Observational Study

Medicine

OPEN

A visualization analysis of global research trends in targeted therapies for thyroid carcinoma (2013–2023)

Yu Mao, MM[a], Fei Ye, MD, PhD[a], Qin Jiang, MM[a], Sushun Liu, MD, PhD[a], Yi Gong, MD, PhD[a,*]

Abstract

This study aims to analyze and identify primary research trends in targeted therapy for thyroid carcinoma (TC). It seeks to provide a factual foundation for researchers, as TC often presents with advanced stages and aggressive subtypes, leading to unfavorable clinical outcomes. The evolution of targeted therapies introduces promising treatment possibilities, necessitating a bibliometric analysis to better understand the current state and trends in this field. A comprehensive bibliometric analysis was conducted using data from the Web of Science Core Collection (WOSCC). Advanced search queries established a literature database, and the analysis was performed using tools such as VOSviewer, CiteSpace, Tableau, and Microsoft Excel. The study focused on publications from 2013 to 2023, examining patterns, geographical contributions, institutional output, and influential journals. The analysis identified 763 publications on TC targeted therapy during the study period, with significant contributions from the United States, China, and Italy, and the United States leading in output. Research activity peaked in 2021, showing overall fluctuating growth. Key contributing institutions included the University of Texas MD Anderson Cancer Center and the University of Pisa. Notable journals, such as *Cancers* and *Thyroid*, were among the most cited, underscoring their impact in the field. The study highlighted an increase in global research output and robust international collaborations, particularly among the leading contributing countries. This bibliometric analysis provides a comprehensive overview of significant contributions and trends in targeted therapy research for TC. It identifies key development processes and research hotspots, offering valuable insights to guide future research directions. The findings aim to stimulate further studies and foster advancements in this critical area of oncology.

Abbreviations: ATC = anaplastic thyroid carcinoma, ATP = adenosine triphosphate, IRTC = iodine-refractory thyroid carcinoma, NSCLC = Non-Small Cell Lung Cancer, TC = thyroid carcinoma, TKIs = tyrosine kinase inhibitors, WOSCC = Web of Science Core Collection.

Keywords: bibliometric analysis, CiteSpace, targeted therapy, thyroid carcinoma, VOSviewer

1. Introduction

Thyroid carcinoma (TC) is one of the most common carcinomas of the endocrine system and its incidence is increasing every year.[1,2] While the majority of individuals diagnosed with TC have a favorable prognosis, factors such as advanced clinical stage[3] and highly aggressive subtypes[4,5] remain linked to unfavorable clinical outcomes. Targeted therapies, through their intervention in the molecular mechanisms of carcinoma cells, selectively disrupt or inhibit their survival and proliferation.[6,7] This not only enriches therapeutic options for this patient group but also infuses new vitality into the traditional treatment paradigm.

The field of targeted therapies for TC is currently undergoing rapid growth and evolution. However, it faces various challenges, including the development of therapeutic resistance[8] and the complexity of specific molecular targets.[9] Within this dynamic landscape, a substantial body of research literature explores diverse therapeutic strategies, biomarkers, and clinical trial results. Upon searching major databases, we discovered that despite literature reviews by several scholars,[10–12] the exploration of targeted therapies for TC from a bibliometric perspective is limited. Bibliometric analysis, as a systematic approach, scrutinizes, cleanses, and mines this wealth of quantitative information using mathematical and statistical tools.[13–15] This process not only assesses elements such as citations, authors, journals, and keywords but also aids researchers in fully comprehending the development and impact of scholarly research.

The authors have no funding and conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

This study did not require the approval of an ethics committee since we analyzed a secondary database.

[a] *Department of Thyroid Surgery, the Second Xiangya Hospital, Central South University, Changsha, P.R. China.*

** Correspondence: Yi Gong, Department of Thyroid Surgery, the Second Xiangya Hospital, Central South University, Changsha, Hunan 410011, P.R. China (e-mail: gongyi5226@csu.edu.cn).*

How to cite this article: Mao Y, Ye F, Jiang Q, Liu S, Gong Y. A visualization analysis of global research trends in targeted therapies for thyroid carcinoma (2013–2023). Medicine 2025;104:11(e41835).

Received: 25 September 2024 / Received in final form: 18 February 2025 / Accepted: 21 February 2025

http://dx.doi.org/10.1097/MD.0000000000041835

By providing key quantitative indicators, bibliometric analysis offers a comprehensive and objective perspective, deepening our understanding of the current state of research in TC targeted therapy. It enables the systematic assessment of patterns, trends, and influential contributions, thereby contributing valuable insights for future research and decision-making.

2. Methods

2.1. Data collection

To conduct bibliometric analysis, we established a database designed for retrieving relevant literature. An advanced search strategy was implemented within the Web of Science Core Collection database (WOSCC)(https://access.clarivate.com). WOSCC served as the chosen data source, and each document record included both the full record and cited references. It is the most common bibliometric database.[16] We conducted a search and export operation on April 22, 2024. The strategy searched was (TS=("thyroid carcinoma" or "thyroid cancer") AND TS=("targeted therapy" or "targeted therapies")) and restricted the search to the period between January 1, 2013, and December 31, 2023. To address potential search bias, we implemented specific constraints, such as restricting the scope of literature to include only articles and reviews and confining the language of publication to English. As a result, the final compilation of literature databases consisted of 763 retrieved documents. Two authors independently conducted the literature search and downloading tasks. The detailed retrieval process is illustrated in Figure 1.

2.2. Data analysis

In this research, VOSviewer (v1.6.19), CiteSpace (v6.2.R4), Tableau (version 10.5.0), and Microsoft Excel were utilized for the analysis. VOSviewer,[17] a software application, primarily focuses on constructing and visualizing bibliometric networks. It enables the creation and visualization of co-occurrence networks, emphasizing key terms extracted from scientific literature. CiteSpace provides dynamic visualizations to reveal structural and temporal complexities in scientific domains.[18,19] For comprehensive research and result validation, this study integrated multiple software tools for mapping cooperation networks (authors, institutions, and countries), keywords co-occurrence, and clustering documents through co-citation, along with coupling of literature sources. We use Tableau to track publication trends and volumes in different countries. Tableau is a data visualization tool that facilitates comprehensive analysis of scientific maps.

3. Results

3.1. Trends in publication outputs

During the period from 2013 to 2023, our research identified a total of 736 studies on targeted therapy in thyroid carcinoma (TC), comprising 442 articles and 294 reviews. The growth trend of annual research output is illustrated in Figure 2, showing fluctuating but generally increasing numbers from 2013 to 2021, peaking in 2021 with 114 papers – a significant rise compared to previous years. However, a decline followed in 2022, with 97 papers making up 12.14% of the total. In 2023, the number of publications recovered to 107, accounting for 13.39% of the total, suggesting renewed research interest.

This publication trend aligns with the annual citation frequency trends, also depicted in Figure 2. A notable citation peak occurred in 2016, with 11,144 citations. This sharp rise was largely driven by the 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer,[20] authored by Haugen et al and published in *Thyroid*. As a comprehensive update on thyroid cancer management, the guidelines became a cornerstone reference in the field, heavily cited in subsequent research. Between 2013 and 2014, citation frequency steadily increased but began declining after 2020, reaching a low of 270 in 2023. This decline may be attributed to the slow citation accumulation of newer publications and shifts in research focus. Together, these trends highlight dynamic changes in academic output and influence,[21] with the 2016 citation peak and 2023 low being particularly notable.

3.2. Geographical and institutional distribution

Publications related to targeted therapies for TC come from 55 countries and regions and 1159 institutions. According to Table 1, The United States takes the lead with 263 papers, constituting 27.25% of the total. China follows with 167 papers, accounting for 17.31%. Other major contributors include Italy, Germany, and France. Overall, publications from China, the United States, and Italy collectively make up 55.34% of the total output. Notably, these publications cover a wide range of research methods and designs, from basic scientific research to

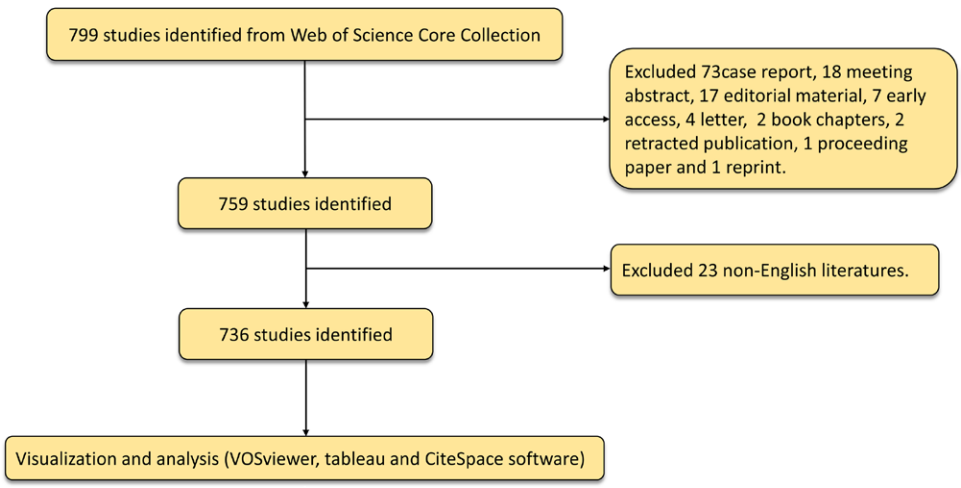


Figure 1. Process for literature screening.

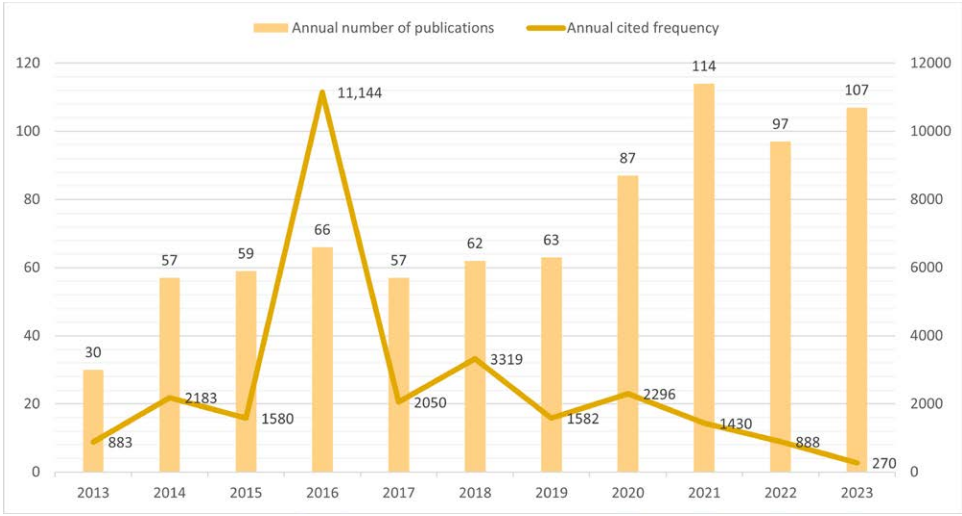


Figure 2. Annual research output of targeted therapy in TC. TC = thyroid carcinoma.

Table 1

The top 10 countries and regions on research of targeted therapy in TC

Rank	Country	Publications	Proportion of publications (%)	Citations	Citations per publications (%)
1	USA	263	27.25	18677	30.22
2	China	167	17.31	2568	4.16
3	Italy	104	10.78	11742	19.00
4	Germany	42	4.35	1328	2.15
5	France	39	4.04	9661	15.63
6	Japan	36	3.73	878	1.42
7	Spain	24	2.49	743	1.20
8	South Korea	23	2.38	666	1.08
9	Canada	22	2.28	9345	15.12
10	England	22	2.28	1094	1.77

TC = thyroid carcinoma.

clinical practice. The countries and regions exhibit a broad and deep range of collaborative relationships. A total of 55 countries and regions were included in this study, and Figure 3A illustrates the collaborative network involving these 55 countries and regions, each contributing to the research landscape with at least 1 publication. The size of the circle represents the number of publications, while the color indicates the level of research activity across different years. Figure 3B shows the world map of publications, incorporating data from 20 countries and regions, and depicts a varying distribution of research output across different countries and regions, each with a minimum of 10 publications.

Figure 4 displays the institutional co-occurrence maps, incorporating a total of 1159 institutions in this study. After setting the minimum number of documents to 4, we are left with 92 institutions, with a predominant number from the United States, China, and Italy. The larger nodes suggest institutions with a higher number of collaborations or publications. The University of Texas MD Anderson Cancer Centre published 53 papers, followed by the University of Pisa and Memorial Sloan-Kettering Cancer Centre with 26 and 25 papers, respectively. The colors range from blue to red, often indicating the evolution of these collaborations over time, with blue being earlier and red being more recent. This map provide a visual representation of the landscape of institutional collaborations within a specific field or set of publications. They can be particularly useful for identifying key players, emerging trends, and the dynamics of research collaborations over time.

3.3. Journals and co-cited journals

As depicted in Table 2 and Figure 5A, *Cancers* and *Thyroid* prominently featured in the top 336 journals with 32 publications, followed by *Frontiers in Endocrinology* with 23 publications, and *Frontiers in Oncology* with 22 publications. Among the top 10 journals, *Thyroid* firmly holds the top position with the highest impact factor of 6, followed by *Journal of Clinical Endocrinology & Metabolism* with 5. Figure 5A provides a visual representation of 118 journals, each with more than 2 significant publications.By evaluating article connections, co-citation analysis reveals journal impact through co-citation frequency. Among the 3721 co-cited journals, 6 have exceeded 1000 citations. Table 3 illustrates that the *Thyroid* leads with 2822 citations, followed by *Journal of Clinical Endocrinology & Metabolism* with 2770 and *Journal of Clinical Oncology* with 2182. In the top 10, the *New England Journal of Medicine* boasts the highest impact factor at 96.3, trailed by *Annals of Oncology* at 56.7. According to the Journal Citation Report 2022, most of these highly cited journals fall under the Q1 category. Figure 5B showcases a co-citation network map based on a total of 3712 co-cited journals. By setting a minimum citation threshold of 30, 257 journals met the criteria and were included in the visualization. This map aids researchers in identifying pivotal journals crucial to their scholarly contributions, vividly highlighting the concentrated influence and interconnectedness within academic fields.

The dual-map overlay in Figure 6 provides a comprehensive perspective by integrating data across different time points, diverse topics, and correlations within the research field. This facilitates the

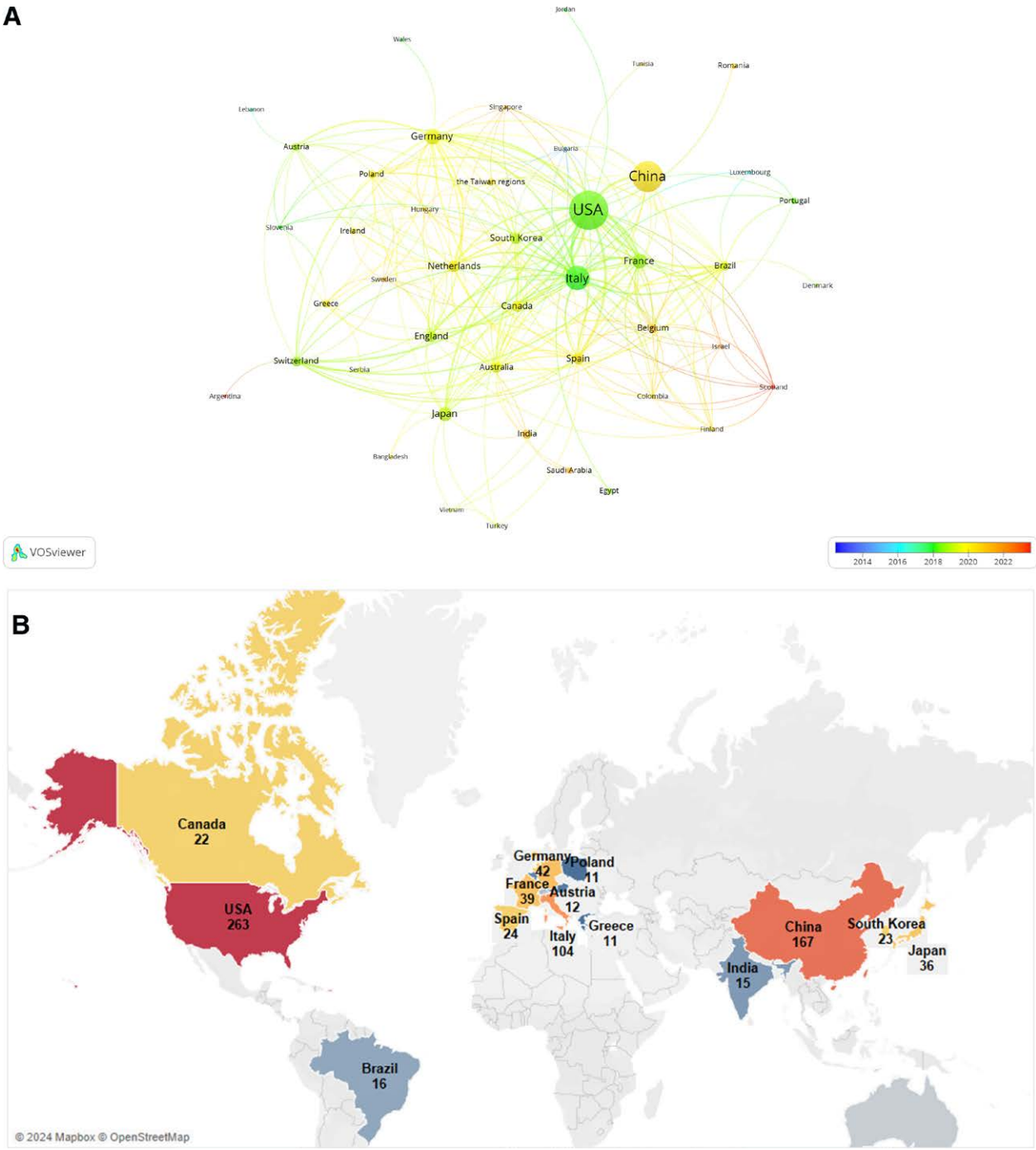


Figure 3. Visualization of collaborating countries (A) and geographical collaboration map (B) pertaining to targeted therapy in TC. TC = thyroid carcinoma.

observation of changes, trends, and correlations, fostering a deeper understanding of the dynamics within the research field. It assists researchers in gaining insights into the development and evolution of academic research. Two prominent citation trajectories are evident: the orange trajectory highlights that articles from Molecular/Biology/Genetics journals are primarily cited by Molecular/Biology/Immunology, while the green trajectory demonstrates the impact of Medicine/Medical/Clinical citations on research from Molecular/Biology/Genetics and Health/Nursing/Medicine journals.

3.4. Subject categories

To better understand the research landscape in TC-targeted therapies, Figure 7 presents the category co-occurrence network knowledge map, illustrating the relationships among key subject categories identified in this study. The size of each node reflects its frequency, with Oncology emerging as the most prominent and central, emphasizing its dominant role in this area. The connections between nodes indicate co-occurrence relationships, illustrating the interdisciplinary nature of TC research. For instance, Endocrinology and Metabolism and Biochemistry and Molecular Biology show significant links to Oncology, underlining their collaborative roles in advancing research on targeted therapies. Nodes highlighted with a purple outer ring represent a betweenness centrality of at least 0.1, signifying their importance in bridging various research domains.[22] Larger betweenness centrality values, such as those observed for Oncology and Pharmacology and Pharmacy, indicate a stronger influence in

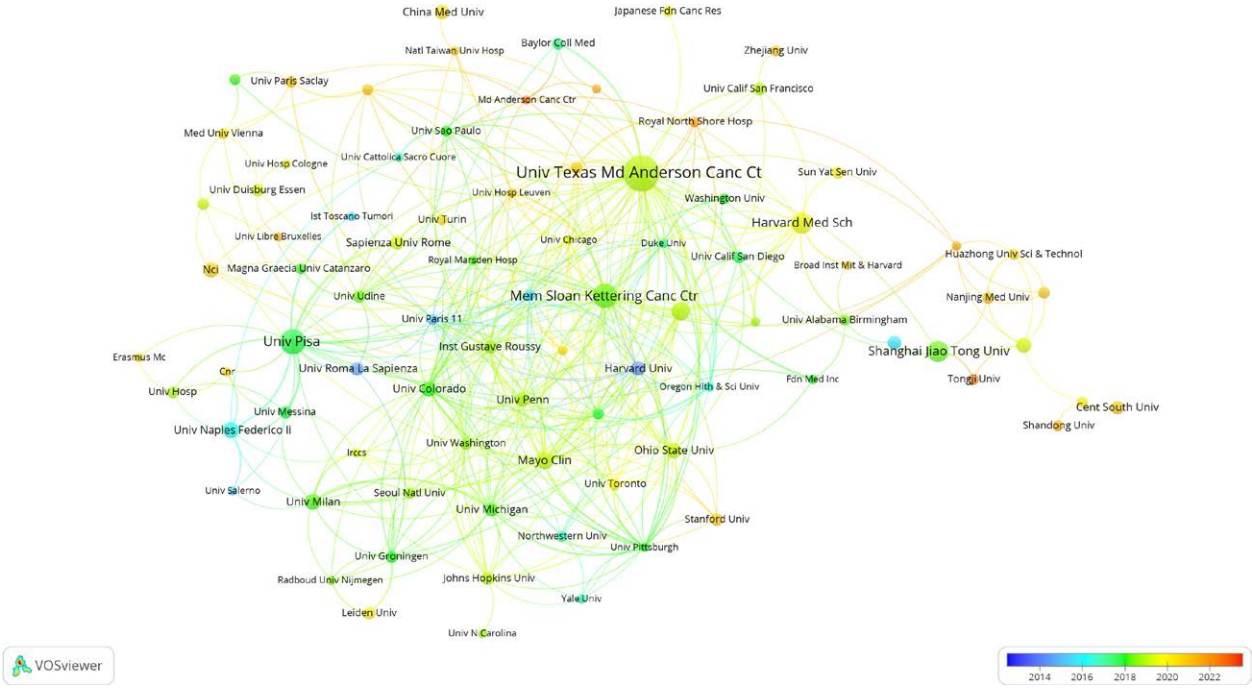


Figure 4. Visualization of research institutions (A) and the proportion of papers published by research institutions from 2013 to 2023 (B) related to targeted therapy in TC. TC = thyroid carcinoma.

Table 2

The top 10 productive journals related to targeted therapy in TC

Rank	Journal	Publications	IF(JCR2023)	JCR quartile
1	Cancers	32	4.5	Q1
2	Thyroid	32	6	Q1
3	Frontiers in Endocrinology	23	3.9	Q2
4	Frontiers in Oncology	22	3.5	Q2
5	Endocrine-Related Cancer	21	4.1	Q2
6	International Journal of Molecular Sciences	17	4.9	Q1
7	Endocrine	12	3	Q2
8	Expert Review of Anticancer Therapy	11	2.9	Q2
9	Oncology Letters	11	2.5	Q3
10	Journal of Clinical Endocrinology & Metabolism	10	5	Q1

TC = thyroid carcinoma.

connecting multiple disciplines. These findings align with the growing trend of interdisciplinary approaches in TC-targeted therapy, which integrate knowledge across biological, pharmacological, and clinical fields. This analysis underscores Oncology as the central research focus, with related disciplines playing supporting roles to drive innovation. Future studies should continue to strengthen these interdisciplinary connections to facilitate breakthroughs in TC-targeted therapies and improve clinical outcomes.

3.5. Authors and co-cited authors

Between 2013 and 2023, the domain of targeted therapies for TC benefited from the contributions of a total of 4309 authors. The top ten authors, outlined in Table 4, are spearheaded by Cabanillas, Maria E. with 29 publications. Antonelli, Alessandro closely follows with 17 publications, and Busaidy, Naifa L. also with 17 publications. A more in-depth analysis reveals a diverse geographical distribution among these leading authors, with Italy boasting the majority at 5 authors, the United States with 4 authors, and France with 1 author each. To describe the collaboration among these researchers, we used VOSviewer software for visualization, setting the minimum number of documents to 3. Each node represents an author, resulting in Figure 8A. To depict the collaboration among these researchers, we employed VOSviewer software to visualize the network, where each node represents an author. Thicker lines indicate more substantial collaboration, and different colors denote various publication years. Figure 8B presents a co-citation network of authors, highlighting the most frequently co-cited scholars in the field. Out of 21,901 co-citation authors, we set the minimum document count to 40, resulting in 96 authors displayed. Leading this list is Schlumberger, Martin, with 389 citations, trailed by Brose, M. S., with 360 citations, and Cabanillas, Maria E., with 338 citations – all summarized in Table 4.

3.6. Co-cited references and reference with citation bursts

Between 2013 and 2023, we amassed a total of 31,740 co-cited references related to TC-targeted therapies. As shown in Figure 9, we set the minimum threshold at 25 co-citations, resulting in a total of 112 references being included in the visualization. To address the frequent citation of specific papers, we constructed co-citation networks and identified conceptual clusters. Table 5 presents the top 10 co-cited references, led by the study from Schlumberger, Martin et al[23] this study finds that lenvatinib significantly improves progression-free survival and response rates in patients with thyroid cancer refractory to iodine-131, though it also increases adverse effects.

Citation bursts are a sudden and significant increase in the number of citations to a particular paper or research area over a period of time.[24] This phenomenon is significant in the evaluation and tracking of scientific research and can help identify the focus of academic attention. Using CiteSpace, we found 191 references in the field of TC targeted therapies that exhibited a significant citation burst. Figure 10 illustrates the top 25 references where the outbreak was most pronounced. The paper by Brose MS[25] mentioned above shows a maximum citation burst

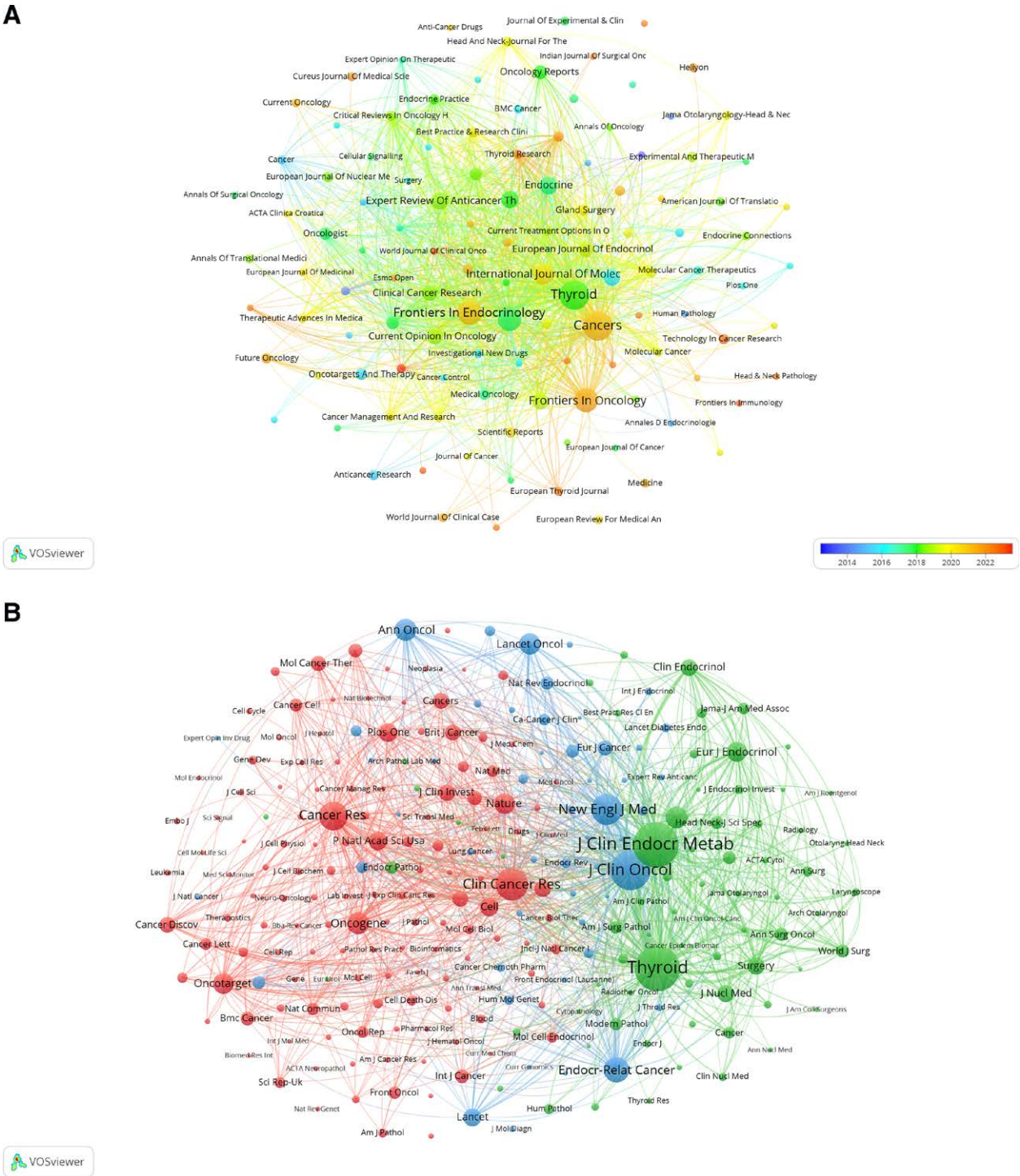


Figure 5. Visualization of contributing journals (A) and co-cited journals (B) in targeted therapy in TC. TC = thyroid carcinoma.

intensity of 22.44 reached between 2015 and 2019. The citation bursts for these references initially occurred in 2009 and ranged in intensity from 9.09 to 22.44, with durations ranging from 1 to 4 years.

3.7. Hotspots and frontiers

The keywords succinctly summarize the basic concepts of the paper and summarize the core areas of the study. We analyzed 1541 author keywords from 736 documents with VOSviewer, of which 112 met the minimum criteria, i.e., at least 3 documents were required for each keyword. Figure 11A illustrates a network visualization map that displays the connections between keyword co-occurrences. The degree of brightness corresponds to the frequency of keyword occurrences. In addition to keywords related to the title of this article, high impact keywords include tyrosine kinase inhibitors (TKIs), anaplastic thyroid carcinoma and differentiated thyroid cancer.

In Figure 11B, cluster analysis via CiteSpace yielded 9 clusters, which are detailed in Figure 11B, ranging from "tyrosine kinase inhibitors" to "molecular mechanisms." The modularity (Q) value above 0.3 and silhouette (S) value above 0.7, obtained in our analysis (Q = 0.338, S = 0.7031), affirm the robustness

and significance of these clusters. Top 25 keywords with the strongest citation bursts are shown in Figure 11C, meaning keywords with a sharp increase in citations over a certain period of time, with the intensity of the bursts indicated, along with the corresponding start and end years. In recent 5 years, the most popular keywords included "dabrafenib," "radioactive iodine," "association guidelines," "positive solid tumors," and "invassion."

4. Discussion

Conventional radiotherapy and chemotherapy are limited in the treatment of TC. Therefore, many studies have shifted their focus to targeted therapies with the aim of exploring more effective treatment strategies. In recent years, extensive research has been focused on delving into the field of targeted therapy for TC. Despite the continued emergence of research findings on this field, there is still a gap in publications centered on bibliometrics. Therefore, to fill this gap, this study conducted a bibliometric and visualization analysis of medical papers on targeted therapy for TC from 2013 to 2023. This study examines 763 publications, investigating essential aspects such as publication trends, geographic distribution, institutions, journals, authors, citations, key hotspots, and noteworthy perspectives within the realm of targeted therapy for TC. This offers a more comprehensive research perspective in the field.

Table 3

Top 10 journals for co-citation of targeted therapy in TC

Rank	Cited journal	Citation	IF(JCR2023)	JCR quartile
1	Thyroid	2822	6	Q1
2	Journal of Clinical Endocrinology & Metabolism	2770	5	Q1
3	Journal of Clinical Oncology	2182	42.1	Q1
4	Clinical Cancer Research	1422	10.4	Q1
5	New England Journal of Medicine	1342	96.3	Q1
6	Cancer Research	1147	12.5	Q1
7	Endocrine Related Cancer	881	4.1	Q2
8	Annals of Oncology	679	56.7	Q1
9	Cancer	679	6.1	Q1
10	Oncogene	660	6.9	Q1

TC = thyroid carcinoma.

Assessing research strength through publication and citation metrics spotlights the United States as a leader in TC-targeted therapy, with significant contributions from 2013 to 2023. Visualized collaboration data reveals a strong partnership between top contributing countries, especially the U.S., China, and Italy. The presence of leading U.S. institutions like MD Anderson and Sloan-Kettering in global research dialogs highlights America's key role in pioneering TC therapies and driving international research collaboration.

Between 2013 and 2023, research on TC targeted therapy was notably published across 336 journals. *Cancers* led with 32 papers, followed by *Thyroid* and *Frontiers in Endocrinology*. The field's interdisciplinarity is evident from co-citation analysis, showing significant cross-disciplinary engagement, particularly in surgery, endocrinology, and genetics. This highlights the growing need for interdisciplinary collaboration to enrich research perspectives. As an emerging research direction, the relatively modest number of papers addressing targeted therapy for TC can be attributed to the nascent stage of the field and the inherent characteristics of the research cycle. As the research deepens and the field matures, we anticipate that pertinent studies will progressively accumulate, contributing significantly to the advancement of TC targeted therapy.

Analyzing scholars in the field allows us to understand the academic landscape comprehensively, helping identify representative and core players. Studying their achievements deepens our grasp of their unique contributions and innovations. This not only clarifies research focus and hotspots but also guides the discipline's strategic development. As shown in Table 4 and Figure 8A, Prof Cabanillas, Maria E is a leader in article publication, which highlights his prominent impact in the field of TC-targeted therapies. According to Web of Science, Professor Cabanillas, Maria E works at the University of Texas MD Anderson Carcinoma Center in the areas of endocrinology and metabolism, oncology, and biology, among others. In 2018, he published an article in the *Journal of Clinical Oncology* with a paper titled "Dabrafenib and Trametinib Treatment in Patients With Locally Advanced or Metastatic BRAF V600-Mutant Anaplastic Thyroid Carcinoma,"[26] a paper that made a significant contribution to research on targeted therapies for TC. This study reported the efficacy and safety of combination therapy with dabrafenib (BRAF inhibitor) and trametinib (MEK inhibitor) in BRAF V600E-mutated anaplastic thyroid carcinoma (ATC). Previously, treatment options for ATC were quite limited, and specific targeted therapies were lacking in the clinic. This study fills the gap in the systemic treatment of ATC with the BRAF V600E mutation, providing a clinically beneficial treatment option for this rare carcinoma. As shown in Table 4

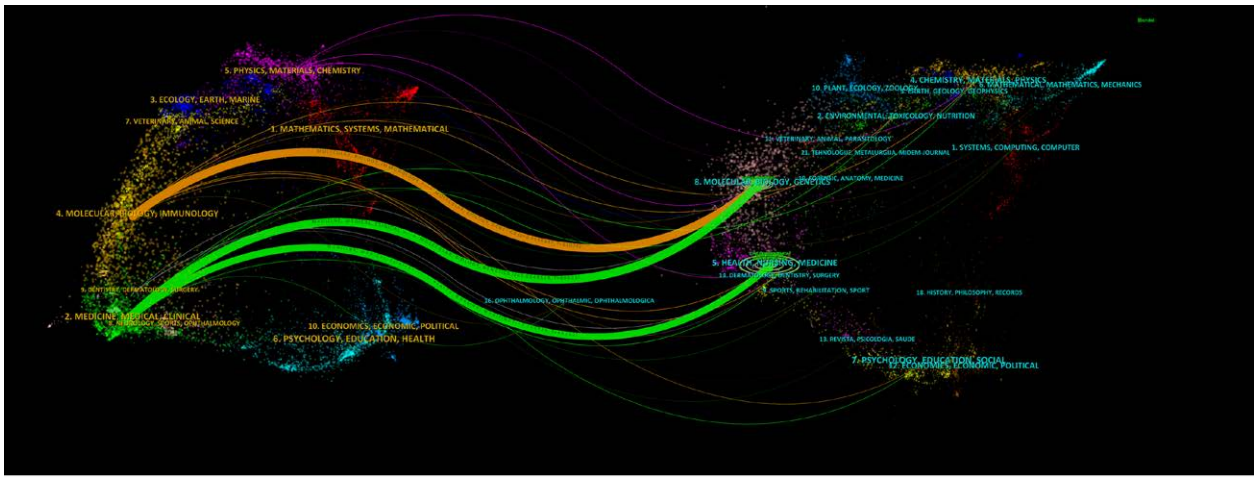


Figure 6. The dual-map overlay of journals for targeted therapy in TC. TC = thyroid carcinoma.

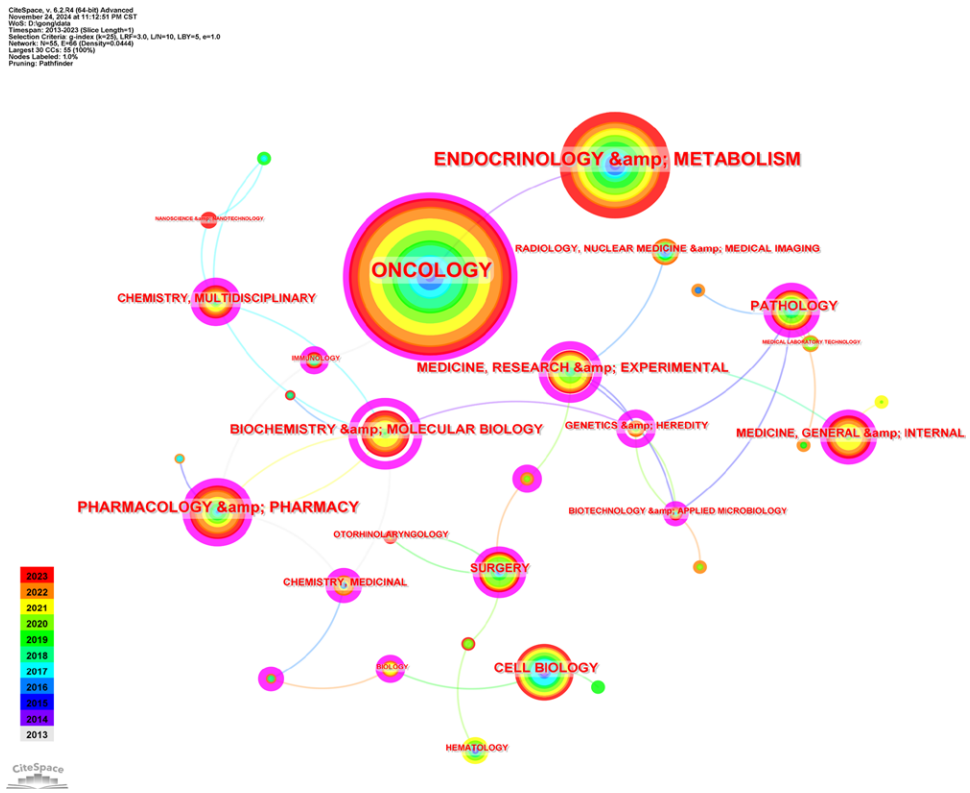


Figure 7. Category co-occurrence network knowledge map for targeted therapy in TC. TC = thyroid carcinoma.

Table 4

Top 10 authors and co-cited authors on research of targeted therapy in TC

Rank	Authors	Location	Publications	Co-cited authors	Location	Citations
1	Cabanillas, Maria E.	USA	29	Schlumberger, Martin	France	389
2	Antonelli, Alessandro	Italy	17	Brose, M. S.	USA	360
3	Busaidy, Naifa L.	USA	17	Cabanillas, Maria E.	USA	338
4	Fallahi, Poupak	Italy	16	Xing, Mingzhao	China	283
5	Ferrari, Silvia Martina	Italy	14	Subbiah, Vivek	USA	280
6	Dadu, Ramona	USA	11	Wells, Samuel	USA	267
7	Materazzi, Gabriele	Italy	11	Elisei, Rossella	Italy	237
8	Subbiah, Vivek	USA	11	Bible, Keith C.	USA	214
9	Schlumberger, Martin	France	10	A.Antonelli, Alessandro	Italy	195
10	Ulisse, Salvatore	Italy	10	Nikiforov, YE	USA	191

TC = thyroid carcinoma.

and Figure 8B, Prof Schlumberger, Marti at the Gustave Roussy Institute is recognized for his contributions to the field of targeted therapy for TC, and his research has been widely cited. The number of citations is 447, reflecting the importance of his research in the international academic community. He was a major contributor to Lenvatinib versus Placebo in Radioiodine-Refractory Thyroid Carcinoma, a phase 3 study investigating the oral inhibitor lenvatinib,[23] which targets a variety of receptors, and which demonstrated significant therapeutic benefits in iodine-refractory thyroid carcinoma (IRTC). advantage. Prof Schlumberger, Marti has been involved in the writing of several guidelines.[20,27,28]

Co-citation analysis is pivotal for identifying impactful research and establishing the network within the academic community, aiding in literature searches and highlighting research trends in TC targeted therapies. Figure 9 and Table 5 reveal a focus on influential trials and guidelines shaping treatment approaches, particularly for challenging differentiated thyroid carcinoma cases like iodine-refractory and metastatic types. Studies on targeted agents, including Sorafenib and Lenvatinib, illustrate their significant role in improving patient outcomes. This underlines the importance of integrated strategies and multi-agent therapies in managing TC, reinforcing the ongoing need for innovative treatments and informing future research directions in the field.

Co-cited references serve as a crucial tool for assessing impact, pinpointing research hotspots, establishing disciplinary networks, and conducting literature searches. This facilitates a comprehensive understanding of the structure and dynamics of the academic community, fostering interdisciplinary cooperation and disciplinary development. As depicted in Figure 9 and Table 5, these publications collectively center on targeted therapies for TC and encompass a variety of widely referenced studies. Firstly, they represent crucial clinical trials or guidelines that furnish the medical community with vital insights into treatment strategies and management. Secondly, these works concentrate on diverse forms of differentiated thyroid carcinoma, including iodine-refractory, locally advanced, or

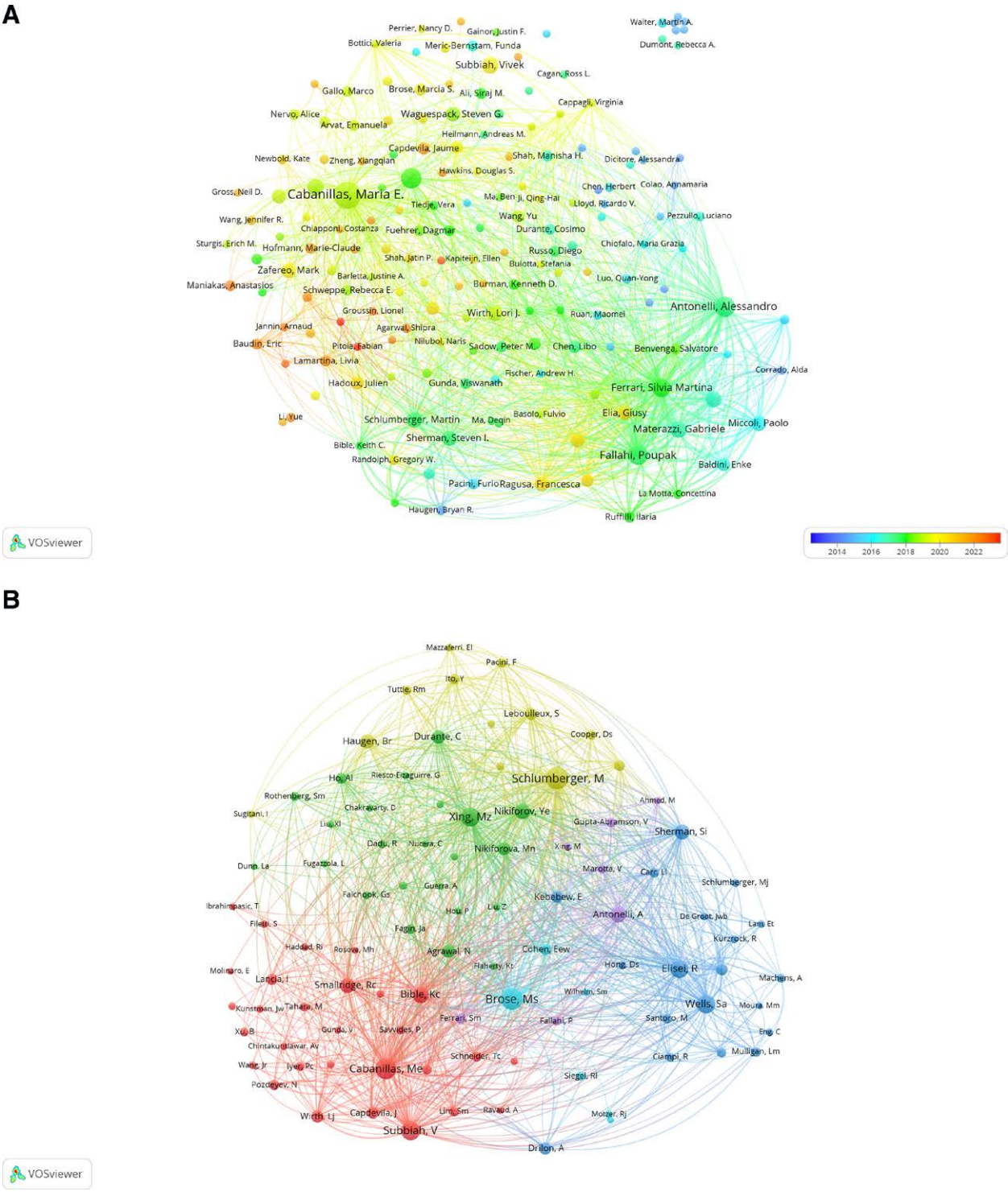


Figure 8. Visualization of authors (A) and co-cited authors (B) on research of targeted therapy in TC. TC = thyroid carcinoma.

metastatic cases, underscoring the pivotal role of targeted therapy in such scenarios. Lastly, these studies involve a spectrum of targeted agents, such as Sorafenib, Vandetanib, Lenvatinib, Cabozantinib, etc.[23,25,26,29–31] Moreover, several of them underscore the clinical effectiveness of targeted therapies and their impact on patient survival, providing substantial evidence to enhance patient prognosis.[32] This emphasizes the critical role of comprehensive treatment strategies and multi-targeted interventions in the management of TC. The comprehensive nature of these contributions reflects the pressing need for more effective TC treatments within the academic community. Additionally, it offers valuable guidance for future research and clinical practices, thereby establishing a solid foundation for the advancement of targeted therapy in the TC field.

The "top 25 references with the strongest citation bursts" are commonly used to identify studies in a specific academic field that have received considerable attention during a certain period, often indicating research hotspots or significant scientific advancements The marked citation bursts of Brose MS et al's 2014 paper signal its major impact, potentially offering

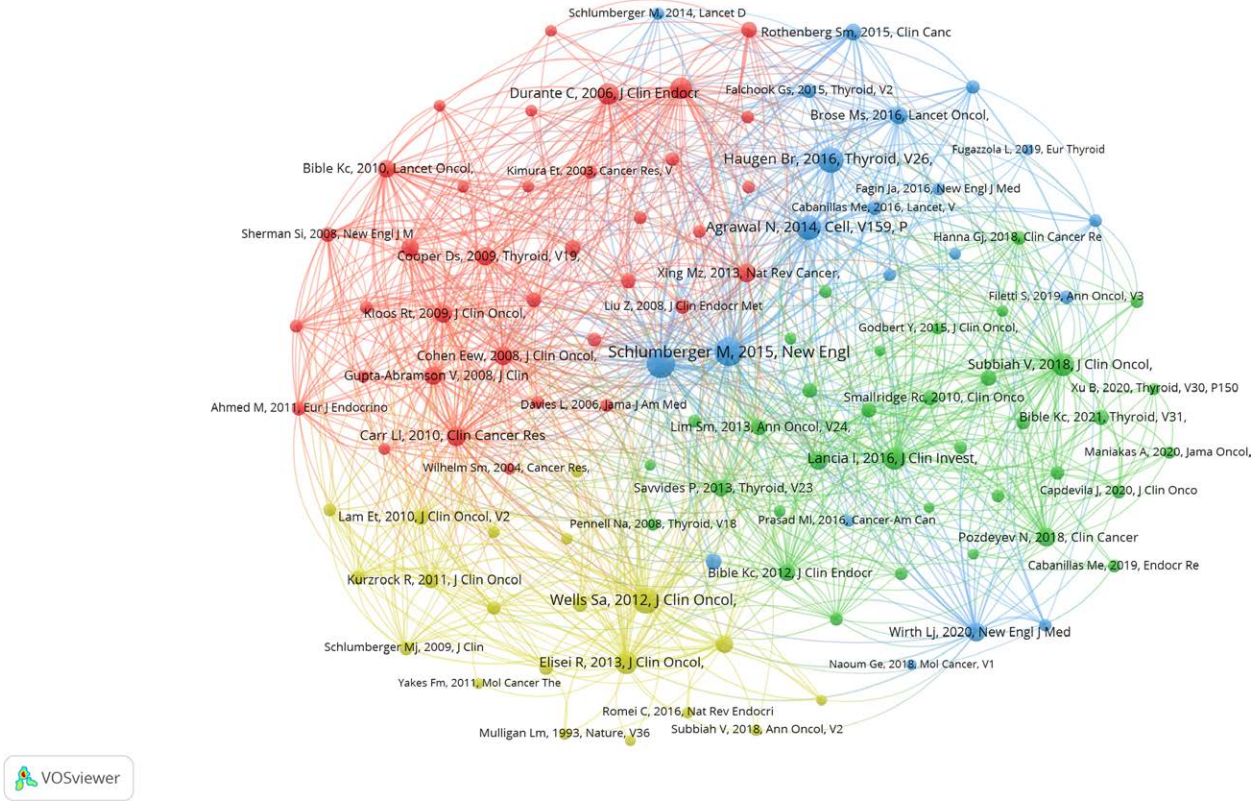


Figure 9. Visualization of co-cited references of targeted therapy in TC. TC = thyroid carcinoma.

groundbreaking clinical trial results that reshaped TC targeted therapy practices. Agrawal N et al.'s work, starting its citation surge later, likely contributed novel genomic understandings, influencing research directions. Haugen BR et al's guidelines, with sustained citations through 2021, reflect their comprehensive approach to thyroid cancer management, continuing to influence diagnostic and treatment strategies. These studies are milestones in the TC field, not just filling existing knowledge gaps but also forging new paths for research and clinical management, reflected in their substantial citation intensities and periods of influence. Their continued relevance in citations underscores their transformative role in the evolving landscape of TC targeted therapies.

10B shows a keyword cluster analysis map of the scientific literature, where keywords are grouped into clusters, each representing a set of closely related topics or concepts. This type of analysis is valuable for identifying research trends, discovering potential research gaps, and providing guidance for future research directions. The keywords in the image can be categorized based on the type of research focus they represent in the field of TC:

4.1. Types of medications and mechanisms of action

This theme is a cluster of keywords for Treatment and Therapy includes "TKIs", "BRAF mutations," and "Molecular Mechanisms." TKIs and BRAF mutations are components of molecular mechanisms that influence cell signal pathways and the molecular regulation of tumor development.

Carcinoma is almost always caused by dysregulated cell signaling pathways leading to uncontrolled proliferation.[33] Tyrosine kinases-receptors catalyze the transfer of phosphate groups from adenosine triphosphate (ATP) to hydroxyl groups in the tyrosine residues of proteins.[34] TKIs as a newly developed class of drugs, are able to block the proliferation of malignant cells by competitively binding to the tyrosine kinases-receptors at the ATP binding pocket site.[35] "TKIs" play a pivotal role in the treatment of TC, particularly in the targeted therapy of IRTC, medullary thyroid carcinoma and ATC.[29,36,37]

These drugs act by inhibiting the activity of tyrosine kinases, which are enzymes that play a central role in the activation of several key signaling pathways within carcinoma cells. The pathways affected include the MAPK/ERK pathway, regulated by "ras" gene mutations and controlling cell proliferation and differentiation[38]; the PI3K/AKT/mTOR pathway, associated with cell survival and metabolism[39,40]; the VEGF/VEGFR pathway, which is key for angiogenesis[41]; the RET signaling pathway, critical in specific types of TCs like medullary thyroid carcinoma.[42,43] Abnormal increases in the activities of tyrosine kinases such as VEGFR, EGFR, and RET are often found in the development of TC. These multi-targeted tyrosine kinase inhibitors, including Sorafenib, Vandetanib, Lenvatinib, and Cabozantinib, effectively target and inhibit these overactive kinases, thereby suppressing tumor growth and offering a more precise and personalized treatment option for thyroid carcinoma.[23,25,29,44] TKIs disrupt these kinases, curtailing tumor growth and offering a more precise, personalized treatment approach. This targeted intervention is vital in managing TC by addressing the specific molecular abnormalities driving its growth.

BRAF mutations, particularly the V600E mutation, play a critical role in the pathogenesis of TC.[45] This specific mutation results in a substitution of valine (V) by glutamic acid (E) at the 600th position in the BRAF protein, leading to its constitutive activation.[46] Normally, BRAF is a part of the MAPK/ERK signaling pathway, which controls cell division and differentiation.[47] However, when mutated, BRAF leads to uncontrolled cell proliferation by continuously signaling cells to grow and divide, even in the absence of external growth signals.[48]

Table 5

Ranking of the top 10 co-cited references for targeted therapy in TC

Rank	Reference	Citation	Year	First author	Journal
1	Lenvatinib versus Placebo in Radioiodine-Refractory Thyroid Cancer	156	2015	Schlumberger, Martin	New England Journal of Medicine
2	Sorafenib in radioactive iodine-refractory, locally advanced or metastatic differentiated thyroid cancer: a randomized, double-blind, phase 3 trial	152	2014	Brose, Marcia S.	Lancet
3	Vandetanib in Patients With Locally Advanced or Metastatic Medullary Thyroid Cancer: A Randomized, Double-Blind Phase III Trial	130	2012	Wells, Samuel A., Jr.	Journal of Clinical Oncology
4	2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer	123	2016	Haugen, Bryan R.	Thyroid
5	Integrated genomic characterization of papillary thyroid carcinoma	113	2014	Agrawal, Nishant	Cell
6	Genomic and transcriptomic hallmarks of poorly differentiated and anaplastic thyroid cancers	100	2016	Lancia, Inigo	Journal of Clinical Investigation
7	Cabozantinib in progressive medullary thyroid cancer	99	2012	Elisei, Rossella	Journal of Clinical Oncology
8	Dabrafenib and Trametinib Treatment in Patients With Locally Advanced or Metastatic BRAF V600-Mutant Anaplastic Thyroid CancerDabrafenib and Trametinib Treatment in Patients With Locally Advanced or Metastatic BRAF V600-Mutant Anaplastic Thyroid Cancer	97	2018	Subbiah, Vivek	Journal of Clinical Oncology
9	Long-term outcome of 444 patients with distant metastases from papillary and follicular thyroid carcinoma: Benefits and limits of radioiodine therapy	91	2006	Durante, C.	Journal of Clinical Endocrinology & Metabolism
10	Selumetinib-Enhanced Radioiodine Uptake in Advanced Thyroid Cancer	89	2013	Ho, Alan L.	New England Journal of Medicine

TC = thyroid carcinoma.

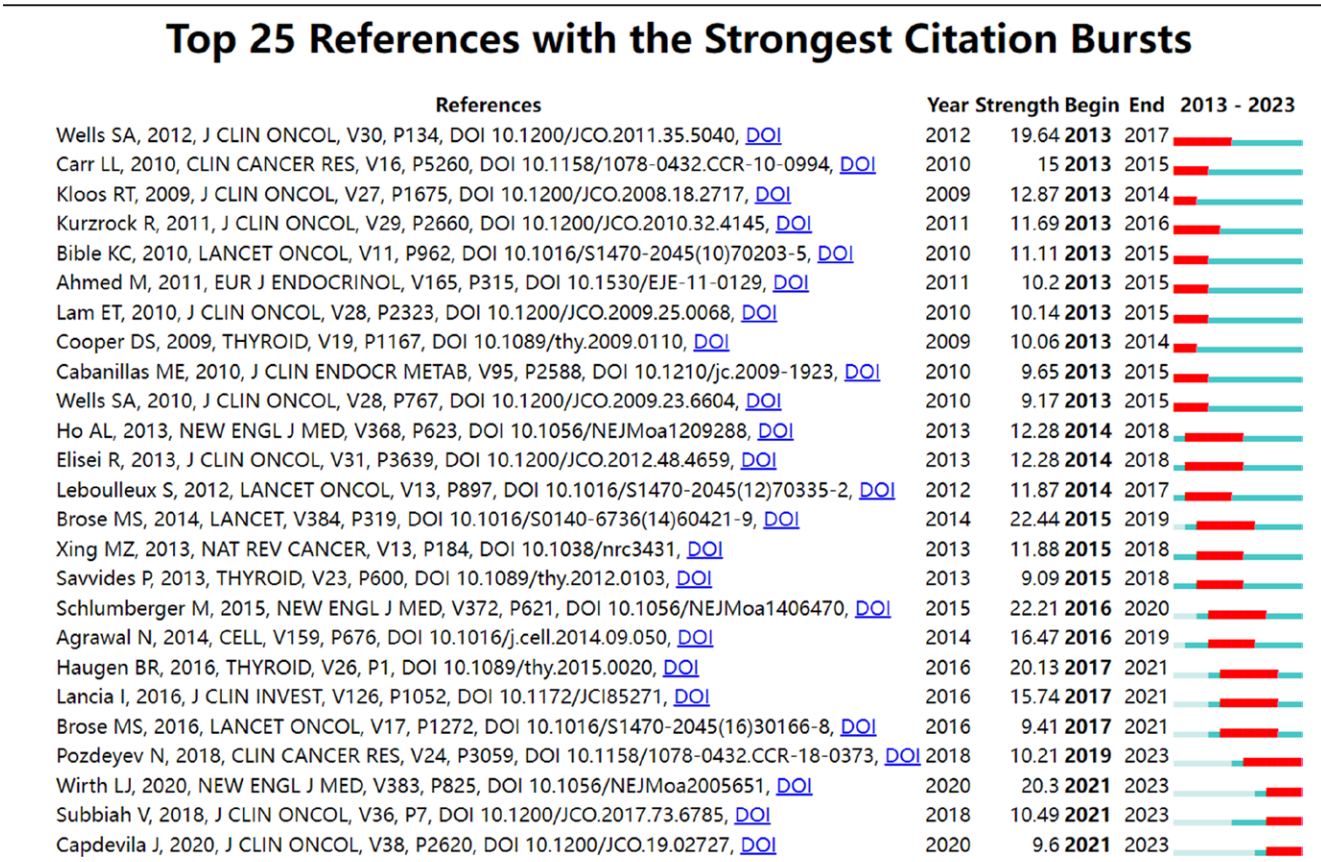
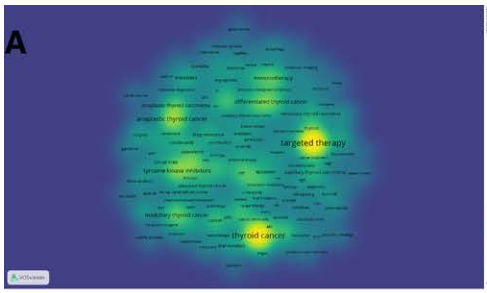
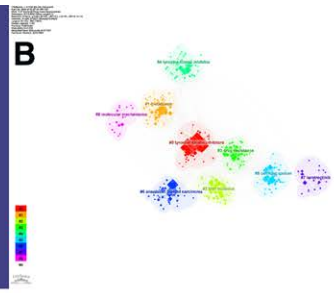


Figure 10. The top 25 references with strong citation bursts of targeted therapy in TC. TC = thyroid carcinoma.

Drugs that target BRAF mutations, known as BRAF inhibitors, are designed specifically to bind to the ATP-binding site of the mutated BRAF protein, effectively inhibiting its kinase activity.[49] This inhibition stops the abnormal growth signal that the mutant protein would otherwise send, thereby halting the proliferation of cancer cells. Examples of such drugs include vemurafenib and dabrafenib. A study found that vemurafenib treatment increased RAI uptake in patients with IRTC, leading to tumor regressions. The drug's efficacy is linked to its inhibition of the MAPK pathway, resulting in upregulated





C Top 25 Keywords with the Strongest Citation Bursts

Keywords	Year	Strength	Begin	End	2013 - 2023
phase ii trial	2013	7.1	2013	2015	
phase ii	2013	6.52	2013	2014	
sorafenib	2013	5.24	2013	2015	
growth factor receptor	2013	3.86	2013	2017	
multiple endocrine neoplasia	2013	3.49	2013	2014	
renal cell carcinoma	2013	3.08	2013	2014	
kinase inhibitors	2013	2.77	2013	2015	
medullary thyroid carcinoma	2013	2.74	2013	2014	
genetic alterations	2013	2.72	2013	2014	
braf(v600e) mutation	2014	4.37	2014	2017	
ret protooncogene	2014	4.07	2014	2017	
high prevalence	2014	3.18	2014	2016	
in vivo	2014	3.01	2014	2018	
papillary carcinomas	2014	2.9	2014	2016	
endothelial growth factor	2014	6.53	2015	2017	
papillary thyroid carcinoma	2013	3.15	2015	2018	
vemurafenib	2016	2.99	2016	2019	
lung cancer	2016	2.98	2016	2018	
lenvatinib	2018	3.34	2018	2020	
cells	2016	3.53	2019	2020	
invasion	2019	3.09	2019	2023	
positive solid tumors	2021	3.94	2021	2023	
association guidelines	2016	3.64	2021	2023	
radioactive iodine	2014	3.55	2021	2023	
dabrafenib	2021	3.02	2021	2023	

Figure 11. Visualization of keywords (A), keyword clusters (B), and top 25 keywords (C) with the strongest citation bursts on research of targeted therapy in TC. TC = thyroid carcinoma.

thyroid-specific gene expression.[50] In a recent clinical phase II trial, dabrafenib combined with trametinib demonstrated efficacy in treating ATC, achieving an overall response rate of 56% among 36 patients and a median duration of response of 14.4 months.[51] This precision makes BRAF inhibitors an invaluable component of personalized cancer treatment strategies, offering hope to patients with previously difficult-to-treat or advanced-stage cancers.

4.2. Specific pathological states and drug responses

This section explores 4 clusters: "Drug Resistance," "Metastasis," "Non-Small Cell Lung Cancer (NSCLC)," and "Larotrectinib." While each focus on distinct challenges, they interlink through shared treatment strategies, highlighting the intricate nature of cancer therapy.

Drug resistance continues to be a major hurdle in the treatment of cancers,[52,53] including TC. Understanding and

overcoming drug resistance is crucial for enhancing therapeutic outcomes and is a key focus of current cancer research. This area of study is essential for developing novel strategies that can prevent or circumvent resistance, ultimately improving patient survival rates.

While lymph node metastasis is common in TC,[54,55] distant metastases, particularly to the lung, brain and bones, are less frequent but significantly worsen prognosis.[55,56] Pulmonary metastases, often asymptomatic initially, are detected through elevated thyroglobulin levels or imaging.[57] Research has identified specific signaling pathways and cell-cell interactions, such as the TGF-beta pathway's role in promoting epithelial-to-mesenchymal transition, that facilitate the migration of cancer cells from the primary tumor site to distant organs.[58,59] Epithelial-to-mesenchymal transition enables thyroid cancer cells to gain migratory and invasive properties, aiding their spread to other parts of the body. Future research in targeted therapy for thyroid cancer should continue to explore these pathways and interactions, focusing on the development of new inhibitors to better manage and potentially prevent metastasis, thereby improving outcomes for patients.

Research in NSCLC significantly informs targeted therapies for thyroid cancer, particularly due to shared resistance mechanisms in molecular pathways. The use of TKIs in NSCLC, effective against mutations like EGFR and ALK, offers a model for overcoming similar resistance in thyroid cancers.[60,61] This interrelation highlights the value of molecular profiling in personalizing cancer treatment, allowing for therapies tailored to specific genetic markers. Leveraging NSCLC research can thus enhance outcomes in TC by improving our understanding and treatment of drug resistance.

With central nervous system activity, Larotrectinib is a highly selective and potent TRK inhibitor.[62] These genetic anomalies are rare but critical drivers of tumorigenesis and are often not amenable to conventional therapeutic modalities. By inhibiting TRK proteins that arise from NTRK fusions, Larotrectinib directly intervenes in the molecular pathways essential for tumor cell survival and proliferation, thereby offering a targeted therapeutic option.[63] Several studies have shown[64,65] that Larotrectinib offers potentially durable responses and a new treatment paradigm that could reduce reliance on more invasive and burdensome conventional therapies. The development and application of targeted therapies like Larotrectinib expand treatment possibilities for thyroid cancer patients, enabling more individuals to benefit from precision medicine tailored to specific genetic profiles. Such stratification enhances the efficacy of treatment regimens, reflecting a significant shift towards individualized cancer therapy based on specific molecular characteristics, and represents a substantial advancement in the therapeutic landscape for TC and beyond.

4.3. Specific types of cancer

This part includes only one cluster: "ATC." ATC stands out as a rare yet notably aggressive variant, notoriously resistant to conventional treatments, thus highlighting the urgent need for groundbreaking, targeted therapeutic research. Due to certain features in the molecular mechanisms of undifferentiated thyroid carcinoma, such as elevated levels of programmed cell death-ligand 1/programmed death-ligand 1 and increased neoangiogenesis via VEGFR/FGFR signaling, the combination of targeted therapies with immunotherapy has emerged as a new focal point.[66–68] For instance, combining lenvatinib with pembrolizumab has indicated a more effective treatment approach compared to single-agent immunotherapy.[69]

5. Limitation

The limitations of this study are that the literature analyzed was obtained only from WOSCC and only English publications were considered. The type of literature covered in this study was limited to articles and reviews. Although this study included all pathologic types of TC, it was not meticulously categorized, which may have biased the data. In addition, bibliometric studies need to be updated to reflect the latest research trends.

6. Conclusions

This study summarizes worldwide research trends on targeted therapy for TC. In this context, the journal *Cancers* published the most relevant research results. The United States are at the forefront of this research field, also in citation count. The University of Texas MD Anderson Carcinoma Center has made notable contributions, publishing a large number of relevant papers. The research frontiers mainly cover specific types of TC, targeted therapies, and drug development. The bibliometric analysis in this paper provides an overview of the current state of research in targeted therapies for TC, identifying key research contributions, trends, and potential directions for future research.

Acknowledgments

Thanks to the editors and reviewers for their hard work and important comments.

Author contributions

Conceptualization: Yu Mao, Fei Ye.
Data curation: Yu Mao, Fei Ye.
Formal analysis: Yu Mao, Fei Ye, Sushun Liu.
Investigation: Qin Jiang.
Project administration: Yi Gong.
Supervision: Yi Gong.
Validation: Sushun Liu.
Visualization: Yu Mao, Qin Jiang.
Writing – original draft: Yu Mao.
Writing – review & editing: Yi Gong.

References

[1] Pstrąg N, Ziemnicka K, Bluyssen H, Wesoły J. Thyroid cancers of follicular origin in a genomic light: in-depth overview of common and unique molecular marker candidates. Mol Cancer. 2018;17:116.
[2] Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin. 2011;61:69–90.
[3] Suzuki K, Iwai H, Utsunomiya K, et al. Efficacy of combination therapy with lenvatinib and radioactive iodine in thyroid cancer preclinical model. Int J Mol Sci . 2022;23:9872.
[4] Jin S, Liu X, Peng D, Li D, Ye Y-N. Differences between cancer-specific survival of patients with anaplastic and primary squamous cell thyroid carcinoma and factors influencing prognosis: a SEER Database Analysis. Front Endocrinol. 2022;13:830760.
[5] Lin C-L, Tsai M-L, Lin C-Y, et al. HDAC1 and HDAC2 double knockout triggers cell apoptosis in advanced thyroid cancer. Int J Mol Sci. 2019;20:454.
[6] Chan BA, Hughes BGM. Targeted therapy for non-small cell lung cancer: current standards and the promise of the future. Transl Lung Cancer Res. 2015;4:36–54.
[7] Ocana A, Pandiella A, Siu LL, Tannock IF. Preclinical development of molecular-targeted agents for cancer. Nat Rev Clin Oncol. 2010;8:200–9.
[8] Comunanza V, Corà D, Orso F, et al. VEGF blockade enhances the antitumor effect of BRAFV600E inhibition. EMBO Mol Med. 2017;9:219–37.
[9] Krug AK, Enderle D, Karlovich C, et al. Improved EGFR mutation detection using combined exosomal RNA and circulating tumor DNA in NSCLC patient plasma. Ann Oncol. 2018;29:2143.

[10] Cabanillas ME, Ryder M, Jimenez C. Targeted therapy for advanced thyroid cancer: kinase inhibitors and beyond. Endocr Rev. 2019;40:1573–604.
[11] Fallahi P, Ferrari SM, Galdiero MR, et al. Molecular targets of tyrosine kinase inhibitors in thyroid cancer. Semin Cancer Biol. 2022;79:180–96.
[12] Ancker OV, Krüger M, Wehland M, Infanger M, Grimm D. Multikinase inhibitor treatment in thyroid cancer. Int J Mol Sci. 2019;21:10.
[13] Yang J, Wu J, Lu H, Wang J, Hou Z. Hotspot analysis and frontier exploration of stem cell research in intervertebral disc regeneration and repair: a bibliometric and visualization study. World Neurosurg. 2024;184:e613–32.
[14] Hou Z, Wang W, Su S, et al. Bibliometric and visualization analysis of biomechanical research on lumbar intervertebral disc. J Pain Res. 2023;16:3441–62.
[15] Li F, Zhang D, Chen J, Tang K, Li X, Hou Z. Research hotspots and trends of brain-computer interface technology in stroke: a bibliometric study and visualization analysis. Front Neurosci. 2023;17:1243151.
[16] Kumar R, Pippal PS, Kumar R, Kumar P, Singh A, Sharma P. The global scenario of hydrogeochemical research on glacier meltwater: a bibliometric and visualization analysis. Environ Sci Pollut Res Int. 2023;30:74612–27.
[17] van Eck NJ, Waltman L. Software survey: VOSviewer, a computer program for bibliometric mapping. Scientometrics. 2010;84:523–38.
[18] Chen C. Searching for intellectual turning points: progressive knowledge domain visualization. Proc Natl Acad Sci USA. 2004;101(Suppl 1):5303–10.
[19] Synnestvedt MB, Chen C, Holmes JH. CiteSpace II: visualization and knowledge discovery in bibliographic databases. AMIA Annu Symp Proc. 2005;2005:724–8.
[20] Haugen BR, Alexander EK, Bible KC, et al. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid. 2016;26:1–133.
[21] Yang J, Wu J, Han T, et al. Global research hotspots and frontiers of myasthenia gravis from 2002 to 2021: a bibliometric study. Medicine (Baltim). 2023;102:e34002.
[22] Zhong Y, Wang J, Liang Z, Han T, Lu H, Hou Z. Bibliometric and visualization analysis of research hotspots and frontiers in endoscopic lumbar discectomy. J Pain Res. 2024;17:2165–90.
[23] Schlumberger M, Tahara M, Wirth LJ, et al. Lenvatinib versus placebo in radioiodine-refractory thyroid cancer. N Engl J Med. 2015;372:621–30.
[24] Zhang J, Chen P, Miao L. A bibliometric and scientific knowledge-map study of the chimeric antigen receptor (CAR) natural killer (NK) cell-related research from 2010 to 2022. Front Immunol. 2022;13:969196.
[25] Brose MS, Nutting CM, Jarzab B, et al; DECISION investigators. Sorafenib in radioactive iodine-refractory, locally advanced or metastatic differentiated thyroid cancer: a randomised, double-blind, phase 3 trial. Lancet. 2014;384:319–28.
[26] Subbiah V, Kreitman RJ, Wainberg ZA, et al. Dabrafenib and Trametinib treatment in patients with locally advanced or metastatic BRAF V600-mutant anaplastic thyroid cancer. J Clin Oncol. 2018;36:7–13.
[27] Cooper DS, Doherty GM, Haugen BR, et al.; American Thyroid Association (ATA) Guidelines Taskforce on Thyroid Nodules and Differentiated Thyroid Cancer. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid. 2009;19:1167–214.
[28] Pacini F, Schlumberger M, Dralle H, Elisei R, Smit JWA, Wiersinga W; European Thyroid Cancer Taskforce. European consensus for the management of patients with differentiated thyroid carcinoma of the follicular epithelium. Eur J Endocrinol. 2006;154:787–803.
[29] Wells SA, Robinson BG, Gagel RF, et al. Vandetanib in patients with locally advanced or metastatic medullary thyroid cancer: a randomized, double-blind phase III trial. J Clin Oncol. 2012;30:134–41.
[30] Elisei R, Schlumberger MJ, Müller SP, et al. Cabozantinib in progressive medullary thyroid cancer. J Clin Oncol. 2013;31:3639–46.
[31] Ho AL, Grewal RK, Leboeuf R, et al. Selumetinib-enhanced radioiodine uptake in advanced thyroid cancer. N Engl J Med. 2013;368:623–32.
[32] Durante C, Haddy N, Baudin E, et al. Long-term outcome of 444 patients with distant metastases from papillary and follicular thyroid carcinoma: benefits and limits of radioiodine therapy. J Clin Endocrinol Metab. 2006;91:2892–9.
[33] Du Z, Lovly CM. Mechanisms of receptor tyrosine kinase activation in cancer. Mol Cancer. 2018;17:58.
[34] Hanks SK, Quinn AM, Hunter T. The protein kinase family: conserved features and deduced phylogeny of the catalytic domains. Science. 1988;241:42–52.
[35] Roskoski R. Properties of FDA-approved small molecule protein kinase inhibitors. Pharmacol Res. 2019;144:19–50.
[36] Busaidy NL, Konda B, Wei L, et al. Dabrafenib Versus Dabrafenib + Trametinib in BRAF-mutated radioactive iodine refractory differentiated thyroid cancer: results of a randomized, Phase 2, Open-Label Multicenter Trial. Thyroid. 2022;32:1184–92.
[37] Capdevila J, Wirth LJ, Ernst T, et al. PD-1 blockade in anaplastic thyroid carcinoma. J Clin Oncol. 2020;38:2620–7.
[38] Boufraqech M, Patel D, Nilubol N, et al. Lysyl Oxidase Is a Key Player in BRAF/mapk pathway-driven thyroid cancer aggressiveness. Thyroid. 2019;29:79–92.
[39] Petrulea MS, Plantinga TS, Smit JW, Georgescu CE, Netea-Maier RT. PI3K/Akt/mTOR: a promising therapeutic target for non-medullary thyroid carcinoma. Cancer Treat Rev. 2015;41:707–13.
[40] Landa I, Ibrahimpasic T, Boucai L, et al. Genomic and transcriptomic hallmarks of poorly differentiated and anaplastic thyroid cancers. J Clin Invest. 2016;126:1052–66.
[41] Schneider TC, Abdulrahman RM, Corssmit EP, Morreau H, Smit JWA, Kapiteijn E. Long-term analysis of the efficacy and tolerability of sorafenib in advanced radio-iodine refractory differentiated thyroid carcinoma: final results of a phase II trial. Eur J Endocrinol. 2012;167:643–50.
[42] de Groot JWB, Links TP, Plukker JTM, Lips CJM, Hofstra RMW. RET as a diagnostic and therapeutic target in sporadic and hereditary endocrine tumors. Endocr Rev. 2006;27:535–60.
[43] Saronni D, Gaudenzi G, Dicitore A, et al. Preclinical evaluation of novel tyrosine-kinase inhibitors in medullary thyroid cancer. Cancers. 2022;14:4442.
[44] Bentzien F, Zuzow M, Heald N, et al. In vitro and in vivo activity of cabozantinib (XL184), an inhibitor of RET, MET, and VEGFR2, in a model of medullary thyroid cancer. Thyroid. 2013;23:1569–77.
[45] Li Y, Su X, Feng C, et al. CYP2S1 is a synthetic lethal target in BRAFV600E-driven thyroid cancers. Signal Transduct Target Ther. 2020;5:191.
[46] Thumar J, Shahbazian D, Aziz SA, Jilaveanu LB, Kluger HM. MEK targeting in N-RAS mutated metastatic melanoma. Mol Cancer. 2014;13:45.
[47] Qu Y, Yang Q, Liu J, et al. c-Myc is Required for BRAFV600E-Induced Epigenetic Silencing by H3K27me3 in Tumorigenesis. Theranostics. 2017;7:2092–107.
[48] Kretschmer N, Durchschein C, Hufner A, Rinner B, Lohberger B, Bauer R. SK119, a novel shikonin derivative, leads to apoptosis in melanoma cell lines and exhibits synergistic effects with vemurafenib and cobimetinib. Int J Mol Sci . 2022;23:5684.
[49] Miao W, Wang Y. Quantitative interrogation of the human kinome perturbed by two BRAF Inhibitors. J Proteome Res. 2019;18:2624–31.
[50] Dunn LA, Sherman EJ, Baxi SS, et al. Vemurafenib Redifferentiation of BRAF Mutant, RAI-refractory thyroid cancers. J Clin Endocrinol Metab. 2019;104:1417–28.
[51] Subbiah V, Kreitman RJ, Wainberg ZA, et al. Dabrafenib plus trametinib in BRAFV600E-mutated rare cancers: the phase 2 ROAR trial. Nat Med. 2023;29:1103–12.
[52] Wen H, Wang H-Y, He X, Wu C-I. On the low reproducibility of cancer studies. Natl Sci Rev. 2018;5:619–24.
[53] Bourzac K. Biology: Three known unknowns. Nature. 2014;509:S69–71.
[54] Roh J-L, Park J-Y, Park CI. Total thyroidectomy plus neck dissection in differentiated papillary thyroid carcinoma patients: pattern of nodal metastasis, morbidity, recurrence, and postoperative levels of serum parathyroid hormone. Ann Surg. 2007;245:604–10.
[55] Randolph GW, Duh Q-Y, Heller KS, et al.; American Thyroid Association Surgical Affairs Committee's Taskforce on Thyroid Cancer Nodal Surgery. The prognostic significance of nodal metastases from papillary thyroid carcinoma can be stratified based on the size and number of metastatic lymph nodes, as well as the presence of extranodal extension. Thyroid. 2012;22:1144–52.
[56] Dinneen SF, Valimaki MJ, Bergstralh EJ, Goellner JR, Gorman CA, Hay ID. Distant metastases in papillary thyroid carcinoma: 100 cases observed at one institution during 5 decades. J Clin Endocrinol Metab. 1995;80:2041–5.
[57] Seifert R, Schäfers MA, Heitplatz B, Kerschke L, Riemann B, Noto B. Minimal extrathyroid extension in papillary micro carcinoma of the thyroid is an independent risk factor for relapse through lymph node and distant metastases. J Nucl Med. 2021;62:1702–9.

[58] Lu W, Kang Y. Epithelial-mesenchymal plasticity in cancer progression and metastasis. Dev Cell. 2019;49:361–74.
[59] Yeung KT, Yang J. Epithelial-mesenchymal transition in tumor metastasis. Mol Oncol. 2017;11:28–39.
[60] Oxnard GR, Janjigian YY, Arcila ME, et al. Maintained sensitivity to EGFR tyrosine kinase inhibitors in EGFR-mutant lung cancer recurring after adjuvant erlotinib or gefitinib. Clin Cancer Res. 2011;17:6322–8.
[61] Katayama R, Shaw AT, Khan TM, et al. Mechanisms of acquired crizotinib resistance in ALK-rearranged lung Cancers. Sci Transl Med. 2012;4:120ra17.
[62] Hamidi S, Hofmann M-C, Iyer PC, et al. Review article: new treatments for advanced differentiated thyroid cancers and potential mechanisms of drug resistance. Front Endocrinol. 2023;14:1176731.
[63] Waguespack SG, Drilon A, Lin JJ, et al. Efficacy and safety of larotrectinib in patients with TRK fusion-positive thyroid carcinoma. Eur J Endocrinol. 2022;186:631–43.
[64] Laetsch TW, DuBois SG, Mascarenhas L, et al. Larotrectinib for paediatric solid tumours harbouring NTRK gene fusions: phase 1 results from a multicentre, open-label, phase 1/2 study. Lancet Oncol. 2018;19:705–14.
[65] Hong DS, DuBois SG, Kummar S, et al. Larotrectinib in patients with TRK fusion-positive solid tumours: a pooled analysis of three phase 1/2 clinical trials. Lancet Oncol. 2020;21:531–40.
[66] Yoo S-K, Song YS, Lee EK, et al. Integrative analysis of genomic and transcriptomic characteristics associated with progression of aggressive thyroid cancer. Nat Commun. 2019;10:2764.
[67] Bastman JJ, Serracino HS, Zhu Y, et al. Tumor-Infiltrating T Cells and the PD-1 checkpoint pathway in advanced differentiated and anaplastic thyroid cancer. J Clin Endocrinol Metab. 2016;101:2863–73.
[68] Chintakuntlawar AV, Rumilla KM, Smith CY, et al. Expression of PD-1 and PD-L1 in anaplastic thyroid cancer patients treated with multimodal therapy: results from a retrospective study. J Clin Endocrinol Metab. 2017;102:1943–50.
[69] Dierks C, Seufert J, Aumann K, et al. Combination of lenvatinib and pembrolizumab is an effective treatment option for anaplastic and poorly differentiated thyroid carcinoma. Thyroid. 2021;31:1076–85.