Review Article

Bibliometric analysis of research relating to radiation-induced lung injury [2001–2020]

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Abstract: Radiotherapy is one of the common means of cancer treatment, especially in the treatment of lung cancer. However, radiation therapy can cause lung tissue radiation lung injury. The study of this disease can reduce its incidence and avoid the occurrence of radiation pulmonary fibrosis. In the past 20 years, the study of radiation-induced lung injury (RILI) has attracted more attention. This paper extracts the main text information of RILI-related literature from WOSCC database from 2001 to 2020, uses Citespace and VOSviewer for visual analysis, and presents the results. We found that in the past 20 years, there have been 4,665 articles on RILI, and the number of articles published reached a peak in 2017. The United States is the main leader in this research field, among which UNIV Texas MD Anderson Cancer Center has published many research results in this field. The most active author is Liao Zhongxing, and the most influential journal is *Int J Radiat Oncol*, which provides a platform for scholars in related fields to publish their articles. Current research focuses mainly on randomized controlled trials related to RILI, the relationship between dose-volume histogram analysis and RILI formation, the protection of normal lung tissue, the effect of stereoscopic radiotherapy on RILI and the pathogenesis of RILI. In the study of the formation mechanism of RILI, the main research directions include the apoptosis mechanism of epithelial and endothelial cells, cytokine cascade theory, immune mechanism regulation process, oxidative stress mechanism, etc.

Keywords: Radiation-induced lung injury (RILI); bibliometric; visual analysis; CiteSpace; VOSviewer

Introduction

Radiotherapy (RT) is a commonly used means of cancer treatment (1), which can also cause damage to normal human tissues (2). In lung cancer patients receiving radiotherapy, 5–20% of patients will develop radiation-induced lung injury (RILI) (3). RILI includes radiation pneumonia (RP) and radiation-induced pulmonary fibrosis (RIFI). The RP stage mainly occurs 1–6 months after radiotherapy (4), and pulmonary tissue fibrosis will gradually appear after 6 months (5), with a poor prognosis. The main symptoms of RP are cough, fever, chest pain, fatigue, and dyspnea, which can significantly affect the quality of life of patients and even lead to death (6). Currently, RILI is mainly in the clinical treatment of glucocorticoid hormones, antibiotics, antioxidants, oxygen and other respiratory support treatment (7), symptomatic radiation-induced lung injury (SRILI) is a serious complication of radical radiotherapy (8), but the side effects of hormone therapy are significant, so we need to find a more suitable
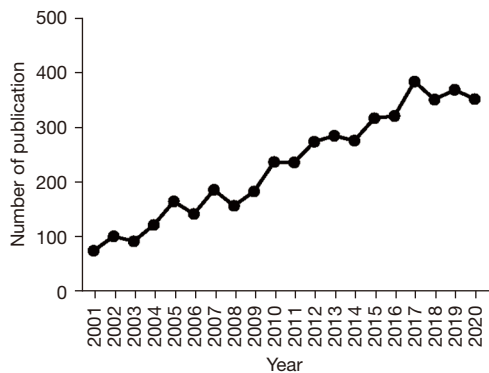
Figure 1 The number of annual publications in RILI research from 2001 to 2020. RILI, radiation-induced lung injury.

treatment. We urgently need to explore the pathogenesis of RILI and develop new therapeutic strategies to prevent and treat this disease. Both CiteSpace (9) and VOSviewer (10) are information visualization software, which can conduct a quantitative analysis of literature and produce visual maps to show hot topics in the research field. At present, no literature has systematically summarized the research status and hot spots of RILI. Therefore, this paper used CiteSpace and VOSviewer software combined with bibliometrics to statistically analyze the studies related to RILI from 2001 to 2020, providing objective guidance for scholars in this field.

Methods

Search method

Data source: Web of Science Core Collection (WOSCC) database, retrieval strategy: TS= ('Radiation-induced lung injury' OR 'RILI' OR 'radioactive lung injury' OR 'RILT' OR 'radio-pulmonary lesion' OR 'Radiation Pneumonitis' OR 'Radiation-induced pulmonary fibrosis' OR 'Radiation pulmonary fibrosis'). Time period: January 2001 to December 2020. Index: SCI-Expand.

Data download

Exports the full record of the search results (including all authors, titles, source journals, keywords) and references in plain text format in WOSCC. Retrieve and download the data within 1 day (January 2, 2021) to avoid changes due to daily database updates.

Analytical methods

CitespaceV 5.7.R2 was used to draw the map of national and institutional cooperation, keyword co-occurrence map, literature, and journal co-citation map, and VOSviewer 1.6.15 was used to draw the map of the author cooperation. In the atlas, nodes represent countries, institutions, keywords, co-cited literature and journals, and links between nodes usually represent cooperation or co-citation relationships. The colors of the nodes and lines change depending on the year. The CiteSpace software is able to present trends and dynamics across the literature and extract key nodes in the research area.

Results

General information and annual publications

A total of 4,665 articles related to RILI were retrieved, with the citation frequency of 107,490, the average citation frequency of 23.04, and H-index of 128. As shown in *Figure 1*, the average number of papers related to RILI is 233 per year, and 2017 is the peak year of publication [386], in 2020, 354 papers were published, with the output remaining at a relatively high level.

Active countries and institutions

The maps of national cooperation (*Figure 2A*, N=42, E=47) and institutional cooperation (*Figure 2B*, N=485, E=701) were generated using CiteSpace software. Researchers from 485 institutions in 42 countries or territories have published articles on RILI. The *Table 1* and *Table 2* listed the top 5 countries and institutions that have contributed the most to research in this field. The largest number of publications in this field are in the United States, where UNIV Texas MD Anderson Cancer Center is an authority in this field. The second most published country is China, and Fudan Univ ranks fourth. Countries such as Spain, South Korea, Switzerland, England, and Sweden all have purple rings, proving significant contributions in this field.

Active authors

We presented the collaborative relationships of the top 100 most active authors in the field and found that there are 13 collaborative teams (*Figure 3*). *Table 3* lists the top 10 most published authors. The two most active authors,
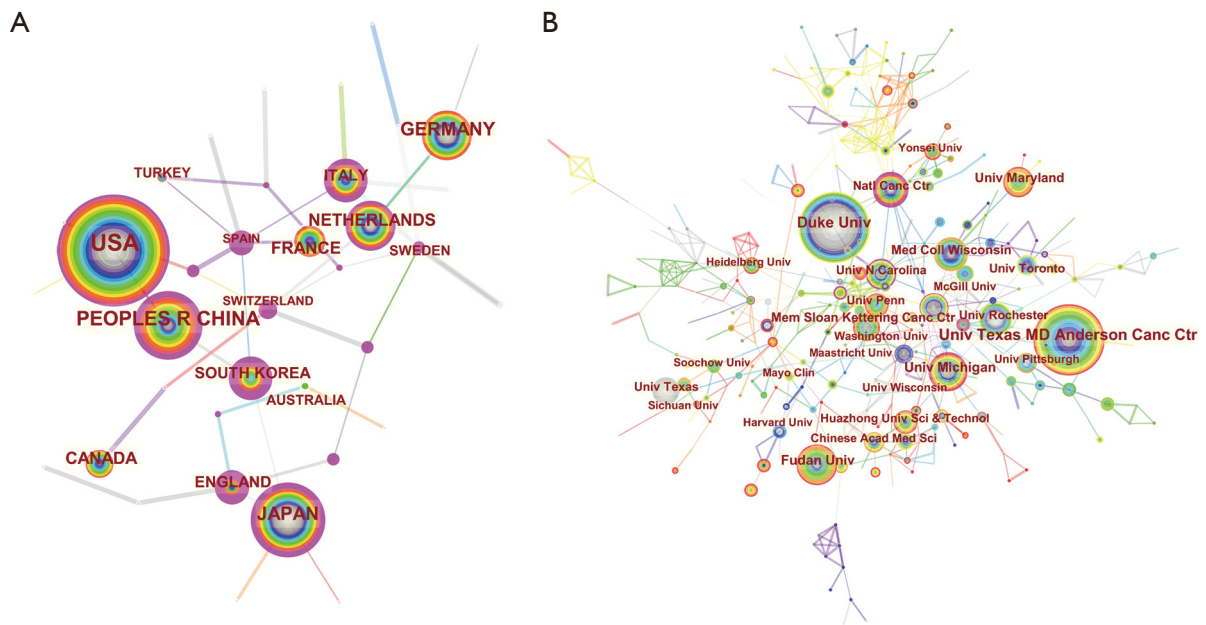
Figure 2 The analysis of active countries and institutions. (A) Network of countries/territories engaged in RILI research; (B) Network of institutions engaged in RILI research. RILI, radiation-induced lung injury.

Table 1 The top 5 countries for centrality and publications in RILI research

Rank	Frequency	Country	Rank	Centrality	Country
1	1,281	USA	1	0.65	Spain
2	584	China	2	0.55	South Korea
3	397	Japan	3	0.5	Switzerland
4	271	Germany	4	0.48	England
5	178	The Netherlands	5	0.38	Sweden

RILI, radiation-induced lung injury.

Table 2 The top 5 institutions for centrality and publications in RILI research

Rank	Frequency	Institution	Rank	Centrality	Institution
1	120	Univ Texas MD Anderson Canc Ctr	1	0.45	Natl Canc Ctr
2	112	Duke Univ	2	0.34	Univ N Carolina
3	65	Univ Michigan	3	0.23	Emory Univ
4	60	Fudan Univ	4	0.22	Univ Calif San Francisco
5	57	Univ Maryland	5	0.21	Vrije Univ Amsterdam

RILI, radiation-induced lung injury.
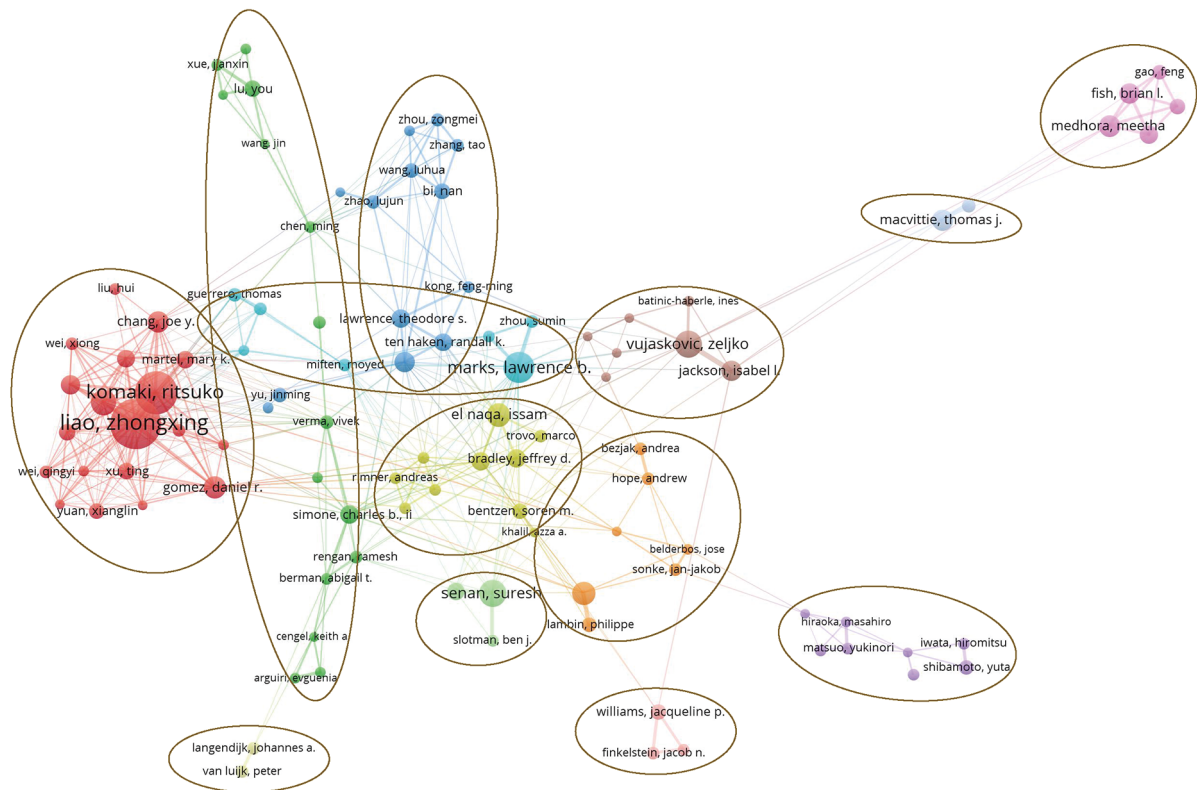
Figure 3 The top 100 active authors in the RILI research: there are 13 clusters. RILI, radiation-induced lung injury.

Table 3 The top 10 authors for publications in RILI research

| Rank	Name	Weight (occurrences)
1	Liao, Zhong Xing	74
2	Komaki, Ritsuko	61
3	Marks, Lawrence B.	40
4	Vujaskovic, Zeljko	35
5	Senan, Suresh	34
6	Mohan, Radhe	31
7	De Ruysscher, Dirk	29
8	El Naqa, Issam	28
9	Gomez, Daniel R.	27
10	Chang, Joey.	25

RILI, radiation-induced lung injury.

Liao Zhongxing and Ritsuko Komaki, are both from The Department of Radiation Oncology of The University of Texas MD Anderson Cancer Center. The third author is

Lawrence B. Marks of Duke University Medical Center.

Keyword co-occurrence and burst

Keyword co-occurrence analysis can display the hot spots of research, and keywords with high frequency are often the main research direction in this field. The top 10 keywords with the highest frequency in 2001–2020 (*Figure 4*) are radiotherapy [985], pneumonitis [810], radiation pneumonitis [589], therapy [580], irradiation [573], radiation-therapy [564], lung cancer [468], toxicity [453], cancer [444], chemotherapy [419].

Strong citation bursts can reveal hot words at the forefront of research. We've listed top 20 keywords with the strongest citation bursts (*Table 4*), including randomized trial, volume histogram analysis, stereotactic body radiotherapy, mechanism, risk factors, lung injury, 3-dimensional conformal radiotherapy, activation, growth factor-beta, non-small cell lung cancer, idiopathic pulmonary fibrosis. Among the latest words to appear in the last five years (*Table 5*) are intensity-modulated radiotherapy,
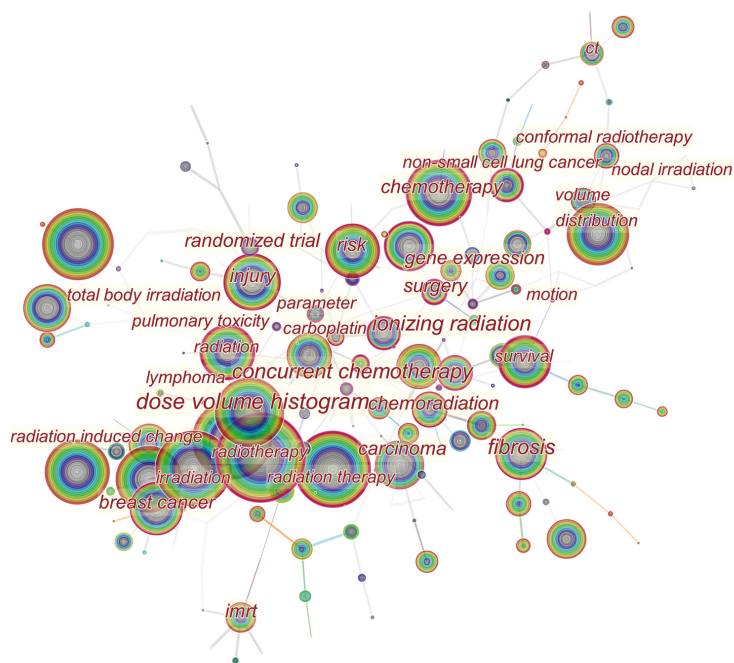
Figure 4 The analysis of keywords in RILI research. RILI, radiation-induced lung injury.

risk factor, damage, activation, cell, impact, pulmonary fibrosis, predictors, etc.

Co-cited journals and references

Co-citation refers to the phenomenon that two papers are jointly cited by one or more later papers. The circles in the figure reflect the citations of the downloaded journals and references. The more citations, the larger the circles, and the color changes with the year. The top 5 journals (*Figure 5*, *Table 6*) and the top 5 references (*Figure 6*, *Table 7*) with the highest citation frequency and the strongest centrality in this field are listed. *Int J Radiat Oncol* ranked highest (2,835, IF=5.859), followed by *Radiother Oncol* (2,004, IF=4.856), and *J Clin Oncol* ranked third (1,725, IF=32.956). *Int J Radiat Oncol* and *J Clin Oncol* are also the two journals with the highest centrality ranking, which proves that these two journals are important in the field of RILI. Robert Timmerman's article published in *JAMA* in 2010 was the most frequently cited, while Andrew J. Hope's article published in *Int J Radiat Oncol* in 2006 ranked the highest for centrality.

Discussion

General information

The number of RILI studies has been increasing year by year, with 4.5 times more published in 2020 than in 2001. Compared with the peak in 2017, the number of articles in 2020 has decreased but still remains at a high level, proving that although a large number of measures and advanced equipment to reduce the effects of radiation have appeared in recent years, such as volume histogram analysis and stereotactic body radiotherapy, the progress of the disease has not been well controlled in essence. The research on RILI has still attracted great attention from scholars. Combined with the emergent word table, it can be speculated that the publication peaks in 2005, 2007 and 2017 may be associated with volume histogram analysis, 3-dimensional conformal radiotherapy (3D-CRT), Stereotactic body is related to radiotherapy.

Both the United States and China are countries that have published extensively in this field, but the United States has a long research history, while China has published more articles recently and has a short research history in this field.

Table 4 Top 20 keywords with the strongest citation bursts

Keywords	Strength	Begin (year)	End (year)	2000–2020
Randomized trial	23.95	2001	2020	
Volume histogram analysis	20.57	2004	2020	
Normal tissue	19.95	2001	2020	
SBRT	16.64	2013	2020	
Mechanism	15.68	2015	2020	
Risk factor	15.57	2016	2020	
Lung injury	14.6	2014	2020	
Dose volume histogram	14.09	2001	2020	
3-dimensional conformal radiotherapy	13.93	2007	2020	
Activation	13.84	2016	2020	
Stereotactic body radiotherapy	13.11	2015	2020	
Concurrent	13.06	2015	2020	
Growth factor beta	12.85	2001	2020	
Non-small cell lung cancer	12.41	2003	2020	
Parameter	12.39	2006	2020	
Concurrent chemotherapy	12.36	2008	2020	
Bone marrow transplantation	12.09	2001	2020	
Management	12.01	2012	2020	
Idiopathic pulmonary fibrosis	11.51	2017	2020	
Docetaxel	11.37	2018	2020	

SBRT, stereotactic body radiation therapy.

This may be due to the late introduction of radiotherapy technology. Spain has a high centrality, which means that the country's scholars publish papers that are recognized and cited by a wide range of scholars.

In terms of the number of publications, the authors who contributed the most were Liao Zhongxing and Ritsuko Komaki. The authors' collaborative map shows that they have formed a collaborative group to study predictors of RP and different fibrosis patterns in RILI. Liao Zhongxing's early research was on the formation process of RP (11) and the distribution of its key sites (12), This laid the foundation for subsequent RILI studies on relevant targets. In addition, he found the correlation between transforming growth factor β1 (TGFβ1) and RP at the gene level, and proposed that TGFβ1 could be used as a reliable predictor of RP (13). His findings are supported by recent studies which have also demonstrated that TGF-β1 is an important fibrotic growth factor and can be produced by a variety of cell types.

Ritsuko Komaki demonstrated the advantages of 3D-CRT technology, which has been shown to reduce side effects and increase the therapeutic dose to tumors, and may better control tumor progression. Three radiological fibrosis patterns that differ from traditional RILI are introduced to help scholars understand and correctly interpret CT scan results after 3D-CRT (14). These works provide important value for clinical diagnosis and treatment. Lawrence B. Marks, whose work is mainly related to the exploration of the mechanism of RILI formation, demonstrated that the production of reactive oxygen species promotes RILI (3). It can be seen from the cluster diagram of authors' cooperation relationship that there are 13 relatively independent research groups, which may be related to their geographical location and have a certain impact on the academic communication among the

11172

Wang et al. Bibliometric analysis of research relating to RILI

Table 5 The strongest citation bursts keywords after 2016

| Keywords	Strength	Begin (year)	End (year)	2000–2020
Intensity modulated radiotherapy	3.95	2016	2020	
Risk factor	15.57	2016	2020	
Damage	7.38	2016	2020	
Activation	13.84	2016	2020	
Cell	9.28	2016	2020	
Impact	10.52	2017	2020	
Idiopathic pulmonary fibrosis	11.51	2017	2020	
Pulmonary fibrosis	3.39	2017	2020	
Docetaxel	11.37	2018	2020	
Disease	12.68	2018	2020	
Predictor	8.04	2018	2020	
Carboplatin	7	2018	2020	
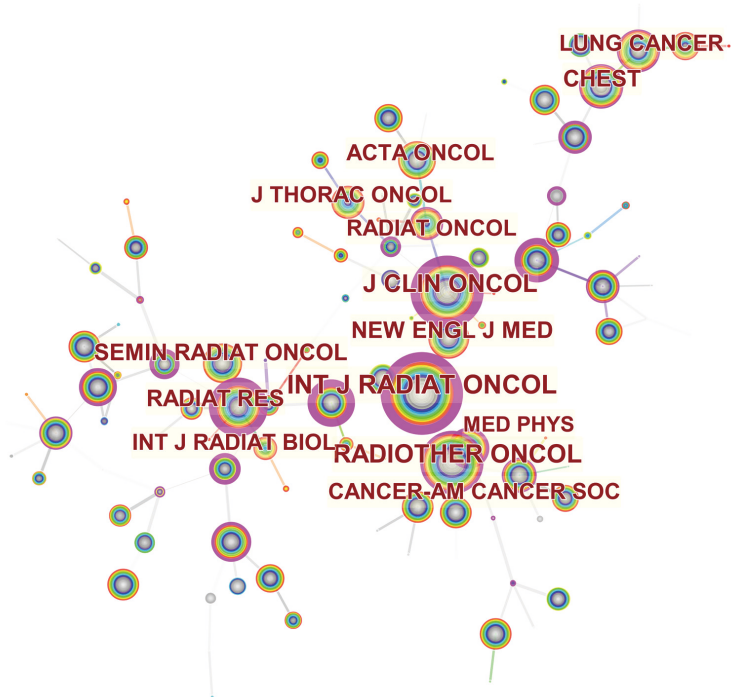
Figure 5 The analysis of co-cited journals: co-citation network of journals from publications in RILI research. RILI, radiation-induced lung injury.

Table 6 The top 5 co-cited journals in RILI research

Rank	Frequency	Journal	Rank	Centrality	Journal
1	2,835	*Int J Radiat Oncol*	1	1.11	*Int J Radiat Oncol*
2	2,004	*Radiother Oncol*	2	1.03	*J Clin Oncol*
3	1,725	*J Clin Oncol*	3	0.89	*Radiat Res*
4	1,006	*New Engl J Med*	4	0.81	*Int J Radiat Biol*
5	904	*Chest*	5	0.61	*Brit J Cancer*

RILI, radiation-induced lung injury.
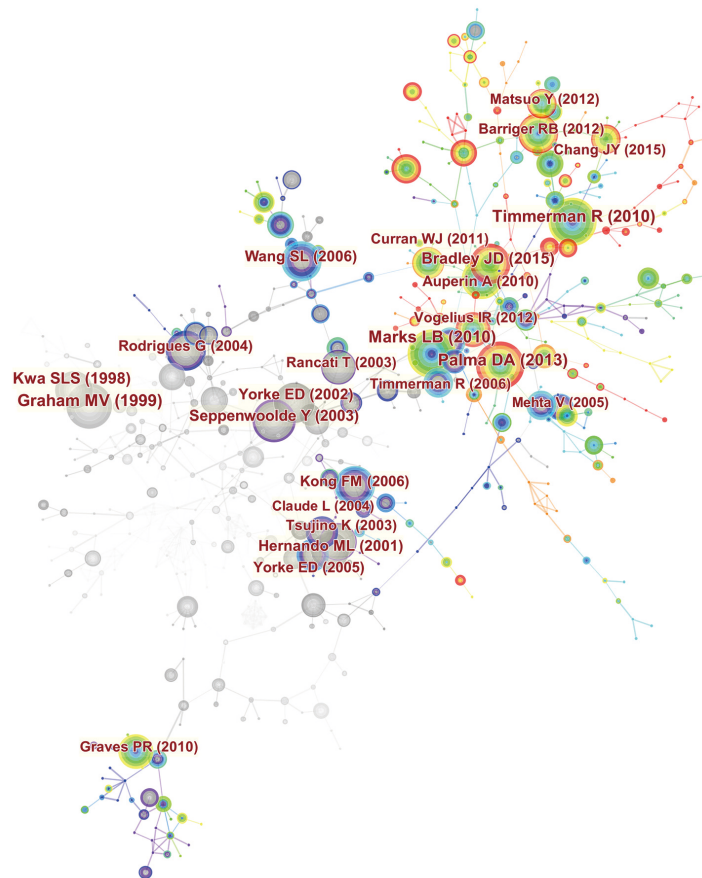
Figure 6 The analysis of co-cited references: co-citation network of references from publications in RILI research. RILI, radiation-induced lung injury.

groups.

Citation information

Int J Radiat Oncol is the journal of centralization and the highest number of publications, the publication direction is mainly related to tumor radiation therapy, molecular radiation biology, tumor sensitization and normal tissue protection, dosing and conformal radiation therapy and other research progress, providing the direction for RILI field academic paper publication.

The most frequently cited article was published by

11174

Wang et al. Bibliometric analysis of research relating to RILI

Table 7 The top 5 co-cited references in RILI research

Rank	Frequency	Reference	Rank	Centrality	Reference
1	156	Timmerman R, 2010, *JAMA-J Am Med Assoc*, V303, P1070	1	0.5	Hope AJ, 2006, *Int J Radiat Oncol*, V65, P112
2	155	Palma DA, 2013, *Int J Radiat Oncol*, V85, P444	2	0.43	Chang DT, 2006, *Int J Radiat Oncol*, V65, P125
3	146	Graham MV, 1999, *Int J Radiat Oncol*, V45, P323	3	0.41	Ang KK, 1998, *Semin Radiat Oncol*, V8, P230
4	143	Marks LB, 2010, *Int J Radiat Oncol*, V76, P0	4	0.39	Yamada M, 1998, *Eur J Cancer*, V34, P71
5	116	Bradley JD, 2015, *Lancet Oncol*, V16, P187	5	0.36	Robnett TJ, 2000, *Int J Radiat Oncol*, V48, P89

RILI, radiation-induced lung injury.

Robert Timmerman in *JAMA* Journal in 2010 (15), which found that the 3-year survival rate of inoperable NSCLC patients receiving SBRT was 55.8%, with a high local tumor control rate and moderate treatment-related morbidity, this provides a basis for the applicability of SBRT. The most centrality article was published by Andrew J. Hope in *Int J Radiat Oncol* in 2006 (16), which evaluated the clinical, dosimetry, and spatial parameters related to RP, and emphasized the importance of lower tumor and dosimetry information in the prediction of RP incidence, which was also confirmed in subsequent studies (17).

Research frontiers

Based on the keyword co-occurrence atlas and strong citation bursts analysis, the top five hotspots were: (I) randomized controlled trials (RCT) related to radioactive lung injury (23.95); (II) dose-to-volume histogram analysis and the relationship between RILI formation (20.57); (III) protection of normal lung tissue (19.95); (IV) the effectiveness of stereotactic radiotherapy for RILI (16.64); (V) the mechanism of RILI formation (15.68). Randomized controlled trials, protection of normal tissues, and dose-volume histogram analysis have been popular for 20 years. Stereotactic radiotherapy, RILI research mechanism, risk factors, activation pathways and so on have only become new research hotspots in the past five years.

As for the research mechanism of RILI, according to the relevant literature review, scholars could conduct research from the following perspectives: (I) apoptosis mechanism of epithelial and endothelial cells: Celine Almeida found that after receiving radiotherapy, lung tissues will experience

vascular wall thickening, inflammatory cell accumulation, collagen deposition, and local fibrosis, etc., and suggested that epithelial-mesenchymal transition (EMT) may play an important role in the development of RIFI (18). Fibroblasts in the alveolar lumen aggregate and secrete angiotensin and hydrogen peroxide to induce apoptosis of alveolar epithelial cells (19). (II) Cytokine cascade theory: at the cellular level, radiation can induce the production of a large number of pro-inflammatory and pro-fibrotic factors (20), which will continue for a long and slow time after the end of radiotherapy. Among them, TGFβ1 and tumor necrosis factor α (TNF-α) play a key role, and multiple pathways such as Nrf2-ARE and TGF-β1/Smad are involved in cytokine initiation. (III) Immune mechanism regulation process: helper T cell 1/Helper T cell 2 (Th1/Th2) imbalance plays an important role in the occurrence of RP and pulmonary fibrosis. In the initial stage of radiation injury, Th1 cells are activated and release IFN-γ, which is associated with acute inflammatory response (21). (IV) Oxidative stress mechanism: Izumi found that (22) Suplatast Tosilate can reduce pulmonary fibrosis and improve the survival rate after radiation by inhibiting the radiation-induced intracellular ROS and DNA double-strand breaks, down-regulating the levels of oxidative stress markers and cytokines of inflammation and fibrosis in the lungs of irradiated mice. Nuclear factor-erythrocyte 2-related factor 2 (Nrf2) is a key transcriptional regulator of the antioxidant cascade (23) and has been shown to modulate life span in mice after chest irradiation (24).

Therefore, through the regulation of EMT process, TGF-β1/Smad pathway, Th1/Th2 balance, Nrf2 and other key transcription regulatory factors related to

antioxidant cascade reaction, as well as the exploration of RILI related predictors, we can explore and verify the mechanism of action of different drugs and further explain the pathogenesis of RILI. It is of great significance for the research and development of new drugs, the prevention of RILI and the improvement of radiotherapy effect, and is a hot research direction of scholars at present.

The literature source in this study was WOSCC database, and the literature retrieval only included English literature. Follow-up research could also include other medical literature databases for more comprehensive research. This study used CitespaceV and VOSviewer software to make a visual analysis of the included literature, which can only provide scholars with some possible research hotspots. In the future, more in-depth literature retrieval and more rigorous scientific research on hot topics are needed.

Conclusions

This study summarizes the research status of RILI in the past 20 years. RILI's research publications are increasing year by year, and cooperation between countries and institutions is not close enough. This study provides help for scholars to find partners and important literature in this field, provides direction for publishing journals, and guides identifying research hotspots in this field.

Acknowledgments

Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/apm-21-1682). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All information is supplementary and does not contain any personal information, therefore informed consent was not required.

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11176

Wang et al. Bibliometric analysis of research relating to RILI

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