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Visual analysis of global research on neoadjuvant and adjuvant strategies in NSCLC from 2013 to 2023

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► ***Original article***

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ABSTRACT

Background: Although combination treatment strategies have significantly improved and achieved impressive results, the 5-year survival rate of non-small cell lung cancer (NSCLC) still remains undesirable. Given the rapidly burgeoning concept of neoadjuvant and adjuvant strategies in cancer for increasing the therapeutic benefit, we aimed to explore the importance and trends of adjuvant strategies in NSCLC. ***Materials and Methods:*** We performed a visual analysis to evaluate published literature (707 papers) in the field of neoadjuvant and adjuvant strategies in NSCLC from January 1, 2013 to July 6, 2023, and acquire a comprehensive understanding of the field. VOSviewer was used to construct bibliometric networks for 707 related literatures. ***Results:*** the counts of publications and the evolution of citations concerning neoadjuvant and adjuvant strategies in NSCLC from 2013 to 2023 indicated the increasing interest and investment in the field of NSCLC neoadjuvance and adjunctive strategies. We detected that the majority of academic papers on neoadjuvant and adjuvant strategies for NSCLC were published in high-quality journals. A keyword screening of the relevant literature showed that the research on neoadjuvant and adjuvant strategies for NSCLC was mainly related to chemotherapy. China and United States were particularly influential and highly prolific in this field. ***Conclusion:*** Given this rapidly expanding realm, the neoadjuvant and adjuvant strategies may further improve the prognosis of NSCLC. The visual analysis will promote the development of research on neoadjuvant and adjuvant strategies in NSCLC and provide a reference for further research in this field.

INTRODUCTION

Nowadays, cancer is acknowledged as a significant worldwide public health issue that has a negative impact on human health [1-5]. Among all human cancers, lung cancer ranks first in terms of both mortality and morbidity [6, 7]. According to the recent global cancer statistics, more than 2 million people are newly diagnosed with lung cancer annually and lung cancer cases in Asia account for about 50% [8]. Furthermore, the frequency of early-stage cancer has grown with increasing screening, and surgically resectable disease currently accounts for only 25–30% of newly diagnosed lung cancer [9]. Although combination treatment strategies including surgery, targeted therapy, immunotherapy, radiotherapy, and chemotherapy have significantly improved and achieved impressive results, the 5-year survival rate of NSCLC remains poor [10-12]. The main reason is that most patients are first diagnosed at the middle or late stages, when surgery is no longer a viable option. Recently, efforts have been made to change patients' stages and raise the percentage of patients who receive a surgical cure by examining neoadjuvant and adjuvant methods [9, 13]. In addition, many patients experience recurrence after lung cancer resection. In this case, adjuvant chemotherapy has a modest survival advantage and improves the cure rate [9]. Immunotherapy with immune checkpoint blockade has emerged as a neoadjuvant treatment strategy for advanced NSCLC, and neoadjuvant checkpoint blockade is well tolerated and reduces morbidity and mortality [14]. In order to improve the prognosis of early-stage lung cancer, systemic therapy is implemented at different points in time. Neoadjuvant therapy refers to medications that are administered before surgery, whereas adjuvant therapy refers to treatment after surgery. At present, a variety of drugs including the combination of vulilumab and ipilimumab, atezolizumab, pembrolizumab, etc., are used in NSCLC patients as adjuvant and neoadjuvant chemotherapy [15].

Visual analysis is a scientific and quantitative research method that is used to explore the contributions and collaborations of countries or regions, authors, and journals over time and across

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topics by analyzing the publications in that field [16-20]. In addition, visualization may convert data into an understandable format and draw attention to key aspects of the data, such as abnormalities and similarities. Compared with traditional literature reviews, these visual representations can provide an objective and comprehensive overview and allow readers to quickly perceive the emerging aspects of data [21-24].

Increasing evidence has revealed that this approach has been successfully used to evaluate research trends in multiple diseases, including spine, sepsis, diabetes, and shoulder-related pain syndrome [25]. However, there are not many previous studies to evaluate the trends of neoadjuvant and adjuvant strategies in NSCLC. This is the first bibliometric analysis that we are aware of that evaluates the status and trends of adjuvant and neoadjuvant therapy in NSCLC and provides reference and direction for treatment strategies in this area.

MATERIALS AND METHODS

Data source

To ensure the quality and accessibility of the data, the Web of Science Core Collection-Science Citation Index Expanded (SCI-Expanded) database was chosen to retrieve and extract the articles or reviews related to neoadjuvant and adjuvant strategies for NSCLC from January 1, 2013 to July 6, 2023. The following terms and strategies were used: ((((TS= Neoadjuvant Therapy) OR (TS= Neoadjuvant Therapy topic)) AND (TS= Carcinoma, Non-Small-Cell Lung) OR (TS= Carcinoma, Non-Small-Cell Lung topic)) AND LA=(English)) AND PY= (2013-2023)) AND DT= (Article OR Review). Ultimately, a total of 707 studies were retained, downloaded, and saved as a download.txt, including fully recorded and cited references.

Bibliometric analysis

Bibliometric analysis is a powerful and statistical tool that can reflect the current state of scholarly development and distribution trends of publications over time and across topics through analyzing empirical and quantitative data [18]. In this study, the selected 707 papers were exported and saved as plain text. To conduct a comprehensive analysis, the WoSCC's own analysis tools, namely CiteSpace 6.2.R4, VOSviewer, and R-Bibliometrix 4.6.1 were employed to conduct the visual analysis.

The bibliometric networks were constructed and visualized with VOSviewer, and all keywords, institutions, countries, and the authors' data from WoSCC were examined using VOSviewer in order to produce the co-occurrence maps. The visual knowledge networks are comprised of several nodes and links, and different-node types can highlight key characteristics, including authors, references, countries/regions, journals, institutions, and keywords [26]. The size of a node indicates the occurrence of publications related to this element. In addition, the lines connecting the nodes represent the relationship between the elements, and thicker lines represent a closer relationship [27, 28].

RESULTS

Annual growth trend of publications on neoadjuvant and adjuvant strategies in NSCLC

The study contained 707 papers, including 569 articles and 138 reviews. According to figure 1, the counts of publications and the evolution of citations concerning neoadjuvant and adjuvant strategies in NSCLC increased steadily from 2013 to 2022; however, it is worth noting that the evolution of publications and citations decreased from 2022 to 2023, which may be because the data was only collected until July 2023. In particular, prior to 2020, the annual publication count was comparatively low, indicating that the field of study continues to be in its early stages. The number of annual publications started to rise quickly after that, with 2021 and 2022 showing the highest growth, indicating increasing interest and investment in the field of neoadjuvant and adjuvant strategies in NSCLC.

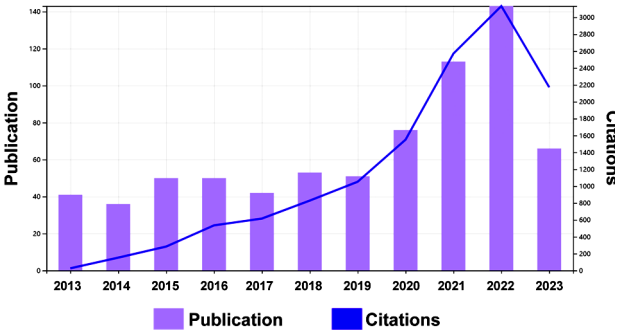

Figure 1. Annual trends of publications and the evolution of citations for neoadjuvant and adjuvant strategies in NSCLC from 2013 to 2023.

Analysis of journals

Information about journals that have published research papers on "neoadjuvant and adjuvant strategies in NSCLC" helps researchers understand which journals are addressing neoadjuvant and adjuvant strategies. From January 1, 2013 to July 6, 2023, 707 papers were published in 206 journals. As listed in table 1, the top three productive journals were Frontiers in Oncology (n=38, 5.37%), Annals of Thoracic Surgery (n=35, 4.95%), and the Journal of Thoracic Disease (n=31, 4.38%). Furthermore, Journal of Clinical Oncology was the most cited journal with 2,672 citations, followed by the Journal of Thoracic Oncology, with an average of 1,995 citations, indicating their high academic standing in the field of neoadjuvant and adjuvant strategies research. Notably, Lancet had the highest impact factor (IF=202.731), indicating its high publication

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quality in this field of study. In addition, 85% of these journals belonged to Q1, 5% to Q2, and 10% to Q3, indicating that most academic papers on neoadjuvant and adjuvant strategies in NSCLC are published in high-quality journals.

Analysis of authors and cited authors

Over the past decade, a total of 4,347 researchers were involved in the research related to neoadjuvant and adjuvant strategies in NSCLC, and the 10 most productive and cited authors in the research field are listed in table 2. 20.65% of all papers were published by the top 10 researchers, who together wrote 146 articles. WANG J from the University of Alberta in Canada was the most productive author with the highest number of published papers (19, 2.69%), followed by CASCONE T from the University of Texas MD Anderson Cancer Center in USA, CHEN C from the University of Zhengzhou in China, and SEPESI B from Texas MD Anderson Cancer Center in USA, with 16 publications of each (Table 2). Among them, it is worth noting that PARRA ER from the University of Texas MD Anderson Cancer Center in USA was the most cited, indicating his significant contributions in the field of neoadjuvant and adjuvant strategies research in NSCLC. In addition, as shown in figure 2, the visual analysis about the cooperative relationship of authors reveals that the authors who collaborate frequently correspond to closely coordinated clusters with the same color. Therefore, to keep pace with the latest developments in this area, these authors should be given more attention and priority. It also informs the search for suitable research partners and industry authorities in the future.

Table 1. The top 10 most productive journals related to neoadjuvant and adjuvant strategies in NSCLC from 2013 to 2023.

Rank	Journals	Articles	IF (JCR 2023)	JCR quartile	Cited Journals	Citation	IF (JCR 2023)	JCR quartile
1	FRONTIERS IN ONCOLOGY	38	5.738	Q2	J CLIN ONCOL	2672	50.717	Q1
2	ANNALS OF THORACIC SURGERY	35	5.102	Q1	J THORAC ONCOL	1995	20.121	Q1
3	JOURNAL OF THORACIC DISEASE	31	3.005	Q3	ANN THORAC SURG	1413	5.102	Q1
4	LUNG CANCER	30	15.283	Q1	NEW ENGL J MED	1312	176.079	Q1
5	TRANSLATIONAL LUNG CANCER RESEARCH	28	17.012	Q1	LANCET ONCOL	986	54.433	Q1
6	CLINICAL LUNG CANCER	23	15.283	Q1	J THORAC CARDIOV SUR	824	1.756	Q3
7	EUROPEAN JOURNAL OF CARDIO-THORACIC SURGERY	22	4.534	Q1	LUNG CANCER	784	15.283	Q1
8	THORACIC CANCER	20	8.972	Q1	LANCET	745	202.731	Q1
9	CANCERS	19	4.544	Q1	ANN ONCOL	672	51.769	Q1
10	JOURNAL OF THORACIC AND CARDIOVASCULAR SURGERY	12	8.049	Q1	EUR J CARDIO-THORAC	660	4.534	Q1

IF: impact factor; JCR: Journal Citation Reports; Q1: JCR quartile 1; Q2: JCR quartile 2; Q3: JCR quartile 3.

Table 2. The 10 most productive and cited authors related to neoadjuvant and adjuvant strategies in NSCLC from 2013 to 2023.

Rank	Author	Publication	Country	Insitution	Cited author	Cited frequency	Country	Insitution
1	WANG J	19	Canada	University of Alberta	PARRA ER	210	USA	University of Texas MD Anderson Cancer Center
2	CASCONE T	16	USA	University of Texas MD Anderson Cancer Center	PROVENCIO M	206	Spain	Hospital Universitario Puerta de Hierro-Majadahonda
3	CHEN C	16	China	Zhengzhou University	SWISHER SG	187	USA	University of Texas M. D. Anderson Cancer Center
4	SEPESI B	16	USA	Texas MD Anderson Cancer Center	WISTUBA II	181	USA	University of Texas M. D. Anderson Cancer Center
5	SWISHER SG	16	USA	University of Texas M. D. Anderson Cancer Center	FORDE PM	176	USA	Johns Hopkins Kimmel Cancer Center
6	HEYMACH JV	13	USA	University of Texas M. D. Anderson Cancer Center	BRAHMER JR	174	USA	Johns Hopkins Kimmel Cancer Center
7	WISTUBA II	13	USA	University of Texas M. D. Anderson Cancer Center	PATAER A	169	USA	University of Texas M. D. Anderson Cancer Center
8	YANG Y	13	China	Yancheng Teachers University	AWAD MM	162	USA	Dana-Farber Cancer Institute
9	PROVENCIO M	12	Spain	Hospital Universitario Puerta de Hierro-Majadahonda	KALHOR N	158	USA	University of Texas M. D. Anderson Cancer Center
10	WANG CL	12	China (Taiwan)	Kaohsiung Medical University	CASCONE T	155	USA	University of Texas M. D. Anderson Cancer Center

Analysis of keywords

Commonly, keywords are highly concentrated content of publications, and to some extent, either the growth of keywords expanded in publications or the increasing frequency of keywords within a certain period could simply and directly be considered as an important characteristic for assessing the cutting-edge topics and emergent trends of the field. Table 3 indicates that the top 10 keywords that were most frequently used were: chemotherapy (167), survival

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(161), surgery (152), open label (133), preoperative chemotherapy (117), therapy (92), radiotherapy (91), multicenter (87), phases-III (82), and induction chemotherapy (81). It can be seen from the time line of keyword occurrence frequency, "chemotherapy, surgery and survival" was always the more frequently occurring keywords at each period whose dynamic curve was similar with the general output growth (figure 3A).

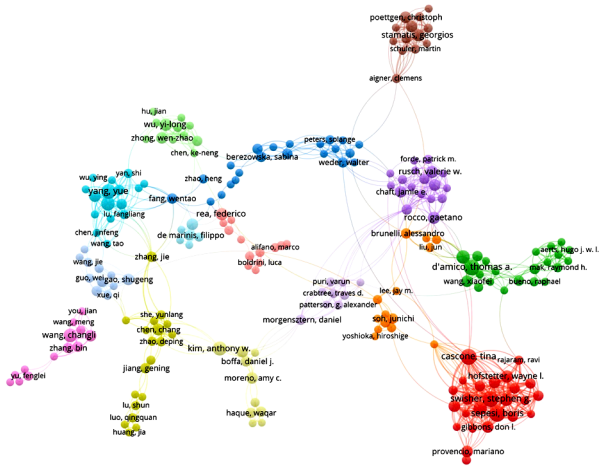

Figure 2. Visual analysis of author partnerships in VOSviewer. The cooperation relationships among authors involved in neoadjuvant and adjuvant strategies in NSCLC from 2013 to 2023. Nodes of different colors represent authors in different clusters, and the size of the nodes indicates how often they appear.

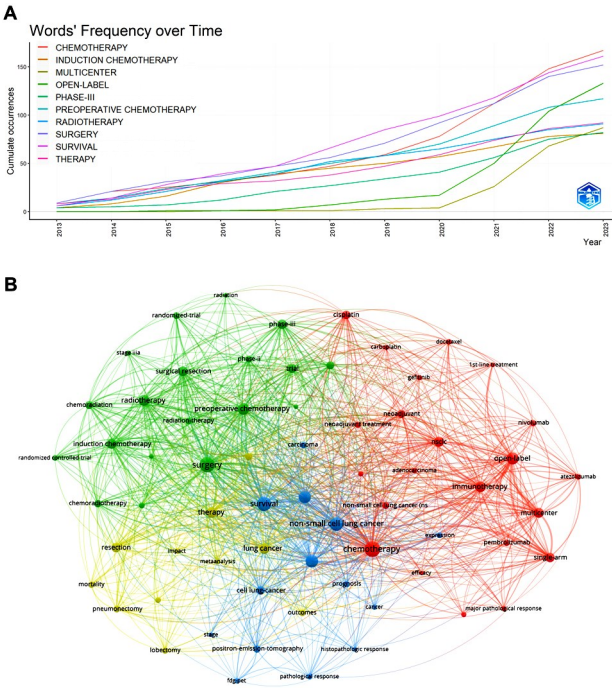

Figure 3. Relevant keyword analysis of neoadjuvant and adjuvant strategies in NSCLC. (A) Timeline dynamic curve view of the keyword; (B) The cluster analysis of keywords involved in neoadjuvant and adjuvant strategies in NSCLC from 2013 to 2023. Visualization of collaborative networks for keywords in VOSviewer. The graph shows keywords that appear more than 20 times. The nodes of different colors represent the keywords of different clusters, and the size of the nodes indicates their frequency.

To build the relationship of keywords based on the publications, the co-occurrence analysis was implemented by the VOS viewer and the trends and current topics of research areas were established by the keywords network map. The keywords were represented by different circles, and the size of the circle was proportional to the number of keyword occurrences. In addition, if two keywords appear in the same publication, the two circles will be connected by the line and the thickness of the lines will reflect the close relationship between the keywords.

A total of 2,024 keywords were extracted from 707 publications, and 258 keywords with a number of occurrences ≥20 were included in the co-occurrence analysis. These keywords were classified into four clusters (figure 3B). The red cluster mainly represented the research associated with chemotherapy in NSCLC, and the blue cluster was mainly concerned with survival of NSCLC. The green cluster mainly focused on the study of surgery, while the yellow cluster was mainly related to the research of therapy in the fields. The highly frequent occurrences of keywords were "chemotherapy," "survival," "surgery," and "open label," suggesting that the study of neoadjuvant and adjuvant strategies in NSCLC was primarily concerned with chemotherapy.

Table 3. Top 10 keywords in neoadjuvant and adjuvant strategies in NSCLC from 2013 to 2023.

Rank	Keywords	Occurrences
1	Chemotherapy	167
2	Survival	161
3	Surgery	152
4	Open-label	133
5	Preoperative chemotherapy	117
6	Therapy	92
7	Radiotherapy	91
8	Multicenter	87
9	Phase-III	82
10	Induction chemotherapy	81

Analysis of references

In this study, 707 papers were included, and the top 10 highly-cited articles are listed in table 4. The most cited article was published in 2009 by Albain *et al.*, with a total number of citations being 166, followed by Forde *et al.* and Burdett *et al.*, with 153 and 146 citations, respectively.

Analysis of institutions

The CiteSpace and VosViewer were used to map the cooperation between the institutions in neoadjuvant and adjuvant strategies of NSCLC. As seen in table 5, the University of Texas MD Anderson Cancer Center (UT MDA), USA, had the most publications, followed by the University of Texas System, USA and the Udice French Research University, France.

In the visual network, the importance of nodes was determined by measuring their centrality, and a

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critical node was highlighted. The connections between institutions are reflected by lines between nodes. As shown in figure 4, several institutions were highlighted, and the most productive institution UT MDA from USA collaborated closely with other organizations. These findings suggest that UT MDA generates a large number of excellent studies and makes great achievements in the field of neoadjuvant and adjuvant strategies research. To keep up with the latest developments in the field, more considerable attention should be given to the institution.

Table 4. Top 10 cited article related to neoadjuvant and adjuvant strategies in NSCLC from 2013 to 2023.

Rank	Article Title	Source Title	Authors	Year	DOI	Cited
1	Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: a phase III randomised controlled trial	Epub	Albain KS, Swann RS, *et al.*	2009	10.1016/S0140-6736(09)60737-6	166
2	Neoadjuvant PD-1 Blockade in Resectable Lung Cancer	NEW ENGL JMED	Patrick M Forde, Jamie E Chaft, *et al.*	2018	10.1056/NEJMOA1716078	153
3	Preoperative chemotherapy for non-small-cell lung cancer: a systematic review and meta-analysis of individual participant data	LANCET	Burdett	2014	10.1016/S0140-6736(13)62159-5	146
4	Pathological response after neoadjuvant chemotherapy in resectable non-small-cell lung cancers: proposal for the use of major pathological response as a surrogate endpoint	LANCET ONCOL	Matthew D Hellmann, Jamie E Chaft, *et al.*	2014	10.1016/S1470-2045(13)70334-6	123
5	Neoadjuvant chemotherapy and nivolumab in resectable non-small-cell lung cancer (NADIM): an open-label, multicentre, single-arm, phase 2 trial	LANCET ONCOL	Provencio M, Nadal E, *et al.*	2020	10.1016/S1470-2045(20)30453-8	115
6	Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE Collaborative Group	JCLIN ONCOL	Pignon JP, Tribodet H, *et al.*	2008	10.1200/JCO.2007.13.9030	104
7	Histopathologic response criteria predict survival of patients with resected lung cancer after neoadjuvant chemotherapy	JTHORAC ONCOL	Pataer A, Kalhor N, *et al.*	2012	10.1097/JTO.0B013E318247504A	102
8	The IASLC Lung Cancer Staging Project: Proposals for Revision of the TNM Stage Groupings in the Forthcoming (Eighth) Edition of the TNM Classification for Lung Cancer	J Thorac Oncol	Goldstraw P, Chansky K, *et al.*	2016	10.1016/j.jtho.2015.09.009	101
9	Neoadjuvant atezolizumab and chemotherapy in patients with resectable non-small-cell lung cancer: an open-label, multicentre, single-arm, phase 2 trial	Lancet Oncol	Shu CA, Gainor JF, *et al.*	2020	10.1016/S1470-2045(20)30140-6	101
10	Randomized controlled trial of resection versus radiotherapy after induction chemotherapy in stage IIIA-N2 non-small-cell lung cancer	J Natl Cancer Inst	Van Meerbeeck JP, Kramer GW, *et al.*	2007	10.1093/jnci/djk093	85

Table 5. Top 10 productive institutions related to neoadjuvant and adjuvant strategies in NSCLC from 2013 to 2023

Rank	Institutions	Publications
1	UTMD ANDERSON CANCER CENTER	122
2	UNIVERSITY OF TEXAS SYSTEM	104
3	UDICE-FRENCH RESEARCH UNIVERSITIES	70
4	PEKING UNION MEDICAL COLLEGE	48
5	CENTRAL SOUTH UNIVERSITY	47
6	UNIVERSITE PARIS CITE	46
7	SUN YAT SEN UNIVERSITY	42
8	CHINESE ACADEMY OF MEDICAL SCIENCES - PEKING UNION MEDICAL COLLEGE	39
9	MEMORIAL SLOAN KETTERING CANCER CENTER	39
10	SAMSUNG MEDICAL CENTER	37

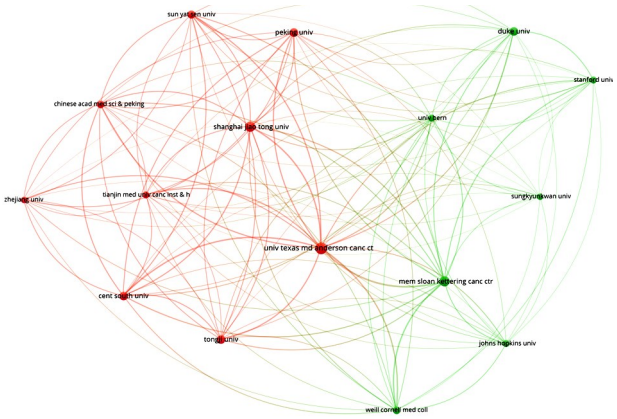

Figure 5. The cooperation relationships among institutions involved in neoadjuvant and adjuvant strategies of NSCLC in each country from 2013 to 2023. Visualization of the collaborative network of productive institutions in VOSviewer. Nodes of different colors represent institutions in different clusters, and the size of the nodes indicates how often they appear.

DISCUSSION

According to the data published by the Global Cancer Observatory (GLOBOCAN2020), in 2020, approximately 2.2 million cases worldwide were initially diagnosed with lung cancer, comprising 11.4% of all diagnosed malignant cancers, and NSCLC comprises >85% of all lung cancers. The number of deaths was approximately 1.8 million, accounting for 18.0% of all tumor-related deaths [2, 11, 29].In the past decade, many studies have reported neoadjuvant and adjuvant strategies for non-small cell lung cancer to increase surgical cure rates as well as patient survival rates through various combination therapies [30, 31].

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In this study, based on the literature from January 1, 2013 to July 6, 2023, we examined the research on adjuvant strategies research in NSCLC by using a bibliometric approach. In all, 707 articles relating to adjuvant strategies research in NSCLC from the SCIE of the WoS were analyzed by VOSviewer and R-Bibliometrix 4.6.1. Finally, we conducted a visual analysis to analyze the current state and scientific trends in the field of neoadjuvant and adjuvant strategies research in NSCLC and acquire a comprehensive understanding of the field, including the authors, journals, annual publications, citations, institutions, keywords, and references. Based on these data, the spatial and temporal distribution, author contributions, and research hotspots of the field are evaluated.

This study provides a systematic bibliometric review of the field and shows a significantly upward trend in the volume of publications and the evolution of citations concerning neoadjuvant and adjuvant strategies in NSCLC from 2013 to 2022. It is worth noting that the evolution of publications and citations decreased from 2022 to 2023 which may be related to the fact that the data is only collected until July 2023. These findings indicate that this field has attracted increasing interest and attention from researchers.

The total number of publications or citations of institutions represents its academic influence. In the past 10 years, as far as the institutions are concerned, with 122 publications, the University of Texas MD Anderson Cancer Center (UT MDA) from USA has contributed to the highest number of publications, which was identified as the major contributor and most influential institution in the field. Furthermore, the University of Texas System from USA (n=104) and the Udice French Research University from France (n=70) have ranked second and third, respectively, in terms of the total number of publications, which indicates that the two institutions have also made great contributions and deserve scholars' attention.

Most authors were devoted to the research on neoadjuvant and adjuvant strategies in NSCLC. From the perspective of the authors, it was seen that Wang from the University of Alberta in Canada published 19 articles in total and had the greatest publication impact in the field. In addition, Parra from the University of Texas MD Anderson Cancer Center, USA, was the most cited author, indicating that they have considerable academic influence and made outstanding contributions. Moreover, the visual analysis about the cooperative relationship of authors reveals that there is a close relationship between the authors with prolific publications or academic influence.

The co-occurrence of keywords and clustering analyses revealed that the most relevant keywords were chemotherapy, followed by survival, surgery, open-label, preoperative chemotherapy, therapy, radiotherapy, multicenter, phase-III, and induction chemotherapy, proving that chemotherapy plays an important role in the neoadjuvant and adjuvant strategies in NSCLC and has attracted the interest of scholars worldwide. For chemotherapy-related neoadjuvant strategies for NSCLC, the U.S. Food and Drug Administration (FDA) approved neoadjuvant nivolumab in combination with platinum-doublet treatment in 2022 [32]. In 2023, the FDA approved neoadjuvant pembrolizumab in combination with platinum-containing chemotherapy for resectable NSCLC [33], followed by pembrolizumab as monotherapy in the adjuvant treatment of all programmed cell death 1 ligand 1 (PD-L1) layers [34, 35]. A phase II NEOSTAR clinical trial conducted by the University of Texas MD Anderson Cancer Center showed that neoadjuvant chemotherapy with nivolumab in combination with ipilimumab in patients with surgically resected tumors resulted in a favorable pathologic response [36, 37]. In the Phase II study of IMpower 030, the combination of atezolizumab and chemotherapy showed significant activity in the neoadjuvant setting of patients with NSCLC [38]. At present, more and more studies are investigating the use of immune checkpoint blockade in neoadjuvant therapy for the treatment of early-stage lung cancer [39, 40]. We are expecting that neoadjuvant and adjuvant strategies could bring another great breakthrough to this field.

To our knowledge, it is the first bibliometric analysis to provide a description of trends in neoadjuvant and adjuvant strategies in NSCLC. This analysis has an objective advantage, as it illustrates trends of development in the field and highlights areas that have not yet been clearly explored.

This study also has some limitations. First, the data was only retrieved from the WoS database and did not include other databases such as PubMed, so some publications may have been inevitably omitted. Second, the study only researched publications in English, which may have a certain impact on the results. Therefore, these publications may not fully represent all studies on neoadjuvant and adjuvant strategies in NSCLC, but the 707 publications in this study may address the offset caused by such small deviations.

CONCLUSIONS

In this study, we analyzed 707 papers in the field of neoadjuvant and adjunctive strategies for NSCLC over the past 20 years using bibliometric analysis. Chemotherapy, survival, surgery, open-label, multicenter, etc. are hot topics in this field. Our research illustrates the basic scientific knowledge of neoadjuvant and adjunctive strategies for NSCLC and the various interrelationships, all of which will provide important clues and references for future

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trends in the field.

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***Author contribution*:** L.M., conceived and designed the experiments. W.Y., and J.Z., contributed significantly to the experiments and arranging data. W.W., W.D., M.C., Q.L., and Z.X., performed data analyses. T.Z. and S.H., wrote the draft manuscript. L.M., revised the manuscript. All authors read and approved the final manuscript.

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