Ewing sarcoma: what trends in recent works? A holistic analysis with global productivity
A cross-sectional study
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Abstract
Advances in the biology of Ewing sarcoma, which continues to be an important cause of mortality, have caused an increase in information in the literature related to the underlying molecular base of the disease and discussions of new treatment approaches. In this study, we aimed to comprehensively analyze the published scientific articles on Ewing sarcoma. The Web of Science database was used to obtain and statistically analysis articles on Ewing sarcoma that were published between 1980 and 2021. Maps of network visualization were used to reveal trending topics, global collaborations, and the most effective studies. Correlation analysis was performed using Spearman's correlation coefficient. A total of 3236 articles were analyzed. The first 3 countries that contributed the most to the literature and cooperated most intensively were USA (1194, 36.8%), Germany (293, 9%), Italy (254, 7.8%). Pediatric Blood & Cancer (n = 122), Cancer (87), Journal of Pediatric Hematology Oncology (71) were among the top 3 journals with the most articles. The most active author was Piero Picci (n = 94). High-income countries have a great effect on the literature on this subject. The most studied trend topics in recent years were pediatric oncology, EWS RNA Binding Protein 1 (EWSR1), EWSR1-FL1, epigenetics, bioinformatics, microRNA, gene expression, metastasis, migration, biomarker, immunotherapy, survival, outcomes, surveillance epidemiology and end results (SEER), nomogram, temozolomide, irinotecan, and drug resistance. Genetic studies, metastasis, immunotherapy, life analyses/nomogram based on new data obtained from SEER, and chemotherapy with irinotecan and temozolomide combination, were seen to be the topics researched in recent years.

Abbreviations: ES = Ewing sarcoma, EWSR1 = EWS RNA Binding Protein 1, GDP = gross domestic product, GDP per capita = gross domestic product per capita, HDI = human development index, NC = number of co-citation, SCI-Expanded = Science Citation Index Expanded, SEER = surveillance epidemiology and end results.

Keywords: bibliometric analysis, Ewing Sarcoma, Ewing’s Sarcoma, trends

1. Introduction

Ewing sarcoma (ES), which was first described in 1921 by James Ewing, is a small, round, blue cell mesenchymal malignancy, which is seen most often in children and young adults.[1,2] The Ewing sarcoma family of tumors includes peripheral primitive, neuroectodermal Ewing sarcoma (ES) tumor, and extraosseous ES.[3] ES is pathologically associated with small round cells and t (11;22) (q24;q12) translocation, with FLI1 of the EWS gene or hybrid transcripts of the ERG gene.[4–7] Most cases of ES include chromosomal translocations resulting in t (11;22) (q24;q12) between chromosome 11 and 22. This exchange encodes EWS/FLI fusion protein. The EWS/FLI formation seems to be a critical oncogenic event in the development of ES.[1,2]

Prognostic factors at the time of diagnosis are metastasis, primary localization, and age. Early diagnosis before metastasis is of critical importance for the better survival of ES patients.[8] The most common regions of metastasis are the lungs and pleural cavity, the skeletal system, and bone marrow, or a combination of these.[7] The most important prognostic factor in ES is metastasis, and while the 5-year survival rate is approximately 70% when there is no metastasis, this rate falls to around 30% when metastasis is present. Despite recorded advances in multi-modal strategies including optimal combination chemotherapy, and the 5-year survival rate of 70% in non-metastatic ES patients, the 5-year survival rate remains <30% for patients with recurrence and/or metastasis.[6,9]

As a treatment strategy for ES, 4 types of standard treatment are used; surgery, radiation therapy, chemotherapy, and high-dose chemotherapy with stem cell salvage. New treatment types have been tested in clinical studies, such as target-directed treatment (monoclonal antibody therapy, kinase inhibitor therapy, NEDD8-activating enzyme inhibitor therapy)
and immunotherapy. For successful treatment, extremely intense chemotherapy is required together with surgery and/or radiation. In the first study between groups of non-metastatic ES, as better results were obtained with the inclusion of doxorubicin, almost all chemotherapy protocols are based on 4 drugs: doxorubicin, cyclophosphamide, vincristine, and dacarbazine.

At the start of the 1980s, following the standard treatment for ES, ifosfamide treatment with or without etoposide, produced noteworthy responses in patients with recurrence. The addition of ifosfamide and etoposide to a standard regimen does not affect the result in patients with metastatic disease, but significantly improves the result in patient with non-metastatic ES, primitive neuroectodermal bone tumor, or primitive bone tumor. The development of cytotoxic chemotherapy since the 1970s has provided improvements in the prognoses of patients with ES in particular. However, despite the establishment of several new targeted drugs and immunotherapies since the 2000s, the desired increase in the prognosis of patients with bone sarcoma has not been seen.

There are various histological types of bone sarcoma and genomic mutations show significant differences according to the histological types. This has created a limitation in the development of new molecular-targeted drugs. Another limitation is in the evaluation of treatment efficacy because of the high rates of pediatric and young adult patients and the difficulty in conducting large-scale randomized clinical trials.

Bone sarcomas constitute only approximately 0.2% of all solid malignancies; ES followed by osteosarcoma are the most frequently seen primary malignant bone cancers. In a study of the incidence using the surveillance, epidemiology, and end results (SEER) database, Esiashvili et al (2008) reported the general age-adjusted ES incidence (per 1 million) for patients aged 1 to 19 years for the years 1973 to 1982, 1983 to 1992, and 1993 to 2004 to be 2.92, 3.07, and 2.72, respectively, and the 5-year survival rates to be 36.4%, 52.7%, and 60.2%, respectively.

Advances in the biology of ES, which continues to severely affect the quality of life of patients, and to be a significant cause of mortality, have caused an increase in information in the literature related to the underlying molecular base of the disease and discussions of new treatment approaches. However, despite the rise in the number of publications worldwide about ES, there has been no bibliometric research on this subject. Bibliometric is the analysis of scientific publications using statistical methods. Using the statistical analysis results of many articles in literature, bibliometric studies provide a holistic summary of the subject to researchers interested in the subject by presenting the most active institutions, authors, and journals, international collaborations, and trend topics studied in recent years. In this study, we used statistical and bibliometric techniques to conduct a comprehensive analysis of the scientific papers on Ewing sarcoma that were published between 1980 and 2021.

2. Material and methods

2.1. Search strategy

Web of Science Core Collection (WoS by Clarivate Analytics: https://www.webofknowledge.com) database was used for literature search. Keywords (search in article title) to access all published articles about Ewing Sarcoma were Ewing sarcoma, Ewing's sarcoma, Ewing sarcoma, Ewing-like sarcoma, Ewing sarcomas, Ewing's sarcoma. The years evaluated are 1980 to 2021 (Due to different access dates, search results may differ slightly, accessed April 20, 2022). The search was carried out in all research areas, VOSviewer (Version 1.6.18, Leiden University’s Center for Science and Technology Studies) software was used for trend analysis, cluster analysis, bibliometric network visualizations and citation analysis.

This article was not ethical approval is not necessary because it is a bibliometric analysis of published articles. Because the current study which did not involve any clinical trials and patient consent.

2.2. Statistical analysis

The Statistical Package for the Social Sciences (Version 22.0, SPSS Inc., Chicago, IL, License: Hitit University) software was used to conduct statistical analyses. A world map displaying the global article productivity of nations on Ewing sarcoma was generated using the website (https://app.datawraper.de). The Exponential Smoothing estimator, which incorporates seasonal smoothing, was used in Microsoft Office Excel to calculate the potential number of articles that could be published over the next 5 years based on past article trends. Before the correlation analysis, the data were tested for normal distribution using the Kolmogorov–Smirnov test. Since the data were not normally distributed, the effect of some economic development indicators (gross domestic product [GDP], gross domestic product per capita [GDP per capita], human development index [HDI]) on the productivity of the article on Ewing sarcoma was examined using the Spearman correlation coefficient (data sourced from the World Bank).

P value < .05 was accepted for a statistically significant correlation.

3. Results

As a result of the literature scan of all the research areas published on the subject of ES between 1980 and 2021 in the WoS database, a total of 5883 publications were identified. Of these publications, 55% (n = 3236) were Articles, 30.7% (n = 1805) Meeting Abstracts, 5.3% (n = 311) Review Articles, 3.4% (n = 199) Letters, 1.5% (n = 89) were Proceedings Papers and the rest were in other publication types (Editorial Materials, Notes, Books, Book Chapters, Early Access, News Items, Corrections, Additions, Discussions, Retracted Publications). The bibliometric analyses of these were limited to 3236 articles published under the category of “Article,” with all other publication types being disregarded. Of these articles, 90% (n = 2906) were scanned in Science Citation Index Expanded (SCI-Expanded) and 9% (n = 290) in the Emerging Sources Citation Index, and the remaining small number in the Book Citation Index—Science, Index Chemicus and Social Sciences Citation Index. The language of publication of the articles was English in 95.4% (n: 3086) and other languages (French [n = 60], German [51], Spanish [19], Russian [11], Japanese [2], Turkish [2], Chinese [1], Croatian [1], Italian [1], Polish [1], Portuguese [1]) in the others. In the 3236 articles, the h-index was 115, the average number of citations per article was 24.71, and there were 79,965 total citations (without self-citations: 54,798).

3.1. Research areas with the most published articles on Ewing sarcoma

The 16 most active research areas with 50 or more articles published on Ewing sarcoma were Oncology (n = 1531, 47.3%), Pediatrics (403, 12.4%), Surgery (347, 10.7%), Pathology (332, 10.2%), Radiology Nuclear Medicine Medical Imaging (246, 7.6%), Hematology (245, 7.5%), Cell Biology (244, 7.5%), Orthopedics (212, 6.5%), Medicine General Internal (184, 5.6%), Biochemistry Molecular Biology (165, 5%), Genetics Heredity (144, 4.4%), Clinical Neurology (118, 3.6%), Medicine Research Experimental (103, 3.1%), Multidisciplinary Sciences (81, 2.5%), Otorhinolaryngology (54, 1.6%), and Pharmacology Pharmacy (31, 1.5%), respectively.
3.2. The development of articles according to years

Figure 1 shows a bar graph showing the number of articles published each year. The statistically estimated results and the Exponential Smoothing estimation model used to estimate the number of articles to be published in the next 5 years are shown in Figure 1. According to the exponential model determined as the most successful estimation model when seasonal correction was taken into consideration, it was estimated that 196 (95% confidence interval: 171–221) articles on the subject of ES would be published in 2022, and 240 (95% CI: 194–286) in 2026 (Fig. 1).

3.3. Active countries

The distribution of the number of articles according to country is shown on a world map, and the top 15 countries contributing most to literature are presented as a bar graph in Figure 2. The top 15 countries with the most articles were USA (1194, 36.8%), Germany (293, 9%), Italy (254, 7.8%), France (215, 6.6%), Japan (215, 6.6%), China (192, 5.9%), India (192, 5.6%), Spain (181, 5.5%), United Kingdom (173, 5.3%), Austria (108, 3.3%), Canada (107, 3.3%), Netherlands (106, 3.2%), Turkey (106, 3.2%), Switzerland (83, 2.5%), and South Korea (53, 1.6%), respectively (Fig. 2). International collaboration analysis and cluster analysis was applied to the 54 countries found to have international collaboration among writers and the 80 countries that produced at least 2 articles on the subject of ES. The top 10 countries with the highest ratings in terms of global cooperation [total link strength], which represents the capacity for cooperation among 54 countries: USA [454], Germany [338], Italy [228], France [213], Spain [210], Austria [191], England in United Kingdom [181], Netherlands [181], Switzerland [141], Canada [113]. The density map according to the strength of collaboration is shown in Figure 3a and the cluster analysis results are shown in Figure 3b. According to the cluster analysis results, 12 different clusters were formed related to international collaboration (Cluster 1: Argentina, Brazil, Finland, Nepal, Norway, Philippines, Portugal, South Korea, Sweden, Uruguay, Cluster 2: Egypt, India, Indonesia, Israel, Japan, Pakistan, Saudi Arabia. Cluster 3: Austria, Czech Republic, Denmark, Netherlands, Scotland, Switzerland. Cluster 4: Bulgaria, Chile, Colombia, Cuba, Germany, Italy. Cluster 5: Lebanon, New Zealand, Qatar, USA. Cluster 6: Australia, Hungary, Jordan. Cluster 7: England, Serbia, Slovakia. Cluster 8: France, Luxembourg, Thailand. Cluster 9: Canada, China, Singapore. Cluster 10: Mexico, Poland, Russia. Cluster 11: North Ireland, Spain, Turkey. Cluster 12: Belgium, Greece, Ireland).

3.4. Correlation analysis

It was found that there was a strong positive correlation between a nation’s GDP, GDP per capita, and HDI scores and the number of articles it produced about ES ($R = 0.743, P < .001$; $R = 0.724, P < .001$, $R = 0.700, P < .001$, respectively).

3.5. Authors who have published the most articles on Ewing sarcoma

The top 10 most active authors on Ewing sarcoma were Picci P. (n = 94), Dirksen U. (73), Jurgens H. (75), Scotlandi K. (63), Ferrari S. (49), Lessnick SL. (49), Bacci G. (48), Kovar H. (45), Delattre O. (43), and Manara MC. (38), respectively.

3.6. Active institutions that have published the most articles on Ewing sarcoma

League of European Research Universities (n = 197), University of Texas System (170), Unicancer (federation of French comprehensive cancer centers, n = 139), University of Munster (139), National Institutes of Health USA (132), UTMD Anderson Cancer Center (127), Harvard University (124), NIH National Cancer Institute (122), University Of California System (110), Ulice French Research Universities (103), Rizzoli Orthopedic Institute (98), Mayo Clinic (84), Institut Curie (83), and PSL Research University Paris (University Paris Sciences & Lettres, n = 81) were the top 15 institutions that produced the most articles on Ewing sarcoma.

3.7. Active journals on Ewing sarcoma

The 3236 papers on ES that have been published have appeared in 914 different journals. In Table 1, the top 60 journals with at
least 10 articles published are listed along with the total number of citations they have received and the average number of citations per article.

### 3.8. Citation analysis on Ewing sarcoma

The 25 articles that received the most citations according to the total number of citations within the 3236 articles published on the subject of ES are shown in Table 2. The last column of Table 2 displays the articles’ annual average number of citations.

### 3.9. Co-citation analysis on Ewing sarcoma

In the list of references of all the 3236 articles, there were found to be citations in a total of 41,985 studies. The first 6 most influential studies with the most co-citations (>200 citations) among these studies were the studies of Delattre et al (1992) (number of co-citation [NC] = 393), Grier et al (2003) (NC = 354), Cotterill et al (2000) (NC = 341), Delattre et al (1994) (NC = 266), Nesbit et al (1990) (NC = 218), Ewing (1921) (NC = 203), respectively.[4,8,11,13,20,21]

### 3.10. Trend topics on Ewing sarcoma

In the 3236 articles published on the subject of ES, 4134 different key words were used. Table 3 displays the frequency of 97 different key words appearing in at least 8 different articles. Figure 4 displays the network visualization map displaying the outcomes of the cluster analysis performed on these key words. As a result of the cluster analysis, 11 different clusters were formed on ES topics. Figure 5a displays the trend network visualization map developed to identify trend topics, and Figure 5b displays the citation network visualization map created to identify the topics with the highest citations.
there was seen to be some regional international collaboration. When the authorship collaboration was examined, although Austria, England, the Netherlands, Switzerland, and Canada, be developed countries; the USA, Germany, Italy, France, Spain, South Korea). The other 3 countries (China, India, Turkey) were developing countries with large economies at GDP level. According to the results of the model formed with exponential smoothing estimation taking seasonal correction into consideration, the number of studies to be published in the next 5 years showed an exponentially increasing trend in the number of articles on the subject of ES that are expected to be published. When the article distribution of countries was looked at, 12 of the 15 countries that contributed the most to literature were developed countries (USA, Germany, Italy, France, Japan, Spain, United Kingdom, Austria, Canada, Netherlands, Switzerland, South Korea). The other 3 countries (China, India, Turkey) were developing countries with large economies at GDP level. According to the results of the analysis of correlation, there is a high positive correlation between the production of articles on the topic of ES and the GDP, GDP per capita, and HDI values. The results of the correlation analysis showed a high level of significant correlation between production of articles on the subject of ES and GDP, GDP per capita, and HDI values. Thus it can be said that the level of development of a country and the size of the economy are factors with an effect on article productivity. In the evaluation of the international collaboration analysis results, the leading countries were determined to be developed countries; the USA, Germany, Italy, France, Spain, Austria, England, the Netherlands, Switzerland, and Canada. When the authorship collaboration was examined, although there was seen to be some regional international collaboration based on geographical proximity, global collaboration was observed to be more common in the production of articles. Pediatr Blood Cancer, Cancer, Journal of Pediatric Hematology Oncology, Cancer Research, Journal of Clinical Oncology, Oncogene, Plos One, Clinical Cancer Research and Oncotarget were found to be the journals that published the most articles on Ewing sarcoma, respectively. It can be recommended that authors in the process of research or wishing to publish on the subject of ES should first give consideration to the journals presented in Table 1. According to the average amount of citations per article obtained in the citation analyses of the journals, the New England Journal of Medicine (Average citation per article = 404), Nature Genetics (269), Plos Genetics (229), Nature Reviews Disease Primers (223), Nature Medicine (195), Cancer Discovery (177), Molecular and Cellular Biology (164), Small (158), Human Molecular Genetics (156), Journal of Clinical Oncology (133), Proceedings of the National Academy of Sciences of the United States of America (119), Lancet Oncology (113), Pediatric Clinics of North America (110), Molecular Cell (109), Journal of Clinical Investigation (108), and American Journal of Surgical Pathology (103) were the journals with the greatest influence on Ewing sarcoma. Researchers who wish to see a greater impact of their work which is to be published should consider these journals first. When the articles under analysis were compared based on the overall number of citations received, the study with the most citations was determined to be the article entitled “Addition of ifosfamide and etoposide to standard chemotherapy for Ewing's sarcoma and primitive neuroectodermal tumor of bone” by Grier et al (2003), published in the New England Journal of Medicine. This was followed by the article entitled “Prognostic factors in Ewing's tumor of bone: Analysis of 975 patients from the European Intergroup Cooperative Ewing's Sarcoma Study group” by Cotterill et al (2000), published in

### Table 1

The 60 most active journals that have published 10 or more articles on Ewing Sarcoma.

| Journals                                    | RC   | C    | AC   |
|---------------------------------------------|------|------|------|
| Pediatric Blood & Cancer                    | 122  | 2360 | 19.3 |
| Cancer                                      | 87   | 6042 | 69.4 |
| Journal of Pediatric Hematology Oncology    | 71   | 1131 | 15.9 |
| Cancer Research                             | 61   | 4776 | 78.3 |
| Journal of Clinical Oncology                | 59   | 7828 | 132.7|
| Oncogene                                    | 53   | 3040 | 57.4 |
| Plos One                                    | 50   | 1548 | 31.0 |
| Clinical Cancer Research                    | 49   | 2158 | 44.0 |
| Oncotarget                                  | 43   | 976  | 22.7 |
| International Journal of Radiation Oncology| 37   | 1517 | 41.0 |
| Medical and Pediatric Oncology              | 36   | 817  | 22.7 |
| International Journal of Cancer             | 36   | 1122 | 31.2 |
| Clinical Orthopaedics and Related Research  | 33   | 799  | 24.2 |
| Skeletal Radiology                          | 33   | 486  | 14.7 |
| European Journal of Cancer                  | 32   | 1184 | 37.0 |
| Cancer Genetics and Cytogenetics            | 29   | 1644 | 56.7 |
| Klinische Padiatrie                         | 24   | 288  | 12.0 |
| British Journal of Cancer                   | 23   | 707  | 30.7 |
| Human Pathology                             | 23   | 903  | 39.3 |
| Journal of Cancer Research and Clinical Oncology | 23   | 532  | 23.1 |
| Ewing Sarcoma: Methods and Protocols        | 22   | 15   | 0.7  |
| Journal of Surgical Oncology                | 22   | 289  | 13.1 |
| Oncology Reports                            | 22   | 292  | 13.3 |
| Bone Marrow Transplantation                 | 20   | 309  | 15.5 |
| Cancers                                     | 20   | 46   | 2.3  |
| American Journal of Surgical Pathology      | 19   | 1965 | 103.4|
| BMC Cancer                                  | 19   | 362  | 19.1 |
| Oncology Letters                            | 19   | 81   | 4.3  |
| Pathology Research and Practice             | 18   | 228  | 12.7 |
| Journal of Pathology                        | 16   | 650  | 40.6 |

| Journals                                    | RC  | C    | AC   |
|---------------------------------------------|-----|------|------|
| Molecular Cancer Therapeutics               | 16  | 340  | 21.3 |
| Pediatric Hematology and Oncology          | 16  | 127  | 7.9  |
| Frontiers in Oncology                       | 15  | 142  | 9.5  |
| Journal of Bone and Joint Surgery-American Volume | 15  | 637  | 42.5 |
| Annals of Oncology                          | 14  | 418  | 29.9 |
| Molecular Cancer Research                   | 14  | 410  | 29.3 |
| American Journal of Pathology              | 13  | 1170 | 92.0 |
| Japanese Journal of Clinical Oncology       | 13  | 173  | 13.3 |
| Journal of Clinical and Diagnostic Research | 13  | 23   | 1.8  |
| Tumor                                       | 13  | 129  | 9.9  |
| Cureus                                      | 12  | 13   | 1.1  |
| Journal of Pediatric Surgery                | 12  | 177  | 14.8 |
| Modern Pathology                           | 12  | 722  | 60.2 |
| Virology Archive                           | 12  | 374  | 31.2 |
| International Journal of Oncology          | 12  | 159  | 13.3 |
| Acta Oncologica                             | 11  | 264  | 24.0 |
| Biochemical and Biophysical Research \    Communications | 11  | 347  | 31.5 |
| Medicine                                    | 11  | 13   | 1.2  |
| International Journal of Surgery Case Reports | 11  | 12   | 1.1  |
| International Journal of Surgical Pathology | 11  | 90   | 8.2  |
| Acta Orthopaedica Scandinavica             | 10  | 70   | 7.0  |
| American Journal of Clinical Oncology-Clinical Trials | 10  | 130  | 13.0 |
| American Journal of Roentgenology          | 10  | 407  | 40.7 |
| Anticancer Research                         | 10  | 109  | 10.9 |
| Diagnostic Molecular Pathology             | 10  | 398  | 39.8 |
| Genes Chromosomes & Cancer                 | 10  | 651  | 65.1 |
| Journal of Laryngology and Otology         | 10  | 120  | 12.0 |
| Scientific Reports                         | 10  | 75   | 7.5  |
| Spine                                      | 10  | 429  | 42.9 |
| Indian Journal of Medical and Paediatric Oncology | 10  | 7    | 0.7  |
the Journal of Oncology.[14] Then the article entitled “A second Ewing’s-sarcoma translocation, t(21;22), fuses the EWS gene to another ETS-family transcription factor, ERG” by Sorensen et al (1994) published in Nature Genetics.[15] The fourth and fifth most effective articles were by Ambrose et al (1991) and Hu-Lieskovská et al (2005), respectively.[22,23]

When the articles were assessed based on the average annual number of citations, the most effective study was determined to be by Grünewald et al (2018),[24] followed by the above-mentioned study by Grier et al (2003). The third most effective study was the article entitled “Randomized controlled trial of interval-compressed chemotherapy for the treatment of localized Ewing sarcoma: a report from the Children’s Oncology Group” by Womer et al (2012), published in the Journal of Clinical Oncology.[25]

According to the numbers of co-citations of all the articles, the most effective articles were determined to be those by Delattre et al (1992), Grier et al (2003), Cotterill et al (2000), Delattre et al (2011),[26,27] respectively.

![Table 2](image-url)

The top 25 most cited articles on Ewing Sarcoma.

| No | Article                                                                 | Author                  | Journal                      | PY | TC | AC  |
|----|------------------------------------------------------------------------|-------------------------|------------------------------|----|----|-----|
| 1  | Addition of ifosfamide and etoposide to standard chemotherapy for Ewing’s sarcoma and primitive neuroectodermal tumor of bone | Grier HE, et al         | New England Journal Medicine | 2003 | 804 | 40.2 |
| 2  | Prognostic factors in Ewing’s tumor of bone: Analysis of 975 patients from the European Intergroup Cooperative Ewing’s Sarcoma Study group | Cotterill SJ, et al     | Journal of Clinical Oncology | 2000 | 649 | 28.22 |
| 3  | A second Ewing’s-sarcoma translocation, t(21;22), fuses the EWS gene to another ETS-family transcription factor, ERG | Sorensen PHB, et al     | Nature Genetics              | 1994 | 605 | 20.86 |
| 4  | MIC2 is a specific marker for Ewings-sarcoma and peripheral primitive neuroectodermal tumors - evidence for a common histogenesis of Ewings-sarcoma and peripheral primitive neuroectodermal tumors from MIC2 expression and specific chromosome aberration | Ambros IM, et al        | Cancer                      | 1991 | 526 | 16.44 |
| 5  | Sequence-specific knockdown of EWS-FLI1 by targeted, nonviral delivery of small interfering RNA inhibits tumor growth in a murine model of metastatic Ewing’s sarcoma | Hu-Liesková S, et al    | Cancer Research              | 2005 | 458 | 25.44 |
| 6  | Ewing sarcoma 11;22 translocation produces a chimeric transcription factor that requires the DNA-binding domain encoded by FLI1 for transformation | May WA, et al           | Proceedings of the National Academy of Sciences of the United States of America | 1993 | 454 | 15.13 |
| 7  | The ewings-sarcoma EWS/FLI-1 fusion gene encodes a more potent transcriptional activator and is a more powerful transforming gene than FLI-1 | May WA, et al           | Molecular and Cellular Biology | 1993 | 426 | 14.2 |
| 8  | A variant Ewing’s-sarcoma translocation (7→22) fuses the EWS gene to the ETS gene ETV1 | Jeon IS, et al          | Oncogene                    | 1995 | 421 | 15.04 |
| 9  | Chromosomes in ewings-sarcoma:1. An evaluation of 85 cases and remarkable consistency of t(11→22) (q24→q12) | Turcarel C, et al       | Cancer Genetics and Cyto genetics | 1988 | 404 | 11.54 |
| 10 | Multimodal therapy for the management of primary, nonmetastatic Ewings-sarcoma of bone - a long-term follow-up of the 1st intergroup study | Nesbit ME, et al        | Journal of Clinical Oncology | 1990 | 401 | 12.15 |
| 11 | Randomized controlled trial of interval-compressed chemotherapy for the treatment of localized Ewing sarcoma: a report from the Children’s Oncology Group | Womer Richard B, et al | Journal of Clinical Oncology | 2012 | 362 | 32.91 |
| 12 | Multidisciplinary treatment of primary Ewing’s-sarcoma of bone - a 6-year experience of a European cooperative trial | Jungens H, et al        | Cancer                      | 1988 | 356 | 10.17 |
| 13 | Primitive neuroectodermal tumor and Ewing’s sarcoma | Dehner LP               | American Journal of Surgical Pathology | 1993 | 348 | 11.6 |
| 14 | EWS-FL11 fusion transcript structure is an independent determinant of prognosis in Ewing’s sarcoma | De Alava E, et al       | Journal of Clinical Oncology | 1998 | 333 | 13.32 |
| 15 | Changes in incidence and survival of Ewing sarcoma patients over the past 3 decades - Surveillance Epidemiology and End Results data | Esiashvili N, et al     | Journal of Pediatric Hematology Oncology | 2008 | 326 | 21.73 |
| 16 | DNA-binding and transcriptional activation properties of the EWS-FLI-1 fusion protein resulting from the t(11;22) translocation in Ewing sarcoma | Bailly RA, et al        | Molecular and Cellular Biology | 1994 | 309 | 10.66 |
| 17 | Osteosarcoma, chondrosarcoma, and Ewing’s sarcoma | Damron Timothy A, et al | Clinical Orthopaedics and Related Research | 2007 | 305 | 19.06 |
| 18 | Primary disseminated multifocal Ewing sarcoma: results of the Euro-EWING 99 trial | Ladenstein R, et al     | Journal of Clinical Oncology | 2010 | 288 | 22.15 |
| 19 | A small molecule blocking oncogenic protein EWS-FLI1 interaction with RNA helicase A inhibits growth of Ewing’s sarcoma | Erkizan Hayriye V, et al | Nature Medicine | 2009 | 283 | 20.21 |
| 20 | Localized Ewing tumor of bone: final results of the cooperative Ewing’s sarcoma study CESS 86 | Paulussen M, et al      | Journal of Clinical Oncology | 2001 | 274 | 12.45 |
| 21 | Immunohistochemical analysis of Ewing’s-sarcoma cell-surface antigen P33/32MIC2 | Felling er, EJ, et al   | American Journal of Pathology | 1991 | 272 | 8.5 |
| 22 | Genomic landscape of Ewing sarcoma defines an aggressive subtype with co-association of STAG2 and TP53 mutations | Tirode F, et al          | Cancer Discovery             | 2014 | 271 | 30.11 |
| 23 | Fusion between CIC and DUX4 up-regulates PEA3 family genes in Ewing-like sarcomas with t(4;19) (q35;q13) translocation | Kawamura-Saito M, et al | Human Molecular Genetics | 2006 | 269 | 15.82 |
| 24 | Ewings-sarcoma - ten-year experience with adjuvant chemotherapy | Rosen G, et al          | Cancer                      | 1981 | 266 | 6.33 |
| 25 | Multimodal therapy for the management of nonpelvic, localized Ewing’s-sarcoma of bone - intergroup study ESS-II | Burget EO, et al        | Journal of Clinical Oncology | 1990 | 265 | 8.03 |

AC = Average citations per year, PY = Publication year, TC = Total citation.
Table 3
The 97 most frequently used keywords in articles on Ewing Sarcoma.

| Keywords                                      | Number of uses | Keywords                                      | Number of uses | Keywords                                      | Number of uses |
|-----------------------------------------------|----------------|-----------------------------------------------|----------------|-----------------------------------------------|----------------|
| Ewing sarcoma (or Ewing’s sarcoma)            | 1578           | Rhabdomyosarcoma                              | 21             | Skull                                         | 11             |
| Chemotherapy                                  | 151            | Translocation                                 | 21             | Ewing-like sarcoma                            | 10             |
| Peripheral (primitive) neuroectodermal tumor(s) | 114            | Pelvis                                        | 19             | Head and neck                                 | 10             |
| Radiotherapy (or radiation therapy)           | 114            | Bone                                          | 18             | Nomogram                                      | 10             |
| Sarcoma                                       | 82             | Kidney                                        | 18             | Pregnancy                                     | 10             |
| Surgery                                       | 82             | Pathology                                     | 17             | Temozolomide                                  | 10             |
| Immunohistochemistry                          | 81             | Fluorescence in situ hybridization            | 16             | Tumor                                         | 10             |
| Metastasis (or metastases)                   | 67             | Neuroblastoma                                 | 16             | Vincristine                                   | 10             |
| Extraosseous Ewing (or Ewing’s) sarcoma      | 66             | Oncology                                       | 16             | Angiogenesis                                  | 9              |
| Child (or children, childhood)                | 63             | p53                                           | 16             | Bone sarcoma                                  | 9              |
| Osteosarcoma                                  | 60             | SEER                                           | 16             | Case report                                   | 9              |
| Prognosis                                     | 60             | Cancer                                         | 15             | Epigenetics                                   | 9              |
| Apoptosis                                     | 54             | Fish                                           | 15             | Gene expression                               | 9              |
| Ewing sarcoma family of tumors (or ESFT)      | 51             | Immunotherapy                                  | 15             | Inotrope                                      | 9              |
| Survival (or survival analysis)               | 51             | Relapse                                        | 14             | Metastatic disease                            | 9              |
| Magnetic resonance imaging (or MRI)          | 48             | Cytogenetics                                   | 13             | Pediatric cancer                              | 9              |
| Prognostic factor (s)                         | 45             | Doxorubicin                                    | 13             | Risk factors                                  | 9              |
| Extraosseous Ewing (or Ewing’s) sarcoma      | 43             | Bone neoplasms                                 | 12             | Spinal cord compression                       | 9              |
| EWS-FLI1                                      | 41             | Childhood cancer                               | 12             | Staging                                       | 9              |
| PNET                                          | 41             | Chromosomal translocation                      | 12             | Synovial sarcoma                              | 9              |
| Bone tumor (s)                                | 38             | EWS                                           | 12             | Therapy                                       | 9              |
| Outcome (s)                                   | 38             | EWSR1-FLI1                                     | 12             | Trail                                         | 9              |
| Pediatric (s)                                 | 36             | High-dose chemotherapy                         | 12             | Bioinformatics                                | 8              |
| CD99                                          | 35             | Microma                                       | 12             | Drug resistance                               | 8              |
| Adult (s)                                     | 32             | Migration                                      | 12             | Etoposide                                     | 8              |
| Treatment                                     | 32             | Neoadjuvant chemotherapy                       | 12             | Flow cytometry                                | 8              |
| Computed tomography (or CT)                  | 28             | Neoplasms                                      | 12             | Hand                                          | 8              |
| Diagnosis                                     | 28             | Pediatric oncology                             | 12             | Ilosfamide                                    | 8              |
| EWSR1                                         | 26             | Recurrence                                     | 12             | Neuroectodermal tumors                        | 8              |
| Biomarker (s)                                 | 24             | Cell cycle                                     | 11             | Radiology                                     | 8              |
| Local control                                 | 24             | Cytopathology                                  | 11             | Soft tissue sarcoma                           | 8              |
| Spine                                         | 24             | FLI1                                           | 11             | Drug resistance                               | 8              |
| RT-PCR                                        | 22             | Mandible                                       | 11             | Flow cytometry                                | 8              |

CD99 = cluster of differentiation 99, EWSR1 = EWS RNA Binding Protein 1, MRI = magnetic resonance imaging, PNET = Primitif Nöroektodermal Tüümör, RT-PCR = A real-time reverse transcription-polymerase chain reaction, SEER = surveilance epidemiology and end results.

Figure 4. Network visualization map for cluster analysis based on keyword analysis performed to identify clustering of Ewing sarcoma. Each color represents a different cluster. Similar keywords are colored together in a cluster. The greater the number of times the keyword is used in articles, the larger the area of the circle it represents.
et al (1994), Nesbit et al (1990), and Ewing (1921).\cite{4,8,11,13,20,21}

It can be recommended that orthopedists and other researchers interested in ES read these articles first.

When the results of the keyword analysis were reviewed, the most studied topics on Ewing sarcoma from the past to the present were chemotherapy, radiotherapy, pediatric cancer, surgery, immunohistochemistry, metastasis, extraskeletal Ewing sarcoma, osteosarcoma, prognosis, apoptosis, survival analysis, magnetic resonance imaging, prognostic factors, extrasosseous Ewing sarcoma, EWS-FLI1, Primitif Nöroektodermal Tümörler (PNET), cluster of differentiation 99, adults, treatment, computed tomography, diagnosis, EWS RNA Binding Protein 1 (EWSR1), biomarker(s), local control, spine, a real-time reverse transcription–polymerase chain reaction, rhabdomyosarcoma, and translocation. In the evaluation of the cluster analysis results, the subjects were seen to be distributed among 11 different clusters. It was determined that the most cited keywords were immunohistochemistry, local control, translocation, EWS-FLI1, neuroblastoma, rhabdomyosarcoma, SEER, p53, cell cycle, therapy, ESFT, microRNA, risk factors, temozolomide, irinotecan,
high-dose chemotherapy, flow cytometry, chromosomal translocation, neoadjuvant chemotherapy, apoptosis, and a real-time reverse transcription–polymerase chain reaction. The analysis performed to identify trending topics revealed that pediatric oncology, EWSR1, EWSR1-FL1, epigenetics, bioinformatics, microRNA, gene expression, metastasis, migration, biomarker, immunotherapy, survival, outcomes, surveillance epidemiology and end results (SEER), nomogram, t(11;22), and drug resistance were the most studied trend topics in recent years. The subjects researched in recent years were genetic studies, metastasis, immunotherapy, life analyses/nomogram based on new data obtained from SEER, and chemotherapy with irinotecan and temozolomide combination.

In literature, there is no previous bibliometric study on the subject of ES, and therefore, this study is the first comprehensive bibliometric research to have been conducted on this subject. A limitation of the study could be said to be that only the WoS database was used. There are relative advantages of databases over each other. The reason for not selecting the PubMed database was that citation analysis cannot be made with this database. In the Scopus database, in addition to the SCI-Expanded and E-SCI indexes, studies published in some low-impact journals are indexed. In the WoS database, only articles published in journals indexed in the SCI-Expanded, E-SCI, and Social Sciences Citation indexes are indexed. Moreover, the use of >1 database in bibliometric analyses conducted on high level articles diminishes the reliability of the results. Therefore, the selection of only the WoS database constitutes a response to the limitations.

5. Conclusion

The results of this study demonstrated an increasing trend for article productivity. High-income countries have a great effect on the literature on this subject. The analysis conducted to identify trend topics revealed that pediatric oncology, EWSR1, EWSR1-FL1, epigenetics, bioinformatics, microRNA, gene expression, metastasis, migration, biomarker, immunotherapy, survival, outcomes, surveillance epidemiology and end results (SEER), nomogram, t(11;22), and drug resistance were the most studied trend topics in recent years. Genetic studies, metastasis, immunotherapy, life analyses/nomogram based on new data obtained from SEER, and chemotherapy with irinotecan and temozolomide combination, were seen to be the topics researched in recent years. The statistical analysis results of this study of 3236 articles on the subject of Ewing sarcoma can be a useful resource for orthopedists and other researchers in respect of the past and current trends, and showing global productivity.

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Author contributions

Each author fulfills each of the authorship requirements. Hassa E: participated in the design of the study and in the acquisition and interpretation of data, performed the statistical analysis, and drafted the final version of the manuscript. Alıcı T: participated in the design of the study and in the acquisition and interpretation of data, performed the statistical analysis, and drafted the final version of the manuscript.

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