Global Research on Osteosarcoma, 1999–2019: A Bibliometric and Visual Analysis

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Research

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Abstract

Background

Osteosarcoma is a primary malignant bone tumor that occurs in children and adolescents. Increasing numbers of scholars have studied its development and treatment. To fully understand the current status of osteosarcoma research and global trends therein, we performed a bibliometric and visual analysis of osteosarcoma studies published between 1999 and 2019.

Methods

We searched the Web of Science database for publications on osteosarcoma. The basic characteristics of this sample of publications, such as H indices, annual outputs, languages of publication, and authors, journals, institutions, and countries of origin, were determined. Co-citation, collaboration, and keyword co-occurrence were analyzed using CiteSpace software.

Results

The sample comprised 16,934 articles. The number of publications increased annually. H indices and total numbers of citations were far higher for articles from the United States than for those from other countries. Among institutions, the largest proportion of articles originated from Shanghai Jiaotong University. R. Gorlick was the author with the highest H index and total number of citations. Oncology Letters published the largest number of articles and Cancer Research was the most frequently cited journal. The five most frequently appearing keywords were “osteosarcoma,” “cancer,” “expression,” “apoptosis,” and “metastasis.” The analysis generated 10 major clusters of keywords and 23 clusters of co-cited references.

Conclusions

The findings of this study have guiding significance for researchers seeking cooperating institutions and partners for osteosarcoma research, popular journals and important literature in the field, an understanding of the knowledge base for this research, and up-to-date identification of research hotspots and trends.

Keywords: osteosarcoma, bibliometric, citespace, visual analysis, co-citation

1. Background

Osteosarcoma (OS) is a primary bone malignancy encountered frequently in children and adolescents, commonly in the metaphyses of long bones (e.g., distal femur, proximal tibia and proximal humerus) [1]. In elderly patients, OS is usually considered to be a secondary tumor attributable to the sarcomatous transformation of Paget's disease or other benign bone lesions [2]. Distant metastasis occurs before the definitive diagnosis of OS in about 15% of patients, and more than 85% of such metastases are in the lung [3]. At present, the clinical treatment of OS is primarily surgical, with adjunctive chemoradiotherapy and biotherapy. In recent years, immunotherapy [4, 5], molecular targeted therapy [6, 7], and cancer stem cell therapy [8, 9] have been used increasingly for the treatment of this disease. Although the 5-year survival

rate of patients with OS has increased significantly with the improvement of treatment and clinical management, therapeutic effects remain unsatisfactory in patients with metastatic and recurrent OS [10]. Thus, abundant research has been conducted on the occurrence, development, and treatment of OS, and the body of literature has grown. However, no summary or analysis of the status of global OS research or changes in its focus has been published.

Bibliometrics is an observational method used to assess the status of research and quality of publications on given topics; it can be used to study growth, development, and communication, and to identify the most influential and pioneering research, in particular fields. In the medical field, it has been applied to research on spinal surgery, arthroscopy, and surgical oncology, as well as many other topics [11–13]. CiteSpace is a widely used bibliometrics and visual analysis tool developed recently by Chen et al. [14]. It is based mainly on co-citation analysis and pathfinding network algorithms, applied to explore key paths in bodies of literature and to identify points of inflection in the evolution of knowledge on particular topics. It is also used to analyze global research hotspots in given disciplines and explore trends in research development through the application of a series of visualization techniques [15].

In this study, we used the Web of Science Core Collection (WoSCC; <http://www.webofknowledge.com>) tools and CiteSpace software to analyze the literature on OS published between 1999 and 2019. The aim was to fully understand the current situation and global trends in OS research, to provide a reference and foundation for theory development for subsequent scholars.

2. Materials And Methods

2.1. Data source and retrieval strategy

On 19 December 2019, we searched the WoSCC for publications related to OS using the topic (TS) keyword "osteosarcoma*" OR "osteogenic sarcoma*," file type "article," and search period of 1999 to 2019. The search generated 16,934 document records for review.

2.2. Bibliometrics and visual analysis

First, we conducted a WoS-based analysis to understand the basic features of the publications in the sample, such as the H index; annual output; all authors, journals, institutions, and countries/regions of origin; and languages of publication. The H index and total number of citations reflect the quality and academic influence of publications at the institution or author level [16].

Then, we performed a visual analysis using the CiteSpace software. This analysis generated visual knowledge networks consisting of nodes (representing, e.g., authors, countries, institutions, or references cited) connected by lines (representing cooperation, co-existence, or co-citation), with representation of temporal patterns and the degree of node centrality, or key role in collaboration and co-citation networks. Network cluster analysis of co-cited references and co-occurrence keywords was performed. The identification of frequently used keywords is often performed to determine directions of development and research foci in a given field. The results of this analysis were manifested as two indicators generated by

CiteSpace – the module (Q) value and average silhouette (S) value – which reflect the network structure and cluster clarity, respectively. In general, Q values range from 0 to 1, with larger values indicating better network clustering. Q values > 0.3 indicate a significant network cluster structure. S values range from – 1 to 1, and reflect the homogeneity of network clusters, with values closer to 1 indicating greater homogeneity; S values > 0.5 are considered to reflect reasonable clustering results.

Timeline maps reflect mainly the historical evolution and interrelationship of clusters, and time zone maps show the evolution of research over time, revealing “hotspots” and developmental trends. Research hotspots in fields with strong temporal characteristics can also be identified by analyzing high-frequency keywords. We performed in-depth analysis of these maps and corresponding data to explain the evolution of OS research and identify hotspots emerging at different times.

The knowledge base is composed of co-cited literature, and the research front is composed of the literature in which knowledge base components are cited. In CiteSpace, we identified clusters, named according to nominal terms extracted from the citing literature, which can be considered to comprise the research frontier. We analyzed the most cited and central articles in each of the top 10 co-citation clusters to determine the knowledge base for each research frontier.

3. Results

3.1. Publication output

Of the 16,934 articles included in the study, about 98% ($n = 16,583$) were written in English. Between 1999 and 2018, the number of publications increased annually, from 459 to 1559. This number decreased slightly in 2019 to 1424 (Fig. 1).

3.2. Country-level distribution and cooperation

The articles originated from 120 countries; the 10 countries producing the most publications, with H indices and citation frequencies, are listed in Table 1. Researchers in China published the most articles ($n = 4783$), followed by those in the United States ($n = 4533$) and Japan ($n = 1695$). The United States had the highest H index value and total citation frequency. Figure 2A shows the top 10 national cooperation networks by co-occurrence time. The top three networks identified were China ($n = 4780$), the United States ($n = 4507$), and Japan ($n = 1685$). In terms of centrality, the top three countries were England (0.16), the United States (0.15), and Canada (0.12; Fig. 2B). Extensive cooperation was also identified among countries (Fig. 2D). China’s important research partners included the United States, Canada, Britain, and Australia; researchers in the United States cooperated with those in Korea, Germany, Russia, Australia, and other countries; and those in Japan established partnerships with India, Poland, China, and the United States, among others. The top three countries in terms of periods of rapid increases in the number of publications were China (2015–2019), Japan (1999–2006), and the United States (2000–2002; Fig. 2C).

Table 1

Top 10 countries in terms of the number of publications, H index, and total citation frequency

Rank	Publications	Country	H-index	Country	Sum of times cited	Country
1	4783	China	139	United States	138166	United States
2	4533	United States	75	Italy	56812	China
3	1695	Japan	75	Germany	32931	Japan
4	1012	Italy	73	Japan	26433	Italy
5	936	Germany	72	China	25797	Germany
6	757	England	72	England	20899	England
7	615	France	64	Canada	15709	France
8	528	Canada	62	France	14607	Canada
9	487	South Korea	56	Australia	11459	Netherlands
10	425	India	53	Netherlands	10846	Australia

3.3. Institution-level distribution and cooperation

Articles in the sample originated from 10,247 institutions. Table 2 lists top 10 academic institutions in terms of the number of publications, H index, and total citation frequency. Researchers in the University of Texas system published the most articles ($n = 440$), followed by those at Shanghai Jiao Tong University ($n = 379$) and those in the University of California system ($n = 368$). In terms of the H index and total citation frequency, the top three institutions were Harvard University, the National Institutes of Health, and the University of Texas system. In terms of co-occurrence, the top three institutions were Shanghai Jiao Tong University ($n = 364$), China Medical University ($n = 235$), and the National Cancer Institute ($n = 205$; Fig. 3A). In terms of centrality, the top three institutions were the National Cancer Institute (0.22), Massachusetts General Hospital (0.2), and Harvard University (0.13; Fig. 3B). In terms of publication intensity in certain periods, the top three institutions were the University of Texas system (1999–2007), Jilin University (2015–2019), and Nanjing Medical University (2016–2019). Extensive cooperation among institutions was also identified (Fig. 3D).

Table 2

Top 10 institutions in terms of the number of publications, H index, and total citation frequency

Rank	Publications	Institution	H-index	Institution	Sum of times cited	Institution
1	440	University of Texas System	66	Harvard University	13641	National Institutes of Health
2	379	Shanghai Jiaotong University	60	University of Texas System	13602	Harvard University
3	368	University of California System	59	National Institutes of Health	13474	University of Texas System
4	361	Harvard University	56	University of Texas MD Anderson Cancer Center	11008	University of California System
5	327	University of Texas MD Anderson Cancer Center	56	Memorial Sloan-Kettering Cancer Center	10641	Memorial Sloan-Kettering Cancer Center
6	305	Istituto Ortopedico Rizzoli	55	University of California System	10453	National Cancer Institute
7	295	National Institutes of Health	54	National Cancer Institute	9830	Istituto Ortopedico Rizzoli
8	258	University of London	52	Istituto Ortopedico Rizzoli	9546	Memorial Sloan-Kettering Cancer Center
9	246	Institut National de la Sante et de la Recherche Medicale,INSERM	49	University of London	8778	University of London
10	218	NIH National Cancer Institute	48	Institut National de la Sante et de la Recherche Medicale,INSERM	7645	Institut National de la Sante et de la Recherche Medicale,INSERM

3.4. Author-level distribution and cooperation

In total, 54,423 authors published articles related to OS. Table 3 lists the top 10 authors in terms of the number of publications, H index, and total citation frequency. Y. Wang published the most articles (n = 173), followed by Y. Zhang (n = 154) and P. Picci (n = 153). In terms of the H index and citation frequency, the top three authors were R. Gorlick, P. Picci, and S. Ferrari. In terms of co-occurrence, the top three authors were R. Gorlick (n = 94), H. Tsuchiya (n = 88) and P. Picci (n = 77; Fig. 4A). In terms of centrality, the top four authors were W. Liu (0.11), P. Picci (0.06), R. M. Hoffman (0.06), and L. Wang (0.06; Fig. 4B). In terms of publication intensity, the top three authors were G. Bacci (1999–2005), P. Picci (1999–2005), and P. F. M. Choong (2007–2011; Fig. 4C). Extensive cooperation among institutions was also identified (Fig. 4D).

Table 3
Top 10 authors in terms of the number of publications, H index, and total citation frequency

Rank	Publications	Author	H-index	Author	Sum of times cited	Author
1	173	Y.Wang	47	R.Gorlick	6384	R.Gorlick
2	154	Y.Zhang	42	P.Picci	5829	P.Picci
3	153	P.Picci	38	S.Ferrari	4313	S.Ferrari
4	137	Y.Liu	35	G.Bacci	4116	G.Bacci
5	129	R.Gorlick	34	PCW. Hogendoorn	3550	PCW. Hogendoorn
6	118	L.Wang	33	M.Serra	3306	Y.Wang
7	115	J.Wang	32	Y.Wang	3292	JH.Healey
8	114	Y.Li	32	JH.Healey	3142	A.Longhi
9	109	H.Tsuchiya	31	A.Longhi	3024	M.Serra
10	103	S.Ferrari	29	F.Bertoni	2649	F.Bertoni

3.5. Journal-level distribution and co-occurrence

In total, 2338 journals published articles related to OS. Table 4 lists the top 10 journals according to the number of publications. The top three journals were Oncology Letters (n = 303 articles), PLoS One (n = 288), and Clinical Orthopaedics and Related Research (n = 269). The journal with the highest impact factor (4.15) among the top 10 journals was Clinical Orthopaedics and Related Research. Figure 5 shows the journal citation network. The top three journals in terms of citation frequency were Cancer Research, the Journal of Clinical Oncology, and the Journal of Biological Chemistry. In terms of centrality, the top three journals were Cancer Research, the Journal of Clinical Oncology, and Oncotarget.

Table 4
Top 10 journals in terms of the number of publications

Rank	Publications(%)	Journal	Impact Factor
1	303(1.789)	Oncology Letters	1.871
2	288(1.701)	Plos One	2.776
3	269(1.589)	Clinical Orthopaedics And Related Research	4.154
4	259(1.529)	Oncology Reports	3.041
5	231(1.364)	Anticancer Research	1.935
6	231(1.364)	Oncotarget	0
7	212(1.252)	Molecular Medicine Reports	1.851
8	199(1.175)	Pediatric Blood & Cancer	2.486
9	185(1.092)	Biochemical And Biophysical Research Communications	2.705
10	185(1.092)	International Journal of Oncology	3.571

3.6. Keyword co-occurrence

The five most frequently occurring keywords were “osteosarcoma,” “cancer,” “expression,” “apoptosis,” and “metastasis” (Fig. 6A). Ten keyword clusters were generated, with a Q value of 0.8269 and S value of 0.8009, indicating a significant cluster structure and reasonable clustering results, respectively (Fig. 6B). Table 5 shows the main keywords in each cluster. The three keywords whose use increased most rapidly during the study period were “invasion” (2016–2019), “osteoblast” (1999–2010), and “migration” (2016–2019; Fig. 6C). Figure 6D shows keywords who use expanded rapidly in recent years, including “nanoparticle tumor,” “supervisor,” and “signaling pathway.” Table 6 shows research hotspots according to keyword time zones. Figure 7 shows timeline and time zone maps of keyword co-occurrence.

Table 5
Ten major keyword clusters

Cluster Number	Cluster Label	Main Keywords	Mean Year
0	Cell Line	Mutation, P53, Nude mice, Human sarcoma, Transport, Squamous cell carcinoma	2002
1	Surgery	Extremity, Neoadjuvant chemotherapy, Adjuvant chemotherapy, Experience, Preoperative chemotherapy	2002
2	Tumor	Osteosarcoma,MRI,Metastasis,Kidney, Galectin-1	2003
3	Osteosarcoma	Differentiation, Messenger rna,Stem cell, Alkaline phosphatase, Osteogenesis, Cell differentiation	2002
4	Autophagy	Migration,Invasion,Apoptosis,Tumor suppressor,Mir-100, Wnt/ β -catenin	2010
5	Metastasis	VEGF,Microrna,Cell,Angiogenesis,Long noncoding rna,	2008
6	Methotrexate	Chemotherapy,Doxorubicin,Model,Survival,Canine,Cisplatin	2003
7	Parathyroid hormone	Osteoblast;Protein kinase;Osteosarcoma cell; Calcium channels; Intracellular store; Phosphate transport; Functional expression	2000
8	In vitro	Nf-kappa b;Tumor growth;Signaling pathway;Prostate cancer;Nanoparticle; Drug delivery; Smooth muscle cell;	2006
9	Radiotherapy	Reconstruction;Endoprosthesis;Malignant tumor;Survival;Fracture;Humerus;Upper extremity; Management; knee	2003

Table 6
Research hotspots according to keyword time zones

Year	Keywords
1999	osteosarcoma,cancer,expression,apoptosis,chemotherapy,proliferation,growth,survival,bone,in vitro,cell,breast cancer,activation,differentiation,gene,protein,prognostic factor,prognosis,gene expression,inhibition,extremity,bone tumor,experience,neoadjuvant chemotherapy,osteosarcoma cell,children,in vivo,doxorubicin,p53,soft tissue sarcoma,cisplatin,osteoblast,identification,receptor,surgery,diagnosis,adjuvant chemotherapy,mutation,messenger rna,induction,high dose methotrexate,parathyroid hormone,cell line,preoperative chemotherapy,rat,amplification,extracellular matrix,alkaline phosphatase,bone resorption,protein kinase c,binding,disease,invitro,multidrug resistance
2000	metastasis,therapy,dog,resection,dna,osteoblast like cell,fibroblast,cytokine,transgenic mice,
2001	ewings sarcoma,immunohistochemistry,methotrexate,cell cycle
2002	mechanism,angiogenesis,chondrosarcoma,death,amputation,neoplasm,growth factor,nonmetastatic osteosarcoma,tissue,
2003	limb salvage,reconstruction,management,soft tissue,protocol,
2004	pathway,high grade osteosarcoma,
2005	monoclonal antibody
2006	cancer cell,phosphorylation,gene therapy
2007	nf kappa b,breast cancer cell,metastase
2010	osteoblast differentiation,endothelial growth factor ,cytotoxicity,adhesion,
2011	invasion,resistance,ewing sarcoma
2012	radiotherapy,risk,
2013	migration,lung cancer
2014	microrna ,progression ,down regulation,epidemiology,mesenchymal stem cell,
2015	cell proliferation,hepatocellular carcinoma,gastric cancer,tumor growth
2016	colorectal cancer,stem cell,
2017	nanoparticle,tumor suppressor,signaling pathway,epithelial mesenchymal transition
2018	long noncoding rna ,autophagy,
2019	inhibitor

3.7. Reference co-citation

The analysis revealed co-citation of 579 articles. Tables 7 and 8 list the top 10 most cited and most central articles, respectively. Twenty-three clusters representing leading OS research topics, including “multifocal

osteosarcoma," "survival," and "osteocalcin," were identified. The generated network structure had a Q value of 0.8905 and S value of 0.5184, indicating a significant cluster structure and reasonable clustering results (Fig. 8).

Table 7
Top 10 cited references in terms of co-citation counts

Rank	Co-citation Counts	Cited Reference	Author	Journal
1	504	Osteosarcoma incidence and survival rates from 1973 to 2004: Data from the Surveillance, Epidemiology, and End Results Program	L.Mirabello	Cancer
2	470	The epidemiology of osteosarcoma	G.Ottaviani	Cancer Treatment And Research
3	429	Osteosarcoma treatment - where do we stand? A state of the art review.	A.Luetke	Cancer Treatment Reviews
4	277	Osteosarcoma: Current Treatment and a Collaborative Pathway to Success.	M.S.Isakoff	Journal of Clinical Oncology
5	254	Prognostic factors in high-grade osteosarcoma of the extremities or trunk: An analysis of 1,702 patients treated on neoadjuvant cooperative osteosarcoma study group protocols	S.S.Bielack	Journal of Clinical Oncology
6	233	Translational biology of osteosarcoma	M.Kansara	Nature Reviews Cancer
7	188	Osteosarcoma: a review of diagnosis, management, and treatment strategies.	D.S.Geller	Clinical Advances In Hematology&Oncology
8	178	New molecular insights into osteosarcoma targeted therapy	J.L.Yang	Current Opinion In Oncology
9	176	A Meta-Analysis of Osteosarcoma Outcomes in the Modern Medical Era	D.C.Allison	Sarcoma
10	164	The molecular pathogenesis of osteosarcoma: a review.	M.L.Broadhead	Sarcoma

Table 8
Top 10 cited references in terms of centrality

Rank	Centrality	Cited Reference	Author	Journal
1	0.76	High-resolution mapping of amplifications and deletions in pediatric osteosarcoma by use of CGH analysis of cDNA microarrays	J.A. Squire	Genes Chromosomes&Cancer
2	0.74	Gene amplifications in osteosarcoma - CGH microarray analysis	J.Atiye	Genes Chromosomes&Cancer
3	0.72	Genomic signatures of chromosomal instability and osteosarcoma progression detected by high resolution array CGH and interphase FISH.	S.Selvarajah	Cytogenetic And Genome Research
4	0.65	Updates on the cytogenetics and molecular genetics of bone and soft tissue tumors: osteosarcoma and related tumors	A.A.Sandberg	Cancer Genetics And Cytogenetics
5	0.53	Molecular pathogenesis of osteosarcoma.	M.Kansara	DNA And Cell Biology
6	0.47	DNA sequence copy number increase at 8q: A potential new prognostic marker in high-grade osteosarcoma	M.Tarkkanen	International Journal of Cancer
7	0.46	Inhibition of platelet-derived growth factor-mediated proliferation of osteosarcoma cells by the novel tyrosine kinase inhibitor STI571	E.C. McGary	Clinical Cancer Research
8	0.39	Current treatment of osteosarcoma	W.S. Ferguson	Cancer Investigation
9	0.32	Treatment of nonmetastatic osteosarcoma of the extremity with preoperative and postoperative chemotherapy: a report from the Children's Cancer Group	A.J. Provisor	Journal of Clinical Oncology
10	0.31	Gains and losses of DNA sequences in osteosarcomas by comparative genomic hybridization	M.Tarkkanen	Cancer Research

4. Discussion

4.1. OS research status and global publication quality

In the past 20 years, the number of articles on OS published annually has increased gradually, reflecting steady development of research in this field. The growth rate has accelerated since 2011, but the number

of articles published annually decreased slightly in 2019, possibly because the search period for this study did not fully cover 2019.

The numbers of publications from researchers in China and the United States were far greater than those from researchers in other countries. H indices and total numbers of citations were far higher for articles from the United States than for those from other countries; these metrics were not satisfactory for China, indicating that the quality of publications from researchers in China needs to be improved. Overall, these findings indicate that the core of OS research and the greatest contributions to its development are situated in the United States, with additional important contributions originating from other developed countries in Europe and North America.

The leading 10 of 10,247 institutions at which OS research is conducted account for 12.9% of publications in our sample, and 90% of these institutions are in Europe and the United States. Thus, OS research is conducted at many institutions worldwide, but most research results are disseminated by institutions in developed countries. The six institutions with the highest H indices, and seven of the top 10 institutions in terms of the total number of citations, are in the United States, again reflecting the quality and influence of research institutions in this country.

Among authors, China's Y. Wang and Y. Zhang led in terms of the number of publications, and the United States' R. Gorlick led in terms of the H index and total number of citations. The analysis identified no single lead researcher or team in this field. Given the significant impacts of the top 10 authors, in terms of the H index and total number of citations, in OS research, interested scholars should pay close attention to research trends and progress in this group.

The co-occurrence analysis revealed broad cooperation among countries, primarily by researchers in China and the United States. Although China's current academic influence is relatively small, Chinese scholars focus on communication and cooperation with other countries. As China showed the most rapid growth in publications in this field, the academic standards and influence of researchers in China will likely improve in the next few years. The United Kingdom had the most intermediate centrality, indicating that British researchers play key roles in international cooperation. In summary, we identified broad and close relationships among countries, institutions, and authors. Such academic exchange promotes the development of OS research.

4.2. Research hotspots and trends

The analysis of high-frequency keywords identified 10 clusters. Useful information can be extracted via in-depth interpretation of the data presented in Table 5. For example, the p53 mutation or p53-mediated phase pathway affects the proliferation and metastasis of OS cells. The effect of neoadjuvant chemotherapy combined with surgical treatment of OS has been investigated. Micro-RNA-100 or the Wnt/ β -actin signaling pathway affects the invasion and migration of OS cells. Micro-RNA and long non-coding RNA affect the apoptosis, autophagy, and development of OS cells. Other topics of study contained within research hotspots include the expression of nuclear factor- κ B in OS, nanoparticles as antitumor drug carriers for OS treatment, and prosthesis-based reconstruction after OS resection.

Hotspots of OS research published in 1999–2006 formed 10 clusters encompassing research on diverse topics with rich content. Fewer hotspots were identified for 2007–2010, and topics of research shifted in this period to nuclear factor- κ B and osteoblast differentiation, among others. During 2011–2019, the number of hotspots decreased further with the main foci being radiotherapy, micro-RNA, nanoparticles, tumor suppressors, signaling pathways, and long noncoding RNA. In general, the pathogenesis of OS, factors influencing its proliferation and metastasis, the curative effects of various treatments, and the analysis of prognosis were consistently research foci throughout the study period, with research on nanoparticles and signaling pathways emerging recently. These recent hotspots reflect ongoing progress in OS treatment and point to future trends in nano-medicine and targeted therapy.

4.3. Research frontiers and knowledge base

The co-citation analysis yielded 23 clusters representing the OS research frontiers. The most cited and central articles in the top 10 co-citation clusters are described here to characterize the knowledge base for these research frontiers.

Nonmetastatic OS

A 1997 study [17] described good histological responses to preoperative chemotherapy among patients with nonmetastatic OS, with an 8-year postoperative event-free survival (EFS) rate of 81% and overall survival rate of 87%; those with poor histological responses had an 8-year postoperative EFS rate of 46% and overall survival rate of 52%. The authors concluded that EFS and survival were related directly to the histological response to neoadjuvant chemotherapy in these patients [17]. Bacci et al. [18] reported that age, the serum alkaline phosphatase level, tumor volume, surgical margins, and histological response are of independent prognostic value for nonmetastatic OS of the extremities.

Survival

Bielack et al. [1] found that tumor site and size, primary metastasis, response to chemotherapy, and surgical remission had independent prognostic value for survival in 1702 consecutive patients with newly diagnosed high-grade OS of the trunk or limbs. Meyers et al. [19] showed that the addition of ifosfamide to standard chemotherapy (cisplatin, doxorubicin, and high-dose methotrexate) did not enhance EFS, but that the addition of muramyl tripeptide to chemotherapy might improve EFS, in patients with newly diagnosed OS. Goorin and colleagues [20] reported no advantage of preoperative chemotherapy in terms of the EFS of patients with OS.

Osteocalcin

Ducy et al. [21] identified an osteoblast-specific cis-acting element, termed OSE2, in the osteocalcin promoter and cloned the cDNA encoding Osf2/Cbfa1, the protein that binds to OSE2. They demonstrated that Osf2/Cbfa1 is an osteoblast-specific transcription factor and regulator of osteoblast differentiation [21]. Using a Cbfa1-mutated mouse model, Komori et al. [22] showed that Cbfa1 is essential for

osteoblasts and bone formation, and may regulate a variety of genes, including those related to osteocalcin and osteopontin.

Systems biology

Atiye et al. [23] identified OS-related amplicons and reported that 12Q amplicons seem to occur much more frequently than previously assumed. These data are valuable for further electrophoresis research. Using high-resolution array comparative genomic hybridization combined with interphase fluorescence in-situ hybridization, Selvarajah and colleagues [24] characterized the genomic imbalance and chromosomal instability associated with OS, providing important insight into the mechanisms that produce complex genomes in patients with this disease.

Zoledronic acid

A 2005 study demonstrated that the combined use of zoledronic acid and ifosfamide promoted tumor regression and tissue repair in rats with OS, providing a new direction for combined OS treatment [25]. Ory et al. showed that zoledronic acid significantly reduced OS-induced lung metastasis and prolonged the survival of mice with OS [26]. In a molecular-level study, the same research group demonstrated that zoledronic acid activates the s-phase checkpoint and mitochondrial pathways of DNA damage through apoptosis-inducing factor and endonucleo-g translocation, bypassing these potential mutations to inhibit OS cell proliferation and inducing cell death [27].

Ezrin

Khanna et al. [28] showed that ezrin, a member of the ezrin/radixin/moesin family, was necessary for metastasis in a mouse model of OS, that early metastasis depended on mitogen-activated protein kinase activation, and that high ezrin expression correlated significantly with poor prognosis in patients with OS. Other researchers found that ezrin-mediated metastasis is related to the mTOR/S6KI/4E-BP1 pathway, and that blockade of this pathway with rapamycin significantly inhibited lung metastasis in mice with OS [29]. These results provide a suitable target for the treatment of OS metastasis.

Chemotherapy

A 2006 review focused on the mechanisms of drug resistance and ways to overcome such resistance in the course of chemotherapy for OS, which has helped researchers and clinicians understand bottlenecks in this chemotherapy and identify coping strategies [30]. A European study revealed no difference in the survival of patients with operable non-metastatic carcinoma receiving the two-drug (doxorubicin and cisplatin) regimen and the T10 multidrug regimen; the authors recommended that the two-drug regimen be the first-choice therapy because of its short course and good tolerance [31].

Amputation

Research has focused on the identification of treatment plans for patients with high-grade OS of the extremities that avoid amputation and improve long-term survival. Preoperative chemotherapy can shrink

the tumor volume, which is conducive to limb salvage. Bacci and colleagues [32] showed that the postoperative local recurrence rate was related closely to the quality of the surgical resection margins and chemotherapy response in 540 patients with non-metastatic OS of the extremities. They reported that limb-salvage surgery is successful only when sufficient surgical margins are obtained; otherwise, immediate amputation should be considered, especially in cases of poor histological response to preoperative chemotherapy.

P-glycoprotein

Baldini et al. [33] found that high P-glycoprotein levels significantly increased the risk of adverse events, and that the P-glycoprotein level was not related to the degree of necrosis after preoperative chemotherapy, in patients with high-grade OS.

Pigment epithelium–derived factor

A 2007 study demonstrated the multi-target roles of pigment epithelium–derived factor (PEDF) in inhibiting tumor growth, angiogenesis, and metastasis in two in-situ OS models (rat UMR-106-01 and human SAOS-2) [34]. Takenaka et al. showed that PEDF can induce tumor cell apoptosis and inhibit the expression of vascular endothelial growth factor (VEGF) in human OS MG63 cells, preventing angiogenesis [35]. These studies have demonstrated the broad potential of PEDF use in OS treatment.

4.4. Study limitations

This study has certain limitations. First, the results of our analysis may be biased by our reliance on the WoS database, as other databases may contain different bodies of literature. Second, differences may exist between the results of the bibliometric analysis and real research conditions. For example, the analysis may not have properly captured the impacts of some recently published high-quality papers because of the low frequency of citations. Thus, future research should not be based on a single database, and should focus on recently published articles.

5. Conclusions

This study provides a comprehensive view of the status of OS research in the past 20 years. The volume of global publications has increased annually, and many academic exchanges among researchers and institutions have occurred. We believe that this research has important guiding significance for researchers seeking cooperating institutions and partners for OS research, popular journals and important literature in the field, an understanding of the knowledge base for this research, and up-to-date identification of research hot spots and trends.

Abbreviations

OS
Osteosarcoma;

WOSCC

The Web of Science Core Collection;

TS

Topic;

WOS

The Web of Science;

EFS

Event-free survival;

OSE2

Osteoblast-specific cis-acting element-2;

PEDF

Pigment epithelium-derived factor;

VEGF

Vascular endothelial growth factor;

Declarations

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Authors' contributions

YB L designed the study; YP C performed data collection; BX W analyzed the data and performed the statistical analysis. YB L drafted the initial manuscript. HW critically reviewed and revised the manuscript. All authors read and approved the final Manuscript

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Competing interests

The authors declare that they have no competing interests.

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Figures

Figure 1

Annual number of publications on osteosarcoma, 1999–201

Figure 2

Country-level co-occurrence findings. A. Top 10 countries in terms of co-occurrence counts. B. Top 10 countries in terms of centrality. C. Countries showing the strongest bursts in publication. D. Collaboration network. For all visual analysis graphics, the size of each point reflects the frequency of occurrence or reference. Colors in the nodes and lines represent different years. The node with the most centrality and considered to be a key point in the network is indicated in purple.

Figure 3

Institution-level co-occurrence findings. A. Top 10 institutions in terms of co-occurrence counts. B. Top 10 institutions in terms of centrality. C. Institutions showing the strongest bursts in publication. D. Cooperation network.

Figure 4

Author-level co-occurrence findings. A. Top 10 authors in terms of co-occurrence counts. B. Top 10 authors in terms of centrality. C. Authors showing the strongest bursts in publication. D. Cooperation network.

Figure 5

Journal-level co-occurrence findings. A. Top 10 journals in terms of co-occurrence counts. B. Top 10 journals in terms of centrality.

Figure 6

Keyword co-occurrence findings. A. Top keywords in terms of co-occurrence counts. B. Cluster map of keyword co-occurrence. C. Keywords showing the strongest bursts in usage. D. Keywords showing the strongest bursts in usage in recent years.

Figure 7

A. Co-occurrence timeline atlas of keywords. B. Co-occurrence time zone map of keywords.

Figure 8

Co-citation of references. A. Top 10 references in terms of co-citation counts. B. Cluster map of reference co-citation. C. Top 20 references showing the strongest bursts in co-citation.