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Research article

Research landscape of radiotherapy for nasopharyngeal carcinoma from 1959 to 2022: A bibliometric analysis

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ABSTRACT

Background: Radiotherapy, as the main treatment method for nasopharyngeal carcinoma (NPC), has evolved over time, but there has been no bibliometric study on NPC radiotherapy to date. In our study, the scientific achievements of NPC radiotherapy around the world were evaluated by bibliometric analyses, and the previous research hotspots and future trends are described.
Methods: Original articles related to NPC radiotherapy were obtained from the Web of Science Core Collection. To identify research hotspots and future trends, countries/regions, institutions, journals, references, authors, and keywords were evaluated and visualized by Excel, VOSviewer, and CiteSpace.
Results: From 1959 to 2022, 7139 original articles were collected. The annual publications showed an increasing trend, especially after 2011. China had the most publications (n = 3719, 52.09 %). Sun Yat-sen University has the most publications and citations among institutions. Jun Ma is most productive and SR Baker has the highest co-cited centrality. *International Journal of Radiation Oncology-Biology-Physics* is the core journal, with most publications, citations and co-citations. Analysis of keywords showed intensity-modulated radiotherapy and chemo-radiotherapy were the main keywords, and multicenter showed the strongest burst.
Conclusion: NPC radiotherapy has attracted increasing attention, and precision and artificial intelligence may be the future trends in this field.

1. Background

Nasopharyngeal carcinoma (NPC), characterized by distinct geographical distribution and particularly prevalent in east and southeast Asia, is an epithelial carcinoma that originates from the inner lining of the nasopharyngeal mucosa and is commonly found in

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the pharyngeal recess (fossa of Rosenmüller), which is distinct from other epithelial head and neck tumors, but originates from similar cell or tissue lineages with them [1]. The clinical behavior of NPC depends on its histological subtype. Epstein-Barr virus (EBV) infection is associated with it in approximately 70–80 percent of cases, and treatment does not vary by histological subtype. Mortality associated with NPC has improved over the last decade due to early detection and advances in treatment [2].

Radiotherapy is the primary treatment for NPC, especially in non-metastatic disease [1,3]. With the development of science and technology, photon-based radiotherapy has experienced traditional two-dimensional (2D) radiotherapy and three-dimensional (3D) conformal radiotherapy, and developed into intensity modulated radiation therapy (IMRT), which is the most commonly used for NPC at present [4,5]. The exploration of advanced radiotherapy techniques such as volumetric modulated arc radiation therapy (VMAT), proton therapy, carbon-ion radiotherapy and boron capture neutron therapy in the treatment of NPC is also progressing [6–10]. While great progress has been made in the study of radiotherapy for NPC over the past decades, and most studies of radiotherapy for NPC have focused on improving survival and reducing toxicity, it remains difficult to balance the efficacy of radiotherapy with the quality of life for patients [11,12].

Against the background of emphasizing the individualized comprehensive treatment for cancer patients, the exploration of radiotherapy combined with other treatments (chemotherapy, immunotherapy, etc.) seems to have become the current mainstream development direction for research on NPC [1]. On the basis of treatment strategies that combine multiple treatment modalities, balancing efficacy and adverse effects seems to become more difficult [13].

In this study, we applied bibliometric analysis to analyze the countries, institutions, journals, authors, references and keywords of documents related to NPC radiotherap, which no scholars explored before, for the purpose of systematically assessing the current status and research trends in NPC. The bibliometric analysis of NPC radiotherapy was carried out using quantitative research methods and visualization tools including VOSviewer [14–16] and CiteSpace [17–19], taking literature systems and biometric characteristics as the study objects.

2. Methods

2.1. Data retrieval strategy

The literature of original research on NPC and radiotherapy from 1900 to Oct. 2022 was searched from the Science Citation Index-Expanded (SCIE) of the Web of Science Core Collection (WoSCC). As one of the most professional and authoritative citation databases, WoSCC has a powerful index function, which contains basic information such as author, institution, country/region, funding institution, author keywords, as well as reference information. The search was conducted until Oct. 30, 2022, and only English original articles were collected. The following keywords were used in the database retrieval by Boolean search operators: ((TS=(carcinoma) OR TS=(cancer) OR TS=(tumor) OR TS=(neoplasm) OR TS=(sarcoma)) AND LA=(English) AND DT=(Article)) AND ((TS= (radiation therapy) OR TS= (radiation treatment) OR TS=(radiotherapy) OR TS=(RT)) AND LA=(English) AND DT=(Article)) AND ((TS= (nasopharyngeal) OR TS=(nasopharynx) OR TS=(rhinopharyngeal)) AND LA=(English) AND DT=(Article)). The search history is presented in Table S1. In this study, the impact factor (IF) of journals from the Journal Citation Reports (https://jcr.clarivate.com), and the H-index for journals was obtained from Scimago Journal & Country Rank (https://www.scimagojr.com).

2.2. Statistical and bibliometric analysis

The descriptive statistical analysis and generating graphs were performed on Microsoft Office Excel 2016 (Microsoft, Redmond, WA, USA), and an exponential regression model was used to evaluate the trends of annual publications by it. VOSviewer (1.6.18) and CiteSpace V (5.8.R3) were used for bibliometric visualization.

VOSviewer is a software developed by van Eck and Waltman for constructing and visualizing bibliometric networks, which was used to perform the co-citation analysis of authors/references/journals, co-occurrence analysis of author keywords, and co-authorship analysis of countries/institutions/authors.

CiteSpace, as another widely used bibliometric tool, was applied to perform co-authorship analysis among institutions, citation burst analysis of keywords, and timeline view analysis of co-cited references (label clusters with tiles, keywords and abstracts). The parameter settings of CiteSpace were as follows: time span = Jan. 1959–Dec. 2022, slice length = 1, selection criteria = top 50 per slice, node types = (reference/institution/keyword), pruning = (pathfinder and pruning the merged network), and visualization = (cluster view-static and show merged network).

3. Results

3.1. Analysis of the annual trend in publications on NPC radiotherapy

On the basis of the WoSCC database, 7139 publications related to NPC radiotherapy between 1900 and October 31, 2022 are included in this study, with the earliest published in 1959. With the exponential linear regression model, the annual publication volume of NPC radiotherapy showed an upward trend over time (Fig. 1, R2figR2 = 0.8849). It had a relatively stable growth before 2011, and a relatively rapid growth after that. Annual publications related to NPC radiotherapy exceeded 100 in 1996, 200 in 2002, and 500 in 2012, doubling in nine years. While the number of publications declined in 2018, the overall trend remained on the increase. This reveals that interest of scholars in NPC radiotherapy is gradually increasing, and it has become a research hotspot.

3.2. *Analysis of publications by countries/regions, institutions and authors*

In order to identify leaders in NPC radiotherapy research, we analyzed the countries/regions, institutions, and authors to which publications in this field belong from 1959 to 2022. Fig. 2A shows the top 10 countries/regions in terms of total number of NPC radiotherapy publications and their citations. China ranked first with 3719 publications (52.09 %) and 76,875 citations, the United States ranked second with 1190 publications (16.67 %) and 50,789 citations, and Taiwan ranked third with 597 publications (8.36 %) and 16,729 citations (Table 1). Although China has the largest number of publications, the analysis of collaborative relationships between countries reveals that the country/region with the highest total link strength (TLS) is the United States, followed by China, and Canada in third place (Fig. 2B).

The details of the top 10 active institutions are listed in Table 1, with Sun Yat-sen University in China having the largest of 1045 publications (Fig. 3A, S = 0.9337, (Q, S) = 0.7002) and 25720 citations, obviously higher than any other institutions. The second one was the University of Hong Kong (252 publications and 10026 citations). The Chinese University of Hong Kong and Fudan University were tied for third with 230 publications, but the number of citations of the Chinese University of Hong Kong (13,397 citations) was significantly higher than that of Fudan University (5412 citations). In addition, the partnership among institutions shows that Sun Yat-sen University has closest cooperation with institutions in the field, with the highest TLS = 1141 (Fig. 3B).

The top 10 productive authors and the top 10 co-cited authors with centrality related to NPC radiotherapy from 1959 to 2022 are shown in Table 2. The visualization of cooperative partnerships between authors based on the number of publications is shown in Fig. 4A. The top ten authors were all from China, among which Jun Ma had the most publications (n = 238), the most citations (n = 8488), and the highest TLS value of 2297. Ying Sun ranked second with 212 publications, 6992 citations and a TLS value of 2088. Among the top 10 co-cited authors, six were from the United State. In terms of centrality for co-cited authors, SR Baker from the United States was ranked first (C = 0.46), KK FU from the United States was ranked second (C = 0.44), and JH Yan from China was ranked third (C = 0.37). The TLS based visualization of the co-cited authors is shown in Fig. 4B, with AWM Lee at the center of the field followed by ATC Chan and DTT Chua.

3.3. *Analysis of journals and co-cited journals*

To identify the authoritative journals in the field of NPC radiotherapy, the journals and co-cited journals in this field were analyzed and their top 10 are listed in detail in Table 3, and half of the top 10 journals with publications and 7 of the top 10 co-cited journals with citations belong to the United States. The top 10 cited and co-cited journals were all classified as Journal Citation Reports (JCR) Q1/Q2 in 2021, except *Oncotarget*, which has not been included in WoSCC database since 2017. According to the network visualization map (Fig. 5A), density map (Fig. 5B) and co-citation network visualization map of journals in this field (Fig. 5C), it is not difficult to find that *International Journal of Radiation Oncology - Biology - Physics*, whose H-index is 257, is the core journal in this field. In the field of NPC radiotherapy, the journal had the most publications (n = 449), the highest total citations of 32,202, and the highest co-citations of 27585 among journals. The second and third most productive journals were *Head and Neck-Journal for the Sciences and Specialties of the Head and Neck* (n = 284) and *Radiotherapy and Oncology* (n = 237). The second and third most co-cited journals were *Journal of Clinical Oncology* (10030 citations) and *Radiotherapy and Oncology* (8817 citations), and *New England Journal of Medicine* had the highest H-index of 1079 and the highest IF of 176.082 among the top 10 journals, which shown its far-reaching impact in the field. However, the IF of the top 10 journals is not more than 10, while top 10 co-cited journals have excellent IFs. Among the top 10 co-cited journals, *New*

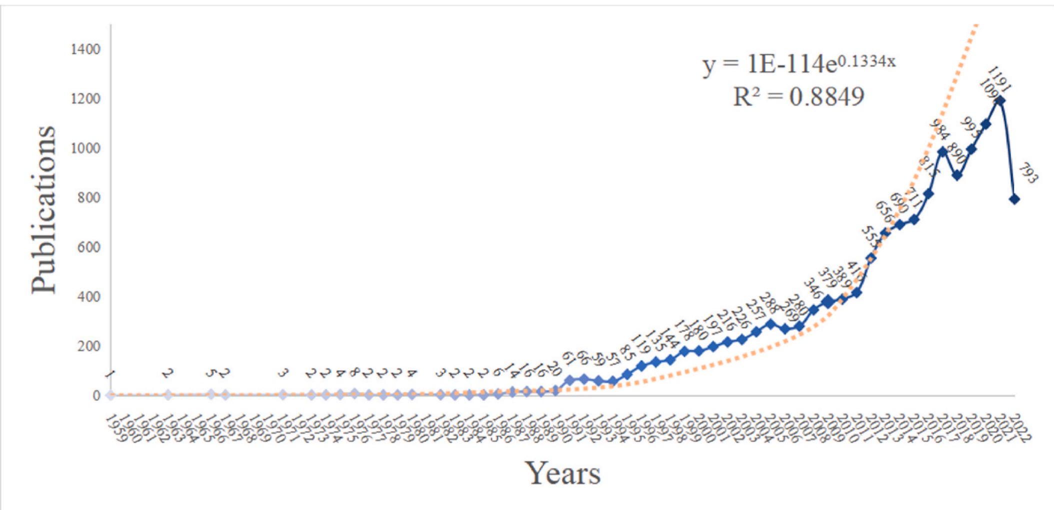

Fig. 1. The annual publications curve showing the annual publication trend and exponential fitting curve of original articles on NPC radiotherapy from 1999 to 2022 in WoSCC database.

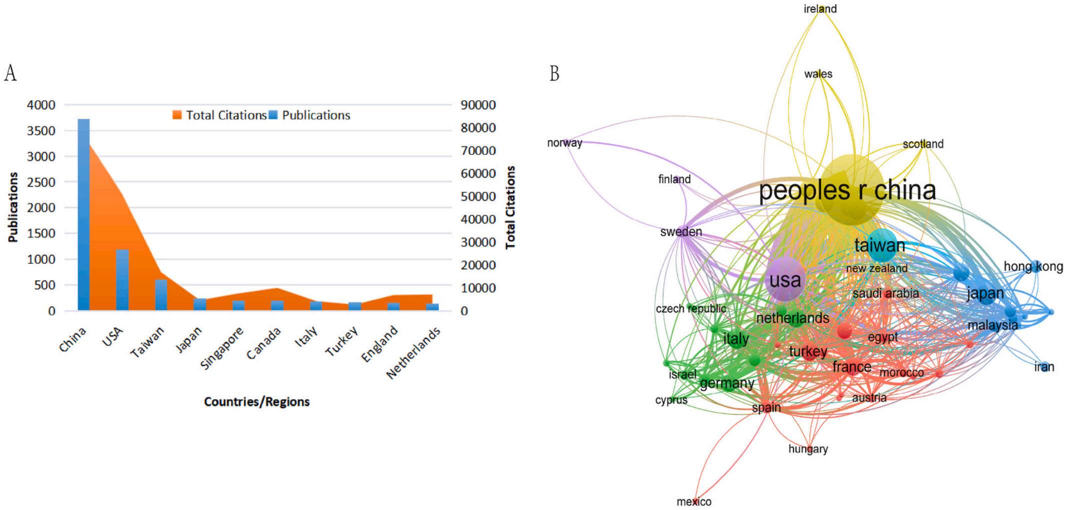

Fig. 2. Visualization of the analyses of countries/regions. (A) The top 10 productive countries/regions and citations of them. (B) Visualization network of the cooperative partnerships between countries/regions conducted by VOSviewer. The nodes with the same color represent the same cluster, implying a close partnership. The larger the node's size or the width of the connecting line, the closer the relative degree of co-occurrence.

Table 1
Top 10 productive countries/regions and institutions related to radiotherapy of NPC.

Rank	Countries/Regions	Documents	Percentage	Citations	TLS	Institutions	Documents	Citations	TLS
1	China	3719	52.09 %	76875	689	Sun Yat-sen University	1045	25720	1141
2	USA	1190	16.67 %	50789	757	The University of Hong Kong	252	10026	347
3	Taiwan	597	8.36 %	16729	180	The Chinese University of Hong Kong	230	13397	321
4	Japan	239	3.35 %	4589	98	Fudan University	230	5412	286
5	Singapore	196	2.75 %	7496	204	Guangxi Medical University	202	3224	215
6	Canada	190	2.66 %	9910	241	Chang Gung University	157	3968	311
7	Italy	186	2.61 %	4189	135	Southern Medical University	154	2247	224
8	Turkey	164	2.30 %	2703	86	Central South University	140	3406	108
9	England	156	2.19 %	6802	157	Fujian Medical University	127	2578	218
10	Netherlands	143	2.00 %	7022	176	Guangzhou Medical University	125	2196	208

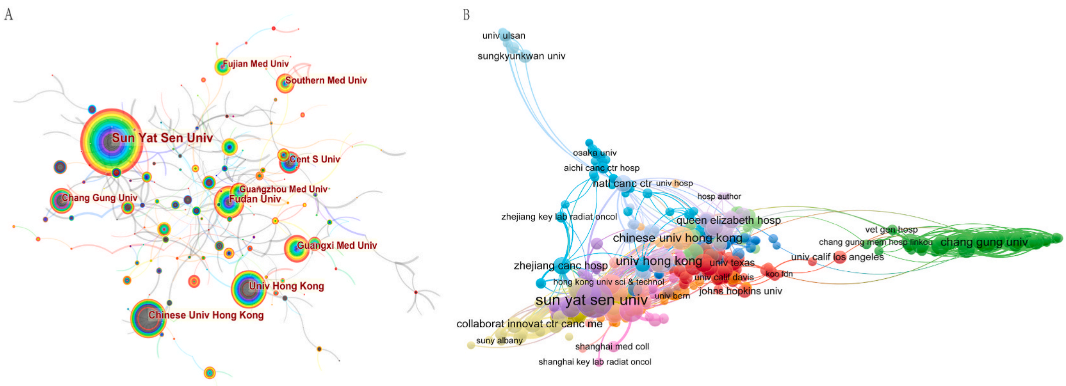

Fig. 3. Visualization for the analyses of institutions. (A) The top 10 productive institutions on NPC radiotherapy original articles. (B) Visualization network of the cooperative partnerships between institutions conducted by VOSviewer.

England Journal of Medicine had the highest IF, followed by *Lancet Oncology* (IF = 54.433) and *Journal of Clinical Oncology* (IF = 50.793).

3.4. Analysis of references and co-cited references

The top 10 references with most citations of NPC radiotherapy research are shown in Table 4. The article "*Chemoradiotherapy versus*

Table 2
The 10 most productive authors and the top 10 co-cited authors with the highest centrality.

Rank	Author	Documents	Countries/ Regions	Citations	TLS	Co-Cited Author	Countries/ Regions	Citations	TLS	Centrality
1	Ma, Jun	238	China	8488	2297	BAKER, SR	USA	41	1026	0.46
2	Sun, Ying	212	China	6992	2088	FU, KK	USA	224	5806	0.44
3	Mai, Hai-qiang	135	China	3095	1487	YAN, JH	China	147	3350	0.37
4	Mao, Yan-ping	117	China	4232	1130	NEEL, HB	USA	97	2179	0.31
5	Tang, Ling-long	112	China	3909	1067	LEVENDAG, PC	Netherlands	205	5382	0.29
6	Chen, Lei	108	China	4006	1056	SYED, AMN	USA	47	1079	0.28
7	Liu, Li-zhi	91	China	3616	790	NOWAK, PJCM	Austria	36	852	0.24
8	Chen, Qiu-yan	90	China	1317	1079	HUNT, MA	USA	136	2703	0.24
9	Lin, Ai-hua	88	China	3670	857	EISBRUCH, A	USA	699	16799	0.23
10	Hu, Chaosu	87	China	1462	372	HO, JHC	Hongkong	257	5381	0.22

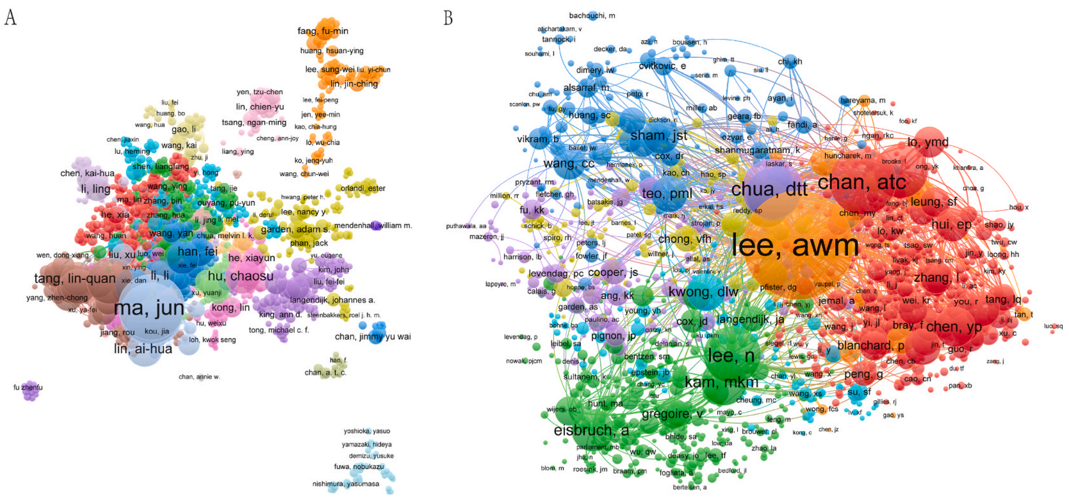

Fig. 4. Authors partnership Network. Visualization network of authors (A) and co-cited authors (B) related to NPC radiotherapy.

radiotherapy in patients with advanced nasopharyngeal cancer: phase III randomized intergroup study 0099" published by Al-sarraf M et al. in *Journal of Clinical Oncology* in 1998 was the most cited (n = 1622). It was far more cited than the second most cited article "*Parotid-sparing intensity modulated versus conventional radiotherapy in head and neck cancer (PARSPORT): a phase 3 multicentre randomised controlled trial*" published by Nutting C et al. (n = 1082) from *Lancet Oncology* in 2011. In addition to the above references, no other references have been cited more than 1000 times. The results reveal that only 12 articles have been cited more than 500 times and 84 articles have been cited more than 200 times in this field. We found that 9 of the 10 most cited articles were clinical studies, and all of them were published before 2007 except for the second, fifth and ninth articles.

The visualized network of co-cited references is shown in Fig. 6A, and the top 10 of them in co-citations are listed in Table 5. The article *"Chemoradiotherapy versus radiotherapy in patients with advanced nasopharyngeal cancer: phase III randomized intergroup study 0099"* published in *Journal of Clinical Oncology* by Al-Sarraf M et al. ranks first with 949 co-citations and has the largest TLS (n = 15,655). In addition, we clustered co-cited references, and the results are presented as a timeline view (Fig. 6B). It reveals that "mean dose" (cluster 0, log-likelihood ratio = 16,717.43, $P < 0.0001$) and "NPC radioresistance" (cluster 57, log-likelihood ratio = 930.32, $P < 0.0001$) were the research hotspots in the past decade, and the former was much more popular than the latter. The mean dose in cluster 0 includes the mean dose of NPC radiotherapy and chemotherapy, while cluster 57 includes the radioresistance of NPC tissues and cells in clinical and laboratory studies. Looking at the past two decades, in addition to the previously mentioned clusters 0 and 57, "treatment result" (cluster 2, log-likelihood ratio = 5318.94, $P < 0.0001$) and "parotid gland" (cluster 3, log-likelihood ratio = 22,567.15, $P < 0.0001$) are also research hotspots in the field of NPC radiotherapy.

3.5. *Keyword analysis of citation burst and co-occurrence*

The keyword co-occurrence analysis with VOSviewer can clarify the co-occurrence relation between keywords and identify hot topics in the NPC radiotherapy field. As shown in Table 6, the top 20 keywords of co-occurrence frequency mainly involved radiotherapy, chemotherapy and prognosis of NPC. A visualization of the network for the top 50 co-occurrence keywords is shown in

Table 3
The top 10 productive journals and the top 10 co-cited journals with TLS about radiotherapy of NPC.

Rank	Journals	Countries	Publications	Citations	TLS	H-index	IF	JCR	Co-Cited Journals	Countries	Co-Citations	TLS	H-index	IF	JCR
1	International Journal of Radiation Oncology - Biology - Physics	USA	449	32202	12847	257	8.013	Q1	International Journal of Radiation Oncology - Biology - Physics	USA	27585	722047	257	8.013	Q1
2	Head and Neck-Journal for the Sciences and Specialties of the Head and Neck	USA	284	6703	4316	127	3.821	Q1	Journal of Clinical Oncology	USA	10030	322812	574	50.739	Q1
3	Radiotherapy and Oncology	Netherlands	237	9616	5224	163	6.901	Q1	Radiotherapy and Oncology	Netherlands	8817	283208	163	6.901	Q1
4	Oral Oncology	England	194	3661	3778	121	5.972	Q1	Cancer	USA	8799	320943	315	6.921	Q1
5	Radiation Oncology	England	155	2611	2432	78	4.309	Q2	Head and Neck-Journal for the Sciences and Specialties of the Head and Neck	USA	5466	219900	127	3.821	Q1
6	Cancer	USA	150	9441	4282	315	6.921	Q1	Cancer Research	USA	3199	112111	466	13.312	Q1
7	Frontiers in Oncology	Switzerland	131	526	1754	102	5.738	Q2	Laryngoscope	USA	3117	218156	157	2.970	Q2
8	Oncotarget	USA	123	2239	1930	148	5.168 (2016)	Q2 (2016)	Oral Oncology	England	3087	109849	121	5.972	Q1
9	Plos One	USA	120	2734	1571	367	3.752	Q2	New England Journal of Medicine	USA	2482	92989	1079	176.082	Q1
10	BMC Cancer	England	111	2012	2006	139	4.638	Q2	Lancet Oncology	England	2317	84610	355	54.433	Q1

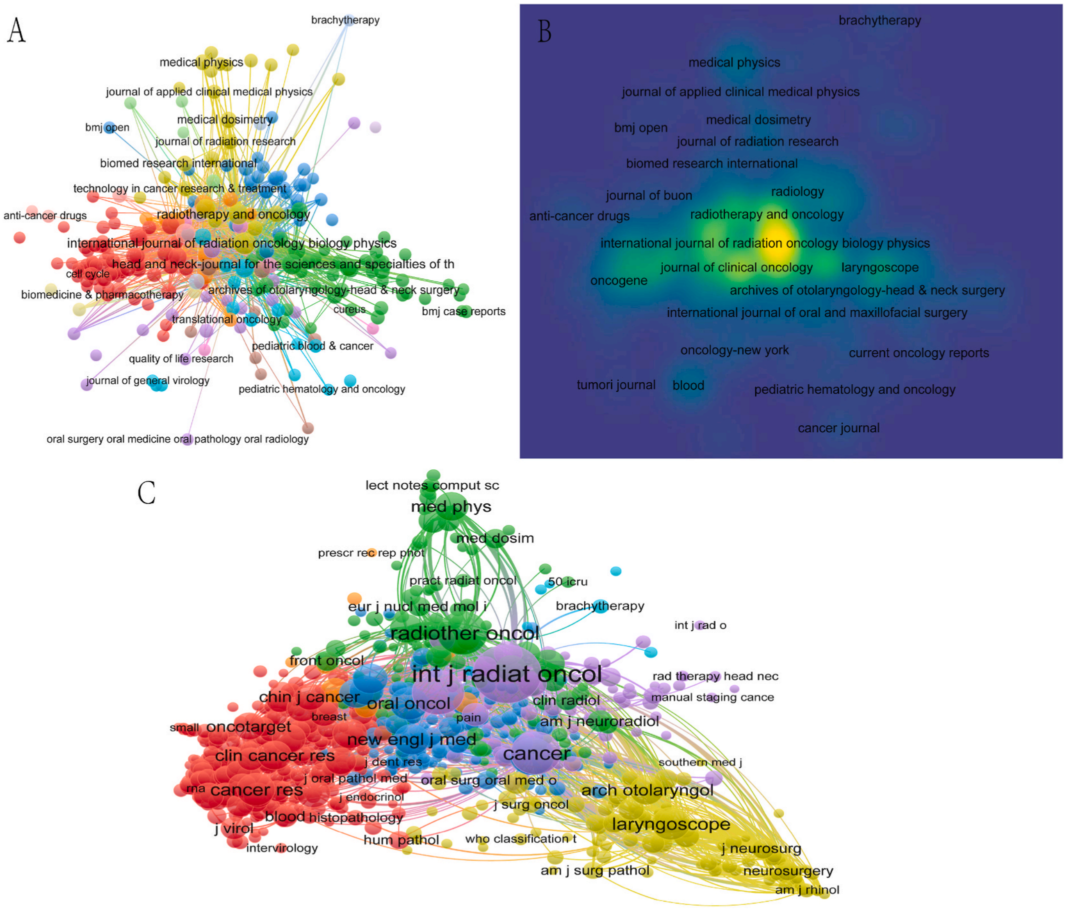

Fig. 5. Visualization of the analyses of journals and co-cited journals. Visualization network and density map of journals (A and B) and network of co-cited journals (C) related to NPC radiotherapy. In the density map, brighter nodes indicate greater journal influence.

Fig. 7A. Obviously the core nodes of the five clusters represented by different colors in the figure are "nasopharyngeal carcinoma", "survival", "intensity-modulated radiotherapy" and "head and neck" cancer "and" chemoradiotherapy ".

The top 25 keywords with the strongest citation bursts resulting from the analysis of keyword citation burst in NPC radiotherapy from 1959 to 2022 are listed in Fig. 7B from top to bottom in terms of burst strength. The analysis, carried out by CiteSpace, includes the burst intensity and duration, which can reflect the research hotspots of NPC radiotherapy in a certain period. We found that nine of these keywords bursts ended in 2022, and they lasted less than six years. This reveals that they may be emerging research hotspots in recent years. The keyword with strongest burst was the "multicenter" (Strength = 71.46), followed by "outcome" (Strength = 53.21), and "irradiation" (Strength = 44.57), "local control" (Strength = 31.02) and "proliferation" (Strength = 26.63) rank from third to fifth. In addition, the keyword "failure" has been burst for the longest time (23 years), which may mean that it has been a hot topic related to NPC radiotherapy for years.

4. Discussion

In recent years, bibliometric analysis has been widely used by scholars to shed light on the current and evolving trends in cancer research [20–22]. Although currently excellent local-regional control rates have been achieved with the use of IMRT, the management of failure remains one of the greatest challenges for NPC, so it is necessary to identify current and future hotspots of NPC radiotherapy research [23,24]. As we understood, this study is the first systematic literature search and bibliometric analysis for NPC radiotherapy research, and illustrates past research hotspots and future research trends.

Due to the unique epidemiology of NPC, which includes race, striking geographical distribution, dietary habits of susceptible populations, Epstein-Barr virus (EBV) infection, genetic and environmental risk factors, it is not surprising that China ranks first in the number of publications (52.09 %) on NPC radiotherapy [1,2,25]. The top 10 most productive institutions are all from China and are concentrated in the southeastern coastal region, which also indicates the dominance of China in the field. It is obvious that China is engaged in extensive cooperation with other countries/regions in this field, and the Sun Yat-sen University ranks first in the publications and citations and is the leader of NPC radiotherapy research in the world with far more publications and citations than other

Table 4
Top 10 most cited original articles concerning NPC radiotherapy.

Rank	Title	Journal	First Author	Year	Citations
1	Chemoradiotherapy versus radiotherapy in patients with advanced nasopharyngeal cancer: phase III randomized intergroup study 0099	Journal of Clinical Oncology	Al-Sarraf, M	1998	1622
2	Parotid-sparing intensity modulated versus conventional radiotherapy in head and neck cancer (PARSPORT): a phase 3 multicentre randomised controlled trial	Lancet Oncology	Nutting, C	2011	1082
3	Intensity-modulated radiotherapy in the treatment of nasopharyngeal carcinoma: an update of the UCSF experience	International Journal of Radiation Oncology - Biology - Physics	Lee, N	2002	772
4	Quantification of plasma Epstein-Barr virus DNA in patients with advanced nasopharyngeal carcinoma	New England Journal of Medicine	Lin, JC	2004	605
5	Head and neck squamous cell carcinoma: update on epidemiology, diagnosis, and treatment	Mayo Clinic Proceedings	Marur, S	2016	600
6	Phase III study of concurrent chemoradiotherapy versus radiotherapy alone for advanced nasopharyngeal carcinoma: positive effect on overall and progression-free survival	Journal of Clinical Oncology	Lin, JC	2003	586
7	Quantitative analysis of cell-free Epstein-Barr virus DNA in plasma of patients with nasopharyngeal carcinoma	Cancer Research	Lo, YMD	1999	585
8	Retrospective analysis of 5037 patients with nasopharyngeal carcinoma treated during 1976–1985 - overall survival and patterns of failure	International Journal of Radiation Oncology - Biology - Physics	Lee, AWM	1992	521
9	Induction chemotherapy plus concurrent chemoradiotherapy versus concurrent chemoradiotherapy alone in locoregionally advanced nasopharyngeal carcinoma: a phase 3, multicentre, randomised controlled trial	Lancet Oncology	Sun, Y	2016	516
10	Xerostomia and quality of life after intensity-modulated radiotherapy vs. conventional radiotherapy for early-stage nasopharyngeal carcinoma: initial report on a randomized controlled clinical trial	International Journal of Radiation Oncology - Biology - Physics	Pow, E	2006	509

institutions.

We identified influential experts related to NPC radiotherapy by publications and citations of authors and centrality of co-cited authors. The top 10 authors are all from China and most of them belong to Sun Yat-sen University, which provides evidence for the dominant position of China, especially Sun Yat-sen University, in NPC radiotherapy research. Despite such great publications and citations by scholars from mainland China, five of the top 10 co-cited authors with centrality are from the United States, while one is from mainland China and he does not rank within the top 10 of publications and citations. Thus, the influence of the United States in the research of NPC radiotherapy remains strong.

4.1. Limitations and future research directions

According to the results of the journals and co-cited journals analysis, the *International Journal of Radiation Oncology - Biology - Physics* is the most core journal for NPC radiotherapy research. *Intensity-modulated radiotherapy in the treatment of nasopharyngeal carcinoma: an update of the UCSF experience*, published by N Lee et al., in 2002, is by far the most cited article on NPC radiotherapy in the journal, and the article lays the foundation for IMRT to become a common treatment for NPC by revealing its excellent local area control and better protection of neighboring organs [26]. Apart from it, three other papers published in the journal ranked in the top 10 most cited and co-cited references, which also had a significant impact on NPC radiotherapy research. AMN Lee et al. performed a retrospective analysis of 5037 NPC patients from Queen Elizabeth Hospital in Hong Kong between 1976 and 1985. Based on a large number of patients and long-term observation, they made a detailed analysis of the characteristics of patients, their failure pattern and survival rate, and they concluded that the improvement of technical precision and dose control of radiotherapy, prophylactic irradiation of patients with negative lymph nodes, improved computed tomography and flexible endoscopy for local evaluation, adjuvant chemotherapy, etc., are beneficial to improve the survival rate of patients, and provide a more solid foundation for future clinical trials to improve treatment [27]. The study of E Pow et al. revealed in 2006 that IMRT was significantly superior to conventional radiotherapy in terms of parotid gland preservation and improvement of life quality in early-stage disease [28]. Based on this, more and more scholars began to focus on side effects and the life quality of NPC patients after radiotherapy. Compared with 2D radiotherapy, IMRT has a greater improvement in the treatment effect of nasopharyngeal cancer patients, mainly manifested as a higher local tumor control rate in nasopharyngeal cancer patients, especially in early T stage patients, as revealed by SZ Lai et al. from the team of Ma Jun [29]. It is obvious that the research published in *International Journal of Radiation Oncology - Biology - Physics has* greatly promoted the popularization of advanced techniques of NPC radiotherapy and the change of treatment strategies.

4.2. Challenges in clinical application and further recommendations

Another well-known journal in the field of radiotherapy, *Radiotherapy and Oncology*, also has a significant influence on NPC radiotherapy research. Although there are fewer publications related to NPC radiotherapy in this journal than in *Head and Neck-Journal for the Sciences and Specialties of the Head and Neck* (237 vs. 284), publications in this field published in *Radiotherapy and Oncology* are cited far above in another (9616 vs. 6703). However, none of the publications from *Radiotherapy and Oncology* ranks in the top 10 most

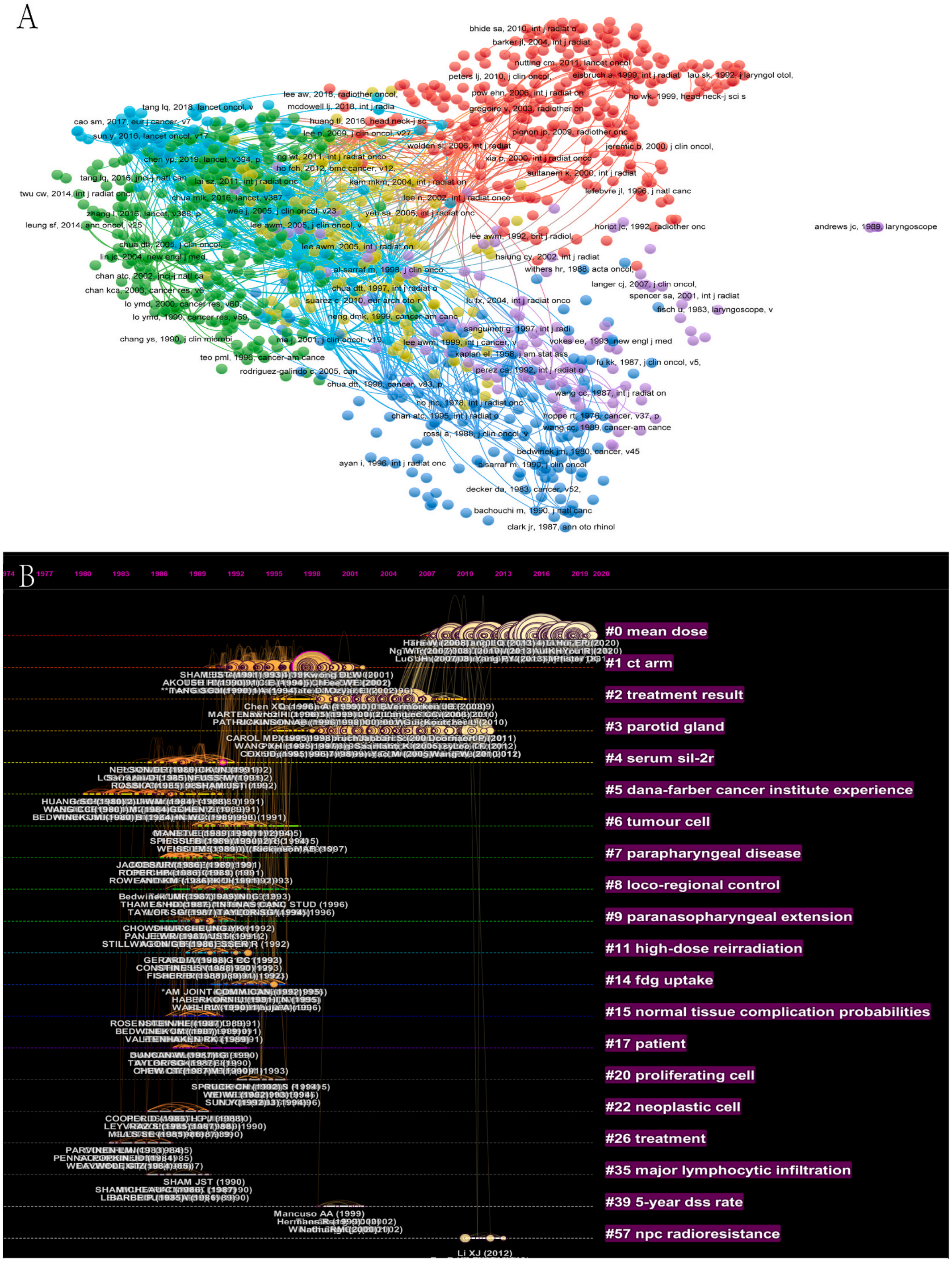

Fig. 6. The co-cited references related to NPC radiotherapy. (A) Visualization network of co-cited references. (B) The timeline view of co-cited references related to NPC radiotherapy with relevant clusters.

cited and co-cited references. The same situation applies to *Cancer*, and only 150 publications on NPC Radiotherapy were published in it (ranking eighth) with the total citations of 9441 (ranking fourth) after *Radiotherapy and Oncology*. Nevertheless, the high citation frequency of their publications in NPC radiotherapy research indicates that they have had a profound impact in the field.

Although there are few publications on NPC radiotherapy in the *Journal of Clinical Oncology* (n = 63), some key studies have been published in it. Based on its second rank in both cited and co-cited journals and an article from it ranked first in both cited and co-cited references, *Journal of Clinical Oncology* highlights its key position in NPC radiotherapy research. A randomized phase III trial published

Table 5
Top 10 co-cited references involved in NPC radiotherapy.

Rank	Title	Year	First Author	Journal	IF	Co-citations	TLS
1	Chemoradiotherapy versus radiotherapy in patients with advanced nasopharyngeal cancer: phase III randomized intergroup study 0099	1998	Al-Sarraf, M	Journal of Clinical Oncology	50.739	949	15655
2	Intensity-modulated radiotherapy in the treatment of nasopharyngeal carcinoma: an update of the UCSF experience	2002	Lee, N	International Journal of Radiation Oncology - Biology - Physics	8.013	529	8719
3	Phase III study of concurrent chemoradiotherapy versus radiotherapy alone for advanced nasopharyngeal carcinoma: Positive effect on overall and progression-free survival	2003	Lin, JC	Journal of Clinical Oncology	50.739	439	7671
4	Nasopharyngeal carcinoma	2005	Wei, WI	Lancet	202.731	417	4654
5	How does intensity-modulated radiotherapy versus conventional two-dimensional radiotherapy influence the treatment results in nasopharyngeal carcinoma patients?	2011	Lai, SZ	International Journal of Radiation Oncology - Biology - Physics	8.013	389	5854
6	Intensity-modulated radiation therapy with or without chemotherapy for nasopharyngeal carcinoma: Radiation therapy oncology group phase II trial 0225	2009	Lee, N	Journal of Clinical Oncology	50.739	370	6146
7	Induction chemotherapy plus concurrent chemoradiotherapy versus concurrent chemoradiotherapy alone in locoregionally advanced nasopharyngeal carcinoma: a phase 3, multicentre, randomised controlled trial	2016	Sun, Y	Lancet Oncology	54.433	359	5907
8	Nasopharyngeal carcinoma	2016	Chua, MLK	Lancet	202.731	353	3255
9	Nasopharyngeal carcinoma	2019	Chen, YP	Lancet	202.731	352	3399
10	Nonparametric-estimation from incomplete observations	1958	Kaplan, EL	Journal of the American Statistical Association	4.369	345	5123

Table 6
Top 20 co-occurrence keywords involved in the research of NPC radiotherapy.

Rank	Keywords	Occurrences	TLS	Rank	Keywords	Occurrences	TLS
1	Nasopharyngeal Carcinoma	3601	4503	11	EBV	171	242
2	Radiotherapy	1300	2028	12	Cisplatin	160	344
3	Intensity-Modulated Radiotherapy	873	1409	13	Metastasis	130	238
4	Head and Neck Cancer	690	1004	14	Cancer	122	186
5	Prognosis	450	879	15	Nasopharynx	119	159
6	Chemoradiotherapy	442	921	16	Apoptosis	117	162
7	Chemotherapy	322	691	17	Quality of Life	114	229
8	Survival	215	457	18	Radiation	110	150
9	Induction Chemotherapy	194	462	19	Xerostomia	105	187
10	Magnetic Resonance Imaging	183	293	29	Prognostic Factor	102	202

in the *Journal of Clinical Oncology* in 1998 compared chemoradiotherapy with radiotherapy alone for patients with NPC and found that chemoradiotherapy was superior to radiotherapy alone in terms of progression-free survival (PFS) and overall survival (OS) for patients with advanced NPC [30]. This study is the one mentioned above that ranks first in both cited (n = 1622) and co-cited (n = 949) references. Another phase III study published in the same journal in 2003 by JC Lin et al. confirmed the conclusion of the previous study [31]. They have laid a solid foundation for the clinical application and research of concurrent chemoradiotherapy for NPC, and promoted the change of treatment strategy for NPC. It is interesting to note that only three of the top 10 cited and co-cited references were published in the last decade, and two of them were reviews. The only one original article of the three papers, a multicenter Phase III clinical trial published in 2016 in *Lancet Oncology* by Y Sun et al., revealed that the addition of induction chemotherapy to concurrent chemoradiotherapy may benefit patients with locally advanced NPC [32].

Clustering based on co-cited references helps scholars understand research hotspots in a particular field over a certain period of time. In order to clarify the research hotspots, we analyzed the references related to NPC radiotherapy from 1959 to 2022 and their significance according to the timeline. We found that the cluster 0 ″mean dose" was the most popular research direction in recent years, which contained most publications among clusters (n = 2653). Studies in cluster 0 mainly focused on adjuvant chemotherapy, detectable plasma EBV DNA, curative radiotherapy, tumor response, T4 NPC, and 5-year disease-free survival (DFS). With the innovation of radiotherapy technology, especially the popularization of IMRT, scholars who have broken the limitations in recent years have focused on the actual average total dose and fractionated dose delivered to the gross tumor volume (GTV), the clinical target volume (CTV) and the average dose delivered to organs at risk (OARs) in NPC radiotherapy research, they were designed to avoid unnecessary irradiation of low-risk areas for reducing a range of toxic side effects such as dysphagia, xerostomia and radiation-induced facial lymphedema, while improving patients' survival [33–36]. This means that in recent years, research on NPC radiotherapy has focused on dosimetry. Whether it is the improvement of the GTV/CTV dose and boundaries or the dose limitation of OARs, the ultimate

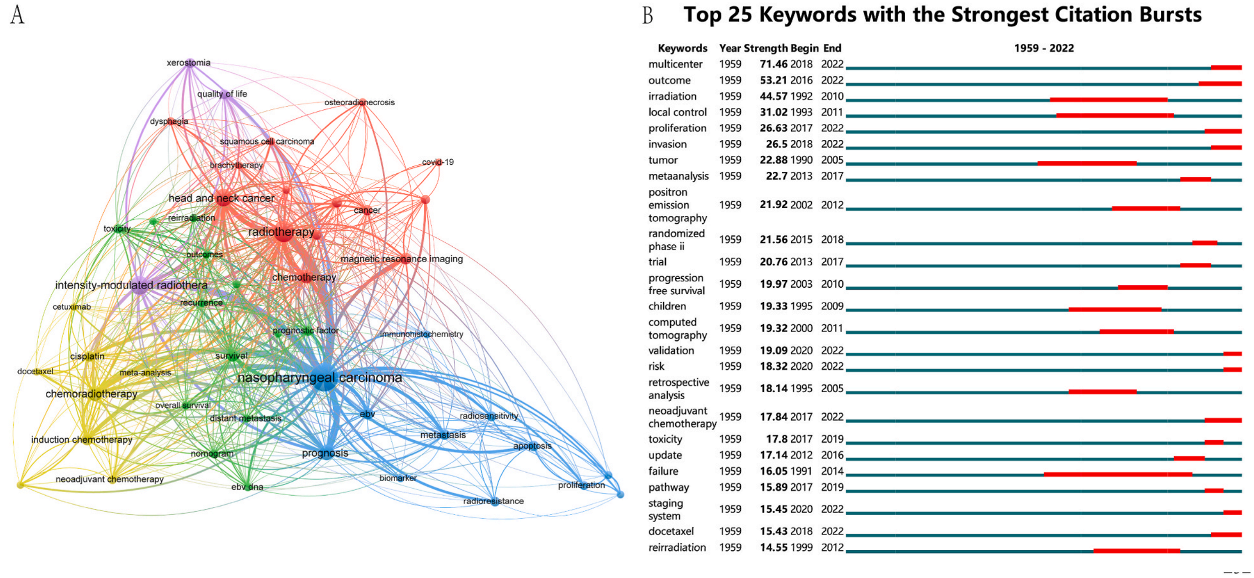

Fig. 7. Visualization of core author keywords related to NPC radiotherapy. (A) Network visualization of top 50 author keywords. (B) Top 25 keywords with the strongest citation bursts in publications.Red indicates the time when the keyword was mainly present.

goal is to achieve the best dose distribution to maintain a balance between quality of life and survival, and scholars are still searching for that balance, and may continue to do so for a long time [37–39]. In the contemporary era with various tumor treatment methods, radiotherapy alone has long been unable to meet the needs of NPC treatment, and radiotherapy in combination with chemotherapy/immunotherapy has become the current mainstream. It seems that the current research on the dose/pattern of radiotherapy has reached a bottleneck. Academics have shown great enthusiasm for studying the dose/pattern of chemotherapy/immunotherapy in combination with radiotherapy for NPC, and future research in this field may focus on a combination treatment strategy of multiple drugs and radiotherapy in the absence of radiotherapy technological innovations [40–44]. Due to the association of EBV infection with the pathogenesis of NPC and the concentration of plasma EBV DNA has impact on the treatment and tumor progression of NPC, it has been studied as a biomarker for years [45,46]. To guide more effective treatment strategies, the exploration of various biomarkers, including EBV, clinical/imaging features, etc., may be a research trend in the future [47–49].

Looking at clusters 2 and 3 with larger sample sizes in recent years, scholars seem never to reduce their concern about the toxic side effects and various outcomes of treatment. This also has been confirmed by citation burst and co-occurrence analysis of keywords. Over time, scholars no longer only pay attention to the OS of NPC patients after radiotherapy, but also a variety of outcomes, including DFS, PFS, disease-specific survival (DSS), distant metastasis-free survival (DMFS), loco-regional relapse free survival (LRRFS), etc., have gradually been paid attention, which means a more comprehensive and objective evaluation of treatment efficacy [50,51]. Since NPC patients have a longer survival time after treatment, demand of patients for better life quality is increasing. As an unavoidable problem in radiotherapy, toxicity has always been a very vexing problem and is also a hot topic in recent years according to the citation burst analysis of keywords (Strength = 17.8). In the background, radiotherapy preserving efficacy and attenuating toxicity gradually becomes the research trend of scholars. The team of ZX Lin and the team of JJ Pan and SJ Lin from China have made prominent contributions to preserve efficacy and attenuate toxicity radiotherapy of NPC. The team of SJ Lin and JJ Pan proposed the concept of reduced target volume by reducing the scope of subclinical lesions for the first time in the world in 2009, and subsequently updated their research results in 2014 and 2022, which was regarded as an improved volume reduction pattern for NPC radiotherapy without affecting the efficacy [52–54]. The team of ZX Lin tends to conduct a series of studies on a specific OAR, and their research on the thyroid in NPC radiotherapy has had a great international impact. They carefully evaluated the correlation between the size of thyroid glands and the changes of related hormones in NPC patients after radiotherapy, and concluded that the radiation-induced changes depend on the average thyroid dose and the correlation between thyroid antibodies and thyroid hormones in radiation-induced hypothyroidism, and proposed to reduce thyroid dose in NPC radiotherapy [55,56]. The comparison of radiation dose risk for thyroid and pituitary gland, and follow-up of thyroid volume and hormone up to 48 months after radiotherapy further supported the previous conclusions [57,58]. The radiation-induced hypothyroidism prediction model/nomogram to guide more effective thyrotoxic reduction radiotherapy strategies was also developed by them [59,60]. Although the two teams have given us two directions to explore preserve efficacy and attenuate toxicity of NPC radiotherapy, advance patterns remain to be further studied.

We find that positron emission tomography (PET, Strength = 21.92) is also a core keyword in NPC radiotherapy research. The currently advocated individual radiotherapy is in essence precision radiotherapy which means preserving effect and reducing toxicity, and the use of PET can make the treatment more accurate no matter before, during and after NPC radiotherapy [61–63]. There are two main directions in NPC radiotherapy research of PET in recent years. One is PET, used for NPC, combined with artificial intelligence (AI) such as deep learning for early cancer detection, diagnosis, classification and grading, molecular characterization of tumors, prediction of patient prognosis and treatment response, personalized therapy, automated radiotherapy workflow, etc [64–66]. Another direction is to treat imaging guidance of PET as a biomarker for biology-guided radiotherapy (BGRT) [67]. BGRT has been shown to benefit patients with NPC, and PET without the use of the unconventional tracer 18F-fluorodeoxyglucose has been shown to have the potential to direct clinical BGRT [68,69]. Rapid advances in functional and biological imaging, predictive biomarker/assays, the development of BGRT induced by different biomarkers, and the advantages of BGRT in individualized precision therapy indicate that BGRT may be one of long-term goals for the development of NPC radiotherapy [70].

5. Conclusions

In conclusion, precision is the vital goal for cancer treatment, especially in radiotherapy. The pursuit of precision strike treatment strategies that preserve efficacy and attenuate toxicity is a continuing hot topic in NPC radiotherapy. Based on this, the exploration of the application of AI in radiotherapy, radiotherapy in combination with other therapies and the BGRT depending on various biomarkers are likely to be long-term research trends in the near future for NPC radiotherapy.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Data availability statement

Data included in article/supplementary material is referenced in the article.

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CRediT authorship contribution statement

Kaichun Huang: Writing – original draft, Data curation. **Xinqing Yang:** Writing – review & editing, Validation, Project administration. **Cuidai Zhang:** Visualization, Formal analysis. **Xuejia Liu:** Visualization. **Yingji Hong:** Data curation. **Qingxin Cai:** Visualization, Data curation. **Mei Li:** Data curation. **Zhixiong Lin:** Writing – review & editing, Validation, Supervision, Project administration, Funding acquisition, Conceptualization. **Yizhou Yang:** Writing – original draft, Validation, Project administration, Methodology, Conceptualization.

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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List of abbreviations

2D	two-dimensional
3D	three-dimensional
AI	artificial intelligence
BGRT	biology-guided radiotherapy
CTV	clinical target volume
DFS	disease-free survival
DMFS	distant metastasis-free survival
DSS	disease-specific survival

EBV	Epstein-Barr virus
GTV	gross tumor volume
IF	impact factor
IMRT	intensity modulated radiation therapy
JCR	Journal Citation Reports
LRRFS	loco-regional relapse free survival
NPC	nasopharyngeal carcinoma
OARs	organs at risk
OS	overall survival
PFS	progression-free survival
SCIE	Science Citation Index-Expanded
TLS	total link strength
VMAT	volumetric modulated arc radiation therapy
WoSCC	Web of Science Core Collection

Appendix A. Supplementary data

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