article

Global research trends in the treatment of squamous cell carcinoma over the past decade: A bibliometric analysis

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ABSTRACT

Objective: This study aims to identify research trends and hot spots in the treatment of Squamous Cell Carcinoma (SCC) over the past decade using bibliometric analysis.
Methods: Data were extracted from the Web of Science Core Collection, including Science Citation Index Expanded (SCI-Expanded), Social Sciences Citation Index (SSCI), and Emerging Sources Citation Index (ESCI). The data underwent manual cleaning to remove inaccuracies and irrelevancies, followed by transformation into an analyzable format via the VOSviewer software. This tool facilitated the visualization of co-occurrence networks and keyword maps, highlighting the relationships and the prominence of research themes.
Results: A total of 46448 authors from 7374 institutions across 108 countries contributed to the literature, reflecting a broad international effort. The study documented a consistent increase in SCC-related publications up to 2020, with some variability in subsequent years. Notably, the United States, Germany, China, the United Kingdom, and France were predominant in this research area. The University of Texas MD Anderson Cancer Center and the University of Pittsburgh were leading contributors in terms of publication volume and citation impact. Key journals included 'Oral Oncology' and 'Clinical Cancer Research', which were central to the dissemination of high-impact research. Our keyword analysis identified three major research clusters focused on molecular mechanisms, clinical treatment strategies, and emerging interests in immunotherapeutic approaches.
Conclusions: The extensive collaboration and the increasing publication trend underscore the growing global commitment to advancing SCC treatment. The high level of engagement from top institutions and the concentration of research in influential journals reflect the field's dynamic evolution towards innovative and effective treatment modalities. This study provides a valuable overview for researchers, guiding future studies towards areas of high impact and emerging trends in SCC treatment. The findings advocate for enhanced focus on personalized medicine and combination therapies, which are poised to improve outcomes for SCC patients.

1. Introduction

Squamous cell carcinoma (SCC) is an invasive epithelial malignancy originating from the squamous cell layer of the skin epithelium.[1] It can occur in various parts of the body, including the skin, lips, mouth, esophagus, urinary tract, prostate, lungs, vagina, and cervix. In the ocular and periocular region, it may affect the conjunctiva, cornea, and eyelid skin, mainly the lower lid.[2] SCC is the second most common malignant tumor of the eyelids after basal cell carcinoma, accounting for approximately 3.4%–12.6% of eyelid malignancies.[3] It exhibits a higher prevalence in the black population and is the second most common in Hispanic and Asian individuals.[4] The primary causes of SCC in people of color are chronic scarring process, and inflammatory conditions. Individuals of color predominantly develop SCC in areas with limited sun exposure, while Caucasians often develop it in skin areas chronically exposed to the sun.[5–7] Other risk factors for SCC include Human Papilloma Virus (HPV),

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immunosuppression, a high-fat diet, smoking, alcohol consumption and exposure to chemical carcinogens.[8,9] Genetic disorders such as xeroderma pigmentosum, albinism, or preexisting chronic skin lesions also pose risks.

SCC varies in morphology depending on its location. Eyelid SCC typically begins as small red patches and progresses to papillary or ulcerative lesions. It often lacks pain and progresses slowly, which makes it prone to misdiagnosis. As the tumor grows, it may cause orbital apex syndrome, leading to visual impairment.[10] In the late stage, it can metastasize to the brain and cause symptoms and signs of central nervous system damage. Surgery is generally the preferred treatment for SCC. In cases with unclear tumor margins or residual tumors, supplementary treatments such as cryotherapy, local chemotherapy, photodynamic therapy, and radiotherapy should be considered.

Bibliometrics is a quantitative method used to visualize the intricate patterns and relationships within vast pools of scholarly literature.[11] It is employed to describe and analyze the dynamics and development of specific disciplines or research fields and to create clear knowledge maps. The Web of Science (WoS), a high-quality digital literature resource database, was created by Clarivate Analytics (United States) in 1997,[12–14] covers a wide range of scholarly publications across various disciplines and features meticulous indexing processes. WoS is widely accepted by many researchers and is considered the most suitable database for bibliometric analysis.[15]

In this study, we conducted a quantitative analysis of the literature on SCC treatment from 2014 to 2023 using VOSviewer software based on the WoS Core Collection database. Our aim was to explore the current status of research on SCC treatment and provide references for further study.

2. Method

For this study, data was retrieved on May 1, 2024, from the WoS database, which includes SCI-Expanded, ESCI, and SSCI indices. The study topics were selected based on Title, Abstract, Keywords, and Keywords Plus (TS = ("squamous cell carcinoma" AND "Treatment" AND "human")). The criteria were refined by language (English) and document type (Article), covering the period from 2014 to 2023. Manual data cleaning involved identifying and removing inaccurate or irrelevant portions of the dataset, which were then replaced.

The retrieved articles were saved as a plain text file, including full records and cited references, and converted into an executable format using the "Data/Import/Export" function of VOSviewer (1.6.20; Leiden University). The data was standardized by identifying and handling duplicate records and removing unnecessary information. Subsequently, the relationships between articles and the importance of keywords were analyzed. Finally, co-occurrence networks and keyword maps were generated. The sizes of the nodes were determined based on the number of documents in which they simultaneously appear. Links between nodes represented relationships, and clusters were classified with different colors.

3. Result

3.1. Annual publications distribution

The number of publications per year from 2014 to 2023 is shown in Fig. 1. The graph displays an overall upward trend in the number of publications, with some fluctuations in recent years. There were 572 publications in 2014, with a steady increase noted until 2017, reaching 739 publications. However, there was a slight decrease in 2018, with the number dropping to 673 publications. The figures rebounded in 2019 and continued to rise, peaking at 842 publications by 2020, followed by a minor decrease to 803 publications in 2021 and a more significant drop to 740 publications in 2023.

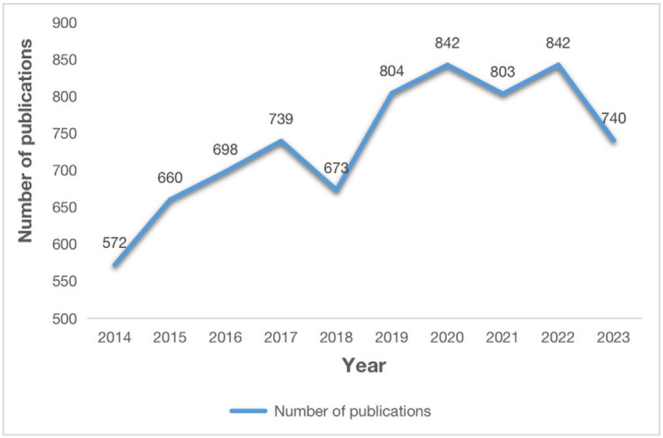

Fig. 1. The number of publications per year from 2014 to 2023. The vertical axis shows the number of publications, while the horizontal axis indicates the years.

3.2. Distribution of research authors, institutions, and countries

The papers used in this study were authored by 46448 researchers from 7374 organizations across 108 countries, published in 7897 papers, and included 203288 cited references from 14347 journals.

The top 10 most productive authors in the field of SCC treatment research over the last decade are presented in Table 1. Each author is listed by rank based on their contribution to the field and provides details on the number of documents they have authored, the total citations received, and the average citations per publication. Adam S. Garden ranks as the top contributor with 44 documents and the highest total citations at 1643, achieving an average of 37.34 citations per publication. Erich M. Sturgis, despite being ranked 9th in terms of document count (30), has the highest average citation per publication at 48.30, indicating highly influential work. The second-highest average citation rate (43.93) was Jack Phan with 28 documents, suggesting significant impact relative to the number of publications. David I. Rosenthal and Steven J. Frank, ranked 3rd and 2nd respectively, also have substantial contributions with 1353 and 875 citations and high average citations per publication (35.61 and 24.31 respectively). The authors ranked 6 through 10, except Erich M. Sturgis, each have fewer than 30 documents but maintain a solid citation impact, with averages ranging from 19.08 to 28.63 citations per publication.

The top 5 countries included the USA, Germany, China, the UK, and France. The top 10 most productive institutions are shown in Table 2, ranked by the number of publications they have produced, the total number of citations received, and the average number of citations per publication. The University of Texas MD Anderson Cancer Center tops the list with the highest number of publications (324) and the highest

Table 1
The top 10 most productive authors contributed of Squamous cell carcinoma researching in last decade.

Rank	Author	Documents	Citations	Average Citation/ Publication
1	Adam S Garden	44	1643	37.34
2	Steven J Frank	36	875	24.31
3	David I Rosenthal	38	1353	35.61
4	Clifton D Fuller	39	576	14.77
5	Jack Phan	28	1230	43.93
6	G Brandon Gunn	29	640	22.07
7	William H Morrison	24	687	28.63
8	Abdallah S R Mohamed	25	477	19.08
9	Erich M Sturgis	30	1449	48.30
10	Stephen Y Lai	26	594	22.85

Table 2
The top 10 most productive institutions of Squamous cell carcinoma researching in last decade.

Rank	Institutions	Publications	Citations	Average Citation/ Publication
1	University Texas MD Anderson Cancer Center	324	17309	53.42
2	Washington University	146	6758	46.29
3	University of Pittsburgh	153	8793	57.47
4	Memorial Sloan Kettering Cancer Center	172	8660	50.35
5	University of Michigan	156	7585	48.62
6	Johns Hopkins University	136	6621	48.68
7	UC San Francisco	106	5633	53.14
8	Ohio State University	119	5690	47.82
9	National Cancer Institute	102	5383	52.77
10	Harvard Medical School	112	3266	29.16

total citations (17309), achieving an average citation rate of 53.42 per publication, which highlights its leading position in research output and impact. The University of Pittsburgh shows the highest average citation per publication (57.47) among the top 10, with 153 publications and 8793 citations, indicating highly influential research despite a lower total publication count compared to MD Anderson. Memorial Sloan Kettering Cancer Center, the University of Michigan, and Johns Hopkins University also feature prominently, with each institution maintaining a strong average citation rate (above 48), showing significant research impact per publication. Institutions like UC San Francisco and Ohio State University demonstrate substantial citation efficiency with average citations per publication over 47, indicating that the quality and impact of their research are well recognized, even if their total output and citations are lower than some others.

3.3. Journals

The top 10 most valuable sources of SCC treatment research in the last decade are shown based on their value in the field, presumably determined by a combination of factors such as publication count, citations, and average citation per publication (Table 3). The "Oral Oncology" journal has the highest number of publications at 237, followed by "Head and Neck" with 221 publications, suggesting these journals are prominent platforms for research dissemination in this field. There is not a direct correlation between the number of publications and the average citation per publication. "Clinical Cancer Research" tends to be highly influential with the highest average citations per publication (46.33). The relationships between different journals are shown in Fig. 2. It is clear that there are two clusters. The density and number of links, particularly in the red cluster, indicate a high degree of interconnectivity, suggesting robust communication and citation exchange among these journals.

Table 3
The top 10 most valuable sources of Squamous cell carcinoma researching in last decade.

Rank	Source	Publications	Citations	Average Citation/ Publication
1	Oral Oncology	237	5527	23.32
2	Head and Neck	221	3782	17.11
3	Cancer	103	3914	38.00
4	Laryngoscope	104	1815	17.45
5	Jama Otolaryngology Head and Neck Surgery	84	2451	29.18
6	Clinical Cancer Research	130	6023	46.33
7	Cancers	175	1407	8.04
8	International Journal of Radiation Oncology, Biology, Physics	88	2802	31.84
9	Oncotarget	169	5694	33.69
10	Frontiers in Oncology	113	1232	10.90

3.4. Keywords distribution

We set a minimum number of occurrences of a keyword as 80 of the 20438 keywords, 157 keywords meet the threshold. The relationships between various keywords used in research publications are shown in Fig. 3. Three major clusters are marked in red, green, and blue, respectively. The visualization of the keyword co-occurrence network with a timeline overlay reflects a shift towards personalized medicine and the integration of immunotherapy into treatment regimens (Fig. 4). Understanding the evolution of keywords can help clinicians and medical researchers stay updated on the most recent and effective treatment paradigms and diagnostic technologies. The emergence of cemiplimab or pembrolizumab has recently opened novel treatment options for patients with advanced CSCC when both surgery and radiotherapy are not possible or were unsuccessful. There are also many neoadjuvant application models of immunotherapy, including combinations of immunotherapy with chemotherapy, targeted therapy, and radiotherapy.

4. Discussion

The bibliometric analysis of SCC treatment over the last decade shows a steady increase in the volume of literature on SCC treatment before 2020, with slight fluctuations in subsequent years. This growing interest may reflect the ongoing development of new therapeutic approaches and the increasing global burden of SCC. The concentration of research output from institutions in the USA, Germany, China, the UK, and France underscores the critical role of these countries in advancing SCC treatment. This prominence is attributed not only to the relatively high prevalence in Caucasians but also to the strong focus on quality and groundbreaking research in these institutions like the University of Texas MD Anderson Cancer Center and the University of Pittsburgh.

The analysis of journals highlights the key platforms for current SCC treatment research. It is particularly useful for researchers in selecting journals for their work, understanding which journals have the highest impact, and identifying trends in publication and citation within the field of SCC research. The journals listed vary in their focus and scope. For example, some, like "Oral Oncology" and "Head and Neck", might be more specialized for head and neck squamous cell cancers (HNSCCs), and cutaneous squamous cell cancers (CSCC), whereas others like "Cancer" cover a broader range of topics within oncology. The specialization can affect both the number of publications and the average citations per publication. Journals with lower average citations per publication, like "Frontiers in Oncology", might still be critical for the field, possibly representing emerging areas of research or providing platforms for preliminary findings that could pave the way for future breakthroughs. The observed interconnectivity among journals within the clusters highlights a robust exchange of knowledge, fostering a cohesive research community that can accelerate innovation in SCC treatment.

For the analysis of keywords, we used network and overlay visualization. For the network visualization, the keywords formed three main clusters and brought together keywords with similar research topics (Fig. 3). Based on the current SCC treatment research status, the three clusters are analyzed as follows:

Cluster 1 (Red) focuses on molecular and cellular aspects of cancer, including terms such as "TP53", "apoptosis", "proliferation", "expression", and "angiogenesis". These terms are associated with the mechanisms of SCC development and progression. Although SCC can occur in different anatomical locations, its pathogenesis shares commonalities and distinctive features. Histologically, the development and evolution of SCC can be divided into stages, from actinic keratosis to carcinoma in situ, and then to the destruction of the basement membrane. The gene tumor protein p53 (TP53, Aliases: BCC7, LFS1, P53, TRP53) (Gene ID: 7157), located on chromosome 17p13.1,[16] is the most commonly

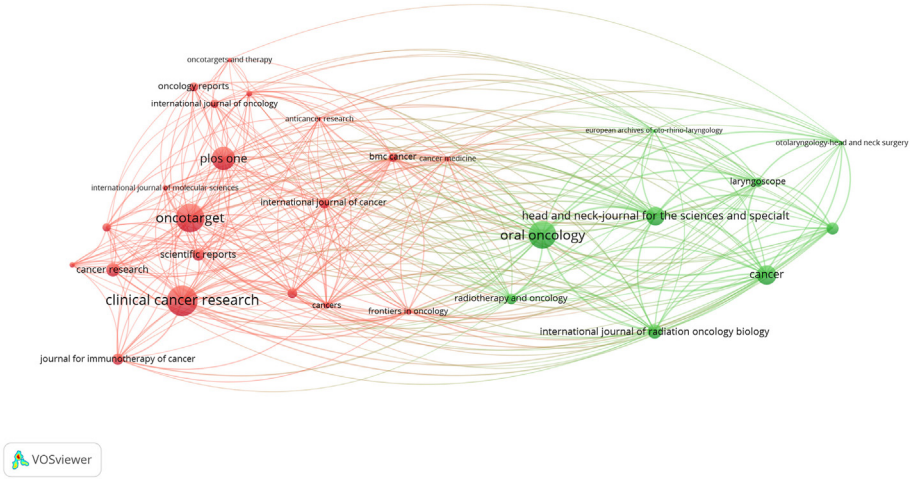

Fig. 2. The bibliographic coupling analysis visualization of sources. Minium documents of a source is set as 50 documents. 29 Journals meet the threshold. Each node represents a journal involved in SCC treatment. The size of each node indicates the number of citations. The lines connecting the nodes represent relationships between these journals. A link suggests that papers from the two connected journals frequently cite each other or are cited together by other works. The colors of the nodes and links generally represent different clusters, indicating journals that are more closely related to each other in terms of their research focus, citation habits, or authorship.

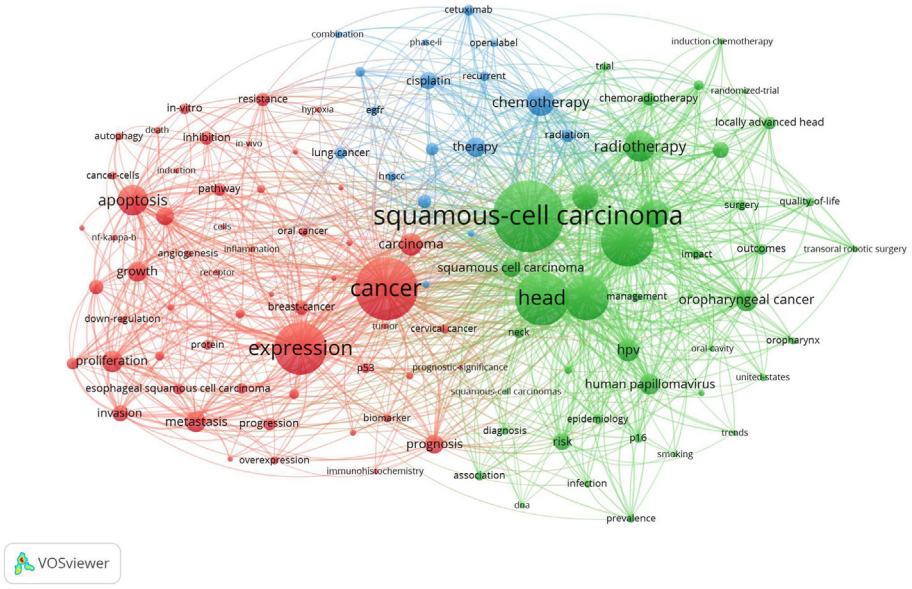

Fig. 3. The bibliographic coupling analysis visualization of keywords. Minimum number of occurrences of keyword is set as 80 of the 20438 keywords, 157 keywords meet the threshold. Each node represents a keyword appearing in the scientific literature. The size of each node indicate the frequency of the keyword's occurrence in the literature. The links between the node indicates the co-occurrence of keywords in the same publications. A thicker or more pronounced link suggests a stronger relationship, meaning those terms frequently appear together.

mutated gene in various SCC. NOTCH1 is regard as the second most commonly mutated gene after TP53.[17,18] The Ras-Raf-MEK-ERK signaling pathway is important for regulating various cellular functions, promoting cell proliferation, malignant transformation, and preventing cell apoptosis.[19] The components of these pathways often change in various types of SCC.[20,21]

Cluster 2 (Green) appears to center around treatment and clinical aspects, with keywords like "surgery", "radiotherapy", "quality of life", and "outcomes". Mohs micrographic surgery (MMS) is the preferred treatment for eyelid SCC. Compared with non-MMS surgery, MMS has a lower local recurrence rate and a higher cure rate. In a comparative study, CSCC treated with MMS had a threefold lower risk of recurrence compared to those treated with standard excision, when adjusted for tumor size and deep tumor invasion.[22] The benefit of MMS in intermediate and high-risk of SCC has been reported. Specifically, MMS was associated with a significantly lower local recurrence rate compared to wide local excision (1.2% vs. 4.0%) in intermediate SCC.[23] For high-risk SCC, MMS alone provides excellent marginal control with low rates of local recurrence (2.9%), nodal metastasis (4.8%), and disease-specific death (1.1%).[24] MMS is more commonly preferred in periocular and eyelid SCC due to the need for precise margin control and tissue preservation, whereas wide local excision is commonly used in oral SCC (OSCC). Additionally, the surgical management of neck nodes in patients with OSCC has been a subject of debate, particularly regarding the contralateral neck.[25,26] Post-surgical reconstruction is often more complex in OSCC due to the functional and cosmetic implications in the oral cavity.[27]

Based on the work of Brodland and colleagues, the National Comprehensive Cancer Network Panel recommends that for low-risk CSCC lesions with a diameter of less than 2 cm, a 4 mm margin excision is required to achieve a 95% clearance rate.[28,29] Otherwise, a 6 mm margin excision is needed to achieve the same result. For CSCCs located in high-risk areas (such as the scalp, ears, eyelids, nose, and lips) or exhibiting other high-risk features (histologic grade $\geq$2, subcutaneous tissue invasion), lesions with a diameter of less than 1 cm, between 1 and 1.9 cm, and 2 cm or greater would require margins of at least 4 mm, 6 mm, and 9 mm, respectively. Currently, European guidelines recommend standard excisions with 6–10 mm peripheral clinical margins for high-risk to very-high-risk CSCCs.[30,31] If the removal is incomplete or surgical margins is insufficient, an additional SCC excision should be performed to minimize the risk of recurrence and metastasis.[32,33] In retrospective study by Galindo-Ferreiro et al., if residual tumor cells are found on or within 1 mm of the lateral or deep margin, it is considered that the resection margin is not completely clear. In this case, further

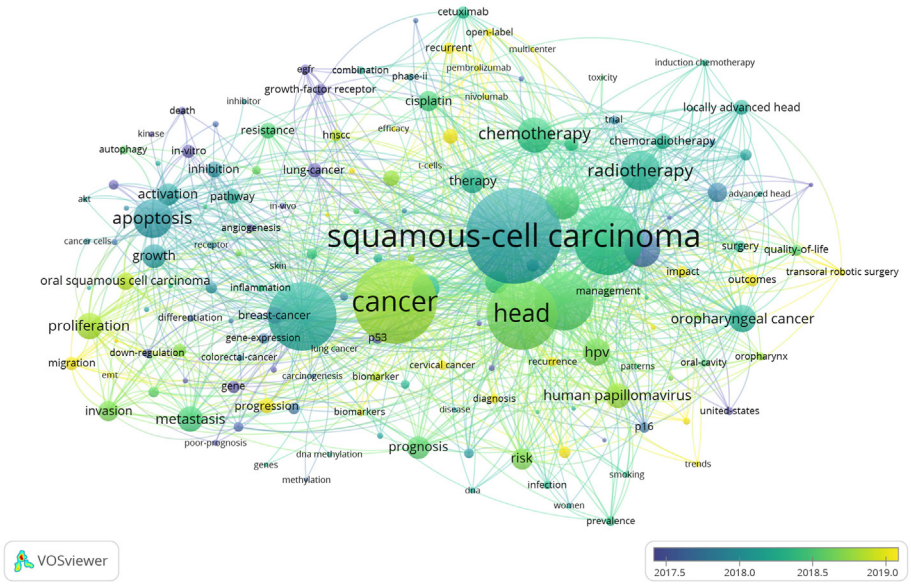

Fig. 4. Visualization of keyword co-occurrence network with a timeline overlay. Minimum number of occurrences of keyword is set as 80 of the 20438 keywords, 157 keywords meet the threshold. The size of a node typically indicates the frequency of the keyword's appearance in the literature, and lines connecting the nodes represent the co-occurrence of these keywords within the same articles. Darker colors (e.g., dark blue) represent keywords that were more prominent earlier in the timeline, while lighter colors (e.g., yellow) indicate keywords that have gained prominence more recently.

surgery or treatment may be needed.[2]

For tumors that invade intraocular or orbital tissues, often cause perineural invasion, postoperative adjuvant radiotherapy should be considered.[34] The two most common types of CSCC radiotherapy are external beam radiation therapy and brachytherapy. However, postoperative radiotherapy also has side effects, including short-term side effects like skin redness, mild discomfort, and fatigue, and long-term side effects non-healing ulcers and cataracts.[35]

Cluster 3 (Blue) includes terms related to systemic therapy, such as "chemotherapy", "cisplatin", and "cetuximab". Targeted therapy and immunotherapy have significantly advanced the treatment landscape for SCC. Targeted therapies, such as epidermal growth factor receptor (EGFR) inhibitors like cetuximab, panitumumab, and erlotinib, have shown promise in reducing tumor burden in locally advanced SCC.[36,37] These therapies work by inhibiting specific pathways that are critical for cancer cell growth and survival, thereby limiting disease progression and improving patient outcomes. Subsequently, researchers have evaluated and continue to develop other targeted therapies, such as trametinib and cobimetinib.[38]

Immunotherapy, particularly with high-affinity PD-1 inhibitors like nivolumab and pembrolizumab, has been a groundbreaking development for patients with platinum-resistant recurrent metastatic HNSCC.[39] These treatments enhance immune system activity to eradicate cancerous cells, can be administered either before surgery (neoadjuvant) or after surgery (adjuvant).[40,41] Clinical trials have demonstrated that combining immunotherapy with chemotherapy (neoadjuvant immunotherapy) can enhance the effectiveness of treatment, resulting in higher response rates and longer patient survival.[42,43] For example, the combination of radiotherapy with nivolumab has been found to be generally safe and effective, providing a robust immune response with minimal adverse effects.[44,45] These advancements underscore the critical role of targeted and immunotherapy in improving the management and outcomes of SCC, offering new hope for patients with advanced or treatment-resistant forms of the disease.

Compared with monotherapy, combination therapy has higher response rates and longer patient survival.[46,47] In some patients, radiotherapy may induce somatic mutations that lead to the generation of new tumor-associated antigens (TAAs) that can serve as targets for a more robust immune response. Radiotherapy combined with nivolumab (NCT02684253 and NCT03349710) is generally safe, with no significant immune-related adverse events for HNSCC.[48] The discovery of more downstream pathways and the use of better combination regimens provide more treatment options to patients with SCC.

5. Conclusions

This bibliometric analysis not only reflects the current status of SCC treatment research but also provides a clear direction for future studies. Understanding emerging trends such as immunotherapy and targeted therapy will be crucial for developing next-generation SCC therapies. By building on the foundations laid by the research of this past decade, researchers can continue to make significant advancements in combating SCC, ultimately leading to better patient care and outcomes.

Study approval

Not Applicable.

Author contributions

The authors confirm contribution to the paper as follows: Conception and design of study: XL, ACR; Data collection: XJ; Analysis and interpretation of results: YG, XH; Drafting the manuscript: XL, WF, LMH; All authors reviewed the results and approved the final version of the manuscript.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Abbreviations

SCC	Squamous Cell Carcinoma
WoS	Web of Science
MMS	Mohs micrographic surgery
HPV	Human Papilloma Virus
TP53	Tumor Protein p53
HNSCCs	Head and Neck squamous cell cancers
CSCC	Cutaneous Squamous Cell Cancer
EGFR	Epidermal growth factor receptor
TKIs	tyrosine kinase inhibitors
TAAs	tumor-associated antigens

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