Child's Nervous System (2019) 35:2339–2346
https://doi.org/10.1007/s00381-019-04254-5

ORIGINAL ARTICLE

The 100 most-cited articles about diffuse intrinsic pontine glioma: a bibliometric analysis

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Received: 22 March 2019 / Accepted: 5 June 2019 / Published online: 15 June 2019

Abstract

Purpose Although the dismal clinical prognosis of diffuse intrinsic pontine glioma (DIPG) has not changed, there has been significant progress in the academic literature made in the biological understanding of this brainstem tumor. The aim of this analysis was to evaluate citation and other bibliometric characteristics of the 100 most-cited DIPG articles in the current literature in order to better understand the current state of our academic efforts in this area.

Methods Elsevier's Scopus database was searched for the 100 most-cited articles that focussed on DIPG. Articles were dichotomized as either primarily basic science (BSc) or clinical (CL) articles. Various bibliometric parameters were summarized and comparison between BSc and CL articles was performed using Pearson's chi-square and Mann–Whitney U tests.

Results Of the 100 most-cited articles, 36 (36%) were BSc and 64 (64%) were CL articles. Overall median values were as follows: citation count, 52 (range, 27–261); citation rate per year, 8.6 (range, 1.7–104); number of authors, 9 (range, 1–63); and publication year, 2011 (range, 1997–2017). Articles were published in a total of 43 different journals and predominately originated in the USA ($n = 67$, 67%). When compared with CL articles, BSc articles reported significantly greater citation count ($P = 0.03$), citations rate per year ($P < 0.01$), number of authors ($P < 0.01$), and more recent years of publication ($P < 0.01$).

Conclusions The 100 most-cited articles about DIPG were characterized in this analysis. Although smaller in overall proportion, BSc articles demonstrated significantly increased bibliometric parameters, supporting the recent dominance of BSc in this field, primarily involving histone biology of the H3K27M mutation. Moving forward, it will be of great interest to see how the findings of these high-impact BSc articles will translate into future high-impact CL articles.

Keywords Diffuse intrinsic pontine glioma · H3 K27M · Bibliometric analysis · Brainstem · Pediatric · Glioma

Introduction

Diffuse intrinsic pontine glioma (DIPG) is a rare, pediatric high-grade glioma (pHGG) of the brainstem and is one of the leading causes of cancer-related morbidity and mortality in children [21, 26]. The median survival of 6–11 months and 2- and 5-year survival estimates are as low as 10 and 2%, respectively [15, 28, 37]. This is, despite radiation therapy, the only established intervention to alleviate tumor burden, as no chemotherapeutic agent to date has been proven effective [11, 36].

In recent years, it has become clear the majority DIPG tumors harbor a somatic mutation in a histone H3 gene, most commonly a H3K27M mutation [5, 23, 39]. This resulted in the reclassification of DIPG tumors to "diffuse midline gliomas of the brainstem with the H3K27M mutation" in the 2016 World Health Organization (WHO) classification of CNS tumors [22]. Consequently, the molecular component of DIPG has emerged as crucial in understanding this disease and how to begin to improve clinical outcomes.

As we continue to build our understanding of DIPG, we rely on the academic literature to gather and disseminate findings as both basic science (BSc) and clinical (CL) articles. BSc articles reflect the growing knowledge pool about what drives DIPG tumorigenesis, and CL articles report how these findings may translate into clinical practice. Currently, a bibliometric analysis

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00381-019-04254-5) contains supplementary material, which is available to authorized users.

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of the DIPG literature has not been conducted, and it is unclear if there exist differences in impact between BSc and CL articles, and furthermore is timely considering the recent advances in the field. This will serve as a benchmark as to where we are now and potentially see changes in the future as we advance our understanding and treatment paradigms. Therefore, the aim of this analysis was to evaluate citation and other bibliometric characteristics of the 100 most-cited DIPG articles in the current literature in order to better understand the current state of our academic efforts in this area.

Methods

Search strategy

The search strategy was designed to capture all possible published indexed articles referring to DIPG. We conducted our electronic search in Scopus from its date of inception to March 2019. Elsevier's Scopus contains indexed articles from approximately 22,000 journals and has been shown to have one of the largest scientific article capture reaches of electronic databases [7]. The database was searched and screened independently by two investigators (VML and EAP) using the following string of terms: (diffuse intrinsic pontine glioma) OR (diffuse midline glioma with H3K27M) OR (H3K27M AND brainstem) OR (DIPG). Any discrepancies were resolved by discussion until consensus was reached.

Selection criteria

Selection criteria were all articles whose focus was DIPG or diffuse midline glioma with H3 K27M mutation that occurs in the < 18-year-old demographic. Articles that described distinctly separate pathologies such as glioblastoma were excluded. Publications were limited to the English language. Ultimately, using the Scopus rank function by citations, we identified the 100 with the most citations that fulfilled the aforementioned criteria.

Data extraction

Articles were dichotomized by two independent investigators (VML and EAP) to be either BSc or CL in nature; BSc articles were ones that primarily described non-human patient–focussed investigations, e.g., histone biology and genome sequencing, whereas CL articles were ones that primarily described outcomes relating to human patients, e.g., biopsy safety and predicting survival outcomes. Any discrepancies were resolved by discussion. The following validated variables were then extracted: article title, authors, journal, Scopus citations, year, citation per year, number of authors, country of origin of the senior author, and study type (BSc or CL) [20].

Statistical analysis

Any comparisons between BSc and CL articles were conducted using Pearson's chi-square test for categorical data and the Mann–Whitney U test for continuous data. Statistical significance was set at two-sided $P < 0.05$. All statistical analyses were performed using STATA 14.1 (StataCorp, College Station, TX).

Results

Search strategy

The initial search of Scopus yielded 525 articles. After ranking by citation count, 100 articles were selected, and we identified 36 (36%) as BSc articles and 64 (64%) as CL articles. The 10 most-cited articles are listed in Table 1, and the whole cohort is detailed in Supplementary Table 1. Within the top 10 most-cited articles, 8 were BSc articles, and 2 were CL articles.

Citations

The median citation was 52 (range, 27–261), with the most-cited article to date the BSc article by Wu et al. [39], published in 2012 with 621 citations: "Somatic histone H3 alterations in pediatric diffuse intrinsic pontine gliomas and non-brainstem glioblastomas" in *Nature Genetics*. This notably was the defining study of the now characteristic H3K27M mutation in DIPG. The most-cited CL article was by Hargrave et al. [11], published in 2006 with 305 citations: "Diffuse brainstem glioma in children: Critical review of clinical trials" in *Lancet Oncology*. These studies were also the most-cited per year by article type, with Wu et al. [39] cited at 104 citations/year and Hargrave et al. [11] cited at 25.4 citations/year. Overall, the median citation per year was 8.6 (range, 1.7–104).

Authors

The median number of authors was 9 (range, 1–63), with the most-authored being the BSc article by Mackay et al. [23], published in 2017 with 63 authors: "Integrated Molecular Meta-Analysis of 1,000 Pediatric High-Grade and Diffuse Intrinsic Pontine Glioma" in *Cancer Cell*. The most-authored CL article was the article by Jansen et al. [16], published in 2015 with 23 authors: "Survival prediction model of children with diffuse intrinsic pontine glioma based on clinical and radiological criteria" in *Neuro-Oncology*. The author with the most overall senior-authored articles was SJ Baker who had 6 articles [17, 30–32, 39, 40].

Table 1 Top 10 most-cited articles about DIPG

Rank	Citations (*n*)	Senior author	Year	Title	Journal
1	621	Baker SJ	2012	Somatic histone H3 alterations in pediatric diffuse intrinsic pontine gliomas and non-brainstem glioblastomas	*Nature Genetics*
2	453	Allis CD	2013	Inhibition of PRC2 activity by a gain-of-function H3 mutation found in pediatric glioblastoma	*Science*
3	340	Hawkins C	2012	K27M mutation in histone H3.3 defines clinically and biologically distinct subgroups of pediatric diffuse intrinsic pontine gliomas	*Acta Neuropathologica*
4	336	Baker SJ	2010	Integrated molecular genetic profiling of pediatric high-grade gliomas reveals key differences with the adult disease	*Journal of Clinical Oncology*
5	329	Baker SJ	2014	The genomic landscape of diffuse intrinsic pontine glioma and pediatric non-brainstem high-grade glioma	*Nature Genetics*
6	305	Bouffet E	2006	Diffuse brainstem glioma in children: Critical review of clinical trials	*Lancet Oncology*
7	220	Hawkins C	2014	Genomic analysis of diffuse intrinsic pontine gliomas identifies three molecular subgroups and recurrent activating ACVR1 mutations	*Nature Genetics*
8	190	Hawkins C	2010	Whole-genome profiling of pediatric diffuse intrinsic pontine gliomas highlights platelet-derived growth factor receptor Î ± and poly (ADP-ribose) polymerase as potential therapeutic targets	*Journal of Clinical Oncology*
9	184	Grill J	2014	Recurrent activating ACVR1 mutations in diffuse intrinsic pontine glioma	*Nature Genetics*
10	166	Kun LE	1999	There is no role for hyperfractionated radiotherapy in the management of children with newly diagnosed diffuse intrinsic brainstem tumors: Results of a pediatric oncology group phase III trial comparing conventional vs. hyperfractionated radiotherapy	*Int J Radiat Biol.**

*International Journal of Radiation Oncology Biology Physics

Year of publication

All articles were published between 1994 and 2017 (Fig. 1). The peak year (median) of the most-cited articles was 16 (16%) articles published in 2011 (Supplementary Table 2). The median years of publication for BSc and CL articles were 2014 and 2011, respectively.

Country of correspondence

Thirteen countries were listed as the location for correspondence of all articles (Fig. 2). The country with the highest contribution was the USA with 67 articles (67%), followed by Canada ($n = 8$, 8%) and the UK ($n = 7$, 7%) (Supplementary Table 3). The USA was the most common for both BSc and CL articles.

Journals

A total of 43 journals contributed to the 100 most-cited articles (Supplementary Table 4). The most common were *Neuro-Oncology* with 14 (14%), *Journal of Neuro-Oncology* with 12 (12%), and *Cancer* with 7 (7%). The most common journals for BSc articles were *Journal of Clinical Oncology*, *Nature Genetics*, and *Neuro-Oncology*, and the most common journal for CL articles was *Journal of Neuro-Oncology*.

Article type comparisons

BSc articles had significantly greater citation counts ($P = 0.03$), citations per year ($P < 0.01$), and median number of authors ($P < 0.01$) and were published significantly later (< 0.01) (Table 2). In terms of proportion published under open access agreement, most-authored articles by a single author,

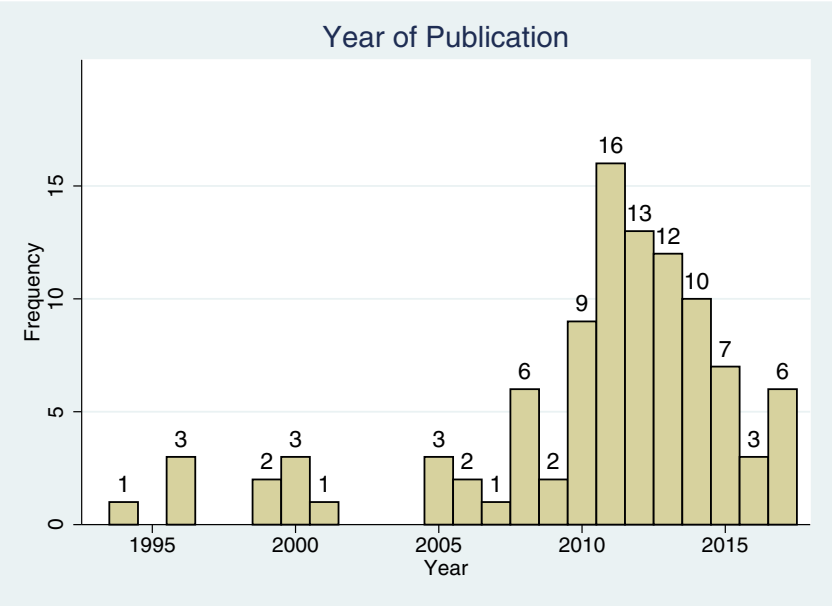

Fig. 1 Distribution of 100 most-cited articles about DIPG based on year of publication

and the USA as the country of correspondence, there was no statistically significant difference between article types.

Discussion

The intention of this bibliometric analysis was to identify the 100 most impactful articles in the literature about DIPG based on citation count. We were able to classify all articles as either BSc or CL articles and showed that they differed in a number of bibliometric parameters, including citation metrics. Overall, BSc articles constituted 36(%) of the 100, and CL articles constituted the remaining 64(%). Interestingly, within the top 10 most-cited articles, there were 8 BSc articles (80%) and only 2 CL articles (20%). These findings illustrate that the research area of DIPG is a dynamic field with overlapping contributions from both BSc and CL articles, most dominantly from the USA.

It would be of little surprise to many in the field that the article published in 2012 by SJ Baker and colleagues [39] was the most-cited. Their seminal findings revolutionized the focus of this tumor type to understanding histone biology. Indeed, this spurred the eventual WHO reclassification of DIPG in 2016 [22]. In fact, six [3, 4, 18, 19, 39, 40] of the 10 most-cited articles about DIPG were BSc articles that referred specifically to histone biology. A pioneer of this work

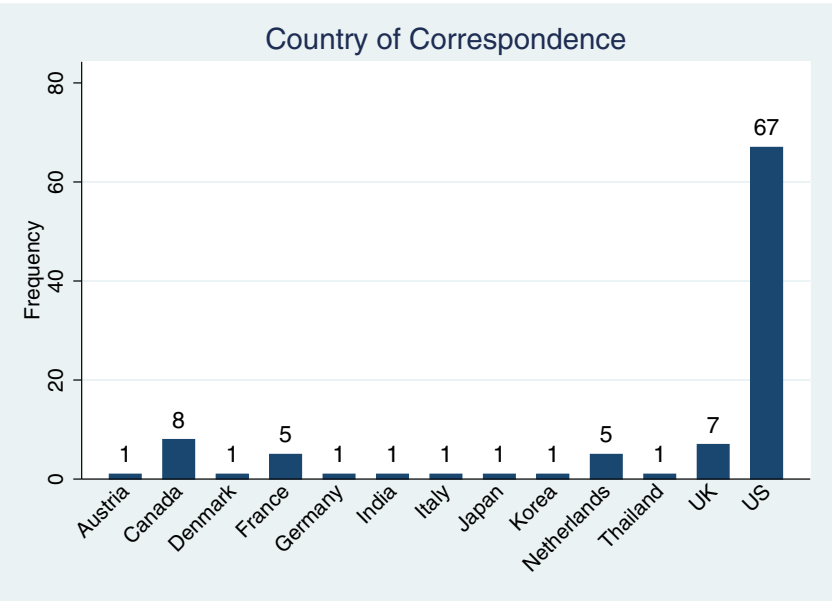

Fig. 2 Distribution of 100 most-cited articles about DIPG based on country of correspondence

Table 2 Comparison of 100 most-cited DIPG articles based on article type, basic science (BSc), and clinical (CL)

Parameter	Article type		*P* value
	BSc (*n* = 36)	CL (*n* = 64)	
Open access, *n* (%)	17 (47%)	22 (34%)	0.21
Citations, median (range)	66 (27–621)	48 (28–305)	0.03
Citations per year, median (range)	11.4 (1.73–104)	6.4 (2.5–66)	< 0.01
Number of authors, median (range)	15 (2–63)	8 (1–23)	< 0.01
Most senior-authored articles by one author, *n* (%)	6 (17%), SJ Baker	4 (6%), CM Kramm	0.10
Year of publication, median (range)	2014 (2010–2017)	2011 (1994–2016)	< 0.01
US as country of correspondence, *n* (%)	23 (64%)	44 (69%)	0.62
Most single journal publications, *n* (%)	4 (11%)*	12 (19%)**	NA

NA, not applicable due to multiple contributors to BSc articles

*Three journals contributed 4 BSc articles each: *Journal of Clinical Oncology*, *Nature Genetics*, and *Neuro-Oncology*

***Journal of Neuro-Oncology*

would be SJ Baker, who was senior author of three [31, 39, 40] of the top 10 most-cited articles, and six [17, 30–32, 39, 40] overall in this cohort of 100 articles, the highest number amongst all senior authors.

The collective impetus of these impactful BSc articles in the DIPG field has led to a significantly greater understanding of the molecular events surrounding tumorigenesis. The characteristic histone mutation H3K27M can occur in several H3 genes including H3F3A and HIST1H3B/C, encoding for variants H3.3 and H3.1, respectively [2, 5, 39]. This substitution mutation results in significant epigenetic reprogramming that has been shown to contribute to tumorigenesis [2, 6, 27, 38]. Evidence accumulated by these impactful studies indicate this occurs primarily due to the global loss of di- and tri-methylation of histone H3K27 (H3K27me2 and H3K27me3) on wild-type histone proteins [1, 19, 25, 34, 38]. This consequent hypomethylation reprograms the epigenetic landscape to be more hospitable to tumorigenic change and ultimately drives tumor proliferation [1].

In the most-cited CL article by Hargrave et al. [11], they described at the time of publication in 2006 the difficulties faced in clinically managing DIPG patients. It was not until 2011 did we see a peak in articles currently within the 100 most-cited ranking, with more BSc articles being published thereafter. Historically, this significant shift in article type reflects the change in focus of DIPG literature. Prior to the landmark histone biology articles, it is likely many of the impactful articles were investigating clinical modalities proven in other adult cancers. Yet with the advent of histone biology emerging by 2011–2012, focus may have shifted to basic science to better understand the workings of DIPG. It is highly likely these discoveries have been spurred by the acceptance of surgical biopsy as feasible in well-selected patients, which provides the biological tissue for molecular studies [10]. As these neurosurgical techniques for biopsy are established further, it is anticipated that greater granularity in the molecular biology of this tumor will be achieved.

One of the older articles in this current list was a CL article by Mandell et al. [24] published in 1999, who showed no role for hyperfractionated radiotherapy in DIPG. Two decades later, we still have not progressed further than standard radiation treatment for DIPG patients. We suspect in the coming years [10, 33], surgical biopsy of the brainstem in DIPG patients may become more mainstream in response to the now clear importance of establishing H3K27M status in these patients. However, one could envision that a liquid biopsy identifying the H3K27M mutation in cerebrospinal fluid may supplant even a surgical biopsy [14, 29]. In addition, new treatment strategies such as convection-enhanced delivery and novel therapies designed to target the histone biology may emerge as the most impactful CL articles of the future [8, 12, 35].

Finally, we do not predict that the contribution of BSc articles in the future will diminish. Although the significance of histone biology has been well established, its interactions across the tumor epigenome and with other molecular mutations require greater investigation. For example, the seventh most-cited article by Hawkins and colleagues [4] in 2014 identified that an activin A receptor, type I (*ACVR1*) mutation contributed to the tumor burden of DIPG. Very recently was it shown that this ACVR1 mutation interacts with the H3K27M mutation to promote DIPG initiation and propagation [13]. Other characteristic mutations in DIPG tissue samples identified by the rise of genome sequencing include tumor protein p53 (*TP53*), platelet-derived growth factor receptor A (*PDGFRA*), and phosphatidylinositol 3-kinase catalytic subunit alpha (*PIK3CA*) [9, 23]. It is yet to be seen if all these targets have translational significance in the future for novel therapeutic targets, and we anticipate it will take some time to be sorted out. Our analysis demonstrated that BSc articles about DIPG have contributions by significantly more authors

than CL articles, highlighting that while such reports are more impactful in terms of citation counts currently, they require a significantly greater concerted multidisciplinary efforts to produce, and therefore, an assumedly longer time to prepare for dissemination.

There are limitations to this study in its current form. Although we performed a search for DIPG-related articles, it is difficult to know if any non-specific pediatric brain tumor articles of relevance to the DIPG field were missed at screening. The challenge here is the definition of relevance. We believe that articles which specifically mentioned any of the terms to which DIPG is referred to warrant inclusion, and articles referring to the management of general pediatric brain tumors were not specific enough about DIPG for our purposes.

The other aspect requiring greater validation in the future is the use of citations as the metric for impact across a field. Similar to the previous point, another challenge is the definition of impact. As impressive as the BSc articles have been in terms of generating new knowledge, they are of arguably little use to a clinician consulting a patient about their management options when targeted therapies are currently not available. Conversely, CL articles describing the safety of brainstem biopsy can alter the course of management. If one considers the scientific literature as an academic pool for scientific knowledge, perhaps bibliometric analyses in DIPG are currently biased towards BSc articles, reflecting that in recent years, more BSc research has been required to further understand DIPG before translation into clinical practice can occur. This suggests we may even be at the precipice of identifying translational interventions, which would be a welcomed outcome.

Conclusions

In this bibliometric analysis, we identified the 100 most-cited articles about DIPG as of March 2019 and showed that there were bibliometric differences between BSc and CL articles. Collectively, the findings indicate that there has been a surge in our molecular understanding of this tumor based on histone biology, and this superseded previous treatment CL articles and may now precede novel histone-based therapies. The preference for BSc articles, with the peak time at the discovery of the H3K27M mutation, points to the field successfully moving in the direction of molecular research and suggests that one reason we have not made more progress in clinic is that our basic science understanding is still evolving. Hopefully, as our scientific understanding matures, we will successfully translate these benchside discoveries to the bedside.

Funding EAP was supported by CTSA Grant Number UL1 TR002377 from the National Center for Advancing Translational Sciences (NCATS).

Compliance with ethical standards

Conflict of interest Other authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this study.

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