

Review Article

The 100 most cited papers on bone metastasis: A bibliometric analysis



Huiyang Li^{a,b}, Haixiao Wu^{b,c}, Maxim A. Abakumov^{b,d,e}, Yao Xu^{b,c}, Yile Lin^{b,c},
Vladimir P. Chekhonin^{b,f}, Karl Peltzer^{b,g}, Kirellos Said Abbas^{b,h}, Shu Li^{b,i,*}, Chao Zhang^{b,c,*}

^a Department of Obstetrics & Gynecology, Tianjin Medical University General Hospital, Tianjin, China

^b The Sino-Russian Joint Research Center for Bone Metastasis in Malignant Tumor, Tianjin, China

^c Department of Bone and Soft Tissue Tumors, Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Center for Cancer, Key Laboratory of Cancer Prevention and Therapy, Tianjin's Clinical Research Center for Cancer, Tianjin, China

^d National University of Science and Technology (MISIS), Moscow, Russia

^e Department of Medical Nanobiotechnology, N.I Pirogov Russian National Research Medical University, Moscow, Russia

^f Department of Basic and Applied Neurobiology, Federal Medical Research Center for Psychiatry and Narcology, Moscow, Russia

^g Department of Psychology, University of the Free State, Turfloop, South Africa

^h Faculty of Medicine, Alexandria University, Alexandria, Egypt

ⁱ Department of Public Service Management, School of Management, Tianjin University of Traditional Chinese Medicine, Tianjin, China

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ABSTRACT

Background: Over the past few decades, a vast number of articles focused on bone metastasis have been published. Bibliometric analysis is helpful to determine the qualities and characteristics and to reveal the influential articles in this field.

Methods: All the databases in Web of Science were utilized to identify articles published from 1961 to 2020. The top 100 most cited articles on bone metastases were involved for degree centrality analysis and analyses on publication time and citations, journals, authors, geographical distribution, research institutions, and research keywords.

Results: The selected articles were published mainly from 1986 to 2015. The 100 most cited articles were selected from a total of 67,451 citations out of 90,502 publications with a density of 50.239 citations/year. Citations per article ranged from 357 to 2167. The leading country was USA, followed by Canada and United Kingdom. The most frequently studied themes were clinical management of bone metastasis from different malignancy origins. A co-authorship analysis revealed an intense collaborative activity between countries and institutions.

Conclusions: This study identified the top 100 most cited articles on bone metastasis. Publication time, area, and theme distribution were thoroughly analyzed. The present study highlighted some of the most influential contributions to the field. Clinical and academic communities have shown a sustained interest in the management of bone metastasis.

1. Introduction

Bone metastasis is a result of the complex interactions between tumor cells and bone cells. It is common in the advanced cancer, such as breast and prostate, with high clinical relevance [1,2]. According to the diagnosis time for bone metastasis, it is divided into synchronous bone metastasis and unsynchronous bone metastasis. For patients diagnosed with synchronous bone metastasis, cardiovascular and cerebrovascular diseases were the leading non-cancer cause of death, followed by COPD, septicemia, infectious and parasitic diseases, etc [3]. In this analysis,

bone metastasis is a general concept without detailed distinguishment. Skeletal-related events (SREs), including bone pain, hypercalcemia, bone fracture, and spinal cord compression, are common complications of bone metastasis, all of these can significantly impact a patient's life quality [4,5].

In the research field of cancer, metastatic process is a complex process, requiring adequate dissemination and homing. The concept of metastatic niche has been gradually developing and accepting. Upon arrival, primary cancer cells established interactions with various bone-resident cells during the process of colonization. Preparation of niche

* Corresponding authors at: Department of Bone and Soft Tissue Tumors, Tianjin Medical University Cancer Institute and Hospital, Tianjin 300070, China (C. Zhang). Department of Public Service Management, School of Management, Tianjin University of Traditional Chinese Medicine, Tianjin, 301617, China (S. Li).

E-mail addresses: lishu@tjutm.edu.cn (S. Li), drzhangchao@tmu.edu.cn (C. Zhang).

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Table 1
List of the 100 most-cited articles.

Rank	Title of the article	Journal	Year	Citation No.	Citation/Year
1	Tumour exosome integrins determine organotropic metastasis [10]	NATURE	2015	2167	433.4
2	Metastasis to bone: Causes, consequences and therapeutic opportunities [11]	NATURE REVIEWS CANCER	2002	2023	112.4
3	A multigenic program mediating breast cancer metastasis to bone [12]	CANCER CELL	2003	1884	110.8
4	Alpha Emitter Radium-223 and Survival in Metastatic Prostate Cancer [25]	NEW ENGLAND JOURNAL OF MEDICINE	2013	1849	264.1
5	Endogenous human microRNAs that suppress breast cancer metastasis [26]	NATURE	2008	1585	132.1
6	Mechanisms of disease: Mechanisms of bone metastasis [27]	NEW ENGLAND JOURNAL OF MEDICINE	2004	1552	97.0
7	Osteonecrosis of the jaws associated with the use of bisphosphonates: A review of 63 cases [28]	JOURNAL OF ORAL AND MAXILLOFACIAL SURGERY	2004	1367	85.4
8	Clinical features of metastatic bone disease and risk of skeletal morbidity [29]	CLINICAL CANCER RESEARCH	2006	1340	95.7
9	Direct decompressive surgical resection in the treatment of spinal cord compression caused by metastatic cancer: a randomised trial [30]	LANCET	2005	1290	86.0
10	Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomised, double-blind study [31]	LANCET	2011	1252	139.1
11	A randomized, placebo-controlled trial of zoledronic acid in patients with hormone-refractory metastatic prostate carcinoma [16]	JNCI-JOURNAL OF THE NATIONAL CANCER INSTITUTE	2002	1208	67.1
12	Metastatic bone disease: clinical features, pathophysiology and treatment strategies [5]	CANCER TREATMENT REVIEWS	2001	1204	63.4
13	Metastatic Behavior of Breast Cancer Subtypes [32]	JOURNAL OF CLINICAL ONCOLOGY	2010	1178	117.8
14	Skeletal complications of malignancy [4]	CANCER	1997	1129	49.1
15	Bisphosphonate-associated osteonecrosis of the jaw: Report of a task force of the American Society for Bone and Mineral Research [33]	JOURNAL OF BONE AND MINERAL RESEARCH	2007	1122	86.3
16	Denosumab Compared With Zoledronic Acid for the Treatment of Bone Metastases in Patients With Advanced Breast Cancer: A Randomized, Double-Blind Study [34]	JOURNAL OF CLINICAL ONCOLOGY	2010	969	96.9
17	Surgical strategy for spinal metastases [35]	SPINE	2001	870	45.8
18	Use of the stromal cell-derived factor-1/CXCR4 pathway in prostate cancer metastasis to bone [36]	CANCER RESEARCH	2002	844	46.9
19	BISPHOSPHONATES PROMOTE APOPTOSIS IN MURINE OSTEOCLASTS IN-VITRO AND IN-VIVO [37]	JOURNAL OF BONE AND MINERAL RESEARCH	1995	821	32.8
20	THE CLINICAL COURSE OF BONE METASTASES FROM BREAST-CANCER [38]	BRITISH JOURNAL OF CANCER	1987	818	24.8
21	Osteonecrosis of the jaw in cancer after treatment with bisphosphonates: Incidence and risk factors [39]	JOURNAL OF CLINICAL ONCOLOGY	2005	808	53.9
22	RANKL-RANK signaling in osteoclastogenesis and bone disease [40]	TRENDS IN MOLECULAR MEDICINE	2006	805	57.5
23	Efficacy of pamidronate in reducing skeletal complications in patients with breast cancer and lytic bone metastases [41]	NEW ENGLAND JOURNAL OF MEDICINE	1996	782	32.6
24	Percutaneous vertebroplasty for osteolytic metastases and myeloma: Effects of the percentage of lesion filling and the leakage of methyl methacrylate at clinical follow-up [42]	RADIOLOGY	1996	759	31.6
25	TGF-beta signaling blockade inhibits PTHrP secretion by breast cancer cells and bone metastases development [43]	JOURNAL OF CLINICAL INVESTIGATION	1999	755	36.0
26	Percutaneous vertebroplasty with polymethylmethacrylate - Technique, indications, and results [44]	RADIOLOGIC CLINICS OF NORTH AMERICA	1998	752	34.2
27	American society of clinical oncology 2003 update on the role of bisphosphonates and bone health issues in women with breast cancer [22]	JOURNAL OF CLINICAL ONCOLOGY	2003	729	42.9
28	Randomized, Double-Blind Study of Denosumab Versus Zoledronic Acid in the Treatment of Bone Metastases in Patients With Advanced Cancer (Excluding Breast and Prostate Cancer) or Multiple Myeloma [45]	JOURNAL OF CLINICAL ONCOLOGY	2011	717	79.7
29	Cancer to bone: a fatal attraction [46]	NATURE REVIEWS CANCER	2011	709	78.8
30	Clinical implications of the osteoprotegerin/RANKL/RANK system for bone and vascular diseases [47]	JAMA-JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION	2004	708	44.3
31	Bisphosphonates: The first 40 years [48]	BONE	2011	707	78.6
32	Percutaneous vertebroplasty for pain relief and spinal stabilization [49]	SPINE	2000	698	34.9
33	Bisphosphonates: From the laboratory to the clinic and back again [50]	BONE	1999	695	33.1
34	Identification of a population of blood circulating tumor cells from breast cancer patients that initiates metastasis in a xenograft assay [51]	NATURE BIOTECHNOLOGY	2013	674	96.3
35	Zoledronic acid versus pamidronate in the treatment of skeletal metastases in patients with breast cancer or osteolytic lesions of multiple myeloma: A phase III, double-blind, comparative trial [52]	CANCER JOURNAL	2001	664	34.9
36	Long-term efficacy and safety of zoledronic acid compared with pamidronate disodium in the treatment of skeletal complications in patients with advanced multiple myeloma or breast carcinoma - A randomized, double-blind, multicenter, comparative trial [53]	CANCER	2003	649	38.2
37	Reduction in new metastases in breast cancer with adjuvant clodronate treatment [54]	NEW ENGLAND JOURNAL OF MEDICINE	1998	625	28.4
38	Evidence for a causal role of parathyroid hormone-related protein in the pathogenesis of human breast cancer-mediated osteolysis [55]	JOURNAL OF CLINICAL INVESTIGATION	1996	616	25.7
39	Malignant bone pain: Pathophysiology and treatment [56]	PAIN	1997	600	26.1
40	Spinal metastases: Indications for and results of percutaneous injection of acrylic surgical cement [57]	RADIOLOGY	1996	594	24.8
41	Common variants on chromosomes 2q35 and 16q12 confer susceptibility to estrogen receptor-positive breast cancer [58]	NATURE GENETICS	2007	592	45.5
42	Regulation of cancer cell migration and bone metastasis by RANKL [59]	NATURE	2006	581	41.5

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Table 1 (continued)

Rank	Title of the article	Journal	Year	Citation No.	Citation/Year
43	The detection of bone metastases in patients with high-risk prostate cancer: Tc-99m-MDP planar bone scintigraphy, single- and multi-field-of-view SPECT, F-18-fluoride PET, and F-18-fluoride PET/CT [60]	JOURNAL OF NUCLEAR MEDICINE	2006	575	41.1
44	Palliative radiotherapy trials for bone metastases: A systematic review [61]	JOURNAL OF CLINICAL ONCOLOGY	2007	574	44.2
45	Receptor activator of nuclear factor kappa B ligand and osteoprotegerin regulation of bone remodeling in health and disease [62]	ENDOCRINE REVIEWS	2008	565	47.1
46	PALLIATIVE RADIOTHERAPY FOR BONE METASTASES: AN ASTRO EVIDENCE-BASED GUIDELINE [23]	INTERNATIONAL JOURNAL OF RADIATION ONCOLOGY BIOLOGY PHYSICS	2011	544	60.4
47	A module map showing conditional activity of expression modules in cancer [63]	NATURE GENETICS	2004	540	33.8
48	Zoledronic acid versus placebo in the treatment of skeletal metastases in patients with lung cancer and other solid tumors: A phase III, double-blind, randomized trial - The zoledronic acid lung cancer and other solid tumors study group [14]	JOURNAL OF CLINICAL ONCOLOGY	2003	522	30.7
49	Pamidronate to prevent bone loss during androgen-deprivation therapy for prostate cancer [64]	NEW ENGLAND JOURNAL OF MEDICINE	2001	520	27.4
50	Bisphosphonates inhibit breast and prostate carcinoma cell invasion, an early event in the formation of bone metastases [65]	CANCER RESEARCH	2000	517	25.9
51	The seed and soil hypothesis revisited-The role of tumor-stroma interactions in metastasis to different organs [66]	INTERNATIONAL JOURNAL OF CANCER	2011	512	56.9
52	IDENTIFICATION OF ENDOHELIN-1 IN THE PATHOPHYSIOLOGY OF METASTATIC ADENOCARCINOMA OF THE PROSTATE [67]	NATURE MEDICINE	1995	508	20.3
53	Randomized trial of short-versus long-course radiotherapy for palliation of painful bone metastases [68]	JNCI-JOURNAL OF THE NATIONAL CANCER INSTITUTE	2005	505	33.7
54	Pamidronate prevents skeletal complications and is effective palliative treatment in women with breast carcinoma and osteolytic bone metastases - Long term follow-up of two randomized, placebo-controlled trials [69]	CANCER	2000	505	25.3
55	STRATIFICATION OF PATIENTS WITH METASTATIC PROSTATE-CANCER BASED ON EXTENT OF DISEASE ON INITIAL BONE-SCAN [70]	CANCER	1988	502	15.7
56	Percutaneous vertebroplasty and kyphoplasty for painful vertebral body fractures in cancer patients [71]	JOURNAL OF NEUROSURGERY	2003	498	29.3
57	Latent Bone Metastasis in Breast Cancer Tied to Src-Dependent Survival Signals [72]	CANCER CELL	2009	491	44.6
58	Radiosurgery for spinal metastases - Clinical experience in 500 cases from a single institution [73]	SPINE	2007	486	37.4
59	Denosumab and bone-metastasis-free survival in men with castration-resistant prostate cancer: results of a phase 3, randomised, placebo-controlled trial [74]	LANCET	2012	482	60.3
60	Long-term efficacy and safety of zoledronic acid in the treatment of skeletal metastases in patients with nonsmall cell lung carcinoma and other solid tumors - A randomized, phase III, double-blind, placebo-controlled trial [75]	CANCER	2004	479	29.9
61	Randomized controlled trial of zoledronic acid to prevent bone loss in men receiving androgen deprivation therapy for nonmetastatic prostate cancer [76]	JOURNAL OF UROLOGY	2003	470	27.6
62	Bisphosphonates inhibit angiogenesis in vitro and testosterone-stimulated vascular regrowth in the ventral prostate in castrated rats [77]	CANCER RESEARCH	2002	468	26.0
63	Long-term prevention of skeletal complications of metastatic breast cancer with pamidronate [78]	JOURNAL OF CLINICAL ONCOLOGY	1998	468	21.3
64	A Novel Classification System for Spinal Instability in Neoplastic Disease An Evidence-Based Approach and Expert Consensus From the Spine Oncology Study Group [24]	SPINE	2010	466	46.6
65	Pamidronate reduces skeletal morbidity in women with advanced breast cancer and lytic bone lesions: A randomized, placebo-controlled trial [79]	JOURNAL OF CLINICAL ONCOLOGY	1999	464	22.1
66	SCORING SYSTEM FOR THE PREOPERATIVE EVALUATION OF METASTATIC SPINE TUMOR PROGNOSIS [80]	SPINE	1990	461	15.4
67	Human prostate cancer metastases target the hematopoietic stem cell niche to establish footholds in mouse bone marrow [81]	JOURNAL OF CLINICAL INVESTIGATION	2011	458	50.9
68	Frequency and risk factors associated with osteonecrosis of the jaw in cancer patients treated with intravenous bisphosphonates [82]	JOURNAL OF BONE AND MINERAL RESEARCH	2008	452	37.7
69	Mechanisms of bone metastasis [83]	CANCER	1997	451	19.6
70	DOUBLE-BLIND CONTROLLED TRIAL OF ORAL CLODRONATE IN PATIENTS WITH BONE METASTASES FROM BREAST-CANCER [84]	JOURNAL OF CLINICAL ONCOLOGY	1993	448	16.6
71	The effect of a single fraction compared to multiple fractions on painful bone metastases: a global analysis of the Dutch Bone Metastasis Study [85]	RADIOTHERAPY AND ONCOLOGY	1999	440	21.0
72	RESULTS OF A RANDOMIZED PHASE-III TRIAL TO EVALUATE THE EFFICACY OF SR-89 ADJUVANT TO LOCAL FIELD EXTERNAL BEAM IRRADIATION IN THE MANAGEMENT OF ENDOCRINE RESISTANT METASTATIC PROSTATE-CANCER [86]	INTERNATIONAL JOURNAL OF RADIATION ONCOLOGY BIOLOGY PHYSICS	1993	430	15.9
73	Percutaneous vertebroplasty: State of the art [87]	RADIOGRAPHICS	1998	428	19.5
74	LONG-TERM RESULTS OF TREATMENT OF 283 PATIENTS WITH LUNG AND BONE METASTASES FROM DIFFERENTIATED THYROID-CARCINOMA [88]	JOURNAL OF CLINICAL ENDOCRINOLOGY & METABOLISM	1986	428	12.6
75	Breast cancer cells interact with osteoblasts to support osteoclast formation [89]	ENDOCRINOLOGY	1999	427	20.3
76	WNT/TCF Signaling through LEF1 and HOXB9 Mediates Lung Adenocarcinoma Metastasis [90]	CELL	2009	425	38.6
77	Bone turnover markers as predictors of skeletal complications in prostate cancer, lung cancer, and other solid tumors [91]	JNCI-JOURNAL OF THE NATIONAL CANCER INSTITUTE	2005	424	28.3
78	Predictive value of bone resorption and formation markers in cancer patients with bone metastases receiving the bisphosphonate zoledronic acid [92]	JOURNAL OF CLINICAL ONCOLOGY	2005	413	27.5

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Table 1 (continued)

Rank	Title of the article	Journal	Year	Citation No.	Citation/Year
79	Incidence, risk factors, and outcomes of osteonecrosis of the jaw: integrated analysis from three blinded active-controlled phase III trials in cancer patients with bone metastases [93]	ANNALS OF ONCOLOGY	2012	411	51.4
80	Breast cancer bone metastasis mediated by the Smad tumor suppressor pathway [94]	PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA	2005	407	27.1
81	Osteoblasts in prostate cancer metastasis to bone [95]	NATURE REVIEWS CANCER	2005	406	27.1
82	Pathologic fractures correlate with reduced survival in patients with malignant bone disease [96]	CANCER	2007	406	31.2
83	Percutaneous image-guided radiofrequency ablation of painful metastases involving bone: A multicenter study [97]	JOURNAL OF CLINICAL ONCOLOGY	2004	402	25.1
84	Randomized Phase II Trial of Denosumab in Patients With Bone Metastases From Prostate Cancer, Breast Cancer, or Other Neoplasms After Intravenous Bisphosphonates [98]	JOURNAL OF CLINICAL ONCOLOGY	2009	394	35.8
85	Bone imaging in metastatic breast cancer [99]	JOURNAL OF CLINICAL ONCOLOGY	2004	391	24.4
86	Zoledronic acid reduces skeletal-related events in patients with osteolytic metastases - A double-blind, randomized dose-response study [100]	CANCER	2001	389	20.5
87	Detection of bone metastases in breast cancer by (18)FDG PET: Differing metabolic activity in osteoblastic and osteolytic lesions [101]	JOURNAL OF CLINICAL ONCOLOGY	1998	389	17.7
88	Tumor-Derived Jagged1 Promotes Osteolytic Bone Metastasis of Breast Cancer by Engaging Notch Signaling in Bone Cells [102]	CANCER CELL	2011	382	42.4
89	BONE METASTASES - PATHOPHYSIOLOGY AND MANAGEMENT POLICY [103]	JOURNAL OF CLINICAL ONCOLOGY	1991	381	13.1
90	Osteoprotegerin inhibits prostate cancer-induced osteoclastogenesis and prevents prostate tumor growth in the bone [104]	JOURNAL OF CLINICAL INVESTIGATION	2001	379	19.9
91	Exosomes from bone marrow mesenchymal stem cells contain a microRNA that promotes dormancy in metastatic breast cancer cells [105]	SCIENCE SIGNALING	2014	378	63.0
92	Bench to bedside: elucidation of the OPG-RANK-RANKL pathway and the development of denosumab [106]	NATURE REVIEWS DRUG DISCOVERY	2012	376	47.0
93	Meta-analysis of dose-fractionation radiotherapy trials for the palliation of painful bone metastases [107]	INTERNATIONAL JOURNAL OF RADIATION ONCOLOGY BIOLOGY PHYSICS	2003	376	22.1
94	Bisphosphonate-associated osteonecrosis of mandibular and maxillary bone - An emerging oral complication of supportive cancer therapy [108]	CANCER	2005	373	24.9
95	Zoledronic acid significantly reduces skeletal complications compared with placebo in Japanese women with bone metastases from breast cancer: A randomized, placebo-controlled trial [15]	JOURNAL OF CLINICAL ONCOLOGY	2005	372	24.8
96	A study of the biological receptor activator of nuclear factor-kappa B ligand inhibitor, denosumab, in patients with multiple myeloma or bone metastases from breast cancer [109]	CLINICAL CANCER RESEARCH	2006	364	26.0
97	Bone-targeted radium-223 in symptomatic, hormone-refractory prostate cancer: a randomised, multicentre, placebo-controlled phase II study [21]	LANCET ONCOLOGY	2007	361	27.8
98	Exosomal miR-135b shed from hypoxic multiple myeloma cells enhances angiogenesis by targeting factor-inhibiting HIF-1 [110]	BLOOD	2014	361	60.2
99	High-dose, single-fraction image-guided intensity-modulated radiotherapy for metastatic spinal lesions [111]	INTERNATIONAL JOURNAL OF RADIATION ONCOLOGY BIOLOGY PHYSICS	2008	359	29.9
100	Update on the Systematic Review of Palliative Radiotherapy Trials for Bone Metastases [112]	CLINICAL ONCOLOGY	2012	357	44.6

required the changes the constant cycle of bone matrix formation and degradation as the prerequisite, leading to the clinical phenotypes of lytic and sclerotic lesions. Meanwhile, the bone microenvironment may even influence primary cancer cells to subsequently metastasis, also known as secondary metastasis, which indicated intricate cancer-bone crosstalk [6].

Till now, bone metastasis has been remaining one of the trickiest clinical challenges that is closely related to a patient's prognosis and life quality. A comprehensive understanding of the molecular mechanisms and clinical management advances in bone metastasis is crucial for providing optimal medical care. Further knowledge in this field is warrant to reveal the pathogenesis, characteristics, and clinical treatment landscape of bone metastasis. However, many open questions are remaining to be addressed to establish individually tailored management approaches.

Bibliometrics is a unique and useful tool for analyzing the quality and characteristics of published articles in a specific field. In 1987, the first bibliometrics analysis of classics from the Journal of the American Medical Association (JAMA) was first published. Recently, it has been widely used in various of different fields to investigate the most important publications or research trends [7]. The purpose of this study was to reveal the top 100 most cited publications in the field of bone metastasis, aiming to analyze the quality and characteristics and to

highlight potential milestones as well as promising research direction of the most cited original papers of the past 6 decades.

2. Materials and Methods

Literature Search and Screening.

The literature search was systematically performed using the Web of Science (WOS) (Clarivate Analytics, USA) 'All Databases'. To enhance the sensitivity, two reviewers (Li Huiyang and Li Shu.) independently identified the top 100 literatures used the same query terms (('bone' OR 'skeletal' OR 'osseous') AND ('metastasis' OR 'metastases' OR 'metastatic')) without any literature type restrictions to search simultaneously. After filtering by language as "English", 91,024 pieces of literature was listed. The selected articles were sorted in descending order according to the total citations (TC). Any disagreement between the 2 reviewers was resolved by consensus involving a third reviewer (Wu Haixiao). Finally, a unanimous decision was made on the list of the top 100 most-cited manuscripts.

2.1. Data extraction and bibliometric parameters

2.1.1. Data analyses and visualization

After identifying the top 100 most-cited articles, records including all

Table 2
Numbers of articles published in each 5-year interval.

Publishing Year	Number of Articles	Total Citations	Mean Citations
1986–1990	4	2209	552.3
1991–1995	5	2588	517.6
1996–2000	20	12,094	604.7
2001–2005	33	24,134	804.5
2006–2010	21	14,090	671.0
2011–2015	17	12,336	725.6

available information from the Web of Science all database, including article title, citation count, citation density, year of publication, authorship, contributing institution, journal of publication, and PMID, etc. From these data, parameters such as the number of times a particular author, institution or country published a T100 article and citation density were obtained. Citation density was calculated as the average number of citations per annum after the work was first published.

The “Visualization of Similarities (VOS) viewer software” is widely used to graphically illustrate the bibliometric parameters in mapping networks, which allow easy visualization of critical elements. The current study used VOS to represent a graphical mapping of keywords as

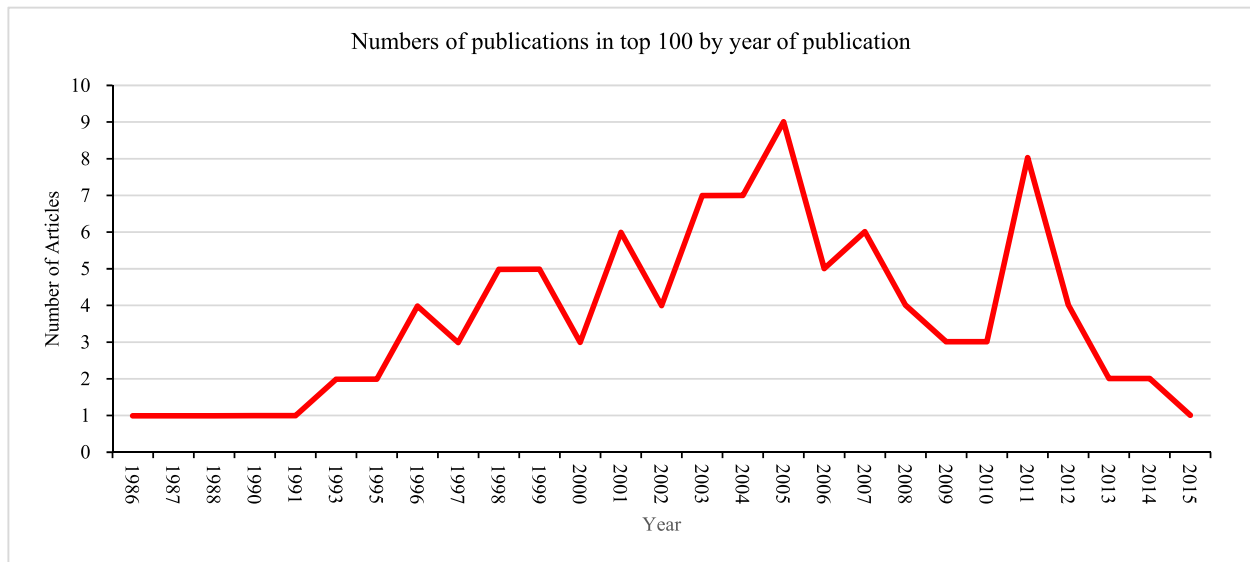


Fig. 1. Numbers of publications in top 100 by year of publication.

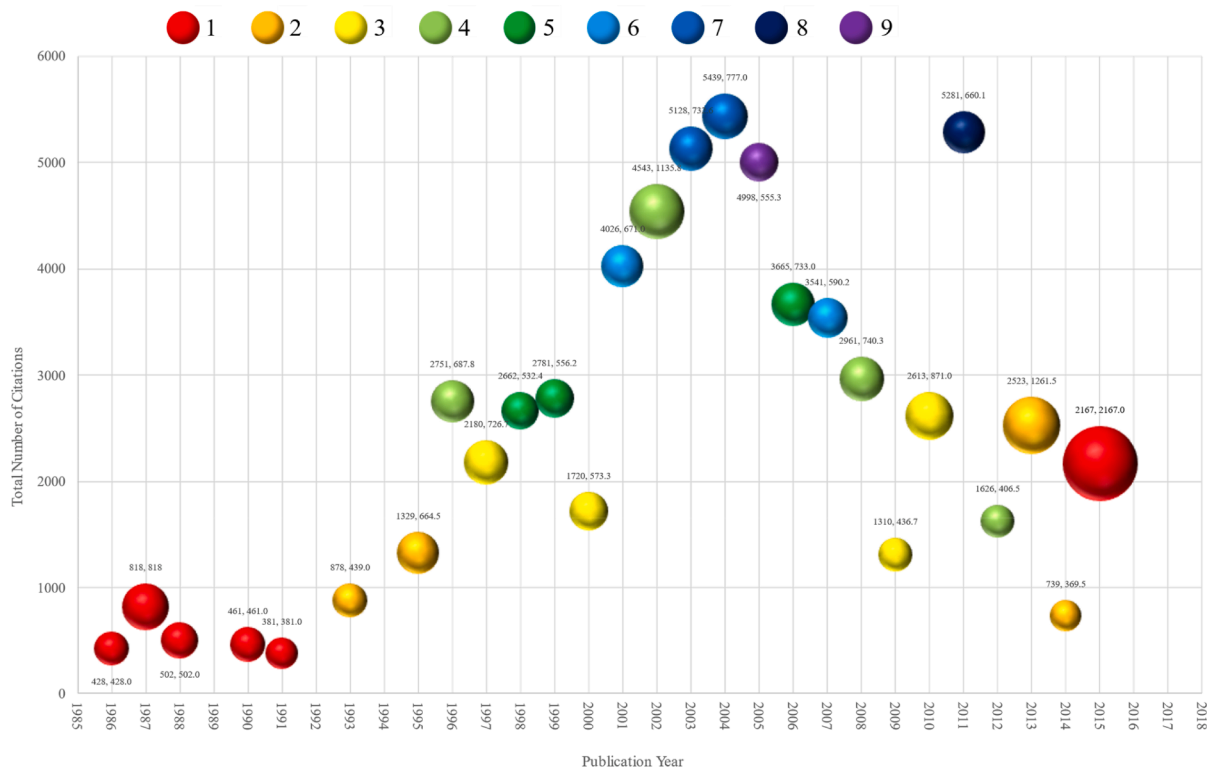


Fig. 2. Bubble plot of published year and citations on the top 100 cited articles on the top 100 cited articles. Note: X-axis: publication year; Y-axis: the total number of citations; bubble size: the average number of citations; colors: the number of articles.

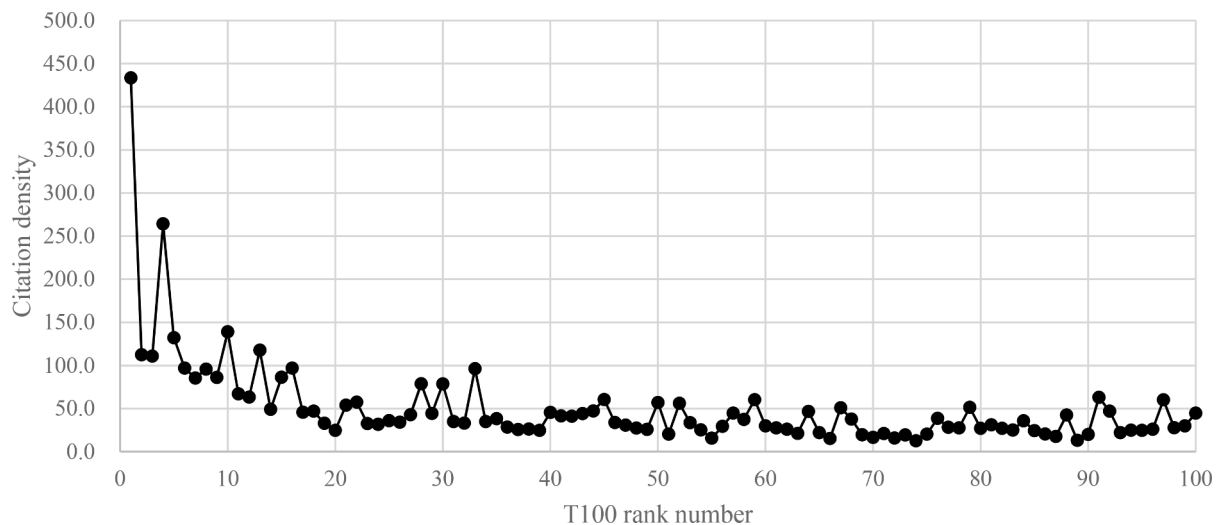


Fig. 3. Distribution of the number of citation per year (density) of each T100 publication.

identified bibliometric analysis to identify the focus of research in recent decades.

Visualization of Similarities (VOS) Viewer 1.6.17 (Leiden University, Leiden, Netherlands) is a software developed and widely used to graphically illustrate for building and visualizing bibliometric parameters in mapping networks. Here, we used it to visualize author collaborations, countries, and contributing institutions. “Full counting” was the counting method. In the visual map, different nodes represented authors, countries, institutions, and keywords. The node size represented the corresponding number or frequency of reference. The links between nodes represented cooperation and co-occurrence relationships. The colors of the nodes and lines represented different clusters or corresponding years or average references.

3. Results

3.1. Article analysis

A total of 90,502 articles were obtained in December 2020 as far back as January 1961. All articles were written in English. Of these, the top 100 articles according to their citation count were demarcated and were presented accordingly (Table 1). Table 2 showed the number of articles published in each 5-year interval. Less than five articles were published before 1990 for each interval, while more than 90 were published after 1995. The largest number of articles published in a single interval was 33, which occurred in 2001–2005. These included guidelines (2), recommendation (1), articles (51), reviews (21), systemic review or meta-analysis (2) and clinical trials (23).

When focus on the first 10 papers (T 10), we found that they brought a total of 16,309 citations, which represents 24.179% of the total citations. All publications included in the T 10 exceed 1200. These T 100 papers comprise a total of 67,451 citations, with a citation density of 50.239.

As noted in Fig. 1, the year that yielded the highest number of influential articles was 2005 ($n = 9$). Most included articles were published after 1995 ($n = 91$). Within the T100, the oldest work is from 1986 (#74) and the most recent which is also the most-cited work is from 2015 (#1). Fig. 2 showed the relationship of publication year (X-axis), the total number of citations (Y-axis), the average number of citations (bubble size), and the number of articles (different colors). In the data label, the former data are the Y value, and the latter is the value of the bubble size. The highest number of citations was in 2004 ($n = 5439$), and the lowest was in 1991 ($n = 381$). In terms of the average number of citations, the highest was 2,167 times in 2015 and the lowest was 381

times in 1991.

It is worth noting that the most cited article (2167 citations) was “Tumour exosome integrins determine organotropic metastasis,” by Hoshino et al., published in Nature in 2015. The article has received an average of 433.4 CY. The last in our list (357 citations) was “Update on the Systematic Review of Palliative Radiotherapy Trials for Bone Metastases,” by Chow et al., published in Clinical Oncology in 2012; it has received an average of 44.6 CY (Fig. 3).

These high-impact most-cited articles were published in 44 different scientific journals. When these articles were compared, Journal of Clinical Oncology was the one with the most publications ($n = 17$), followed by Cancer ($n = 9$). Only 3 Journals in this category belongs to Q3 (Quartile in Category) (Table 3).

For the T100 citations, we summarized the topics and classification of these citations roughly according to article type and specific details, including disease focus, basic or clinical medical research, review, etc. (shown in Table 4).

3.2. Countries or Regions, Institutions, and Authors

In analyzing countries (or regions) and institutions of the authors, the 100 most cited articles were originated from 16 countries or regions, led by USA ($n = 53$), followed by the United Kingdom ($n = 10$), Canada ($n = 9$), and so on. The distribution was illustrated on the world map (Fig. 4). The authors from USA contributed greater than 10 articles. Considering the continents, authors from North America ($n = 62$) published the most articles, followed by Europe ($n = 31$), Asia ($n = 6$) and Oceania ($n = 1$). None of them was published in Africa or South America.

The cooperation among different countries/regions, institutions, and authors is a critical driving force to promote the development of most successful large-scale trials. To this point, there seemed to be close cooperation among different institutions from various countries and regions, especially in North America (Figs. 5–6).

Moreover, authors were classified into greater than 10 clusters in the authors’ collaboration network analysis; several major research teams were identified, mainly including Seam,JJ., Lipton,A., Coleman,RE. (shown in Fig. 7).

4. Discussion

Metastasis is the single most catastrophic complication of human malignancy, while the great avidity for bone always causes painful and untreatable consequences. This bibliometric analysis thoroughly

Table 3
Journals of the 100 most-cited articles.

Journal	No. of articles	Citation count	Impact factor	Quartile in Category [§]
Journal of Clinical Oncology	17	9619	44.544	Q1
Cancer	9	4883	6.86	Q1
New England Journal of Medicine	5	5328	91.245	Q1
Spine	5	2981	3.468	Q1/Q2
International Journal of Radiation Oncology Biology Physics	4	1709	7.038	Q1/Q1
Journal of Clinical Investigation	4	2208	14.808	Q1
Cancer Cell	3	2757	31.743	Q1/Q1
Cancer Research	3	1829	12.701	Q1
Jnci-journal of the National Cancer Institute	3	2137	13.506	Q1
Journal of Bone and Mineral Research	3	2395	6.741	Q1
Lancet	3	3024	79.321	Q1
Nature	3	4333	49.962	Q1
Nature Reviews Cancer	3	3138	60.716	Q1
Bone	2	1402	4.398	Q2
Clinical cancer research	2	1704	12.531	Q1
Nature Genetics	2	1132	38.33	Q1
Radiology	2	1353	11.105	Q1
Annals of Oncology	1	411	32.976	Q1
Blood	1	361	22.114	Q1
British Journal of Cancer	1	818	7.64	Q1
Cancer Journal	1	664	3.36	Q3
Cancer Treatment Reviews	1	1204	12.111	Q1
Cell	1	425	41.582	Q1/Q1
Clinical Oncology	1	357	4.126	Q3
Endocrine Reviews	1	565	19.871	Q1
Endocrinology	1	427	4.736	Q2
International Journal of Cancer	1	512	7.396	Q1
Jama-journal of the American Medical Association	1	708	56.722	Q1
Journal of Clinical Endocrinology & Metabolism	1	428	5.958	Q1
Journal of Neurosurgery	1	498	5.115	Q1/Q1
Journal of Nuclear Medicine	1	575	10.057	Q1
Journal of Oral and Maxillofacial Surgery	1	1367	1.895	Q3
Journal of Urology	1	470	7.45	Q1
Lancet Oncology	1	361	41.316	Q1
Nature Biotechnology	1	674	54.908	Q1
Nature Medicine	1	508	53.44	Q1/Q1/ Q1
Nature Reviews Drug Discovery	1	376	84.694	Q1
Pain	1	600	6.961	Q1
Proceedings of the National Academy of Sciences of the United States of America	1	407	11.205	Q1
Radiographics	1	428	5.333	Q1
Radiologic Clinics of North America	1	752	2.303	Q3
Radiotherapy and Oncology	1	440	6.28	Q1/Q1
Science Signaling	1	378	8.192	Q1/Q1
Trends in Molecular Medicine	1	805	11.951	Q1/Q1/ Q1

[§] Data from the 2020 edition of Journal Citation Reports.

suggested that the clinical community kept the interest focus in bone metastasis. Characteristics of published articles were explored based on specific and reliable parameters. In fact, there has been a relatively rare publications per year before 1995. After 1996, there has been a gradually increased papers involved in bone metastasis until 2015. Another indication of this interest is that all top 10 most cited articles were found to be with more than 1200 citations.

It is a fact that older papers had more chance to be cited [8], and even the most cited papers may had seldom citation after they were published [9]. Here, we presented a study providing a detailed bibliometric analysis of the top 100 most cited articles in bone metastasis, which may

pave the way for further research. These articles were published between 1961 and 2020. Most articles focused on the medical management of different originated bone metastasis, including surgery, radiation therapy and drugs clinical trials mostly.

The top 1 most cited article was published in 2015, entitled *Tumour exosome integrins determine organotropic metastasis*, with 2197 citations [10]. This article provided insight into the possibility of targeting exosome integrins interventions, which may be candidates for blockage of organ-specific metastasis combination therapies. Deciphering the mystery of tumour organotropism apparently has drawn a lot of interest from scholarship worldwide, in the important role of tumour-derived exosomes in determining and mediating future organ-specific metastasis to form favourable niche processes. The top 2 most cited article was published in 2002, entitled *Metastasis to bone: Causes, consequences and therapeutic opportunities*, with 2023 citations [11]. This article provided a thorough overview of the specific cancer avidity for bone, the molecular mechanisms responsible for how they alter the skeletal system physiology, and new potential molecular targets for future drug development. The top 3 most cited article was published in 2003, entitled *A multigenic program mediating breast cancer metastasis to bone*, with 1884 citations [12]. This article aimed to investigate the molecular basis for osteolytic bone metastasis by in vivo selection of highly metastatic breast expression signature in high metastatic cells cancer. Transcriptional profiles were compared of cells with different metastatic potentials in order to identify genes that differ functionally validation of genes overexpressed in these cells was also carried out. This article provided a conceptual framework and experimental evidence for a specific set of genes that mediated the breast cancer cells to metastases to bone. What's more, from the most frequently occurring keywords analysis we can learn that the connection between "bone metastasis" with "breast cancer" and "bone metastasis" with "bisphosphonates" is deep and tight, and these topics have always been the focus of research.

Bisphosphonates are a class of pyrophosphate analogs with a high binding affinity to mineralized bone surfaces, moderating osteoblast-mediated bone production and osteoclast-mediated bone resorption. Typical examples of bisphosphonates are zoledronate, pamidronate, and so on. These bone-specific anti-resorptive agents are often chosen as first-line therapy for patients with diseases of bone loss, such as osteoporosis and cancers that cause osteolysis [11,13]. Clinical trials have made up a relatively important part of the T 100 list. We noticed that 11 clinical trial papers focus on zoledronic acid among the 23 papers reporting clinical trial findings. Among them, the most common topic is the long-term efficacy and safety of zoledronic acid for treating skeletal-related events in patients with bone metastases. Zoledronic acid, denosumab and pamidronate are the most common topic of these articles. Zoledronic acid is the first new-generation bisphosphonate with highly potent demonstrating efficacy in patients with bone metastases from solid tumors not only restricted to breast cancer, such as prostate cancer and non-small-cell lung cancers [14–16].

Denosumab is a human immunoglobulin G2 (IgG2) antibody, with a molecular weight of about 147,000 Da [17]. By targeted inhibiting the action of receptor activator of nuclear factor-kappaB ligand (RANKL), denosumab reduces the biofunction of osteoclasts, thereby moderating bone resorption and increasing bone mineral density, mirroring the action of endogenous osteoprotegerin [18,19]. Pamidronate is a bisphosphonate class of medication, which is a valuable agent in managing hypercalcemia of malignancy, osteolytic bone metastases of breast cancer, and osteolytic lesions of multiple myeloma [20]. Radium-223 (²²³Ra) is a bone-targeted alpha-emitter radionuclide which has been studied as a new treatment option for hormone-refractory prostate patients with bone metastases [21]. Comparative study between zoledronic acid and other drugs, including denosumab (3 papers) and pamidronate (1 paper). While, the efficacy of pamidronate (3 papers), radium-223 (2 papers), and pamidronate (2 papers) cover most of the remaining clinical trials' findings. From the above articles, we can see that factors that may influence scientific interests include not only the

Table 4

Rough summary of topics and classification of the TOP 100 citations.

rank	type	basic medical research	specific field	clinical medical research	biology of metastasis	disease focus	imaging	clinical trail	clinical guidelines	recoomendation	consensus	review	meta-analysis	systemic review
T1	article	✓	tumour exosome		✓									
T2	review				✓							✓		
T3	article	✓			✓	breast cancer metastasis to bone								
T4	clinical trail		alpha emitter radium-223	✓		Metastatic Prostate Cancer		✓						
T5	article	✓				breast cancer metastasis to bone								
T6	review				✓							✓		
T7	article		osteonecrosis of the jaws	✓										
T8	review		clinical features and risk									✓		
T9	clinical trail		direct decompressive surgical resection	✓		spinal cord compression caused by metastatic cancer		✓						
T10	clinical trail		denosumab and zoledronic acid	✓		prostate cancer metastasis to bone		✓						
T11	clinical trail		zoledronic acid	✓		hormone-refractory metastatic prostate cancer		✓						
T12	review		clinical features, pathophysiology and managements									✓		
T13	article		metastatic breast cancer	✓										
T14	review				✓							✓		
T15	recommendation		bisphosphonate-associated osteonecrosis of the jaw							✓				
T16	clinical trail		denosumab and zoledronic acid	✓		breast cancer metastasis to bone		✓						
T17	article		spinal metastases	✓										
T18	article	✓	prostate cancer metastasis to bone											
T19	article	✓	bisphosphonates											
T20	article		breast cancer metastases to bone	✓										
T21	article		bisphosphonates and osteonecrosis of the jaws	✓										
T22	review		RANKL-RANK signaling pathway									✓		
T23	article		pamidronate	✓										
T24	article		Percutaneous vertebroplasty for osteolytic metastases and myeloma	✓										
T25	article	✓			✓									
T26	review		percutaneous vertebroplasty with polymethylmethacrylate									✓		
T27	guideline		bisphosphonates and bone health			female breast cancer			✓					
T28	clinical trail		denosumab and zoledronic acid	✓		cancer (excluding breast and prostate cancer) or multiple		✓						

(continued on next page)

Table 4 (continued)

rank	type	basic medical research	specific field	clinical medical research	biology of metastasis	disease focus	imaging	clinical trail	clinical guidelines	recoomendation	consensus	review	meta-analysis	systemic review
T29	review				✓	myeloma metastasis to bone						✓		
T30	review		osteoprotegerin/RANKL/RANK system									✓		
T31	review		bisphosphonates									✓		
T32	article		Percutaneous vertebroplasty	✓										
T33	review		bisphosphonates									✓		
T34	article	✓												
T35	clinical trail		zoledronic acid and pamidronate	✓		breast cancer or osteolytic lesions of multiple myeloma metastasis to skeleton		✓						
T36	clinical trail		zoledronic acid and pamidronate	✓		breast cancer or osteolytic lesions of multiple myeloma metastasis to skeleton		✓						
T37	article		adjuvant clodronate treatment	✓										
T38	article	✓	breast cancer-mediated osteolysis											
T39	review		pathophysiology and treatment									✓		
T40	article		vertebroplasty of spinal metastases	✓										
T41	article	✓	chromosomal variants in estrogen receptor-positive breast cancer	✓										
T42	article	✓	RANKL and bone metastasis											
T43	article		high-risk prostate cancer	✓			✓							
T44	systemic review		palliative radiotherapy trials for bone metastases											
T45	review		RANKL and osteoprotegerin									✓		
T46	guideline		palliative radiotherapy for bone metastases						✓					
T47	article	✓												
T48	clinical trail		zoledronic acid	✓		lung cancer and other solid tumors metastasis to skeleton		✓						
T49	article		pamidronate and prostate cancer	✓										
T50	article	✓												
T51	review				✓							✓		
T52	article	✓	endothelin-1 in the pathophysiology of metastatic prostate cancer	✓	✓									
T53	clinical trail		radiotherapy for palliation of bone pain	✓		breast or prostate cancer metastasis to bone		✓						
T54	clinical trail		pamidronate	✓				✓						

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Table 4 (continued)

rank	type	basic medical research	specific field	clinical medical research	biology of metastasis	disease focus	imaging	clinical trial	clinical guidelines	recoomendation	consensus	review	meta-analysis	systemic review
T55	article			✓		breast cancer and osteolytic bone metastases	✓							
T56	article			✓										
T57	article	✓			✓									
T58	article		radiosurgery for spinal metastases	✓										
T59	clinical trail		denosumab	✓		castration-resistant prostate cancer		✓						
T60	clinical trail		zoledronic acid	✓		nonsmall cell lung carcinoma and other solid tumors metastasis to skeleton		✓						
T61	clinical trail		zoledronic acid	✓		bone loss in nonmetastatic prostate cancer patient with hormone therapy		✓						
T62	article	✓	bisphosphonates											
T63	clinical trail		pamidronate	✓		breast cancer metastasis to bone		✓						
T64	article		a novel classification system for spinal instability in neoplastic disease	✓							✓			
T65	clinical trail		pamidronate	✓		advanced breast cancer and lytic bone lesions		✓						
T66	article			✓										
T67	article	✓			✓									
T68	article		bisphosphonates and osteonecrosis of the jaws	✓										
T69	review				✓							✓		
T70	clinical trail		clodronate	✓		breast cancer metastasis to bone		✓						
T71	article		fraction on painful bone metastases	✓										
T72	clinical trail		SR-89 adjuvant to local field external beam irradiation	✓		endocrine resistant metastatic prostate-cancer		✓						
T73	review		percutaneous vertebroplasty									✓		
T74	article		differentiated thyroid carcinoma	✓										
T75	article	✓			✓									
T76	article	✓	lung adenocarcinoma metastasis											
T77	article			✓										
T78	article		bone metastases and zoledronic acid	✓										
T79	clinical trail		incidence, risk factors, and outcomes of osteonecrosis of the jaw	✓		osteonecrosis of the jaw								

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Table 4 (continued)

rank	type	basic medical research	specific field	clinical medical research	biology of metastasis	disease focus	imaging	clinical trail	clinical guidelines	recoomendation	consensus	review	meta-analysis	systemic review
T80	article	✓	Breast cancer bone metastasis											
T81	review					prostate cancer metastasis to bone						✓		
T82	article		pathologic fractures and malignant bone disease	✓										
T83	article		ablation therapy for painful bone metastases	✓										
T84	clinical trail		Denosumab	✓		prostate cancer, breast cancer, or other neoplasms metastasis to bone		✓						
T85	review		bone imaging			breast cancer metastasis to bone	✓					✓		
T86	clinical trail		zoledronic acid	✓		osteolytic metastases		✓						
T87	article		detection of bone metastases in breast cancer	✓			✓							
T88	article	✓			✓									
T89	review		pathophysiology and treatment									✓		
T90	article	✓			✓									
T91	article	✓			✓									
T92	review		OPG-RANK-RANKL and denosumab									✓		
T93	meta analysis		palliative radiotherapy for bone metastases										✓	
T94	article		bisphosphonate-associated osteonecrosis	✓										
T95	clinical trail		zoledronic acid	✓		breast cancer metastasis to bone		✓						
T96	article		denosumab	✓										
T97	clinical trail		alpha-emitter radium-223	✓		hormone-refractory prostate cancer metastasis to bone		✓						
T98	article	✓												
T99	article		radiotherapy for metastatic spinal lesions	✓										
T100	review		palliative radiotherapy trials for bone metastases									✓		✓

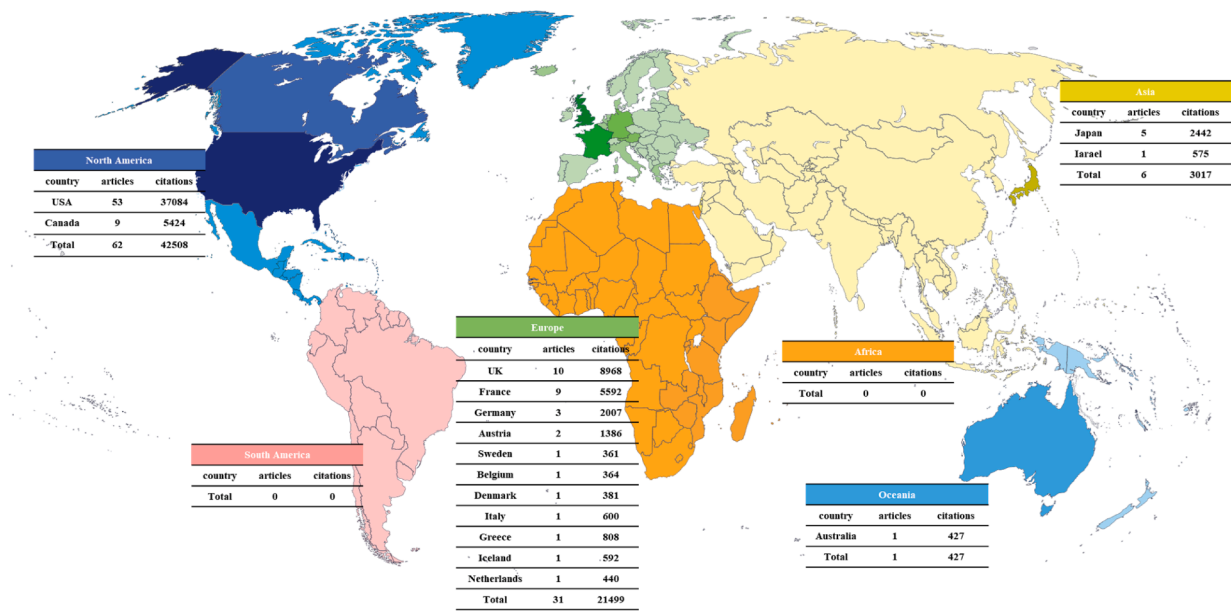


Fig. 4. Worldwide distribution of the top 100 most-cited papers.

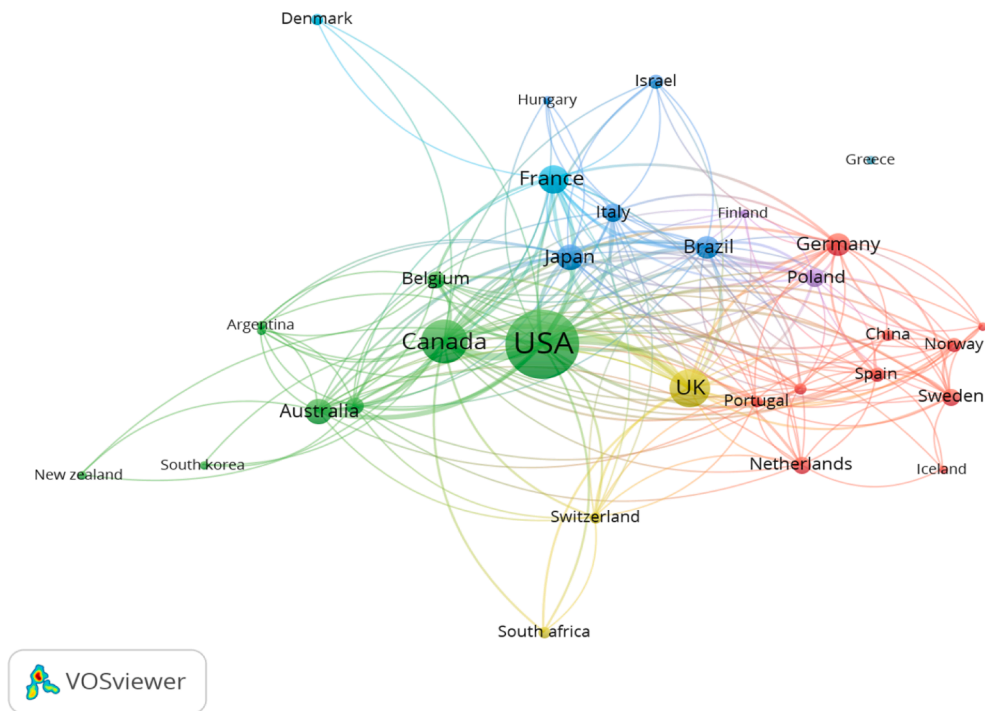


Fig. 5. Bibliographic coupling between countries in the top 100 most-cited papers.

clinical need to solve problems in the real world but also the advances and development of the pharmaceutical industry nowadays.

It is noteworthy that the guideline published in 2003 entitled *American society of clinical oncology 2003 update on the role of bisphosphonates and bone health issues in women with breast cancer (27#)*, recommending a management algorithm for patients diagnosed non-metastatic breast cancer. Meanwhile, this guideline also emphasized the supportive, albeit expensive and non-life-prolonging, benefit of bisphosphonates to patients diagnosed with bone metastases [22]. Beyond the drug management for bone metastases, radiotherapy is also a successful and time-efficient option to palliate pain and/or prevent morbidity. Article #41 published an evidence-based guideline from American Society for Radiation Oncology (ASTRO) focused on palliative

radiotherapy for bone metastases. According to published evidence and expert opinions, it defined the proper use of radiotherapy for patients and physicians regarding the management of bone metastases [23]. Before 2010, neoplastic spinal instability was poorly defined and lacked guidelines in defining the degree of spinal instability. Article #64 generated a consensus of best evidence through a modified Delphi technique to develop a classification system to define neoplastic spinal instability. Based on patient symptoms and radiographic criteria of the spine, a comprehensive classification system was developed aiming to be helpful in predicting spine stability of neoplastic lesions [24].

In our analysis, the involved 100 articles were published in 44 journals, with an impact factor range of 1.895 to 91.245. 90.91% of the journals were categorized in Q1 and Q2 quartile. Only 4 journals were

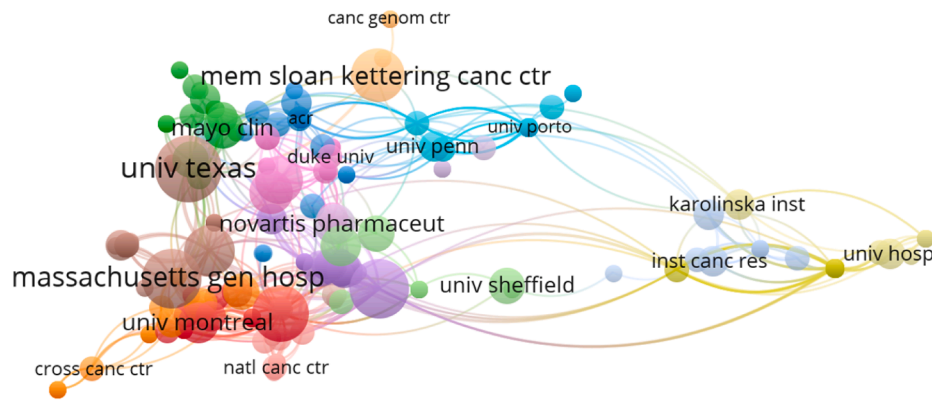


Fig. 6. Bibliographic coupling between institutions in the top 100 most-cited papers.

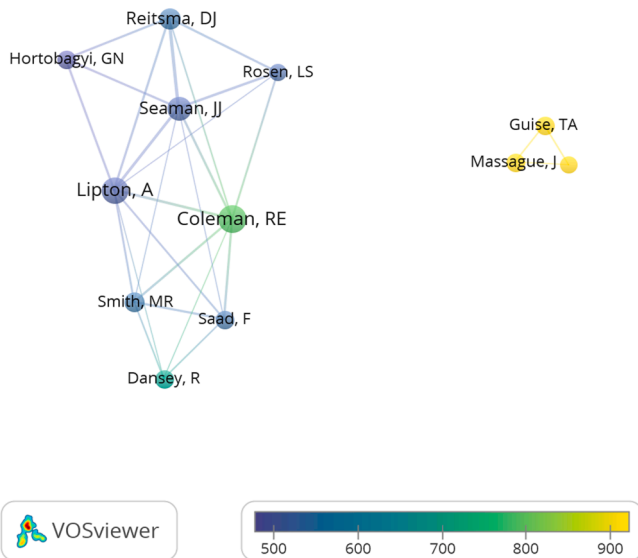


Fig. 7. Co-authorship inter-citation diagram among the 100 most-cited articles.

from Q3 in Category, including *Cancer Journal*, *Clinical Oncology*, *Journal of Oral and Maxillofacial Surgery* and *Radiologic Clinics of North America*. 36% of the most cited articles were published in top 4 journals, including *Journal of Clinical Oncology* (IF = 44.544), followed by *Cancer* (IF = 6.86), *New England Journal of Medicine* (IF = 91.245) and *Spine* (IF = 3.468). It is not surprising that researchers preferred to submit high-quality articles to journals with high impact factors. On the other side, articles published in high-impact factor journals tended to get more citations.

We identified authors from 14 different countries in the top 100 most cited articles. Oncologists all over the world participated in rosacea research, especially in North America and Europe. Scholar from Africa and South America seems not much interested in bone metastasis. Massachusetts General Hospital, Texas State University, and Memorial Sloan-Kettering Cancer Center reflected a great interest in bone metastasis research. Professor Robert E Coleman from the University of Sheffield published the most articles (13 publications, 9847 total citations). From the countries, institutions, and even authors analyses, we

could easily find the authoritative scholarships and key institutions attributed to bone metastasis. The above finding could be attributed to an enhanced opportunity for a general understanding of bone metastasis for new readers about the natural history and trends within the bone metastasis field.

Undoubtedly, there are also some limitations to our analysis. First, as publications are filtered according to citations number, publications in recent years may be of great significance in the field but have a great chance to be ignored and out of the present list for now. Second, this analysis included not only published articles, but also other papers like reviews, meta-analyses, and clinical guidelines or recommendations, which may lead to omission bias. Third, we only included publications in English recorded on the Web of Science, and language and/or database limits may have been omitted.

5. Conclusions

In conclusion, this bibliometric article highlights the top 100 most cited articles in the bone metastasis field over the past 30 years (1986–2015), in terms of their publishing time and citations, journals, authors, geographical distribution, research institutions, and research keywords. We addressed the top 100 cited papers, regardless of publication type. From the aspect of the research theme, we found that clinical management of bone metastasis was one of the issues of global concern. Clinical trials and basic laboratory research are still of great significance and warrant deeper and broader exploration. This data-driven analysis provided a key advantage of a bibliometric review and may be of help in paving the way for further research on bone metastasis. In summary, the research field of bone metastasis looks promising.

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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