

Review Article

Brain Metastases Research 1990–2010: Pattern of Citation and Systematic Review of Highly Cited Articles

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Background. High and continuously increasing research activity related to different aspects of prevention, prediction, diagnosis and treatment of brain metastases has been performed between 1990 and 2010. One of the major databases contains 2695 scientific articles that were published during this time period. Different measures of impact, visibility, and quality of published research are available, each with its own pros and cons. For this overview, article citation rate was chosen. *Results.* Among the 10 most cited articles, 7 reported on randomized clinical trials. Nine covered surgical or radiosurgical approaches and the remaining one a widely adopted prognostic score. Overall, 30 randomized clinical trials were published between 1990 and 2010, including those with phase II design and excluding duplicate publications, for example, after longer followup or with focus on secondary endpoints. Twenty of these randomized clinical trials were published before 2008. Their median number of citations was 110, range 13–1013, compared to 5–6 citations for all types of publications. Annual citation rate appeared to gradually increase during the first 2–3 years after publication before reaching high levels. *Conclusions.* A large variety of preclinical and clinical topics achieved high numbers of citations. However, areas such as quality of life, side effects, and end-of-life care were underrepresented. Efforts to increase their visibility might be warranted.

1. Introduction

Development of brain metastases is a common problem in several subgroups of patients with malignant melanoma, lung, breast, and kidney cancer [1, 2]. Given the large number of patients with brain metastases and important consequences for individual patients and health care systems [3], intense research activity is directed towards prevention and treatment. Significant progress in clinical management has been made during the last two decades [4]. Both local and systemic treatment approaches have been gradually refined. Landmark phase III randomized trials provided the framework for these advances. Eventually, researchers attempt to publish their results in a way that ensures high visibility and allows for broad adoption of the progress achieved. Successful publication is desirable for several reasons related to investigators' career advancement, tenure

track or likelihood of future funding, and might be defined by various measures. Impact factor of journals is a two-edged sword, for example, regarding its correlation with the true scientific or practical impact of let us say radiation technology or neurosurgery advances and the publication bias that strikes negative or inconclusive studies [5–9]. Article download rates might provide some indication for visibility and impact but will depend on presence and quantity of fees charged by the publisher. Another potential measure of quality and impact of research is the citation rate. Landmark or practice-changing research is likely to be cited by successor trials, editorials, review articles, meta-analyses, and guidelines. In our attempt to review the most significant publications relevant for the topics of treatment, diagnosis, and prevention of brain metastases, we relied on citation rates of articles published between 1990 and 2010. Information about highly cited article types can be

useful for preparation of future research projects. Moreover, identification of underrepresented areas might facilitate efforts to increase their visibility.

2. Methods

A systematic search of the abstract and citation database Scopus (Elsevier B.V., <http://www.scopus.com/>) by use of the key words “brain metastases,” “cerebral metastases,” “intracranial metastases,” “central nervous system metastases” or “secondary brain tumor” was performed on November 28th and 29th 2011. Publications related to metastases from extracranial solid tumors in pediatric and adult patients were selected irrespective of language and article type (case report, review, meta-analysis, etc.). In other words, all epidemiologic, diagnostic, therapeutic and preclinical topics were included. Prophylactic cranial irradiation and leptomeningeal carcinomatosis were not included unless for example, an article covered both leptomeningeal and parenchymal brain metastases. Articles dealing with brain metastases and glioma, for example, related to differential imaging diagnosis, were included as well.

3. Results

Overall 2695 publications were identified (69 to 226 per year). Figure 1 shows the numbers of publications per year. After the year 2003, a consistent and substantial increase in the number of published articles is noted, underscoring a considerable increase in interest in this topic. Figure 2 shows the median number of citations of all articles published in a given year (typically 5-6, lowest for recent years of publication). We also stratified all articles by number of citations (0, 1-5, 6-10, 11-25, 26-50, 51-100, >100). Except for the year 2002, most articles belonged to the group with 1-5 citations (24-35%, except for 42% in 2009 and 46% in 2010). In 2002, articles with 11-25 citations comprised the largest subgroup (24% of all articles). Figure 3 shows the proportion of articles without any citation (typically between 15 and 25% of all articles published in a given year; 22% of all 2695 articles). Figure 4 shows the proportion of highly cited articles, arbitrarily defined as more than 25 citations (typically between 15 and 25% of all articles published in a given year, except for recent years; 15% of all 2695 articles).

References [10-116] represent the 5 most cited articles per year. Figure 5 shows the minimum number of citations required to make it into the top 5 of each year (median 82, range 17-122). Table 1 shows the 10 most cited articles overall. Seven of these report on randomized clinical trials. Nine covered surgical or radiosurgical approaches and the remaining one a widely adopted prognostic score. All were published before 2005. Since articles published, for example, in 1990 are more likely to have accumulated a large number of citations than articles published in 2010, the average of the annual numbers of citations was also calculated. For this purpose, 2011 was defined as 0.92 years (11 of 12 months; January-November). Table 2 shows the 11 articles with most citations per year (several had 28 annual citations, which

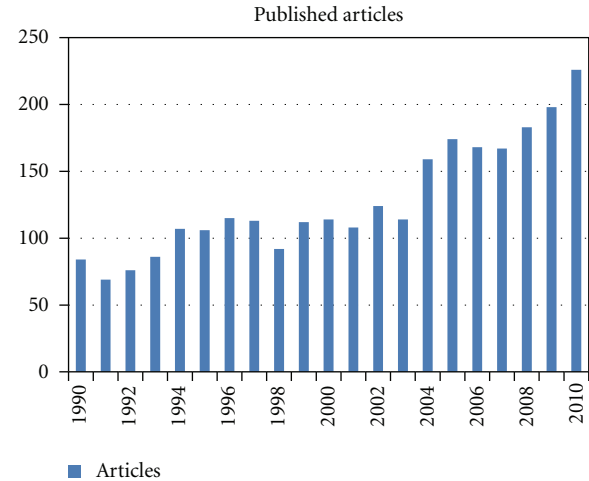


FIGURE 1: Number of articles published per year.

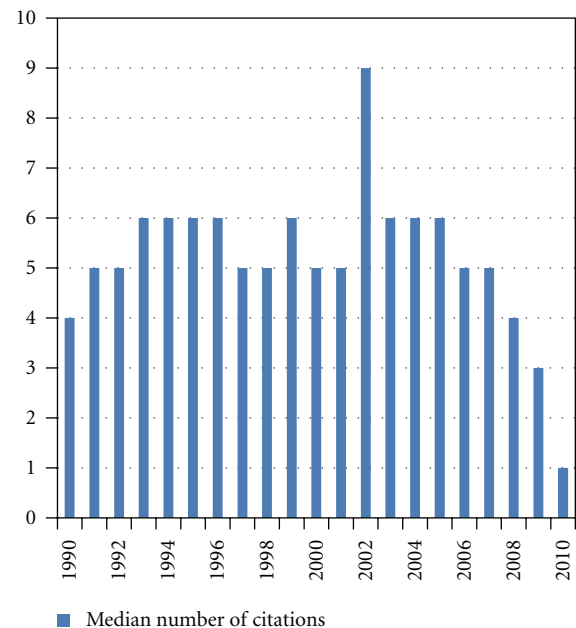


FIGURE 2: Median number of citations (basis: all articles published in a given year).

was the minimum number required for this endpoint). The table contains articles published between 1990 and 2009, but none of the 2010 publications had accumulated enough citations. Six of the articles reported on randomized clinical trials. The same number of publications covered surgical or radiosurgical approaches and 3 brain metastases in patients with breast cancer.

Overall, 30 randomized clinical trials were published between 1990 and 2010, including those with phase II design and excluding duplicate publications, for example, after longer followup or with focus on secondary endpoints. Ten of these were published after 2008. Their median number of citations was 13.5, range 1-82. Twenty randomized clinical trials were published before 2008. Their median number of

TABLE 1: Articles with most citations (absolute count).

Authors and year of publication	Short title	Absolute citation count	Citations per year
Patchell et al. 1990 [10]	Randomized trial of surgery in the treatment of single metastases	1013	85
Gaspar et al. 1997 [11]	RTOG RPA	700	47
Andrews et al. 2004 [12]	Whole brain radiation therapy with or without stereotactic radiosurgery boost (RTOG 9508 randomised trial)	509	64
Patchell et al. 1998 [13]	Randomized trial of postoperative radiotherapy in the treatment of single metastases	487	35
Flickinger et al. 1994 [14]	Multi-institutional experience with stereotactic radiosurgery for solitary brain metastasis	398	22
Kondziolka et al. 1999 [15]	Stereotactic radiosurgery plus whole brain radiotherapy versus radiotherapy alone for patients with multiple brain metastases	396	31
Vecht et al. 1993 [16]	Radiotherapy alone or combined with neurosurgery in single metastases	382	20
Alexander III et al. 1995 [17]	Stereotactic radiosurgery for the definitive, noninvasive treatment of brain metastases	333	20
Noordijk et al. 1994 [18]	The choice of treatment of single brain metastasis should be based on extracranial tumor activity and age	328	18
Mintz et al. 1996 [19]	A randomized trial to assess surgery in addition to radiotherapy in patients with single cerebral metastasis	292	18

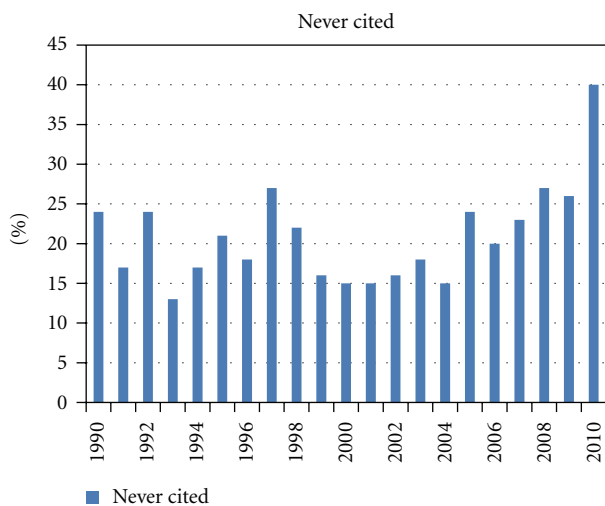


FIGURE 3: Percent of articles without any citation of all articles published in a given year.

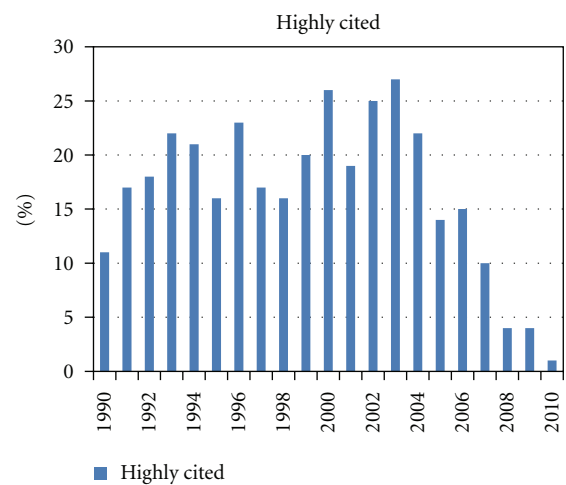


FIGURE 4: Percent of highly cited articles (>25 citations) of all articles published in a given year.

citations was 110, range 13–1013. The most cited articles (top five of each year [10–116]) were published in 35 different scientific journals. Twenty-five articles (23%) were published in the International Journal of Radiation Oncology, Biology, Physics, 14 (13%) in the Journal of Clinical Oncology, 12 (11%) in Cancer, 9 (8%) in the Journal of Neurosurgery, and 6 (6%) in the Journal of Neuro-Oncology.

4. Discussion

This overview is based on a systematic literature search where we decided to apply a broad definition of brain metastases-related publication. It should be kept in mind that not all completed research projects eventually will be published. We acknowledge that some of the selected articles might be

TABLE 2: Articles with most citations per year.

Authors and year of publication	Short title	Citations per year	Absolute citation count
Patchell et al. 1990 [10]	Randomized trial of surgery in the treatment of single metastases	85	1013
Andrews et al. 2004 [12]	Whole brain radiation therapy with or without stereotactic radiosurgery boost (RTOG 9508 randomised trial)	64	509
Aoyama et al. 2006 [20]	Randomized trial of stereotactic radiosurgery plus whole-brain radiation therapy versus stereotactic radiosurgery alone	48	282
Gaspar et al. 1997 [11]	RTOG RPA	47	700
Bos et al. 2009 [21]	Genes that mediate breast cancer metastasis to the brain	42	123
Patchell et al. 1998 [13]	Randomized trial of postoperative radiotherapy in the treatment of single metastases	35	487
Kondziolka et al. 1999 [15]	Stereotactic radiosurgery plus whole brain radiotherapy versus radiotherapy alone for patients with multiple brain metastases	31	396
Bendell et al. 2003 [22]	Central nervous system metastases in women who receive trastuzumab for metastatic breast carcinoma	31	276
Lin et al. 2009 [23]	Multicenter phase II study of lapatinib in patients with brain metastases from HER2-positive breast cancer	28	83
Chang et al. 2009 [24]	Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised trial	28	82
Lin et al. 2008 [25]	Phase II trial of lapatinib for brain metastases in patients with EGFR 2-positive breast cancer	28	108

subject to debate. In this overview, we focused on citation rate. Articles with high numbers of citations are likely those that impressed other clinicians/scientists and had profound influence on clinical practice or future developments in the field. However, the majority of published articles reviewed here received limited attention (22% were not cited at all). In a study covering the Lancet, JAMA, and New England Journal of Medicine, from October 1999 to March 2000, the authors found that presence of industry funding and an industry-favoring result was associated with an increase in annual citation rate of 25.7 (95% confidence interval, 8.5 to 42.8) compared to the absence of both industry funding and industry-favoring results [117]. Higher annual rates of citation were also associated with articles dealing with cardiovascular medicine (13.3 more; 95% confidence interval, 3.9 to 22.3) and oncology (12.6 more; 95% confidence interval, 1.2 to 24.0), articles with group authorship (11.1 more; 95% confidence interval, 2.7 to 19.5), larger sample size and journal of publication.

As stated in the previous section, we evaluated average annual citation rate because the exact time course or kinetics of citation is hard to predict and varies with topic and

journal [118, 119]. Both accumulation of citations of recently published articles and reduced interest in older articles over time pose challenges if reliable quantitative analysis is attempted. We did not account for date of publication, that is, whether an article was published earlier or later during a given year. For the purpose of this overview, the chosen methods are sufficient. Of course, more detailed and quantitative analyses can be performed with the internet-based tools available. Self-citation is likely to influence the final citation count of some generally sparsely cited articles, whereas its impact on highly cited articles might be less pronounced.

Our results are consistent with the assumption that citation rate is gradually increasing for approximately 2-3 years after publication. After several years with large numbers of citations, annual rates for older articles might decline. However, the purpose of this overview was not to explore dynamics of citation count. Given the fact that major scientific journals in the field, for example, Journal of Clinical Oncology and International Journal of Radiation Oncology, Biology, Physics, had steady increases in the number of published issues and articles over this time period and

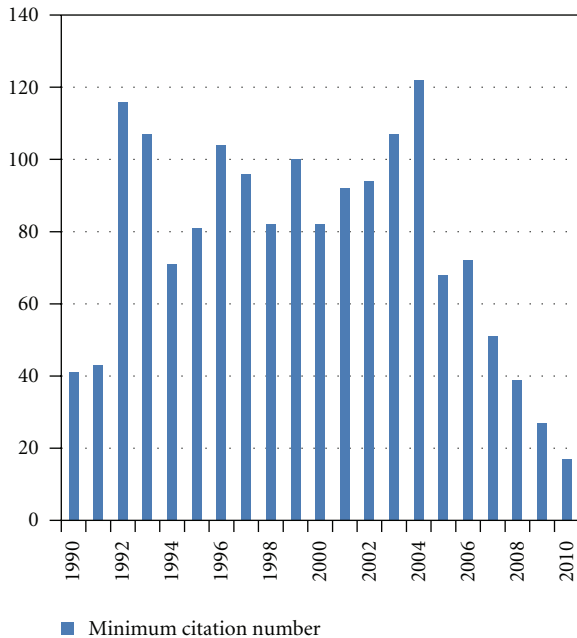


FIGURE 5: Minimum number of citations required to be among the 5 most cited articles in a given year.

that each article contains a certain number of references, the increase in total numbers of publications over time is expected to lead to a parallel increase in citation rates. It is also interesting to note that highly cited research was published in a large number of different scientific journals with or without high impact factor, but always in the English language.

The large diversity of topics covering basically all clinical, preclinical, biological, and technical aspects of the field is noteworthy and mirrors the highly multidisciplinary approach towards brain metastases. Randomized trials, which often were performed by cooperative groups, in part nationwide or on an international level, were cited more often than other studies. This finding underlines the importance of continued support for this type of trials. There has also been major progress in uncovering patients at higher risk for development of brain metastases and predicting the outcome after treatment. In many instances, the latter was also achieved through multi-institutional cooperation. Research in areas such as quality of life, side effects, and end-of-life care was less likely to result in highly cited articles. While this does not mean that such research remains unrecognized or has a generally low likelihood of publication, efforts to increase the number of highly prestigious and cited articles might be warranted.

5. Conclusions

Research activity has increased in the time period between 1990 and 2010, where a large number of highly cited and practice changing studies have been published. Randomized trials were overrepresented among highly cited studies. Multi-institutional and cooperative group projects

contributed importantly to the advancement of the field and were likely to receive high citation counts.

Conflict of Interests

C. Nieder and A. L. Grosu have no conflict of interests. M. Mehta has or has had the following roles in the last 2 years (2011-2012): consultant (Bayer, Bristol-Meyers-Squibb, Elekta, Merck, Novartis, Quark, Tomotherapy, US Oncology, Vertex), member of data safety monitoring boards (Apogenix), member of the board of directors (Pharmacyclics), member of medical advisory boards (Colby, Stemina, Procetus), and speaker (GRACE Foundation, MCM, Merck, priME Oncology, Strategic Edge, WebMD); he also owns stock options in Accuray, Colby, Pharmacyclics, Procetus, and Stemina and patents in WARF/Procetus, and he received royalties from DEMOS Publishers.

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