

# Bibliometric Analysis of the Hundred Most-Cited Publications on Bone Metastases Research

**Tingxiao Zhao**

Zhejiang Provincial People's Hospital <https://orcid.org/0000-0003-0154-3595>

**Yuan Zhang**

Zhejiang Provincial People's Hospital

**Jun Lv**

Zhejiang Provincial People's Hospital

**Meng Ge**

Zhejiang provincial people's hospital

**Zhanqiu Dai**

zhejiang provincial people's hospital

**Haiyu Shao**

zhejiang provincial people's hospital

**Xiaoyan Ding**

zhejiang provincial people's hospital

**Yazeng Huang**

Zhejiang Provincial People's Hospital

**Jun Zhang**

zhejiang provincial people's hospital

**Yao Kang (✉ [kyc0730@163.com](mailto:kyc0730@163.com))**

zhejiang provincial people's hospital <https://orcid.org/0000-0002-4117-271X>

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## Research article

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# Abstract

## Background

Bone metastases (BM) represents a common complication of cancer, patients with BM may experience skeletal complications, such as pathological fractures, spinal cord compression, hypercalcemia, and persisting pain. Currently, there are a large number of publications available on this topic. The purpose of this study was to identify and analyze the 100 most-cited publications on BM research.

## Method

All databases from the Web of Science were searched in a three-step approach. First, the 100 most-cited BM studies were identified using only one term “bone metastases” to allow for comprehensive keyword identification. Second, ten keywords identified from the results of the first search were used to conduct a second search of the databases to yield a separate list of the top 100 cited BM publications. Finally, the results of the two searches were overlapped and duplicated articles were removed. After overlapping, the top 100 most-cited articles on BM were selected for further analysis of title, authorship, source journal, publication year, geographic origin, research institution, number of citations, and subspecialty.

## Results

The 100 most-cited articles were published from 1959 to 2014 in 44 different journals and were cited from 250 to 1707 times. The most influential period was from 2001–2010, which produced 50 out of the top 100 publications. A total of 12 countries contributed to the 100 articles, and the United States topped the list with 48 articles. The majority of publications were in *Journal of Clinical Oncology*, which published 16 articles. In terms of institutional support, a total of 13 institutions each supported at least 2 articles, and the first ranked institution was University of Texas M. D. Anderson Cancer Center (USA) with 8 articles. Regarding subspecialty of the studies, the most frequent studies were “clinical description” with 30 articles, followed by “clinical trial” with 20 articles.

## Conclusion

In this comprehensive review, we identified and analyzed the 100-most-cited articles on BM research by measuring their citation number, and recognized some of the most important contributions by authors, institutions and countries. Furthermore, our study will help researchers and orthopedic surgeons understand the research trends for BM and as an efficient guide for future BM-related research.

## Introduction

Bone metastases (BM) represents a common complication in the most prevalent human cancers, whose incidence reaches 70–95% in multiple myeloma (MM), up to 65–90% in prostate cancer (PC), 65–75% in breast cancer (BC), 17–64% in lung cancer (LC), and 10% in colorectal cancer (CC) [1-4]. Patients with BM may experience skeletal complications including pathological fractures, hypercalcemia, spinal cord and

nerve compression syndromes, and uncontrolled pain that require orthopedic surgery or/and radiotherapy, collectively referred to as skeletal-related events (SREs) [5,6]. These events seriously affect the quality of life (QoL) of patients and patient survival rates [7]. Therefore, the major treatment options for BM patients aim at improving the QoL and reducing SREs. Currently, BM treatments include loco-regional and systemic approaches. The former, mainly represented by focal excision and radiotherapy, are usually performed to relieve bone pain and to prevent pathological fractures. The latter mainly include anabolic agents, inhibitors of bone resorption and radiopharmaceuticals that aim at restoring severely impaired physiological bone turnover in metastatic bone disease patients [8].

In recent years, with the emergence of imaging techniques with improved sensitivity and specificity in the detection of bone injury, the early diagnosis of BM has significantly improved [9]. The diagnosis and management of BM has also gained much interest among surgeons, similarly, fundamental scientific research has also made major breakthroughs in understanding the mechanism involved in the development of BM. Concomitantly, a large number of studies regarding BM have been published.

Bibliometric analysis is a widely accepted approach for identifying high impact scientific studies on medicine and to quantitatively and qualitatively evaluate its academic impact [10,11] This analysis method has been widely performed in the field of orthopedic surgery [12-16]. To the best of our knowledge, there have been no reports on bibliometric analysis on BM to date. Therefore, our objective was to identify the top 100 most-cited studies on BM, and to analyze the characteristics and research trends of the most impactful publications. This bibliographic analysis will augment efforts in research consensus and will enable researchers to better align their research direction to address the issues that require additional research due to the lack of evidence and to tailor their future research on BM.

## **Materials And Methods**

### **Inclusion Criteria**

All available journals from the Web of Science database were searched to identify and analyze the 100 most-cited articles on BM between 1950 and 2020. To be considered for the top 100 list: (1) papers had to focus on the field of BM; (2) papers should be written in English; and (3) the publication date should be between the 1950 and 2020.

### **Exclusion Criteria**

The exclusion criteria included: (1) papers that focused on broad areas with no emphasis on BM; and (2) papers focused on primary bone/spinal tumor.

### **Search strategy and study selection**

As of 5 July 2020, we identified the 100 most-cited BM research studies published between 1950 and 2020, excluding non-English language studies. In order to achieve a higher comprehensiveness and

accurateness of the study, a three-step approach was adopted to search the databases of the Web of Science, as shown in the flow chart in Figure 1.

First, the Web of Science databases was searched using the keyword “bone metastases.” The search produced 85,957 results, which were then ranked in descending order of the total number of citations. In the initial 1200 studies identified, the 100 most-cited papers on BM were selected based on titles and abstracts. The aim was to provide a more comprehensive study of BM, and the title and abstract of the identified 100 studies were systematically analyzed for possible keywords. Combined with other keywords known to be relevant to the field of BM research, a search query composed of a group of 10 keywords was established and used for a second database search by topic. The 10 keywords identified were “bone metastases,” “bone metastasis,” “metastatic bone disease,” “skeletal metastases,” “spinal metastases,” “spinal metastasis,” “metastatic spine disease,” “osseous metastases,” “osteolytic metastases,” and “osteoblastic metastases.”

Second, every search word or phrase was delimited by an OR term, by this means, additional search results were obtained. The second search showed 105,159 results, again were ranked these in descending order of the total number of citations. Of the top 1000 preliminary studies, 100 articles related to BM were selected based on titles and abstracts.

Third, the studies of the two selections were compared, and duplicate studies were removed and the 100 most-cited BM studies were selected for finally analysis.

To ensure consistency of data extraction, two independent authors evaluated the articles for their relevance to BM and the 100 most-cited articles on BM were final determined. Finally, the 100 most-cited articles were then extracted with regard to basic information including: title, authorship, source journal, publication year, geographic origin, research institution, number of citations, and subspecialty.

## Statistical Methods

All data were manually extracted from the Web of Science database and recorded in Microsoft Excel 2016 or further analysis or visualization. VOSviewer (Leiden University, Leiden, the Netherlands) is a commonly used software tool for creating maps for network analysis and visualization. In this study, this software was used to visualize the relationships and the time distribution between the most frequently occurring concepts and keywords.

# Results

## Overview of publications

The 100 most-cited articles involving BM research were cited from 250 to 1707 times in 44 different journals and the mean citation number was 467.5 (**Table 1**). “A multigenic program mediating breast cancer metastasis to bone,” published by Kang et al., was the most-cited article (cited 1707 times). The earliest published article was “Experiences with metastatic neoplasms involving the spinal cord,” which

was published in 1959 by Barron et al. (cited 312 times). The most recent article was “Effect of radium-223 dichloride on symptomatic skeletal events in patients with castration-resistant prostate cancer and bone metastases: Results from a phase 3, double-blind, randomised trial,” published by Sartor et al. in 2017 (cited 312 times).

### Country of publications

The top 100 articles originated from 12 different countries. Authors from the United States contributed 48 articles. European centers from ten countries published 34 articles in total. Among these, 10 articles were from the United Kingdom, 8 articles were from France, 3 articles were from Italy, Sweden, and The Netherlands, 2 articles were from Switzerland and Belgium, and 1 article was from Austria, Denmark and Germany. Authors from Asia and Africa published relatively fewer articles compared to the United States and Europe. Authors from Japan published 5 articles, and Israel 1 articles, respectively. Besides, authors from Canada and Australia published 10 and 1 articles, respectively.

### Year of publication

The publishing period responsible for the largest number of studies was 2001 to 2010 with 50 articles, followed by 1991 to 2000 with 24 articles, 1981 to 1990 with 11 articles, 2011 to 2014 with 10 articles, and the period 1971 to 1980 with 3 articles (**Figure 3**). Notably, only 2 articles were published before 1970.

### Journals of publications

Overall, 44 different journals were represented on the list of the 100 most-cited studies (**Table 2**). The *Journal of Clinical Oncology* was the most popular journal, which was responsible for 16 articles and 7218 total citations. This was followed by *Cancer* with 10 articles with 4888 total citations. *Cancer Research*, *Spine*, *Journal of Neurosurgery*, *Journal of the National Cancer Institute*, and *Cancer Cell* each with 4, 4, 3, 3 and 3 articles, respectively. Although there were only 2 articles on the list which were published in *Lancet*, their mean citations per article was the highest (1106 times per article).

### Authors of publications

Regarding the authors, A Lipton was the most productive author with 11 articles in total, followed by R. E. Coleman with 11 articles. J. E. Brown, G. N. Hortobagyi, F. Saad, J. J. Seaman, J. J. Body, and L. S. Rosen, with 5 articles each (**Table 3**).

### Institutions of publications

In terms of institutional support, a total of 13 institutions each supported at least 2 articles (**Table 4**). The first ranked institution was the University of Texas M. D. Anderson Cancer Center (USA) with 8 articles. The second top ranked institution was Weston Park Hospital with 5 articles. The Memorial Sloan-

Kettering Cancer Center (USA), and the University of Toronto (Canada) were tied for third with 4 articles each.

### **Subspecialty of publications**

Regarding the subspecialty of the studies, the most frequent studies were “clinical description” (n=30), followed by “clinical trial” (n=20), “mechanism” (n=16), “drug efficacy” (n=11) “radiotherapy” (n=7), “evaluation” (n=5), “surgery treatment” (n=4), “detection” (n=3), “murine model” (n=2), and “prediction” (n=2) (**Figure 4**).

### **Keyword analysis of publications**

As shown in **Figure 5**, the 28 terms (defined as being used more than 6 times within titles and abstracts in all of the articles) were classified into 3 clusters: “clinical trial”, “clinical features”, and “basic research”. Among the “clinical trial” cluster, keywords used in the top articles were listed as follows: trial (30 items), time (26 items), event (23 items), week (22 items), and spinal cord compression (20 items). For the cluster of “clinical features”, the primary keywords were as follows: treatment (61 items), survival (29 items), pain (29 items), year (27 items), and site (21 items). In the “basic research” cluster, the primary keywords were as follows: cell (35 items), factor (25 items), breast cancer (25 items), effect (24 items), and therapy (22 items).

As shown in **Figure 6**, VOSViewer assigned colors to keywords according to the average year in which they appeared in the article. In the early stage of BM research, both the biological and clinical fields were the main hotspots. In the early stage of BM research, treatment of BM was the main hotspot. Recent trends showed that the words “SRE”, “zoledronic acid”, “hazard rate”, “denosumab”, and “intension” appeared as keywords articles after 2006. There was most of the key words appear in the “clinical trial” cluster.

## **Discussion**

The present bibliometric analysis determined and characterized the 100 most-cited publications in the Web of Science databases. After identifying the most-cited research articles, we obtained insight into the historic developmental trends in BM research that reflected the great importance and academic concern placed on the study of BM.

Undoubtedly the publishing date will affect citation numbers, the longer periods after the article is published allows for a greater opportunity to be cited. In our study, the most productive period was from 2001 to 2010 with 50 articles. However, only 2 articles were published before 1970. This indicates that the improvement of BM research quality and efficiency promoted an increase in papers and citations in recent years. Notably, no top-cited articles were published after 2015 in our current analysis. We speculated the following possible reasons for this: firstly, because BM has always been a hot research field for researchers and orthopedic surgeons, numerous high-quality articles have already been

published, although, we have only included the top 100 most-cited articles, therefore, articles with relatively fewer citations are not included. Secondly, more recently published articles need time to be cited widely.

In total, 44 different journals published the top 100 most-cited studies, with the *Journal of Clinical Oncology* contributing most studies, followed by *Cancer*. It has been reported that major journals can attract high-quality research articles in their fields, maintaining high the impact factors of these journals [17]. Compared with other similar bibliometric studies, top 100 articles have been published in a greater number of journals, while, the most contributive journals have published fewer articles [18,19]. We speculated that this may be related to more high-quality journals in the field of cancer.

Overall, 12 different countries contributed to the top 100 articles, and the most productive country of article origin was the United States, followed by European centers. In contrast, Asia (Japan, Israel) made a relatively small contribution to the 100 most-cited articles, which indicated that there is still a large gap of scientific studies published between Asian countries and western developed areas. Thus, various countries, especially in developing regions, have to endeavor make greater contributions to be integrated into the world scientific processes.

VOSviewer software was used to analyze the keywords of the main subjects of these 100 articles. The 100 most-cited articles extracted from all database of the Web of Science were classified into 3 clusters: "clinical trial," "clinical features," and "basic research." In the clinical trial cluster, "trial" and "time" were the most frequently appearing keywords on the network map. This finding demonstrated that randomized controlled trials investigating drug therapy are a major research direction in the field of BM. In the clinical features cluster, the most frequently occurring keywords included "treatment," "survival," and "pain" meaning that the clinical efficacy and prognosis of BM patients have been widely studied. Further, in the basic research cluster, "cell," "factor," and "breast cancer" were the most frequently keywords, which illustrated that the research interest was mainly focused on the molecular biology of BM. Generally, molecular mechanisms, treatment, and prognosis were hot topics in the research of BM.

Keyword analysis is an indispensable approach to evaluate the evolution of research hotspots in this field. To the best of our knowledge, this study is the first to visually summarize the evolution of global research trends on BM. Among the 3 keyword clusters "clinical trial," "clinical features," and "basic research," the former is of great interest because of the obvious changes in the research hotspots over the last 20 years. From simple attention to pain control to a series of clinical problems caused by SREs, researchers and surgeons are focusing increasingly on improving prognosis and prolonging the survival of patients with BM [20,21]. In-depth study of the molecular mechanisms, targeted therapies, and immunotherapy have attracted increasing attention, and some studies have led to agents being recommended as first-line drugs by the guidelines, such as denosumab [22]. In addition, in recent years, with the rapid progress of radiotherapy research, especially the emergence of stereotactic body radiation therapy (SBRT), radiotherapy has also received strong research interest from doctors and patients [23,24].

Even so, surgery and chemotherapy still play an irreplaceable role. Thus, it is necessary to review the highly quality articles to understand milestones during the study of BM.

Although this current analysis was relatively comprehensive and objective, it had several limitations. First, the date for literature search was 5 July 2020, theoretically, which could limit the citation numbers by time. Second, besides the Web of Science, Google Scholar and SCOPUS databases could also provide citation data, these databases may display a different number of citations and therefore may provide different analysis results [25]. Third, since the top 100 articles selected are limited to English, we might have overlooked high-impact articles in other languages. Finally, some recently published high-quality articles were not included in this analysis due to their low citation frequency.

In summary, despite its limitations, bibliometric analysis remains one of the best methods to quantify the impact of scientific studies and to quantify the contributions of researchers [26,27]. We believe that this study highlights a series of intellectual milestones in BM research. The present study identified influential authors, institutions, countries, and journals that have made outstanding contributions to BM research. Undoubtedly, this study will provide a catalogue of valuable articles for young researchers and will help scientists to master research hotspots and to determined future academic pursuits.

## Conclusion

The BM literature has grown continuously over the years. The 100 most-cited publications in BM research were searched and analyzed, and the contribution of the authors and their origins were identified. This article provides insight into the development of BM research, and should contribute to help scientists to grasp the international research hotspots on BM research.

## Abbreviations

BM: bone metastases

MM: multiple myeloma

PC: prostate cancer

BC: breast cancer

LC: lung cancer

CC: colorectal cancer

SREs: skeletal-related events

QoL: quality of life

SBRT: stereotactic body radiation therapy

# Declarations

## Acknowledgements

Not applicable.

## Author's contributions

Conceived and designed the study: Yao Kang and Jun Zhang. Revised the protocol: Tingxiao Zhao and Yuan Zhang. Extracted the data: Jun Lv, Meng Ge and Yazeng Huang. Performed the statistical analysis: Zhanqiu Dai, Haiyu Shao, and Xiaoyan Ding. Wrote the manuscript: Tingxiao Zhao and Yuan Zhang. All authors contributed constructive comments on the paper. The authors read and approved the final manuscript.

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## Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

## Ethics approval and consent to participate

Ethics approval is not required due to this work is carried out on open data.

## Consent for publication

Not applicable.

## Competing Interests:

The authors declare that they have no competing interests.

## Device Status/Drug Statement:

The manuscript submitted does not contain information about medical devices

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## Tables

**TABLE 1. The Top 100 Cited Articles on Bone Metastases**

Rank	Author	Title	Journal	Year	Citation	Citation No./Year
1	Kang, Y. B.	A multigenic program mediating breast cancer metastasis to bone	Cancer Cell	2003	1707	100.41
2	Roodman, G. D.	Mechanisms of disease: mechanisms of bone metastasis	New England Journal of Medicine	2004	1347	84.19
3	Coleman, R. E.	Clinical features of metastatic bone disease and risk of skeletal morbidity	Clinical Cancer Research	2006	1122	80.14
4	Patchell, R. A.	Direct decompressive surgical resection in the treatment of spinal cord compression caused by metastatic cancer: a randomised trial	Lancet	2005	1115	74.33
5	Fizazi, K.	Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomised, double-blind study	Lancet	2011	1097	121.89
6	Coleman, R. E.	Metastatic bone disease: clinical features, pathophysiology and treatment strategies	Cancer Treatment Reviews	2001	1048	55.16
7	Coleman, R. E.	Skeletal complications of malignancy	Cancer	1997	1011	43.96
8	Stopeck, A. T.	Denosumab compared with zoledronic acid for the treatment of bone metastases in patients with advanced breast cancer: a randomized, double-blind study	Journal of Clinical Oncology	2010	839	83.90
9	Saad, F.	Long-term efficacy of zoledronic acid for the prevention of skeletal complications in patients with metastatic hormone-refractory prostate cancer	Journal of the National Cancer Institute	2004	784	49.00
10	Taichman, R.	Use of the stromal cell-	Cancer	2002	761	42.28

	S.	derived factor-1/CXCR4 pathway in prostate cancer metastasis to bone	Research			
11	Coleman, R. E.	The clinical course of bone metastases from breast cancer	British Journal of Cancer	1987	755	22.88
12	Hortobagyi, G. N.	Efficacy of pamidronate in reducing skeletal complications in patients with breast cancer and lytic bone metastases. Protocol 19 Aredia Breast Cancer Study Group	The New England Journal of Medicine	1996	746	31.08
13	Yin, J. J.	TGF-beta signaling blockade inhibits PTHrP secretion by breast cancer cells and bone metastases development	Journal of Clinical Investigation	1999	692	32.95
14	Hillner, B. E.	American society of clinical oncology 2003 update on the role of bisphosphonates and bone health issues in women with breast cancer	Journal of Clinical Oncology	2003	688	40.47
15	Tomita, K.	Surgical strategy for spinal metastases	Spine	2001	642	33.79
16	Gilbert, R. W.	Epidural spinal cord compression from metastatic tumor: diagnosis and treatment	Annals of Neurology	1978	637	15.17
17	Henry, D. H.	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	Journal of Clinical Oncology	2011	631	70.11
18	Rosen, L. S.	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	Cancer Journal	2001	618	32.53

19	Cotten, A.	Percutaneous vertebroplasty for osteolytic metastases and myeloma: effects of the percentage of lesion filling and the leakage of methyl methacrylate at clinical follow-up	Radiology	1996	615	25.63
20	Rosen, L. S.	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	Cancer	2003	595	35.00
21	Weilbaecher, K. N.	Cancer to bone: a fatal attraction	Nature Reviews Cancer	2011	577	64.11
22	Thalmann, G. N.	Androgen-independent cancer progression and bone metastasis in the LNCaP model of human prostate cancer	Cancer Research	1994	560	21.54
23	Fleisch, H.	Bisphosphonates. Pharmacology and use in the treatment of tumour-induced hypercalcaemic and metastatic bone disease	Drugs	1991	558	19.24
24	Mercadante, S.	Malignant bone pain: pathophysiology and treatment	Pain	1997	553	24.04
25	Tong, D.	The palliation of symptomatic osseous metastases: final results of the Study by the Radiation Therapy Oncology Group	Cancer	1982	537	14.13
26	Weill, A.	Spinal metastases: indications for and results of percutaneous injection of acrylic surgical cement	Radiology	1996	524	21.83
27	Tokuhashi, Y.	A revised scoring system for preoperative	Spine	2005	520	34.67

		evaluation of metastatic spine tumor prognosis				
28	Even-Sapir, E.	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	Journal of Nuclear Medicine	2006	518	37.00
29	Jones, D. H.	Regulation of cancer cell migration and bone metastasis by RANKL	Nature	2006	500	35.71
30	Chow, E.	Palliative radiotherapy trials for bone metastases: A systematic review	Journal of Clinical Oncology	2007	497	38.23
31	Boissier, S.	Bisphosphonates inhibit breast and prostate carcinoma cell invasion, an early event in the formation of bone metastases	Cancer Research	2000	482	24.10
32	Rosen, L. S.	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	Journal of Clinical Oncology	2003	473	27.82
33	Lutz, S.	Palliative radiotherapy for bone metastases: an astro evidence-based guideline	International Journal of Radiation Oncology Biology Physics	2011	473	52.56
34	Lipton, A.	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	Cancer	2000	469	23.45
35	Soloway, M. S.	Stratification of patients with metastatic prostate	Cancer	1988	459	14.34

		cancer based on extent of disease on initial bone scan				
36	Fourney, D. R.	Percutaneous vertebroplasty and kyphoplasty for painful vertebral body fractures in cancer patients	Journal of Neurosurgery	2003	453	26.65
37	Hortobagyi, G. N.	Long-term prevention of skeletal complications of metastatic breast cancer with pamidronate. Protocol 19 Aredia Breast Cancer Study Group	Journal of Clinical Oncology	1998	445	20.23
38	Theriault, R. L.	Pamidronate reduces skeletal morbidity in women with advanced breast cancer and lytic bone lesions: a randomized, placebo-controlled trial	Journal of Clinical Oncology	1999	439	20.90
39	Hartsell, W. F.	Randomized trial of short-versus long-course radiotherapy for palliation of painful bone metastases	Jnci-Journal of the National Cancer Institute	2005	438	29.20
40	Gerszten, P. C.	Radiosurgery for spinal metastases - Clinical experience in 500 cases from a single institution	Spine	2007	438	33.69
41	Paterson, A. H.	Double-blind controlled trial of oral clodronate in patients with bone metastases from breast cancer	Journal of Clinical Oncology	1993	437	16.19
42	Rosen, L. S.	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	Cancer	2004	434	27.13
43	Zhang, X. H.	Latent bone metastasis in breast cancer tied to src-dependent survival signals	Cancer Cell	2009	424	38.55
44	Mundy, G. R.	Mechanisms of bone	Cancer	1997	413	17.96

## metastasis

45	Steenland, E.	The effect of a single fraction compared to multiple fractions on painful bone metastases: a global analysis of the Dutch Bone Metastasis Study	Radiotherapy and Oncology	1999	411	19.57
46	Schlumberger, M.	Long-term results of treatment of 283 patients with lung and bone metastases from differentiated thyroid carcinoma	The Journal of Clinical Endocrinology and Metabolism	1986	406	11.94
47	Brown, J. E.	Bone turnover markers as predictors of skeletal complications in prostate cancer, lung cancer, and other solid tumors	Jnci-Journal of the National Cancer Institute	2005	392	26.13
48	Coleman, R. E.	Predictive value of bone resorption and formation markers in cancer patients with bone metastases receiving the bisphosphonate zoledronic acid	Journal of Clinical Oncology	2005	379	25.27
49	Kang, Y. B.	Breast cancer bone metastasis mediated by the Smad tumor suppressor pathway	Proceedings of the National Academy of Sciences of the United States of America	2005	370	24.67
50	Tokuhashi, Y.	Scoring system for the preoperative evaluation of metastatic spine tumor prognosis	Spine	1990	367	12.23
51	Cook, G. J.	Detection of bone metastases in breast cancer by 18FDG PET: differing metabolic activity in osteoblastic and osteolytic lesions	Journal of Clinical Oncology	1998	361	16.41
52	Fizazi, K.	Randomized phase II trial of denosumab in patients with bone metastases from prostate cancer, breast cancer, or other neoplasms after	Journal of Clinical Oncology	2009	359	32.64

		intravenous bisphosphonates				
53	Berenson, J. R.	Zoledronic acid reduces skeletal-related events in patients with osteolytic metastases. A double-blind, randomized dose-response study	Cancer	2001	353	18.58
54	Goetz, M. P.	Percutaneous image-guided radiofrequency ablation of painful metastases involving bone: a multicenter study	Journal of Clinical Oncology	2004	352	22.00
55	Logothetis, C. J.	Osteoblasts in prostate cancer metastasis to bone	Nature Reviews Cancer	2005	352	23.47
56	Wu, J. S. Y.	Meta-analysis of dose-fractionation radiotherapy trials for the palliation of painful bone metastases	International Journal of Radiation Oncology Biology Physics	2003	350	20.59
57	Nielsen, O. S.	Bone metastases: pathophysiology and management policy	Journal of Clinical Oncology	1991	349	12.03
58	Saad, F.	Pathologic fractures correlate with reduced survival in patients with malignant bone disease	Cancer	2007	346	26.62
59	Sasaki, A.	Bisphosphonate risedronate reduces metastatic human breast cancer burden in bone in nude mice	Cancer research	1995	344	13.76
60	Kohno, N.	Zoledronic acid significantly reduces skeletal complications compared with placebo in Japanese women with bone metastases from breast cancer: A randomized, placebo-controlled trial	Journal of Clinical Oncology	2005	343	22.87
61	Body, J. J.	A study of the biological receptor activator of nuclear factor-kappa B ligand inhibitor, denosumab, in patients with multiple myeloma	Clinical Cancer Research	2006	341	24.36

		or bone metastases from breast cancer				
62	Nilsson, S.	Bone-targeted radium-223 in symptomatic, hormone-refractory prostate cancer: a randomised, multicentre, placebo-controlled phase II study	Lancet Oncology	2007	339	26.08
63	Young, R. F.	Treatment of spinal epidural metastases. Randomized prospective comparison of laminectomy and radiotherapy	Journal of neurosurgery	1980	339	8.48
64	Fisher, C. G.	A novel classification system for spinal instability in neoplastic disease an evidence-based approach and expert consensus from the Spine Oncology Study Group	Spine	2010	337	33.70
65	Schlumberger, M.	Radioactive iodine treatment and external radiotherapy for lung and bone metastases from thyroid carcinoma	Journal of Nuclear Medicine	1996	336	14.00
66	Hamaoka, T.	Bone imaging in metastatic breast cancer	Journal of Clinical Oncology	2004	336	21.00
67	Price, P.	Prospective randomised trial of single and multifraction radiotherapy schedules in the treatment of painful bony metastases	Radiotherapy and Oncology	1986	333	9.79
68	Saad, F.	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	Annals of Oncology	2012	323	40.38
69	Mirels, H.	Metastatic disease in long bones. A proposed scoring system for diagnosing impending pathologic fractures	Clinical Orthopaedics and Related Research	1989	321	10.35
70	Guise, T. A.	Basic mechanisms	Clinical Cancer	2006	318	22.71

		responsible for osteolytic and osteoblastic bone metastases	Research			
71	Yamada, Y.	High-dose, single-fraction image-guided intensity-modulated radiotherapy for metastatic spinal lesions	International Journal of Radiation Oncology Biology Physics	2008	315	26.25
72	Chow, E.	Update on the systematic review of palliative radiotherapy trials for bone metastases	Clinical Oncology	2012	312	39.00
73	Barron, K. D.	Experiences with metastatic neoplasms involving the spinal cord	Neurology	1959	312	5.11
74	Sethi, N.	Tumor-derived jagged1 promotes osteolytic bone metastasis of breast cancer by engaging notch signaling in bone cells	Cancer Cell	2011	310	34.44
75	Body, J. J.	Intravenous ibandronate reduces the incidence of skeletal complications in patients with breast cancer and bone metastases	Annals of Oncology	2003	307	18.06
76	Maranzano, E.	Effectiveness of radiation therapy without surgery in metastatic spinal cord compression: final results from a prospective trial	International Journal of Radiation Oncology, Biology, Physics	1995	307	12.28
77	Takeshita, F.	Efficient delivery of small interfering RNA to bone-metastatic tumors by using atelocollagen in vivo	Proceedings of the National Academy of Sciences of the United States of America	2005	306	20.40
78	Chang, E. L.	Phase I/II study of stereotactic body radiotherapy for spinal metastasis and its pattern of failure	Journal of Neurosurgery-Spine	2007	304	23.38
79	Boucharaba, A.	Platelet-derived lysophosphatidic acid supports the progression of osteolytic bone	Journal of Clinical Investigation	2004	300	18.75

		metastases in breast cancer				
80	Wong, D. A.	Spinal metastases: the obvious, the occult, and the impostors	Spine	1990	299	9.97
81	Hornberg, E.	Expression of androgen receptor splice variants in prostate cancer bone metastases is associated with castration-resistance and short survival	Plos One	2011	296	32.89
82	Lipton, A.	Superiority of denosumab to zoledronic acid for prevention of skeletal-related events: a combined analysis of 3 pivotal, randomised, phase 3 trials	European Journal of Cancer	2012	290	36.25
83	Serafini, A. N.	Palliation of pain associated with metastatic bone cancer using samarium-153 lexidronam: a double-blind placebo-controlled clinical trial	Journal of Clinical Oncology	1998	290	13.18
84	Kingsley, L. A.	Molecular biology of bone metastasis	Molecular Cancer Therapeutics	2007	286	22.00
85	Arguello, F.	A murine model of experimental metastasis to bone and bone marrow	Cancer Research	1988	286	8.94
86	Gu, Z.	Prostate stem cell antigen (PSCA) expression increases with high gleason score, advanced stage and bone metastasis in prostate cancer	Oncogene	2000	281	14.05
87	Constans, J. P.	Spinal metastases with neurological manifestations. Review of 600 cases	Journal of Neurosurgery	1983	280	7.57
88	Daldrup-Link, H. E.	Whole-body MR imaging for detection of bone metastases in children and young adults: comparison with skeletal	American Journal of Roentgenology	2001	275	14.47

		scintigraphy and FDG PET				
89	Nilsson, S.	First clinical experience with alpha-emitting radium-223 in the treatment of skeletal metastases	Clinical Cancer Research	2005	273	18.20
90	Chen, T. L.	Pharmacokinetics and pharmacodynamics of zoledronic acid in cancer patients with bone metastases	Journal of Clinical Pharmacology	2002	273	15.17
91	Body, J. J.	A phase I study of AMGN-0007, a recombinant osteoprotegerin construct, in patients with multiple myeloma or breast carcinoma related bone metastases	Cancer	2003	271	15.94
92	Bendre, M. S.	Interleukin-8 stimulation of osteoclastogenesis and bone resorption is a mechanism for the increased osteolysis of metastatic bone disease	Bone	2003	270	15.88
93	Deckers, M.	The tumor suppressor Smad4 is required for transforming growth factor beta-induced epithelial to mesenchymal transition and bone metastasis of breast cancer cells	Cancer Research	2006	268	19.14
94	Sartor, O.	Effect of radium-223 dichloride on symptomatic skeletal events in patients with castration-resistant prostate cancer and bone metastases: results from a phase 3, double-blind, randomised trial	Lancet Oncology	2014	264	44.00
95	Thalmann, G. N.	LNCaP progression model of human prostate cancer: androgen-independence and osseous metastasis	Prostate	2000	263	13.15
96	Galasko, C. S.	Mechanisms of bone destruction in the development of skeletal metastases	Nature	1976	262	5.95

97	Murray, L. J.	SU11248 inhibits tumor growth and CSF-1R-dependent osteolysis in an experimental breast cancer bone metastasis model	Clinical & Experimental Metastasis	2003	259	15.24
98	Edelstyn, G. A.	The radiological demonstration of osseous metastases. Experimental observations	Clinical Radiology	1967	259	4.89
99	Lelekakis, M.	A novel orthotopic model of breast cancer metastasis to bone	Clinical & Experimental Metastasis	1999	257	12.24
100	Jacobs, S. C.	Spread of prostatic cancer to bone	Urology	1983	250	6.76

Publishing Years	Articles	Total Citations	Mean Citations
1959	1	312	312
1967	1	259	259
1971-1980	3	1238	412.67
1981-1990	11	4293	390.27
1991-2000	24	11143	464.29
2001-2010	50	24935	498.7
2011-2014	10	4573	457.3

<b>TABLE 3. Journals with More Than One of the Top 100 Cited Articles on Bone Metastases</b>				
Journals	Articles	Total Citations	Mean Citations	Impact Factor
Journal of Clinical Oncology	16	7218	451.13	32.956
Cancer	10	4888	488.8	5.742
Cancer research	6	2701	450.17	9.727
Spine	6	2603	433.83	2.646
Clinical Cancer Research	4	2054	513.5	10.107
International Journal of Radiation Oncology Biology Physics	4	1445	361.25	5.859
Journal of Neurosurgery	3	1072	357.33	3.968
Cancer Cell	3	2441	813.67	26.602
Annals of Oncology	2	630	315	18.274
Clinical & Experimental Metastasis	2	516	258	3.037
Journal of the National Cancer Institute	2	830	415	11.577
Journal of Clinical Investigation	2	992	496	11.864
Journal of Nuclear Medicine	2	854	427	7.887
Lancet	2	2212	1106	60.392
Lancet Oncology	2	603	301.5	33.752
Nature	2	762	281	42.778
Nature Reviews Cancer	2	929	464.5	53.03
Proceedings of the National Academy of Sciences of the United States of America	2	676	338	9.412
Radiology	2	1139	569.5	7.931
Radiotherapy and Oncology	2	744	372	4.856

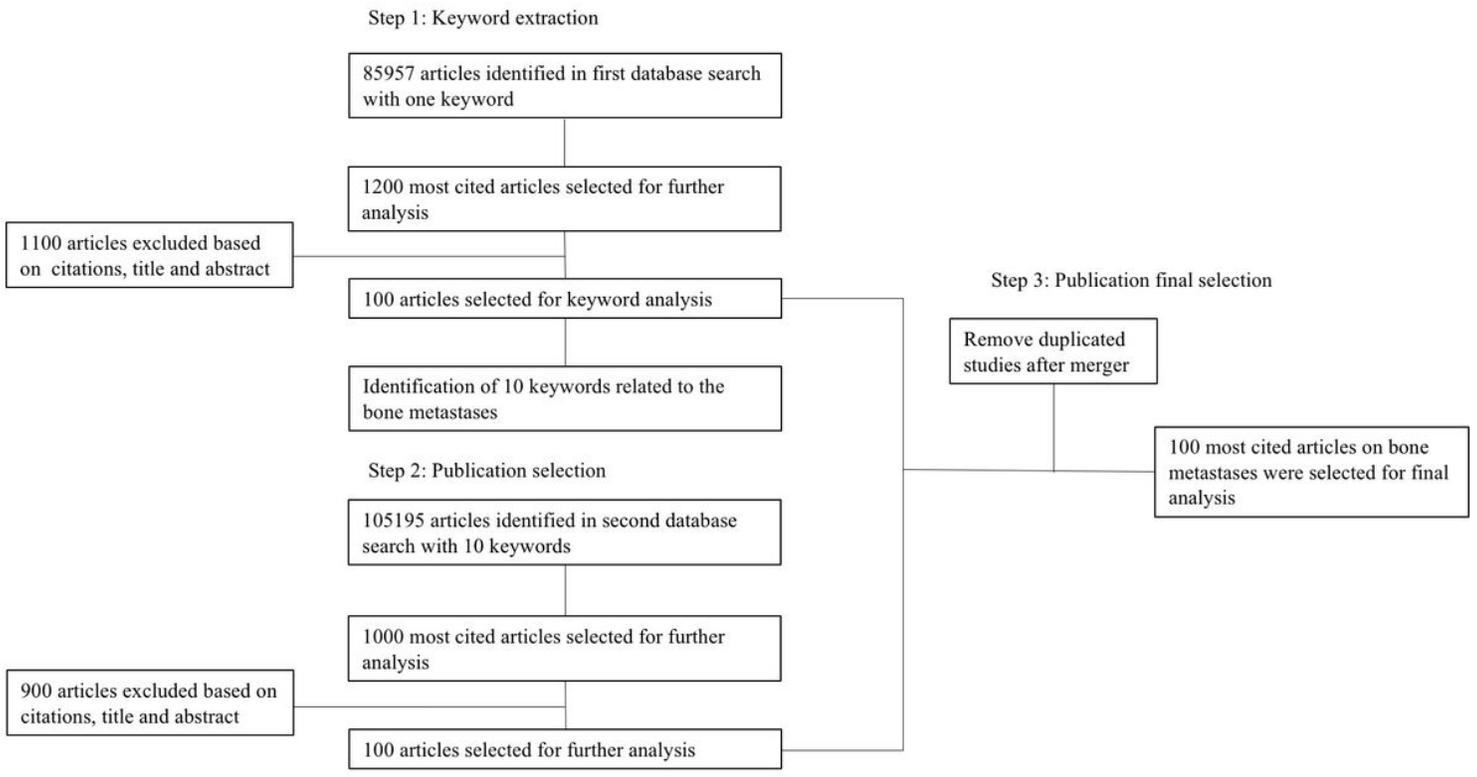
**TABLE 4. Most Frequent Authors of the 100 Most Cited Articles on Bone Metastases**

Authors	Articles	First Author	Last Author	Coauthor	Areas of Interest
Lipton, A.	13	2	0	11	Drug efficacy; Clinical trial; Prediction
Coleman, R. E.	11	5	2	4	Drug efficacy; Clinical trial; Prediction
Brown, J. E.	5	1	0	4	Clinical trial; Prediction
Hortobagyi, G. N.	5	2	0	3	Drug efficacy; Clinical trial; Clinical description
Saad, F.	5	3	0	2	Drug efficacy; Prediction
Seaman, J. J.	5	0	3	2	Clinical trial
Body, J. J.	5	3	0	2	Drug efficacy; Prediction
Rosen, L. S.	5	4	0	1	Clinical trial
Dansey, R.	4	0	1	3	Clinical trial; Clinical description
Fizazi, K.	4	2	0	2	Clinical trial; Clinical description
Gordon, D.	4	0	0	4	Clinical trial
Guise, T. A.	4	1	1	2	Mechanism
Jun, S.	4	0	2	2	Clinical trial
Theriault, R. L.	4	1	0	3	Drug efficacy; Clinical trial

**TABLE 5. Contributing Institutions with More Than Two of the Top 100 Cited Articles on Bone Metastases**

Institutions	Location	Articles	Total Citations
University of Texas M. D. Anderson Cancer Center	USA	8	3635
Weston Park Hospital	United Kingdom	5	4328
Memorial Sloan-Kettering Cancer Center	USA	4	2816
University of Toronto	Canada	4	1745
Cancer Institute Medical Group	USA	3	1502
University of California	USA	3	1238
University of Texas Health Science Center at San Antonio	USA	3	1449
Centre Hospitalier de l'Université de Montréal	Canada	2	1130
Institut Jules Bordet	Belgium	2	612
Joan Karnell Cancer Center	USA	2	735
Nihon University	Japan	2	887
University of Berne	Switzerland	2	821
University of Virginia	USA	2	604

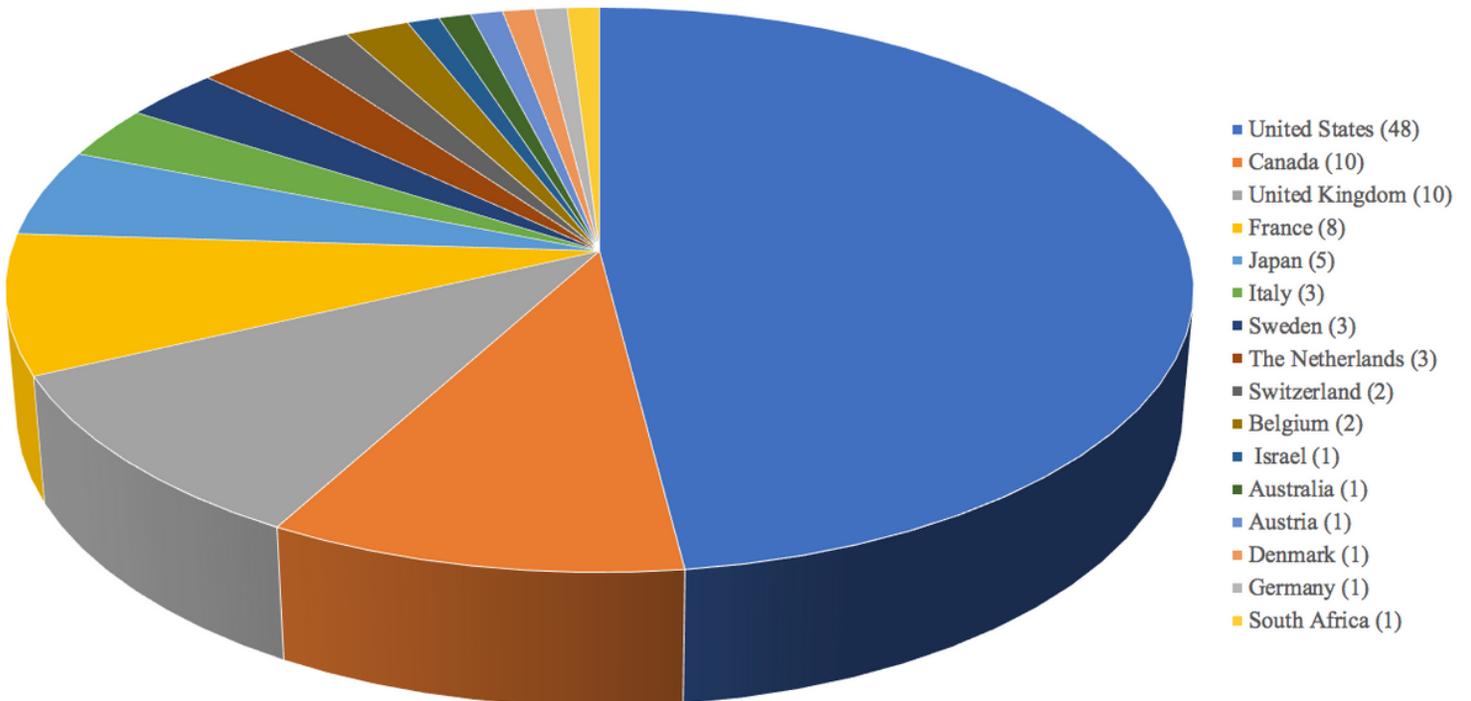
## Figures



**Figure 1**

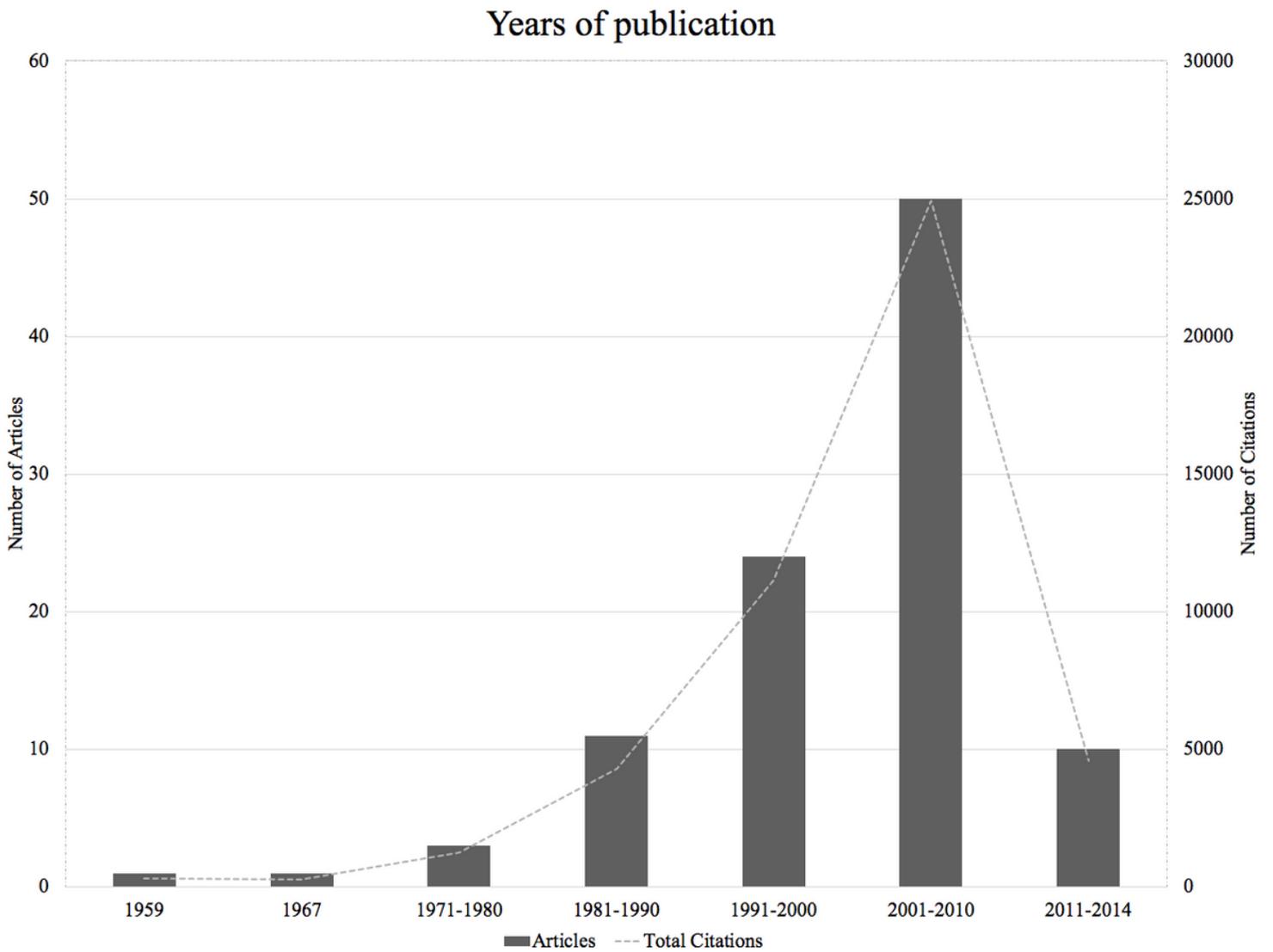
Three-step approach.

Number of Articles



**Figure 2**

Countries of the top 100 cited articles on bone metastases.



**Figure 3**

Publishing years of the top 100 cited articles on bone metastases.

Number of Articles

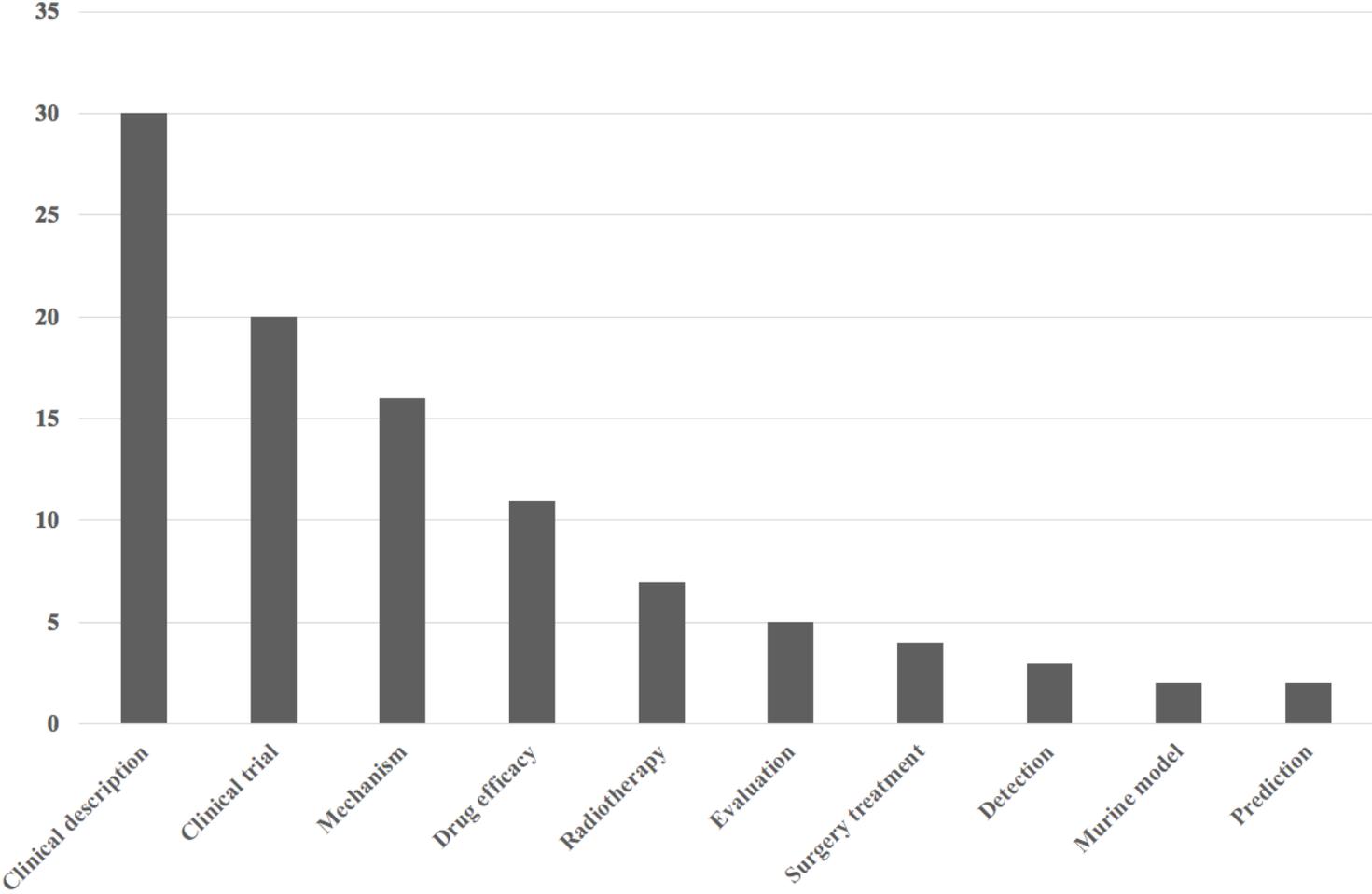


Figure 4

Subspecialty of the top 100 cited articles on bone metastases.



## Figure 6

Distribution of keywords according to when they appeared for the average time.