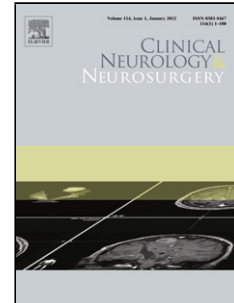


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## Shaping Our Understanding of Medulloblastoma: A Bibliometric Analysis of the 100 Most Cited Articles

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Shaping Our Understanding of Medulloblastoma: A Bibliometric Analysis of the 100 Most Cited Articles.

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## **HIGHLIGHTS**

- Medulloblastoma understanding has changed based on published studies.
- Most of 100-most cited medulloblastoma articles originated from the US.
- Basic science articles were more cited per year than clinical articles.
- Basic science articles were more recent than clinical articles.

## **ABSTRACT**

The clinical management of medulloblastoma has undergone significant transformation since the recent dawn of the molecular era. The aim of this analysis was to evaluate citation and other bibliometric characteristics of the 100 most cited medulloblastoma articles in the literature to better understand the current state of our research efforts into this diagnosis. Elsevier's Scopus database was searched for the 100 most cited articles that focused on medulloblastoma. Articles were dichotomized as either primarily basic science (BSc) or clinical (CL) articles. Various bibliometric parameters were summarized and compared between BSc and CL articles using Pearson's Chi-

square and Mann Whitney U tests. Of the 100 most cited articles, 52 were characterized as BSc articles and 48 as CL articles. Overall median (range) values were as follows: citation count 252 (164-1,270); citation rate per year 17.5 (2.5-110); number of authors 11 (1-135); and publication year 2005 (1925-2014). Articles were published in a total of 40 different journals, and the majority originated in the US (n=60). When compared to CL articles, BSc articles reported significantly greater citation rates per year ( $P<0.01$ ), and more recent years of publication ( $P<0.01$ ). In summary, although similar in overall proportion, BSc articles demonstrated significantly increased bibliometric parameters of impact in this field by the successful clustering molecular subtypes. Moving forward, it will be of great interest to see how the findings from these impactful BSc articles will translate into future clinical initiatives and subsequently high-impact CL articles.

## **KEYWORDS**

medulloblastoma; bibliometric; most cited; impactful; basic science; clinical; sonic hedgehog.

## **INTRODUCTION**

Brain tumors are the most common cause of cancer-related death in children, with medulloblastoma the most common malignant form found in 10-20% of all pediatric brain tumor presentations.<sup>1-3</sup> The current standard of care for medulloblastoma involves surgical resection, craniospinal irradiation, and chemotherapy, with an expected 5-year survival of 70-75% amongst children greater than 3-years-old.<sup>4-6</sup> In the last decade, the disease has been clustered into four distinct molecular subtypes, each of which follows a unique clinical course with a specific therapeutic vulnerability profile.<sup>7,8</sup> This understanding has transformed medulloblastoma from a

histological diagnosis with generic therapeutic approach to one of molecular-guided diagnosis and more finely-targeted management.<sup>9</sup>

The emergence of the molecular era in medicine has directed translational medulloblastoma research, and allowed for dynamic optimization of our practice for treating medulloblastoma - we rely on academic literature to gather and disseminate impactful basic science (BSc) and clinical (CL) findings to benefit the patient. Assessing the most impactful articles to date allows us to profile the progress made in developing our current treatment practices, and perhaps hints at where future impactful work might arise. Therefore, the aim of this bibliometric analysis was to examine the properties of the 100 most cited medulloblastoma articles to date.

## **METHODS**

### *Search strategy*

The search strategy was designed to capture all relevant published indexed articles referring to medulloblastoma. We conducted our electronic search in Scopus in July 2019. Elsevier's Scopus contains indexed articles from approximately 22,000 journals and captures one of the widest range of scientific articles amongst all electronic databases, with articles dating back to the 1800s in some cases.<sup>10</sup> The database was searched and screened for "medulloblastoma" in the Title and Keywords only, to screen out studies principally concerned with larger groups of brain tumors. Any discrepancies were resolved by discussion and consensus between authors.

### *Selection criteria*

All articles whose focus was medulloblastoma were finally incorporated into this study, excluding articles that also described distinctly separate tumor pathologies. Publications were limited to the English language. After sorting Scopus rank function according to citation number, the top 100 were selected.

#### *Data extraction*

Articles were dichotomized as either BSc or CL in nature: CL articles were ones that primarily described outcomes relating to human patient as the principal entity - e.g. predicting survival outcomes, and clinical trials; BSc articles were articles whose principal entity was not the whole human patient, e.g. subgrouping of a molecular element, genetic sequencing, or a distinct molecular mechanism. Any discrepancies resolved by discussion between authors. The following validated labels 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).<sup>11</sup>

#### *Statistical analysis*

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

## **RESULTS**

#### *Search strategy*

Initial search of Scopus yielded 4,083 articles. After ranking by citation count, 100 articles were selected, and we identified 52 (52%) as BSc articles and 48 (48%) as CL articles, with all articles describing outcomes involving pediatric patients, or biological studies using materials from pediatric patients. 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, 7 were BSc articles, and 3 were CL articles.

### *Citations*

Median citation count was 252 (range, 164-1,270) amongst the 100 most cited articles. The most cited article to date was the BSc article by Goodrich et al.<sup>12</sup>, published in 1997 with 1,270 citations; ‘Altered neural cell fates and medulloblastoma in mouse patched mutants’ in *Science*. This notably was the seminal report that laid the foundation for further exploiting the molecular landscape of medulloblastomas. The most cited CL article was by Rudin et al.<sup>13</sup>, published in 2009 with 742 citations; ‘Treatment of medulloblastoma with hedgehog pathway inhibitor GDC-0449’ in *New England Journal of Medicine*. Median citation rate (per year) was 17.5 (range, 2.5-110).

The most cited per year article to date was the more recent BSc article by Taylor et al.<sup>8</sup>, published in 2012 with 110 citations per year; ‘Molecular subgroups of medulloblastoma: The current consensus.’ in *Acta Neuropathologica*. This article has provided a significant reference in recent years given the discovery of the molecular profiles of medulloblastoma. The most cited per year CL article was the same article by Rudin et al.<sup>13</sup> that garnered the greatest number of cumulative citations, with a rate of 74 citations per year.

### *Theme*

Across all studies, the three most common themes of study were tumorigenesis (n=18), molecular biology (n=15), and clinical outcomes (n=13) (Supplementary Table 2). The three most common themes in BSc studies only were tumorigenesis (n=18), molecular biology (n=15) and subgrouping (n=11). The three most common themes in CL studies only were clinical outcomes (n=13), radiation outcomes (n=8) and biomarkers (n=8).

### *Authors*

Median number of authors was 11 (range, 1-135), with the most authored being the BSc article by Northcott et al.<sup>14</sup>, published in 2012 with 135 authors; ‘Subgroup-specific structural variation across 1,000 medulloblastoma genomes’ in *Nature*. The most authored CL article was the article by Gajjar et al.<sup>5</sup>, published in 2006 with 22 authors; ‘Risk-adapted craniospinal radiotherapy followed by high-dose chemotherapy and stem-cell rescue in children with newly diagnosed medulloblastoma (St Jude Medulloblastoma-96): long-term results from a prospective, multicenter trial’ in *Lancet Oncology*. Of all 100 articles, the authors with the most overall senior-authored articles were RJ Gilbertson from Memphis, US (n=6), MD Taylor from Toronto, Canada (n=5), Pfister SM from Heidelberg, Germany (n=4) and Wechsler-Reya RJ from La Jolla, US (n=4).

### *Year of Publication*

All articles were published between 1925-2014 (Figure 1). The earliest article was by Bailey & Cushing ‘Medulloblastoma cerebelli: A common type of midcerebellar glioma of childhood,’ published in *Archives of Neurology and Psychiatry*.<sup>15</sup> Overall, the median year of publication was



2005, and median years of publication for BSc and CL articles were 2009 and 2001 respectively (Supplementary Table 3).

#### *Countries and institutions of origin*

Thirteen countries in total were listed as the location for correspondence (Figure 2). The country with the highest contribution was the US with 60 articles, followed by Canada (n=10), Germany (n=10) and the UK (n=9) (Supplementary Table 4). The US was the most common country of origin for both BSc and CL articles. To identify institutions with the greatest contribution to the 100 most cited articles, the most common origins were then evaluated per country. In the US, St. Jude's Children's Hospital in Memphis, Tennessee was the most common origin of studies (15/60, 25%), followed by the Children's National Medical Center in Washington, DC (6/60, 10%) and the hospitals of Harvard Medical School/MIT in Boston, MA (6/60, 10%). For studies from Canada, 9/10 (90%) originated from Hospital for Sick Children in Toronto. For studies from Germany, 7/10 (70%) originated from the German Cancer Research Center in Heidelberg. For studies originating in the UK, 4/9 (45%) were from the Institute for Cancer Research in Newcastle.

#### *Journals*

A total of 40 journals contributed to the 100 most cited articles (Supplementary Table 5). Overall, the most common were *Journal of Clinical Oncology* with 21, *Nature* with 9, and *Journal of Neurosurgery* with 6 articles. The most common journals for BSc articles were *Nature*, *Cancer Cell*, and *Science*, and the most common journals for CL articles were *Journal of Clinical Oncology*, *Journal of Neurosurgery* and *International Journal of Radiation Oncology Biology Physics*.

*Article type comparisons*

BSc articles trended towards more citations than CL articles, although this was not statistically significant (Table 2). However, the citation rate per year was significantly higher for BSc articles than for CL articles, 31 vs 14 citations per year respectively ( $P < 0.01$ ). Additionally, BSc articles were published significantly later than CL articles, median year 2009 versus 2000 respectively ( $P < 0.01$ ). There was no significant correlation between the article types and the number of authors or the country of origin.

**DISCUSSION**

We conducted a bibliometric analysis of the 100 most cited articles about medulloblastoma to examine the intellectual trends in the understanding and therapeutic approach to this disease. We found the literature to be roughly balanced with respect to basic science versus clinical research in medulloblastoma. Over time, there has been a shift from clinical description to mechanistic study in basic science, spurred by advances in our understanding of the molecular biological features of disease. It was clear that although these studies and findings appealed to a wide range of journals, there have been particular institutions and countries that have been significant contributors to the literature, with St. Jude's Children's Hospital, Tennessee, United States as the most voluminous.

The earliest study in this list was by Bailey & Cushing<sup>15</sup>, who first described medulloblastoma as ‘spongioblastoma cerebelli’, highlighting the predilection of this tumor for the cerebellum and foreshadowing the role histology would play in stratifying this tumor for decades to come. Clinical articles peaked in 2000 based on median year, establishing the multi-modal approach to current standard of care involving surgery, craniospinal irradiation and chemotherapy as the optimal treatment for these tumors.<sup>4,16-20</sup> However, as greater long-term follow-up was obtained, future impactful clinical studies also brought to our attention the cognitive and functional risks associated with such treatments.<sup>21-23</sup>

With the most citations overall, the BSc article by Goodrich et al.<sup>12</sup>, ‘Altered neural cell fates and medulloblastoma in mouse patched mutants,’ published in 1997 exposed how integral the sonic hedgehog (SHH) pathway is to cerebellar development after engineering *Ptch1* deletions in mice to induce medulloblastoma development. In many ways, this study prefaced the explosion in basic science genomic and proteomic discoveries that were to come in the field of medulloblastoma and the shift away from gross clinical description toward a molecular characterization in the understanding of this disease. Within specific countries, we identified specific institutions as major facilitators for this impactful type of medulloblastoma research, highlighting the level of multidisciplinary subspecialization required for an institution to generate significant contributions to this field, which is reflected in the number of authors contributing to such articles. “

It was an early genomics study by Thompson et al.<sup>24</sup> in 2006 that affirmed the suspicion that medulloblastomas consist of biologically distinct subgroups based on transcriptomic differences rather than histology alone. A number of validating basic science studies<sup>25-27</sup>, all of which are

featured in the 100 most cited list, followed Thompson's paper using more advanced technologies and larger cohorts to effectively describe four distinct molecular groups of medulloblastoma. This ultimately cumulated in the publication 'Molecular subgroups of medulloblastoma: The current consensus' by Taylor et al.<sup>8</sup> in 2012 which effectively established the four molecular subgroups used in practice today: the Wnt subtype, the SHH subtype, 'group 3,' and 'group 4' medulloblastomas. Although this publication was ranked second in terms of overall citations, it is arguably the most impactful recent study; accordingly, it had the highest yearly citation rate of all publications analyzed here.

As has become evident in clinical practice, each medulloblastoma subgroup predisposes to a distinct clinical course.<sup>8,26</sup> Therefore, the early works establishing these subgroups are likely to remain impactful for many years to come as we begin to stratify therapy options based on these basic science findings and translate them into the clinical realm. To date, much of the clinical medulloblastoma outcome data that stratifies by the molecular groups derives from patients treated by clinical indications, rather than targeted-therapies towards these now established subgroups.<sup>7,28</sup> In particular, given the very poor prognosis of 'subgroup 3' medulloblastomas, there is still a great need to advance this research, with the expected 5-year overall survival of this subgroup is approximately 50% in children, and 33% in adults.<sup>27,29</sup> We predict that as results of clinical trials studying molecularly-guided therapies and treatment reductions for specific medulloblastoma subtypes are published (e.g. NCT01802567 & NCT01878617), we will see a shift back towards more impactful clinical studies in this field, pending their success.

There are limitations to a bibliometric analysis. Although citation count was used as our metric of impact, how representative this parameter is of mechanistic insight or clinical utility remains controversial. Admittedly, there are other possible measures of impact, such as journal impact factor, and author parameters, including m-quotient, h-index, and authorship value, which provide additional avenues to explore when quantifying impact.<sup>30</sup> Additionally, due to the time it takes to acquire literature citations, it is unclear if the presented proportion of BSc to CL articles reflects the current trends in the recently published literature. It is possible that more meaningful translational CL articles have since been published which incorporate understanding from accumulated BSc data, but have not had the time to accumulate the requisite threshold of citations for inclusion on this list.

## CONCLUSION

Our current understanding of medulloblastoma as a central nervous system tumor has undergone many impactful transitions. Clinical studies preceded a large body of basic science research that shed light onto the molecular properties of this disease. These, in turn, have informed more nuanced clinical practice. By analyzing the most cited studies, we have identified many significant advances have been made with respect to establishing favorable standards of care, including understanding of genetic landscape of this disease with new molecular subgroupings, which are trending to towards clinical translation via outcomes and biomarker research. There remains a need for further significant translational and clinical research integrating these basic science findings to address the malignant medulloblastoma subgroup as well as the long-term sequelae of current treatment modalities. These future clinical studies are likely to be the focus of the next series of

important studies in medulloblastoma research following the successful impact of basic science research on this field.

## Disclosures

The authors report no funding sources or conflict of interest concerning the materials or methods used in this study or the findings specified in this study.

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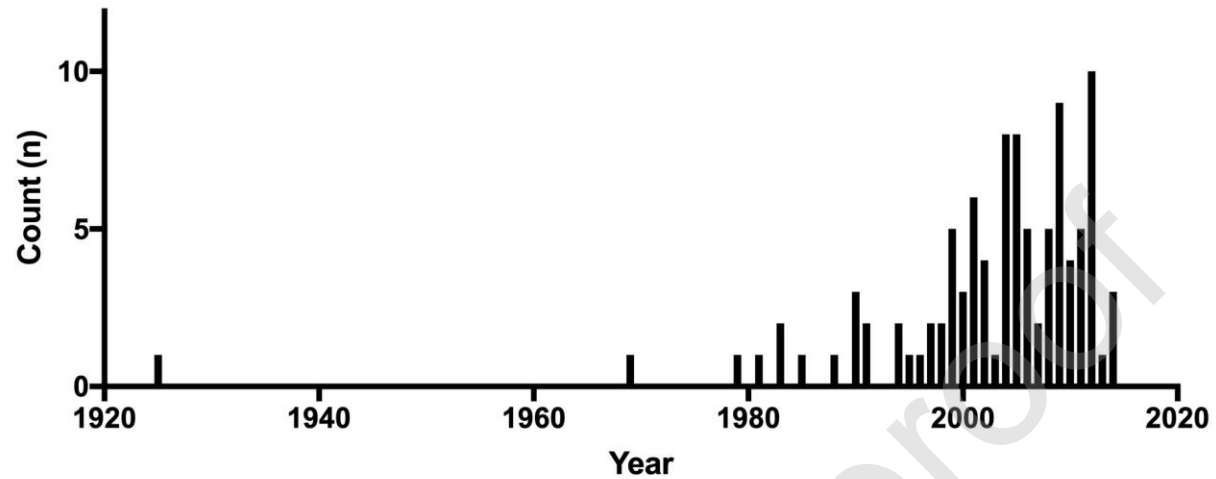
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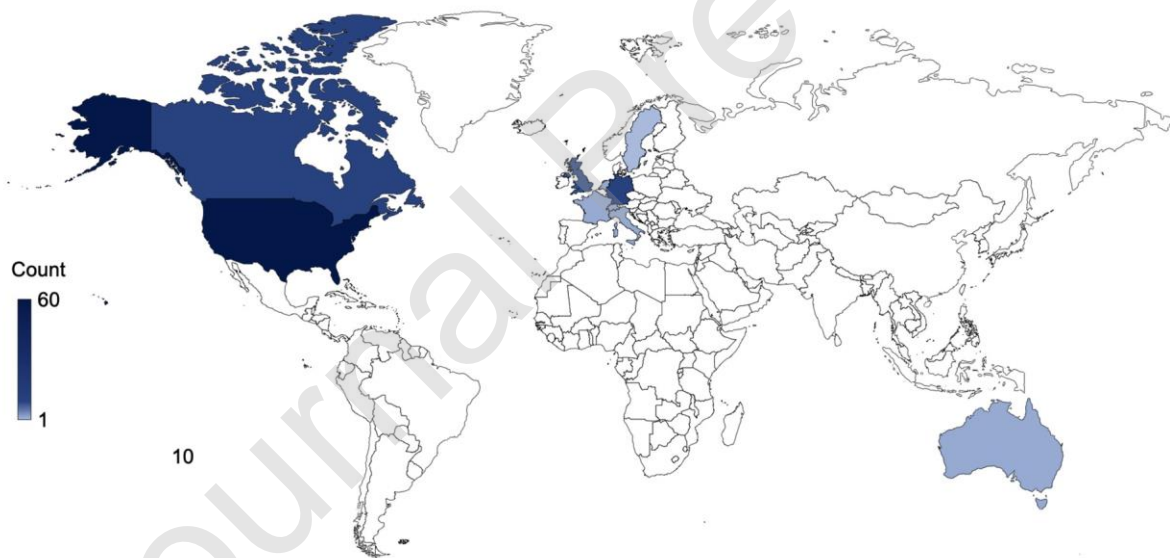
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**Figure 1.** Publication year of 100 most cited medulloblastoma articles.



**Figure 2.** Countries of correspondence of 100 most cited medulloblastoma articles.



**Table 1.** Top 10 most-cited articles about medulloblastoma.

Rank	Citations (n)	Senior author	Year	Title	Journal
1	1270	Scott MP	1997	Altered neural cell fates and medulloblastoma in mouse patched mutants	<i>Science</i>
2	770	Pfister SM	2012	Molecular subgroups of medulloblastoma: The current consensus	<i>Acta Neuropathologica</i>
3	742	Low JA	2009	Treatment of medulloblastoma with hedgehog pathway inhibitor GDC-0449	<i>New England Journal of Medicine</i>
4	690	Taylor MD	2011	Medulloblastoma comprises four distinct molecular variants	<i>Journal of Clinical Oncology</i>
5	652	Beachy PA	2002	Medulloblastoma growth inhibition by Hedgehog pathway blockade	<i>Science</i>
6	601	De Sauvage FJ	2009	Smoothed mutation confers resistance to a hedgehog pathway inhibitor in medulloblastoma	<i>Science</i>
7	553	Hogg D	2002	Mutations in SUFU predispose to medulloblastoma	<i>Nature Genetics</i>
8	506	Gilbertson RJ	2006	Risk-adapted craniospinal radiotherapy followed by high-dose chemotherapy and stem-cell rescue in children with newly diagnosed medulloblastoma (St Jude Medulloblastoma-96): long-term results from a prospective, multicentre trial	<i>Lancet Oncology</i>
9	503	Packer RJ	1999	Metastasis stage, adjuvant treatment, and residual tumor are prognostic factors for medulloblastoma in children: Conclusions from the Children's Cancer Group 921 randomized phase III study	<i>Journal of Clinical Oncology</i>
10	498	Velculescu VE	2011	The genetic landscape of the childhood cancer medulloblastoma	<i>Science</i>

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

Parameter	Article type		P-value
	BSc (n=52)	CL (n=48)	
Citations, median (range)	297 (164-1,270)	232 (166-742)	0.10
Citations per year, median (range)	31 (5-110)	14 (3-74)	<0.01
Number of authors, median (range)	12 (1-135)	9 (1-22)	0.17
Year of publication, median (range)	2009 (1983-2014)	2000 (2001-2012)	<0.01
US as country of origin, n(%)	28 (56%)	30 (63%)	0.49