Glioblastome Multiforme: A Bibliometric Analysis

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Key words
- Bibliometric analysis
- GBM
- Glioblastoma
- Glioblastoma multiforme

Abbreviations and Acronyms
GBM: Glioblastoma multiforme
NIH: National Institutes of Health

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Bibliometric analyses are widely used to gauge the scholarly impact of any scientific publication. We conducted a bibliometric analysis of the 100 most influential articles on glioblastoma multiforme (GBM). We searched Scopus using the keywords "Glioblastoma multiforme," "GBM," Glioblastoma," and "Grade IV glioma." A list of the top 100 articles was prepared. The articles were sorted according to the number of citations. A detailed analysis was carried out to identify the characteristics of the most influential studies. The 100 most cited articles in the field were published over 38 years between 1978 and 2018, with the maximum number of articles published in the 10-year period from 2001 to 2010. The total number of citations for 100 articles was 148,594 and 4.8% were self-citations. Citations ranged from 9624 to 617, with a median of 935 (interquartile range, 906). The top cited articles originated from 22 countries, with the greatest contributions from the United States. *Nature* made the greatest contribution to the research on GBM, with a total of 14 articles, and *Cancer Cell* and *New England Journal of Medicine* were the second biggest contributors. Fifty-seven studies focused on the pathogenesis of GBM. There were 12 authors who had ≥5 articles in the top 100 citation list. Only 31% of the articles were funded by public and private sector organizations. Our analysis highlights the characteristics of the most influential articles on GBM and provides valuable insight into the research that has been conducted in this field.

INTRODUCTION

Bibliometric analyses have emerged as one of the most widely used methods to assess the credibility, quality, and impact of scholarly work.[1,2] One of the measures used for this analysis includes citation frequency, which relates the number of times the article has been cited by researchers.[3] Hence, the most frequently cited article is arguably the one making the most impact on its scientific community. Bibliometrics, although not an infallible technique, can serve as a valuable tool for directing the allocation of resources by funding agencies and for identifying potential underresearched areas in a discipline.[4]

Glioblastoma multiforme (GBM), a malignant primary central nervous system tumor, presents an enigma to clinicians because of its aggressive and heterogeneous nature.[5,6] GBM is characterized as a high-grade grade IV glioma by the World Health Organization.[7] Compared with other forms of gliomas, it is markedly more invasive and infiltrative.[5] The diagnosis of GBM almost invariably portends a dismal prognosis, with even the most rigorous treatment regimens failing to significantly improve the survival.[8] However, the robust clinical research aimed at discovering target-specific drugs heralds the possibility of a better prognosis for patients with GBM in the future.[9] Citation classics have been published in different specialties and various subspecialties[10-13]; however, none has been conducted for GBM research. To fill this knowledge gap, we performed a bibliometric analysis of the most influential studies on GBM.

METHODS

In April 2019, the Scopus library was accessed for citations of all the published articles on GBM. Scopus was used as the database because of its broader coverage of journals compared with the other databases. No time limitation was set for the search and both original and review articles were included. To ensure a comprehensive coverage of all the available literature, studies pertaining to fields other than medicine, studies on nonhuman subjects, and those without abstracts were also included.

Our main keywords for the search "Glioblastoma Multiforme," "GBM," "Glioblastoma," and "Grade IV Glioma" were found using the MeSH (Medical Subject Heading) database. Keywords were searched for in the title, abstract, and keywords of the articles. Articles were first assessed for their suitability for inclusion by title, and in case of any ambiguity, the abstracts and full texts were also reviewed.

Table 1. Top 100 Articles with Their Total Citations and Citations per Year

Rank	Article	Total Citations	Citations per Year
1	Stupp R, Mason WP, Van Den Bent MJ, Weller M, Fisher B, Taphoorn MJ, Belanger K, Brandes AA, Marosi C, Bogdahn U, Curschmann J. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med*. 2005;352:987-996.	9624	687.43
2	Louis DN, Ohgaki H, Wiestler OD, Cavenee WK, Burger PC, Jouvet A, Scheithauer BW, Kleihues P. The 2007 WHO classification of tumours of the central nervous system. *Acta Neuropathol*. 2007;114:97-109.	6057	504.75
3	Singh SK, Hawkins C, Clarke ID, Squire JA, Bayani J, Hide T, Henkelman RM, Cusimano MD, Dirks PB. Identification of human brain tumour initiating cells. *Nature*. 2004;432:396.	4975	331.67
4	Cancer Genome Atlas Research Network. Comprehensive genomic characterization defines human glioblastoma genes and core pathways. *Nature*. 2008;455:1061-1068.	4240	385.45
5	Shweiki D, Itin A, Soffer D, Keshet E. Vascular endothelial growth factor induced by hypoxia may mediate hypoxia-initiated angiogenesis. *Nature*. 1992;359:843.	3793	140.48
6	Li J, Yen C, Liaw D, Podsypanina K, Bose S, Wang SI, Puc J, Miliaresis C, Rodgers L, McCombie R, Bigner SH. PTEN, a putative protein tyrosine phosphatase gene mutated in human brain, breast, and prostate cancer. *Science*. 1997;275:1943-7.	3755	170.68
7	Hegi ME, Diserens AC, Gorlia T, Hamou MF, De Tribolet N, Weller M, Kros JM, Hainfellner JA, Mason W, Mariani L, Bromberg JE. MGMT gene silencing and benefit from temozolomide in glioblastoma. *N Engl J Med*. 2005;352:997-1003.	3737	266.92
8	Bao S, Wu Q, McLendon RE, Hao Y, Shi Q, Hjelmeland AB, Dewhirst MW, Bigner DD, Rich JN. Glioma stem cells promote radioresistance by preferential activation of the DNA damage response. *Nature*. 2006;444:756.	3649	280.69
9	Singh SK, Clarke ID, Terasaki M, Bonn VE, Hawkins C, Squire J, Dirks PB. Identification of a cancer stem cell in human brain tumors. *Cancer Res*. 2003;63:5821-5828.	3567	222.94
10	Stupp R, Hegi ME, Mason WP, van den Bent MJ, Taphoorn MJ, Janzer RC, Ludwin SK, Allgeier A, Fisher B, Belanger K, Hau P. Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial. *Lancet Oncol*. 2009;10:459-466.	3479	347.9
11	Parsons DW, Jones S, Zhang X, Lin JC, Leary RJ, Angenendt P, Mankoo P, Carter H, Siu IM, Gallia GL, Olivi A. An integrated genomic analysis of human glioblastoma multiforme. *Science*. 2008;321:1807-1812.	3412	310.18
12	Verhaak RG, Hoadley KA, Purdom E, Wang V, Qi Y, Wilkerson MD, Miller CR, Ding L, Golub T, Mesirov JP, Alexe G. Integrated genomic analysis identifies clinically relevant subtypes of glioblastoma characterized by abnormalities in PDGFRA, IDH1, EGFR, and NF1. *Cancer Cell*. 2010;17:98-110.	3120	346.67
13	Yan H, Parsons DW, Jin G, McLendon R, Rasheed BA, Yuan W, Kos I, Batinic-Haberle I, Jones S, Riggins GJ, Friedman H. IDH1 and IDH2 mutations in gliomas. *N Engl J Med*. 2009;360:765-773.	2716	271.6
14	Abbott NJ, Rönnbäck L, Hansson E. Astrocyte—endothelial interactions at the blood-brain barrier. *Nat Rev Neurosci*. 2006;7:41.	2410	185.38
15	Wen PY, Kesari S. Malignant gliomas in adults. *N Engl J Med*. 2008;359:492-507.	2346	213.27
16	Steck PA, Pershouse MA, Jasser SA, Yung WA, Lin H, Ligon AH, Langford LA, Baumgard ML, Hattier T, Davis T, Frye C. Identification of a candidate tumour suppressor gene, MMAC1, at chromosome 10q23. 3 that is mutated in multiple advanced cancers. *Nat Genet*. 1997;15:356.	2308	104.91
17	Skog J, Würdinger T, Van Rijn S, Meijer DH, Gainche L, Curry WT Jr., Carter BS, Krichevsky AM, Breakefield XO. Glioblastoma microvesicles transport RNA and proteins that promote tumour growth and provide diagnostic biomarkers. *Nat Cell Biol*. 2008;10:1470.	2297	208.82
18	Louis DN, Perry A, Reifenberger G, Von Deimling A, Figarella-Branger D, Cavenee WK, Ohgaki H, Wiestler OD, Kleihues P, Ellison DW. The 2016 World Health Organization classification of tumors of the central nervous system: a summary. *Acta Neuropathol*. 2016;131:803-820.	2291	763.66
19	Visvader JE, Lindeman GJ. Cancer stem cells in solid tumours: accumulating evidence and unresolved questions. *Nat Rev Cancer*. 2008;8:755.	2231	202.82
20	Plate KH, Breier G, Weich HA, Risau W. Vascular endothelial growth factor is a potential tumour angiogenesis factor in human gliomas in vivo. *Nature*. 1992;359:845.	2004	74.22
21	Chan JA, Krichevsky AM, Kosik KS. MicroRNA-21 is an antiapoptotic factor in human glioblastoma cells. *Cancer Res*. 2005;65:6029-33.	1906	136.14
22	Phillips HS, Kharbanda S, Chen R, Forrest WF, Soriano RH, Wu TD, Misra A, Nigro JM, Colman H, Soroceanu L, Williams PM. Molecular subclasses of high-grade glioma predict prognosis, delineate a pattern of disease progression, and resemble stages in neurogenesis. *Cancer Cell*. 2006;9:157-73.	1751	134.69

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Table 1. Continued

Rank	Article	Total Citations	Citations per Year
23	Galli R, Binda E, Orfanelli U, Cipelletti B, Gritti A, De Vitis S, Fiocco R, Foroni C, Dimeco F, Vescovi A. Isolation and characterization of tumorigenic, stem-like neural precursors from human glioblastoma. *Cancer Res.* 2004;64:7011-7021.	1699	113.27
24	Dang L, White DW, Gross S, Bennett BD, Bittinger MA, Driggers EM, Fantin VR, Jang HG, Jin S, Keenan MC, Marks KM. Cancer-associated IDH1 mutations produce 2-hydroxyglutarate. *Nature.* 2009;462:739.	1673	167.3
25	Wen PY, Macdonald DR, Reardon DA, Cloughesy TF, Sorensen AG, Galanis E, DeGroot J, Wick W, Gilbert MR, Lassman AB, Tsien C. Updated response assessment criteria for high-grade gliomas: response assessment in neuro-oncology working group. *J Clin Oncol.* 2010;28:1963-1972.	1642	182.44
26	Lacroix M, Abi-Said D, Fourney DR, Gokaslan ZL, Shi W, DeMonte F, Lang FF, McCutcheon IE, Hassenbusch SJ, Holland E, Hess K. A multivariate analysis of 416 patients with glioblastoma multiforme: prognosis, extent of resection, and survival. *J Neurosurg.* 2001;95:190-198.	1635	90.83
27	Stummer W, Pichlmeier U, Meinel T, Wiestler OD, Zanella F, Reulen HJ, ALA-Glioma Study Group. Fluorescence-guided surgery with 5-aminolevulinic acid for resection of malignant glioma: a randomised controlled multicentre phase III trial. *Lancet Oncol.* 2006;7:392-401.	1633	125.62
28	Friedman HS, Prados MD, Wen PY, Mikkelsen T, Schiff D, Abrey LE, Yung WK, Paleologos N, Nicholas MK, Jensen R, Vredenburgh J. Bevacizumab alone and in combination with irinotecan in recurrent glioblastoma. *J Clin Oncol.* 2009;27:4733-4740.	1561	156.1
29	Brennan CW, Verhaak RG, McKenna A, Campos B, Noushmehr H, Salama SR, Zheng S, Chakravarty D, Sanborn JZ, Berman SH, Beroukhim R. The somatic genomic landscape of glioblastoma. *Cell.* 2013;155:462-477.	1433	238.83
30	Furnari FB, Fenton T, Bachoo RM, Mukasa A, Stommel JM, Stegh A, Hahn WC, Ligon KL, Louis DN, Brennan C, Chin L. Malignant astrocytic glioma: genetics, biology, and paths to treatment. *Genes Dev.* 2007;21:2683-2710.	1415	117.92
31	Kleihues P, Louis DN, Scheithauer BW, Rorke LB, Reifenberger G, Burger PC, Cavenee WK. The classification of tumors of the nervous system. *J Neuropathol Exp Neurol.* 2002;61:215-225.	1319	77.59
32	Lee J, Kotliarova S, Kotliarov Y, Li A, Su Q, Donin NM, Pastorino S, Purow BW, Christopher N, Zhang W, Park JK. Tumor stem cells derived from glioblastomas cultured in bFGF and EGF more closely mirror the phenotype and genotype of primary tumors than do serum-cultured cell lines. *Cancer Cell.* 2006;9:391-403.	1369	105.31
33	Kleihues P, Burger PC, Scheithauer BW. The new WHO classification of brain tumours. *Brain Pathol.* 1993;3:255-68.	1350	51.92
34	Batchelor TT, Sorensen AG, di Tomaso E, Zhang WT, Duda DG, Cohen KS, Kozak KR, Cahill DP, Chen PJ, Zhu M, Ancukiewicz M. AZD2171, a pan-VEGF receptor tyrosine kinase inhibitor, normalizes tumor vasculature and alleviates edema in glioblastoma patients. *Cancer Cell.* 2007;11:83-95.	1336	111.33
35	Noushmehr H, Weisenberger DJ, Diefes K, Phillips HS, Pujara K, Berman BP, Pan F, Pelloski CE, Sulman EP, Bhat KP, Verhaak RG. Identification of a CpG island methylator phenotype that defines a distinct subgroup of glioma. *Cancer Cell.* 2010;17:510-522.	1292	143.56
36	Walker MD, Green SB, Byar DP, Alexander Jr. E, Batzdorf U, Brooks WH, Hunt WE, MacCarty CS, Mahaley MS Jr., Mealey J Jr., Owens G. Randomized comparisons of radiotherapy and nitrosoureas for the treatment of malignant glioma after surgery. *N Engl J Med.* 1980;303:1323-1329.	1236	31.69
37	Walker MD, Alexander E, Hunt WE, MacCarty CS, Mahaley MS, Mealey J, Norrell HA, Owens G, Ransohoff J, Wilson CB, Gehan EA. Evaluation of BCNU and/or radiotherapy in the treatment of anaplastic gliomas: a cooperative clinical trial. *J Neurosurg.* 1978;49:333-343.	1224	29.85
38	Liu G, Yuan X, Zeng Z, Tunici P, Ng H, Abdulkadir IR, Lu L, Irvin D, Black KL, John SY. Analysis of gene expression and chemoresistance of CD133+ cancer stem cells in glioblastoma. *Mol Cancer.* 2006;5:67.	1223	94.08
39	Libermann TA, Nusbaum HR, Razon N, Kris R, Lax I, Soreq H, Whittle N, Waterfield MD, Ullrich A, Schlessinger J. Amplification, enhanced expression and possible rearrangement of EGF receptor gene in primary human brain tumours of glial origin. *Nature.* 1985;313:144.	1155	33.97
40	Millauer B, Shawver LK, Plate KH, Risaui W, Ullrich A. Glioblastoma growth inhibited in vivo by a dominant-negative Flk-1 mutant. *Nature.* 1994;367:576.	1131	45.24
41	Mellinghoff IK, Wang MY, Vivanco I, Haas-Kogan DA, Zhu S, Dia EQ, Lu KV, Yoshimoto K, Huang JH, Chute DJ, Riggs BL. Molecular determinants of the response of glioblastomas to EGFR kinase inhibitors. *N Engl J Med.* 2005;353:2012-2024.	1113	79.5
42	Kreisl TN, Kim L, Moore K, Duic P, Royce C, Stroud I, Garren N, Mackey M, Butman JA, Camphausen K, Park J. Phase II trial of single-agent bevacizumab followed by bevacizumab plus irinotecan at tumor progression in recurrent glioblastoma. *J Clin Oncol.* 2009;27:740.	1057	105.7
43	Brem H, Piantadosi S, Burger PC, Walker M, Selker R, Vick NA, Black K, Sisti M, Brem S, Mohr G, Muller P. Placebo-controlled trial of safety and efficacy of intraoperative controlled delivery by biodegradable polymers of chemotherapy for recurrent gliomas. *Lancet.* 1995;345:1008-1012.	1044	43.5

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Table 1. Continued

Rank	Article	Total Citations	Citations per Year
44	Vredenburgh JJ, Desjardins A, Herndon JE, Marcello J, Reardon DA, Quinn JA, Rich JN, Sathornsumetee S, Gururangan S, Sampson J, Wagner M. Bevacizumab plus irinotecan in recurrent glioblastoma multiforme. *J Clin Oncol*. 2007;25:4722-4729.	1042	86.83
45	Schwartzentruber J, Korshunov A, Liu XY, Jones DT, Pfaff E, Jacob K, Sturm D, Fontebasso AM, Quang DA, Tönjes M, Hovestadt V. Driver mutations in histone H3. 3 and chromatin remodelling genes in paediatric glioblastoma. *Nature*. 2012;482:226.	1015	145
46	Curran WJ Jr., Scott CB, Horton J, Nelson JS, Weinstein AS, Fischbach AJ, Chang CH, Rotman M, Asbell SO, Krisch RE, Nelson DF. Recursive partitioning analysis of prognostic factors in three Radiation Therapy Oncology Group malignant glioma trials. *JNCI: J Natl Cancer Inst*. 1993;85:704-710.	1015	39.04
47	Gilbert MR, Dignam JJ, Armstrong TS, Wefel JS, Blumenthal DT, Vogelbaum MA, Colman H, Chakravarti A, Pugh S, Won M, Jeraj R. A randomized trial of bevacizumab for newly diagnosed glioblastoma. *N Engl J Med*. 2014;370:699-708.	1009	201.8
48	Chinot OL, Wick W, Mason W, Henriksson R, Saran F, Nishikawa R, Carpentier AF, Hoang-Xuan K, Kavan P, Cernea D, Brandes AA. Bevacizumab plus radiotherapy—temozolomide for newly diagnosed glioblastoma. *N Engl J Med*. 2014;370:709-722.	970	194
49	Patel AP, Tirosh I, Trombetta JJ, Shalek AK, Gillespie SM, Wakimoto H, Cahill DP, Nahed BV, Curry WT, Martuza RL, Louis DN. Single-cell RNA-seq highlights intratumoral heterogeneity in primary glioblastoma. *Science*. 2014;344:1396-1401.	952	190.4
50	Chen J, Li Y, Yu T-S, McKay RM, Burns DK, Kernie SG, Parada LF. A restricted cell population propagates glioblastoma growth after chemotherapy. *Nature*. 2012; 488:522-526.	946	135.14
51	Maher EA, Furnari FB, Bachoo RM, Rowitch DH, Louis DN, Cavenee WK, DePinho RA. Malignant glioma: genetics and biology of a grave matter. *Genes Dev*. 2001;15:1311-33.	924	51.33
52	Dolecek TA, Propp JM, Stroup NE, Kruchko C. CBTRUS statistical report: primary brain and central nervous system tumors diagnosed in the United States in 2005—2009. *Neuro Oncol*. 2012;14:v1-49.	921	131.57
53	Turcan S, Rohle D, Goenka A, Walsh LA, Fang F, Yilmaz E, Campos C, Fabius AW, Lu C, Ward PS, Thompson CB. IDH1 mutation is sufficient to establish the glioma hypermethylator phenotype. *Nature*. 2012;483:479.	918	131.14
54	Aboody KS, Brown A, Rainov NG, Bower KA, Liu S, Yang W, Small JE, Herrlinger U, Ourednik V, Black PM, Breakefield XO. Neural stem cells display extensive tropism for pathology in adult brain: evidence from intracranial gliomas. *Proc Natl Acad Sci U S A*. 2000;97:12846-12851.	882	46.42
55	Bao S, Wu Q, Sathornsumetee S, Hao Y, Li Z, Hjelmeland AB, Shi Q, McLendon RE, Bigner DD, Rich JN. Stem cell—like glioma cells promote tumor angiogenesis through vascular endothelial growth factor. *Cancer Res*. 2006;66:7843-7848.	876	67.38
56	Westphal M, Hilt DC, Bortey E, Delavault P, Olivares R, Warnke PC, Whittle IR, Jääskeläinen J, Ram Z. A phase 3 trial of local chemotherapy with biodegradable carmustine (BCNU) wafers (Gliadel wafers) in patients with primary malignant glioma. *Neuro Oncol*. 2003;5:79-88.	873	54.56
57	Ohgaki H, Dessen P, Jourde B, Horstmann S, Nishikawa T, Di Patre PL, Burkhard C, Schüler D, Probst-Hensch NM, Maiorka PC, Baeza N. Genetic pathways to glioblastoma: a population-based study. *Cancer Res*. 2004;64:6892-6899.	867	57.8
58	Ohgaki H, Kleihues P. Genetic pathways to primary and secondary glioblastoma. *Am J Pathol*. 2007;170:1445-1453.	854	71.17
59	Ohgaki H, Kleihues P. Population-based studies on incidence, survival rates, and genetic alterations in astrocytic and oligodendroglial gliomas. *J Neuropathol Exp Neurol*. 2005;64:479-489.	852	60.86
60	Piccirillo SG, Reynolds BA, Zanetti N, Lamorte G, Binda E, Broggi G, Brem H, Olivi A, Dimeco F, Vescovi AL. Bone morphogenetic proteins inhibit the tumorigenic potential of human brain tumour-initiating cells. *Nature*. 2006;444:761.	845	65
61	Vredenburgh JJ, Desjardins A, Herndon JE, Dowell JM, Reardon DA, Quinn JA, Rich JN, Sathornsumetee S, Gururangan S, Wagner M, Bigner DD. Phase II trial of bevacizumab and irinotecan in recurrent malignant glioma. *Clin Cancer Res*. 2007;13:1253-1259.	831	69.25
62	Ciafre SA, Galardi S, Mangiola A, Ferracin M, Liu CG, Sabatino G, Negrini M, Maira G, Croce CM, Farace MG. Extensive modulation of a set of microRNAs in primary glioblastoma. *Biochem Biophys Res Commun*. 2005;334:1351-1358.	828	59.14
63	Sugahara T, Korogi Y, Kochi M, Ikushima I, Shigematu Y, Hirai T, Okuda T, Liang L, Ge Y, Komohara Y, Ushio Y. Usefulness of diffusion-weighted MRI with echo-planar technique in the evaluation of cellularity in gliomas. *J Magn Reson Imaging*. 1999;9:53-60.	828	41.4
64	Fine HA, Dear KB, Loeffler JS, McBlack PL, Canellos GP. Meta-analysis of radiation therapy with and without adjuvant chemotherapy for malignant gliomas in adults. *Cancer*. 1993;71:2585-2597.	801	30.81
65	Jain RK, Di Tomaso E, Duda DG, Loeffler JS, Sorensen AG, Batchelor TT. Angiogenesis in brain tumours. *Nat Rev Neurosci*. 2007;8:610.	799	66.58
66	Beier D, Hau P, Proescholdt M, Lohmeier A, Wischhusen J, Oefner PJ, Aigner L, Brawanski A, Bogdahn U, Beier CP. CD133+ and CD133— glioblastoma-derived cancer stem cells show differential growth characteristics and molecular profiles. *Cancer Res*. 2007;67:4010-4015.	798	66.5

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Table 1. Continued

Rank	Article	Total Citations	Citations per Year
67	Yung WK, Albright RE, Olson J, Fredericks R, Fink K, Prados MD, Brada M, Spence A, Hohl RJ, Shapiro W, Glantz M. A phase II study of temozolomide versus procarbazine in patients with glioblastoma multiforme at first relapse. *Br J Cancer*. 2000;83:588.	771	40.58
68	Van Meir EG, Hadjipanayis CG, Norden AD, Shu HK, Wen PY, Olson JJ. Exciting new advances in neuro-oncology: the avenue to a cure for malignant glioma. *CA Cancer J Clin*. 2010;60:166-193.	770	85.56
69	Giese A, Bjerkvig R, Berens ME, Westphal M. Cost of migration: invasion of malignant gliomas and implications for treatment. *J Clin Oncol*. 2003;21:1624-1636.	756	47.25
70	Ricci-Vitiani L, Pallini R, Biffoni M, Todaro M, Invernici G, Cenci T, Maira G, Parati EA, Stassi G, Larocca LM, De Maria R. Tumour vascularization via endothelial differentiation of glioblastoma stem-like cells. *Nature*. 2010;468:824.	745	82.78
71	Ohgaki H, Kleihues P. Epidemiology and etiology of gliomas. *Acta Neuropathol*. 2005;109:93-108.	743	53.07
72	Sturm D, Witt H, Hovestadt V, Khuong-Quang DA, Jones DT, Konermann C, Pfaff E, Tönjes M, Sill M, Bender S, Kool M. Hotspot mutations in H3F3A and IDH1 define distinct epigenetic and biological subgroups of glioblastoma. *Cancer Cell*. 2012;22:425-437.	739	105.57
73	Wang R, Chadalavada K, Wilshire J, Kowalik U, Hovinga KE, Geber A, Fligelman B, Leversha M, Brennan C, Tabar V. Glioblastoma stem-like cells give rise to tumour endothelium. *Nature*. 2010;468:829.	733	81.44
74	Clement V, Sanchez P, De Tribolet N, Radovanovic I, Ruiz I Altaba A. HEDGEHOG-GLI1 signaling regulates human glioma growth, cancer stem cell self-renewal, and tumorigenicity. *Curr Biol*. 2007;17:165-172.	733	61.08
75	Du R, Lu KV, Petritsch C, Liu P, Ganss R, Passegué E, Song H, VandenBerg S, Johnson RS, Werb Z, Bergers G. HIF1α induces the recruitment of bone marrow-derived vascular modulatory cells to regulate tumor angiogenesis and invasion. *Cancer Cell*. 2008;13:206-220.	731	66.45
76	Nishikawa R, Ji XD, Harmon RC, Lazar CS, Gill GN, Cavenee WK, Huang HJ. A mutant epidermal growth factor receptor common in human glioma confers enhanced tumorigenicity. *Proc Natl Acad Sci U S A*. 1994;91:7727-7731.	730	29.2
77	Zhao S, Lin Y, Xu W, Jiang W, Zha Z, Wang P, Yu W, Li Z, Gong L, Peng Y, Ding J. Glioma-derived mutations in IDH1 dominantly inhibit IDH1 catalytic activity and induce HIF-1α. *Science*. 2009;324:261-265.	719	71.9
78	Li Z, Bao S, Wu Q, Wang H, Eyler C, Sathornsumetee S, Shi Q, Cao Y, Lathia J, McLendon RE, Hjelmeland AB. Hypoxia-inducible factors regulate tumorigenic capacity of glioma stem cells. *Cancer Cell*. 2009;15:501-513.	715	71.5
79	Daumas-Duport C, Scheithauer B, O'Fallon J, Kelly P. Grading of astrocytomas: a simple and reproducible method. *Cancer*. 1988;62:2152-2165.	711	22.93
80	Wong ET, Hess KR, Gleason MJ, Jaeckle KA, Kyritsis AP, Prados MD, Levin VA, Yung WA. Outcomes and prognostic factors in recurrent glioma patients enrolled onto phase II clinical trials. *J Clin Oncol*. 1999;17:2572-2578.	709	35.45
81	Hochberg FH, Pruitt A. Assumptions in the radiotherapy of glioblastoma. *Neurology*. 1980;30:907-911.	708	18.15
82	Markert JM, Medlock MD, Rabkin SD, Gillespie GY, Todo T, Hunter WD, Palmer CA, Feigenbaum F, Tornatore C, Tufaro F, Martuza RL. Conditionally replicating herpes simplex virus mutant, G207 for the treatment of malignant glioma: results of a phase I trial. *Gene Ther*. 2000;7:867-874.	707	37.21
83	Kanzawa T, Germano IM, Komata T, Ito H, Kondo Y, Kondo S. Role of autophagy in temozolomide-induced cytotoxicity for malignant glioma cells. *Cell Death Differ*. 2004;11:448-457.	705	47
84	Nutt CL, Mani DR, Betensky RA, Tamayo P, Cairncross JG, Ladd C, Pohl U, Hartmann C, McLaughlin ME, Batchelor TT, Black PM. Gene expression-based classification of malignant gliomas correlates better with survival than histological classification. *Cancer Res*. 2003;63:1602-1607.	700	43.75
85	Omuro A, DeAngelis LM. Glioblastoma and other malignant gliomas: a clinical review. *JAMA*. 2013;310:1842-1850.	694	115.67
86	Zundel W, Schindler C, Haas-Kogan D, Koong A, Kaper F, Chen E, Gottschalk AR, Ryan HE, Johnson RS, Jefferson AB, Stokoe D. Loss of PTEN facilitates HIF-1-mediated gene expression. *Genes Dev*. 2000;14:391-396.	691	36.37
87	Parsa AT, Waldron JS, Panner A, Crane CA, Parney IF, Barry JJ, Cachola KE, Murray JC, Tihan T, Jensen MC, Mischel PS. Loss of tumor suppressor PTEN function increases B7-H1 expression and immunoresistance in glioma. *Nature Med*. 2007;13:84.	683	56.92
88	Seoane J, Le HV, Shen L, Anderson SA, Massagué J. Integration of Smad and forkhead pathways in the control of neuroepithelial and glioblastoma cell proliferation. *Cell*. 2004;117:211-223.	677	45.13
89	Beroukhim R, Getz G, Nghiemphu L, Barretina J, Hsueh T, Linhart D, Vivanco I, Lee JC, Huang JH, Alexander S, Du J. Assessing the significance of chromosomal aberrations in cancer: methodology and application to glioma. *Proc Natl Acad Sci U S A*. 2007;104:20007-20012.	676	56.33

Continues

Table 1. Continued

Rank	Article	Total Citations	Citations per Year
90	Stommel JM, Kimmelman AC, Ying H, Nabioullin R, Ponugoti AH, Wiedemeyer R, Stegh AH, Bradner JE, Ligon KL, Brennan C, Chin L. Coactivation of receptor tyrosine kinases affects the response of tumor cells to targeted therapies. *Science.* 2007;318:287-290.	672	56
91	Holland EC, Celestino J, Dai C, Schaefer L, Sawaya RE, Fuller GN. Combined activation of Ras and Akt in neural progenitors induces glioblastoma formation in mice. *Nat Genet.* 2000;25:55-57.	672	35.37
92	Balss J, Meyer J, Mueller W, Korshunov A, Hartmann C, von Deimling A. Analysis of the IDH1 codon 132 mutation in brain tumors. *Acta Neuropathol.* 2008;116:597-602.	661	60.09
93	Silber J, Lim DA, Petritsch C, Persson AI, Maunakea AK, Yu M, Vandenberg SR, Ginzinger DG, James CD, Costello JF, Bergers G. miR-124 and miR-137 inhibit proliferation of glioblastoma multiforme cells and induce differentiation of brain tumor stem cells. *BMC Med.* 2008;6:14.	661	60.09
94	Fulda S, Wick W, Weller M, Debatin KM. Smac agonists sensitize for Apo2L/TRAIL-or anticancer drug-induced apoptosis and induce regression of malignant glioma in vivo. *Nat Med.* 2002;8:808-15.	655	38.53
95	Stupp R, Dietrich PY, Kraljevic SO, Pica A, Maillard I, Maeder P, Meuli R, Janzer R, Pizzolato G, Miralbell R, Porchet F. Promising survival for patients with newly diagnosed glioblastoma multiforme treated with concomitant radiation plus temozolomide followed by adjuvant temozolomide. *J Clin Oncol.* 2002;20:1375-1382.	654	38.47
96	Gabriely G, Wurdinger T, Kesari S, Esau CC, Burchard J, Linsley PS, Krichevsky AM. MicroRNA 21 promotes glioma invasion by targeting matrix metalloproteinase regulators. *Mol Cell Biol.* 2008;28:5369-5380.	647	58.82
97	Norden AD, Young GS, Setayesh K, MuzikanskyA, Klufas R, Ross GL, Ciampa AS, Ebbeling LG, Levy B, Drappatz J, Kesari S. Bevacizumab for recurrent malignant gliomas: efficacy, toxicity, and patterns of recurrence. *Neurology.* 2008;70:779-787.	645	58.64
98	Wu G, Broniscer A, McEachron TA, Lu C, Paugh BS, Becksfort J, Qu C, Ding L, Huether R, Parker M, Zhang J. Somatic histone H3 alterations in pediatric diffuse intrinsic pontine gliomas and non-brainstem glioblastomas. *Nat Genet.* 2012;44:251-253	626	89.43
99	Barth RF, Coderre JA, Vicente MG, Blue TE. Boron neutron capture therapy of cancer: current status and future prospects. *Clin Cancer Res.* 2005;11:3987-4002.	624	44.57
100	Brandsma D, Stalpers L, Taal W, Sminia P, van den Bent MJ. Clinical features, mechanisms, and management of pseudoprogression in malignant gliomas. *Lancet Oncol.* 2008;9:453-461.	617	56.09

Articles with their primary or major focus on glioblastoma or those in which glioblastoma cells were used as specimens were included. Articles that dealt mainly with other types of gliomas were excluded. Selected articles were sorted using the "Cited by" option and the retrieved list was arranged in descending order.

To reduce bias, 2 authors (M.A. and N.H.) conducted independent searches, an approach of methods first introduced by Lim et al.[14] A list of the 100 top cited articles was prepared by both the reviewers and compared for any discrepancies, which were later resolved with consensus.

The retrieved top 100 articles were analyzed both by Scopus and manual screening and the following characteristics were noted for each article: 1) article title, 2) year of publication, 3) citations, 4) citations per year, 5) names of authors with their H-indices, 6) authors' affiliations, 7) journal name with impact factor, 8) country of origin, and 9) article type. For articles with authors from different countries or institutions, the first author's country and institution were noted. Using the approach used by Hachem et al.,[15] articles were classified on the basis of the study type into the following categories: 1) laboratory investigation, 2) review, 3) meta-analysis, 4) guidelines/consensus, and 5) clinical studies (prospective analyses, retrospective analyses, and randomized trials). The impact factor of the journals was extracted from Thomson Reuters Journal Citation Reports. The mean, median, and interquartile ranges were calculated for the total number of citations and the number of citations per year. Tables and charts were prepared using Microsoft Word and Excel, respectively. SPSS version 23.0 (IBM Corp., Armonk, New York, USA) was used to apply tests of significance.

The Pearson moment correlation coefficient was applied to check for any correlation between the impact factor of a journal and the number of its articles in the list. Correlation between the impact factor and the total number of citations of a journal was also assessed. For all statistical tests, a P value of <0.05 was considered significant. Ethical approval was not needed for the study, because it was limited to analyzing previously published data.

RESULTS

Table 1 lists the top 100 articles with their citation counts and citations per year. The total number of citations for 100 articles was 148,594, of which 4.8% were self-citations. Citations ranged from 9624 to 617, with a median of 935 (interquartile range, 906) and an average of 1485.94 citations per article. Citations per year ranged from 18.15 to 763.66, the mean number of citations per year was 124.0733, and the median was 75.905 (interquartile range, 92.1475).

Of the 100 articles, 81 were original articles, 18 were reviews, and 1 was a conference paper (Figure 1). The most cited article was "Radiotherapy plus

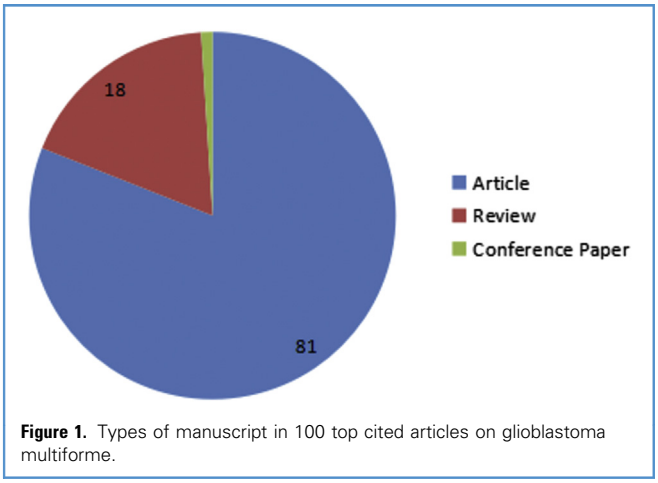

Figure 1. Types of manuscript in 100 top cited articles on glioblastoma multiforme.

concomitant and adjuvant temozolomide for glioblastoma" published in *New England Journal of Medicine* in 2005, with a total of 9624 citations, which helped set the standard of care for management of many patients with GBM. However, when sorted according to citations per year, the most impactful article was found to be "The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary," with an average of 763.66 citations per year, which was published in *Acta Neuropathologica*.

Figure 2 presents the total citations of the top 100 articles in each year. The articles were published over 38 years from 1978 to 2016, with the greatest number of articles published in the 10-year period from 2001 to 2010 (Figure 3).

The top cited articles originated from 22 countries, with the greatest contribution from the United States ($n = 75$) followed by Germany ($n = 19$), Canada ($n = 13$), and Switzerland ($n = 13$). The countrywise contribution of the articles is shown in Figure 4.

Table 2 lists the institutes that contributed ≥6 articles to the list. The institutes that were at the forefront in GBM research were Harvard Medical School ($n = 21$), Dana-Farber Cancer Institute ($n = 16$), and Brigham and Women's Hospital ($n = 15$). The U.S. National Institutes of Health (NIH) was the largest funding sponsor followed by Foundations for the National Institutes of Health and the Goldhirsh Foundation.

A total of 159 authors contributed to the 100 articles. Table 3 shows the top 12 authors in GBM with ≥5 articles in the list. P. Kleihues and D.N. Louis were the leading authors ($n = 8$) followed closely by D.D. Bigner and W.K. Cavenee ($n = 7$). H. Ohgaki had the highest number of articles as the first author ($n = 4$). For the top 12 authors, there was a significant and moderately positive correlation between the H-indices and the number of their articles in the list ($r = 0.593$; $P = 0.042$).

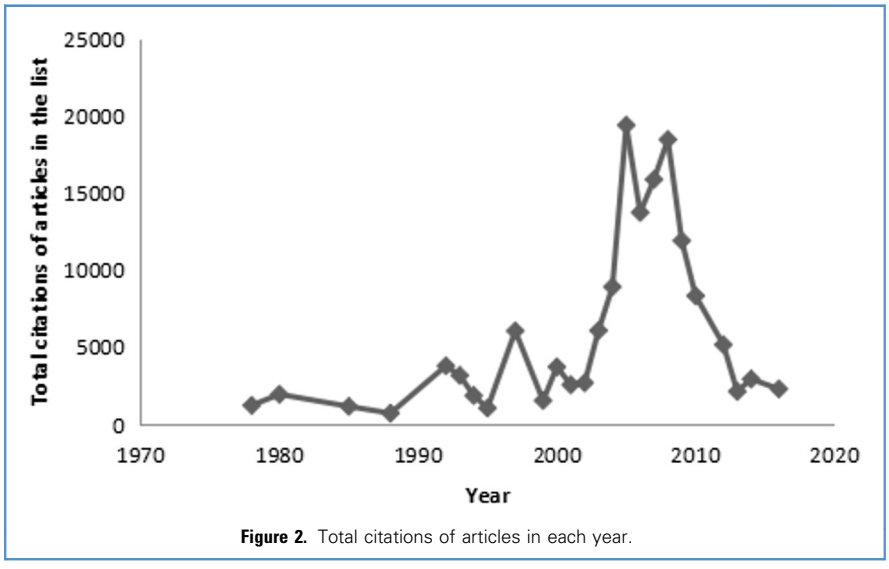

Figure 2. Total citations of articles in each year.

The top cited articles were published in 36 different journals (Table 4) which were further classified into the following categories: 1) general medicine, 2) oncology, 3) neuroscience. 4) basic sciences/biology, and 5) others (journals that did not fit into any of the other 4 categories). Most of the articles were published in oncology-oriented ($n = 34$), general medicine ($n = 27$), and basic sciences/biology ($n = 18$) journals. Only 14 articles were published in neuroscience-specific journals. *Nature* made the greatest contribution to the research on GBM, with a total of 14 articles in the list, and *Cancer Cell* and *New England Journal of Medicine* were the second big contenders. The most frequently cited article came from *New England Journal of Medicine*, with a total of 9624 citations. There was no significant correlation between the impact factor of the journal and the number of its articles in the list ($r = 0.073$; $P = 0.667$). Similarly, there was no correlation between the impact factor of the journals and their total number of citations in the list ($r = 0.138$; $P = 0.416$).

Table 5 shows the classification of the articles on the basis of study type. Articles were classified into 4 study types: 1) laboratory investigations, 2) clinical studies, 3) reviews and meta-analysis, and 4) guidelines/consensus.

Fifty-two of the studies were laboratory investigations that intended to discover the underlying mechanisms leading to both development and progression of the disease, to test the efficacy of the drugs, and to trace prognosis on a cellular and molecular level.

Twenty-seven studies were clinical, including randomized trials and cohort studies (prospective and retrospective). Twelve were randomized clinical trials, 7 of which were prospective whereas the remainder were retrospective. Clinical

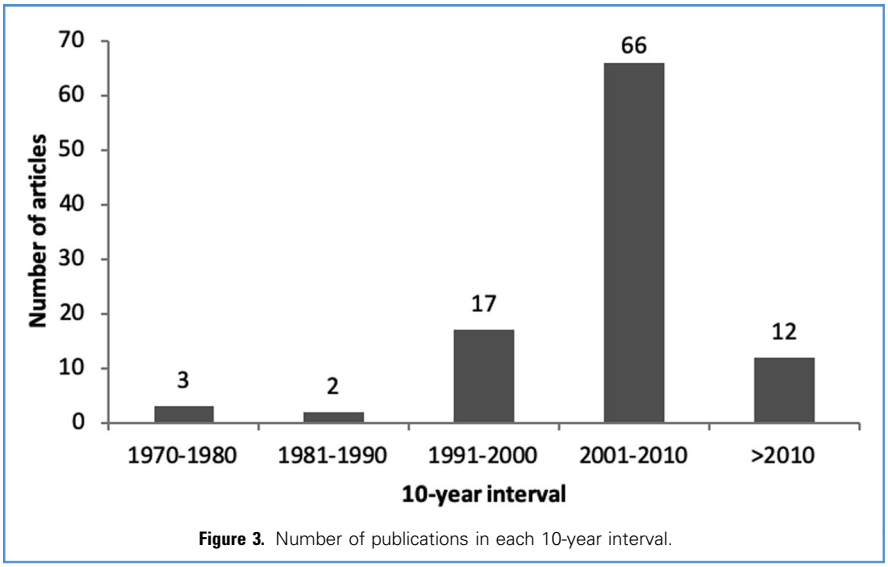

Figure 3. Number of publications in each 10-year interval.

studies are usually devised to test the efficacy and safety profile of the various therapeutic options available and to inspect the effect of tailored approaches on individuals.

Sixteen articles were reviews that summarized all the findings to date on GBM, ranging from pathogenesis to therapeutic regimens. Only one was a meta-analysis that provided the highest evidence-based findings to show which management approach was better.

Five studies outlined general guidelines, recommendations, and consensus developed among the researchers that influence the decision making and clinical practice of the physicians and caregivers.

Fifty-seven studies focused on identifying the key mechanisms leading to the pathogenesis of GBM. These studies included discovering any dysregulation in gene functioning, genetic mutations, deranged biological markers, attenuated transcription factors, and cell surface markers. Besides genetics, a multiple causality model, including both environmental factors and the role of drugs, was also analyzed in these studies. Nine studies devised the classification criteria for variants of GBM and other gliomas. These studies inspected the similarities and differences between different malignant gliomas and tried to identify the causes of heterogeneity of GBM. This classification was mostly devised on the various clinical markers or imaging differences present.

Therapy was categorized into further subgroups including radiotherapy, chemotherapy, and any possible new agents that were proved beneficial in improving the prognostic outcomes. About 38 of the studies included trials and observational studies that tested the existing drug regimens and also evaluated for the safety and efficacy of the developing therapeutic modalities on the tumor

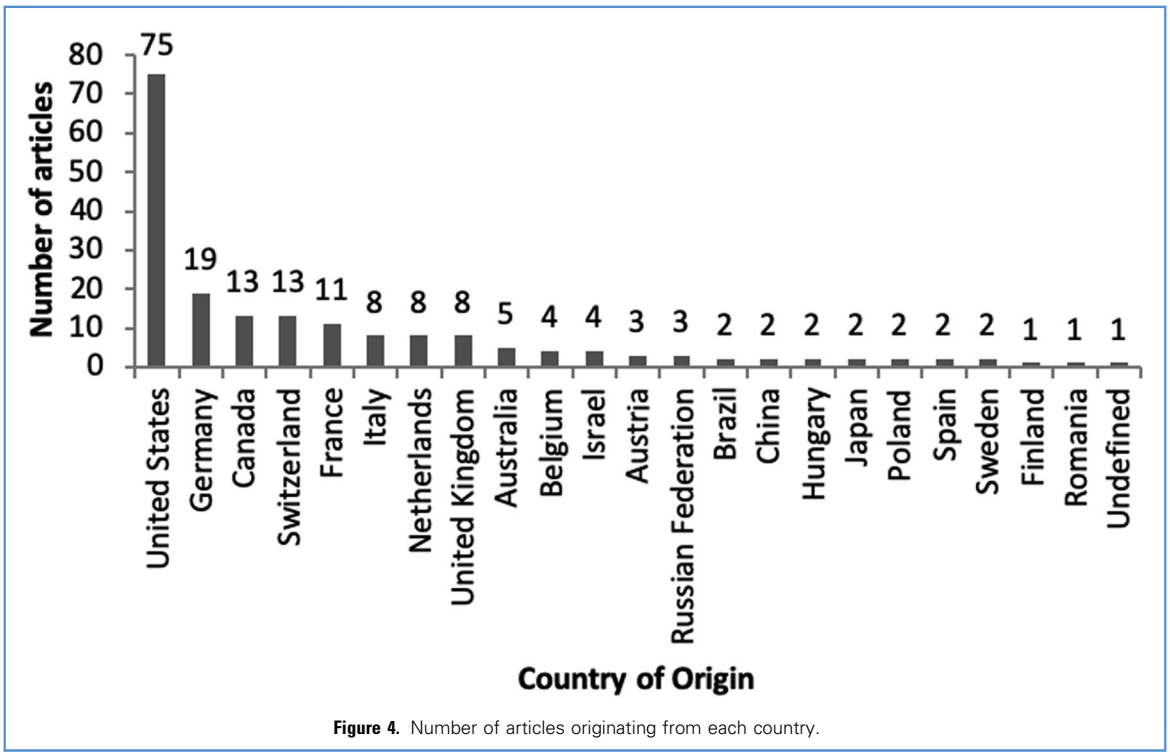

Figure 4. Number of articles originating from each country.

Table 2. Institutions Affiliated with ≥6 Articles in the List

Institution	Number of Articles
Harvard Medical School	21
Dana-Farber Cancer Institute	16
Brigham and Women's Hospital	15
Massachusetts General Hospital	14
University of Texas MD Anderson Cancer Center	12
University of California, San Francisco	12
Memorial Sloan Kettering Cancer Center	10
Massachusetts Institute of Technology	10
Duke University Medical Center	10
University of California, San Diego	9
German Cancer Research Center	8
Broad Institute	7
Howard Hughes Medical Institute	7
International Agency for Research on Cancer	7
Ludwig Institute for Cancer Research San Diego	6
University of Toronto	6
UniversitatsSpital Zurich	6
University of California, Los Angeles	6

progression. About 7 of those studies solely focused on the therapeutic efficacy of radiotherapy, about 22 on chemotherapy, 5 on new agents, 1 on surgical resection, and 16 investigated the outcomes of >1 therapeutic approach.

Imaging was studied in 3 of the studies, 3 on clinical presentation and diagnosis, and 2 on epidemiology. The most cited article "Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma" was a randomized controlled trial and helped set the standard of treatment care for patients with GBM.

DISCUSSION

We present a detailed analysis of the top cited articles on GBM and outline various important research trends and advances in this field. This list can be of tremendous help to clinicians and researchers because it helps to identify landmark research. It can also encourage collaboration among researchers from diverse fields, allowing them to come together and probe further into areas of GBM research. In addition, classification of studies based on themes and article descriptors can serve to identify key areas in GBM, both in which research is ongoing and in which it may be warranted.

Although Percival Bailey and Harvey Cushing introduced the term GBM in 1926,[16] our results found that most of the highly cited studies were not conducted until 1978. The time span that yielded the most cited top 100 articles was 1978–2016. This finding is in contrast to the bibliometrics in other related areas of research such as neurosurgery, malignancies such as breast cancer, and malignant mesothelioma, which listed older articles.[12,17,18] However, specialties such as cardiology and thrombolytic therapy show trends similar to our study, which is not surprising given that these fields, like GBM, are rapidly evolving, and older practices are quickly replaced by newer approaches.

The peak research activity was observed during 2005–2012. In this time frame, 58 articles were published, with 2007 and 2008 being the most monumental years, contributing 12 and 11 articles, respectively, to the list. There was a sharp increase in the number of research articles in the 1990s. This 1990s peak has also been observed in a similar bibliometric analysis on neuro-oncology.[15] The paucity of literature before the 1990s also dictates that most of the research on GBM in terms of diagnostic techniques and therapeutic regimens has been conducted relatively recently. In addition, recent conversations about GBM in the media after the death of high-profile individuals such as Senator John McCain and Senator Edward Kennedy may have sparked the interest of researchers in this field.[19] Increasing incidence of radiation-induced gliomas since the 1960s may also have prompted significant and wide-scale research activity in recent decades.[20]

Because citation count alone is not an adequately reliable measure of the scientific worth of an article, we used citations per year as a more credible parameter for assessing the true impact of an article over the years. When the articles were arranged according to citations per year, the top cited article was found to be a relatively recent article by D.N. Louis et al., published in 2016.[21] This finding affirms that when based on the citation count alone, newer articles are likely to rank lower even if their impact is more than that of older articles. Consistent with other bibliometrics, there seems to have been a decline in the number of articles in the recent years. This finding is because newer articles show less representation in the list of top 100 articles because they tend to be cited less in their initial years of publication and also because there is shorter time span to generate citation rates.[15]

GBM, although primarily a topic of oncology, permeates the disciplines of neurosurgery, neurology, radiotherapy, basic science, and general medicine, which explains the wide variety of journals in which the top cited articles were published. Only a few articles ($n = 14$) were published in neuroscience-specific journals, whereas most were published in oncology, basic sciences, and general medicine journals. This situation is different from the bibliometrics published in other fields, such as cardiology and thrombolytic therapy, in which most of the top articles came from specialty-specific journals because advances in these fields are primarily of interest to researchers and clinicians who are associated with these specialties.[22,23] Hence, the Bradford law, which holds true for these bibliometrics, did not apply to our analysis.[24] This law dictates that authors, to maximize the impact of their article in a field, usually tend to cite a few core specialty-specific journals rather than general medicine journals. This observation implies that GBM is of interest to authors and researchers in a wide variety of disciplines, and research in this field reaches out to a diverse readership, within the domain of both neuroscience and general medicine.

Although generally authors tend to centralize their publications in journals with wider readership and higher impact factor, we did not find a positive correlation between the impact factor of a journal and the number of citations it received. This finding is in contrast to the bibliometric analysis on neuro-oncology, which found a positive correlation between

Table 3. Authors with ≥5 Articles in the List

Author	Total Number of Articles	Affiliation	First Position	Last Position	Others	H-Index
Kleihues P.	8	University of Zurich, Zurich, Switzerland International Agency for Research on Cancer (IARC), Lyon, France	2	5	1	85
Louis D.N.	8	Harvard Medical School	3	1	4	109
Bigner D.D.	7	Duke University, Durham, North Carolina, USA	0	3	4	110
Cavenee W.K.	7	Ludwig Institute for Cancer Research, University of California San Diego, San Diego, California, USA	0	2	5	97
Ohgaki H.	6	International Agency for Research on Cancer (IARC), Lyon, France	4	0	2	76
Wen P.Y.	6	Dana-Farber Cancer Institute Boston, Massachusetts. USA	1	2	3	82
Aldape K.	5	Ontario Cancer Institute University of Toronto, Toronto, Ontario, Canada	0	2	3	103
Brennan C.	5	Memorial Sloan Kettering Cancer Center, New York, New York, United States	0	0	5	65
Ding L.	5	Washington University School of Medicine in St. Louis, St. Louis, Missouri, USA	0	0	5	86
Mikkelsen T.	5	Henry Ford Hospital, Detroit, Michigan, USA	0	0	5	68
Rich J.N.	5	UCLA San Diego, California, USA	0	2	3	79
Stupp R.	5	Multidisciplinary Oncology Center, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland	3	1	1	72

journal impact factor and the number of its citation classics in the list of the top 100 articles.[15] Hence, it can be concluded that an impactful article in GBM garners citations regardless of the journal in which it is published.

Three fourths ($n = 75$) of the articles in our list came from the United States. This finding concurs with the results of several other bibliometric analyses. "Citation classics in neuro-oncology" also showed a similar trend. This much larger contribution of the United States toward GBM research can be attributed, in part, to the large-scale government funding for brain research, which is more than twice that of Europe.[25] In concordance with bibliometric analyses in other areas of research, the contribution from Asian countries was minimal.

However, a small but significant portion of scientific contribution by European countries cannot be ignored, because the top 2 authors in our list are from Switzerland and France, respectively. The increasing incidence of GBM, along with advances in diagnostic techniques, in the developed world[26,27] and underreporting in the developing world[28] may also account for the disparity. The South-East Asian population has also experienced radiation-induced gliomas, particularly Japan, which may justify its participation alongside China, which is low but still significant. However, relative to the perceived incidence, representation of the South-East Asian cohort in the top 100 is low ($n = 4$), which emphasizes that there is a need for the scientific community in the developed world to collaborate with researchers from developing countries.

All the top 4 institutes were Harvard Medical School affiliates and the top 10 institutes were United States base, which is dictated by the trend in funding of brain cancer research according to which Harvard-affiliated institutions come in the top 50 list of NIH-funded institutions.[29] Most of the articles in our list were original articles and <20% were review articles, with only one of them a meta-analysis. More than half of the articles in our list were laboratory investigations and most dealt with the pathogenesis, molecular biology, and genetics of GBM. This finding is not surprising given that much remains to be discovered about the tumor characteristics of GBM. Even as the most common primary brain tumor in adults, GBM is a relatively rare cancer type overall, with heterogeneous molecular and biologic characteristics. As a result, trials are difficult to conduct because funding is not as easily available as is for other forms of cancer, such as breast and lung cancer, which have a higher global prevalence. Furthermore, high-quality laboratory and genetics studies are important because they can help lay down the foundation on which well-designed trials are based.

Only 31% of the articles were funded by public and private sector organizations. Most of the articles received funding from various sources, with NIH emerging as the sole funder for about 10 articles, followed by the Foundation for the National Institutes of Health. Major funding organizations hailed from the United States but there were also significant contributions from other countries. The NIH funding for brain cancers has increased over the years, perhaps because of the increasing incidence of GBM. This increase is in contrast to older diseases, such as diabetes, the funding for which shows a downward trend because standards of care and treatment guidelines have become well established and well known in the scientific community.[30]

Bibliometrics, being a purely quantitative measure, is more reflective of the recognition of an article in the scientific community rather than of its quality and impact on future research. Hence, more robust methods of qualitative assessment such as peer review and methodological

Table 4. Journals with their Impact Factors and Total Number of Articles in the List

Serial No.	Journal Title	Journal Category	Impact Factor	Number of Articles	Total Number of Citations
1	*Nature*	General medicine	41.577	14	27,089
2	*Cancer Cell*	Oncology	22.844	8	11,053
3	*New England Journal of Medicine*	General medicine	79.258	8	22,751
4	*Cancer Research*	Oncology	9.13	7	10,413
5	*Journal of Clinical Oncology*	Oncology	26.303	7	7421
6	*Science*	Basic sciences	3.893	5	9510
7	*Acta Neuropathologica*	Neuroscience	15.872	4	9752
8	*Genes and Development*	Basic sciences/ biology	9.462	3	3030
9	*Lancet Oncology*	Oncology	36.418	3	5729
10	*Nature Genetics*	Basic sciences/ biology	27.125	3	3606
11	*Proceedings of the National Academy of Sciences of the United States Of America*	Others	9.504	3	2288
12	*Cancer*	Oncology	6.537	2	1512
13	*Cell*	Basic sciences/ biology	31.398	2	2110
14	*Clinical Cancer Research*	Oncology	6.217	2	1255
15	*Journal of Neuropathology and Experimental Neurology*	Neuroscience	3.49	2	2231
16	*Journal of Neurosurgery*	Neuroscience	4.318	2	2859
17	*Nature Medicine*	General medicine	32.621	2	1338
18	*Nature Reviews Neuroscience*	Neuroscience	32.635	2	3209
19	*Neuro Oncology*	Neuroscience	9.384	2	1794
20	*Neurology*	Neuroscience	4.649	2	1353
21	*American Journal of Pathology*	Others	4.069	1	854
22	*BMC Medicine*	General medicine	9.088	1	661
23	*Biochemical and Biophysical Research Communications*	Others	2.559	1	828
24	*Brain Pathology*	Others	6.187	1	1350
25	*British Journal of Cancer*	Oncology	5.922	1	771
26	*CA Cancer Journal for Clinicians*	Oncology	244.485	1	770
27	*Cell Death and Differentiation*	Basic sciences/ biology	8	1	705
28	*Current Biology*	Basic sciences/ biology	9.251	1	733
29	*Gene Therapy*	Basic sciences/ biology	3.203	1	707
30	*JAMA Journal of the American Medical Association*	General medicine	47.661	1	694
31	*Journal of Magnetic Resonance Imaging*	Others	3.612	1	828

Continues

Table 4. Continued

Serial No.	Journal Title	Journal Category	Impact Factor	Number of Articles	Total Number of Citations
32	*Journal of the National Cancer Institute*	Oncology	11.238	1	1015
33	*Lancet*	General medicine	53.254	1	1044
34	*Molecular and Cellular Biology*	Basic sciences/ biology	3.813	1	647
35	*Molecular Cancer*	Oncology	7.776	1	1223
36	*Nature Cell Biology*	Basic sciences/ biology	19.064	1	2308
37	*Nature Reviews Cancer*	Oncology	42.784	1	2231

analysis may be combined with bibliometric parameters to give a more holistic insight into research dynamics. Second, although a meticulous search strategy was adopted to prepare a comprehensive list of top cited articles, we might have inadvertently missed some old articles, because Scopus is known to omit citations from before 1980. Some newer articles might also have been missed because there might not be enough time for them to accumulate the required number of citations to be included in the list. One additional limitation is that only 1 database was recruited for the analysis. Although self-citations may be considered a source of potential bias in bibliometrics, the percentage of self-citations in our study is less than that of general medicine (4.8% vs. 6.5%) and, hence, would not have made a considerable influence on our results. These limitations may have a slight impact on the overall results but are unlikely to shift the major trends shown in this article.

Table 5. Classification of Articles Based on Study Type

Types of Study	Number of Articles
Laboratory investigations	51
Clinical Studies	27
Retrospective	8
Prospective	7
Randomized	12
Reviews	16
Meta-analysis	1
Guidelines/consensus	5

CONCLUSIONS

Our bibliometric analysis presents a detailed evaluation of the most influential studies in GBM. This analysis can serve as a benchmark in drawing the attention of researchers worldwide to identify and contribute to the increasing scientific work. Albeit not enough, because of its malignant potential and dismal survival, GBM has managed to attract some financial and technical assistance over the years. Although ongoing research is still concentrated in a few countries, this analysis helps emphasize the significance of devising therapeutic regimens by using a multidisciplinary approach. Because of the increasing incidence and heterogeneity of GBM, it is a prerequisite that new avenues for increased collaboration within the scientific community, and increased funding, are pursued.

REFERENCES

1. Luukkonen T. Invited review article: bibliometrics and evaluation of research performance. *Ann Med*. 1990;22:145-150.
2. Ellegaard O, Wallin JA. The bibliometric analysis of scholarly production: how great is the impact? *Scientometrics*. 2015;105:1809-1831.
3. Moed HF. New developments in the use of citation analysis in research evaluation. *Arch Immunol Ther Exp (Warsz)*. 2009;57:13.
4. Wallin JA. Bibliometric methods: pitfalls and possibilities. *Basic Clin Pharmacol Toxicol*. 2005;97:261-275.
5. Kleihues P, Louis DN, Scheithauer BW, et al. The WHO classification of tumors of the nervous system. *J Neuropathol Exp Neurol*. 2002;61:215-225.
6. Furnari FB, Fenton T, Bachoo RM, et al. Malignant astrocytic glioma: genetics, biology, and paths to treatment. *Genes Dev*. 2007;21:2683-2710.
7. Komori T. The 2016 WHO classification of tumours of the central nervous system: The major points of revision. *Neurol Med Chir (Tokyo)*. 2017;57:301-311.
8. Adamson C, Kanu OO, Mehta AI, et al. Glioblastoma multiforme: a review of where we have been and where we are going. *Expert Opin Investig Drugs*. 2009;18:1061-1083.
9. Agnihotri S, Burrell KE, Wolf A, et al. Glioblastoma, a brief review of history, molecular genetics, animal models and novel therapeutic strategies. *Arch Immunol Ther Exp (Warsz)*. 2013;61:25-41.
10. Yoon DY, Yun EJ, Ku YJ, et al. Citation classics in radiology journals: the 100 top-cited articles, 1945–2012. *Am J Roentgenol*. 2013;201:471-481.
11. Yi F, Ma J, Ni W, et al. The top cited articles on glioma stem cells in Web of Science. *Neural Regen Res*. 2013;8:1431.
12. Ponce FA, Lozano AM. Highly cited works in neurosurgery. Part I: the 100 top-cited papers in neurosurgical journals: A review. *J Neurosurg*. 2010;112:223-232.
13. Yeung AW, Goto TK, Leung WK. At the leading front of neuroscience: a bibliometric study of the 100 most cited articles. *Front Hum Neurosci*. 2017;11:363.
14. Lim KJ, Yoon DY, Yun EJ, et al. Characteristics and trends of radiology research: a survey of original articles published in AJR and Radiology between 2001 and 2010. *Radiology*. 2012;264:796-802.

15. Hachem LD, Mansouri A, Juraschka K, Taslimi S, Pirouzmand F, Zadeh G. Citation classics in neuro-oncology: assessment of historical trends and scientific progress. *Neuro Oncol*. 2017;19:1158-1172.

16. Stoyanov GS, Dzhenkov DL. On the concepts and history of glioblastoma multiforme-morphology, genetics and epigenetics. *Folia Med*. 2018;60:48-66.

17. Glynn RW, Scutaru C, Kerin MJ, Sweeney KJ. Breast cancer research output, 1945-2008: a bibliometric and density-equalizing analysis. *Breast Cancer Research*. 2010;12:R108.

18. Ugolini D, Neri M, Casilli C, et al. A bibliometric analysis of scientific production in mesothelioma research. *Lung Cancer*. 2010;70:129-135.

19. Mia De Graaf. The-brain-cancer-killed-John-McCain-Beau-Biden-Ted-Kennedy. Daily Mail. 2018. Available at: https://www.dailymail.co.uk/health/article-6095427/The-brain-cancer-killed-John-McCain-Beau-Biden-Ted-Kennedy.html. Accessed June 4, 2019.

20. Salvati M, Frati A, Russo N, et al. Radiation-induced gliomas: report of 10 cases and review of the literature. *Surg Neurol*. 2003;60:60-67.

21. Louis DN, Perry A, Reifenberger G, et al. The 2016 World Health Organization classification of tumors of the central nervous system: a summary. *Acta Neuropathol*. 2016;131:803-820.

22. Siddiqi TJ, Usman MS, Khan MS, et al. The 100 most influential papers in the field of thrombolytic therapy: a bibliometric analysis. *Am J Cardiovasc Drugs*. 2017;17:319-333.

23. Shuaib W, Khan MS, Shahid H, Valdes EA, Alweis R. Bibliometric analysis of the top 100 cited cardiovascular articles. *Am J Cardiol*. 2015;115:972-981.

24. Brookes BC. Bradford's law and the bibliography of science. *Nature*. 1969;224:953-956.

25. Sobocki P, Lekander I, Berwick S, Olesen J, Jönsson B. Resource allocation to brain research in Europe (RABRE). *Eur J Neurosci*. 2006;24:2691-2693.

26. Thakkar JP, Dolecek TA, Horbinski C, et al. Epidemiologic and molecular prognostic review of glioblastoma. *Cancer Epidemiol Biomarkers Prev*. 2014;23:1985-1996.

27. Philips A, Henshaw DL, Lamburn G, O'Carroll MJ. Brain tumours: rise in glioblastoma multiforme incidence in England 1995–2015 suggests an adverse environmental or lifestyle factor. *J Environ Public Health*. 2018;2018:7910754.

28. Ohgaki H. Epidemiology of brain tumors. *Methods Mol Biol*. 2009;472:323-342.

29. Top 50 NIH-Funded Institutions of 2018. GEN—Genetic Engineering and Biotechnology News. 2019. Available at: https://www.genengnews.com/a-lists/top-50-nih-funded-institutions-of-2018/. Accessed June 4, 2019.

30. NIH Categorical Spending—NIH Research Portfolio Online Reporting Tools (RePORT). Available at: https://report.nih.gov/categorical_spending.aspx. Accessed June 4, 2019.

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