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Original Article

Bibliometric analysis of the top 100 most-cited articles on astrocytoma

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ABSTRACT

Background: Citation analysis reflects the scientific recognition and influential performance of a published article within its field. We aim to identify the top 100 most-cited articles on astrocytoma using this bibliometric analysis method.

Methods: In May 2020, we performed a thorough search in the Scopus database using the word "Astrocytoma." The top 100 most-cited articles were arranged based on citation count in descending order. The resultant articles were then analyzed with an assessment of pertinent factors.

Results: The most-cited articles on astrocytoma had been cited 23,720 times. The top-cited article received a total of 682 citations, with an average of 34.1 citations annually. The list comprised eight clinical trials, in which the highest cited article received 625 citations. Articles were published from 1975 to 2015 with the 1995–2005 era as the most prolific period. Neuropathology studies were the most studied category, followed by clinical studies. The United States of America was the most significant contributor, with 49 published articles. The University of California San Francisco was the most contributing institution by producing 11 articles. Articles were published in 32 different journals led by the Cancer Research Journal, with a total of 12 publications. Approximately 160 authors contributed to the list in which Scheithauer, B.W. contributed the most with a total of eight articles.

Conclusion: This report clustered the most impactful articles on astrocytoma. It serves as an adequate tool to identify publication trends and helps in achieving evidence-based clinical practice.

Keywords: Astrocytoma, Bibliometric, Citation analysis, Low-grade glioma, Neurosurgery

INTRODUCTION

Astrocytoma (ICD: 9400/3) is a tumor of the central nervous system (CNS) originating from astrocytes, a glial cell with various essential supporting roles. Commonly, astrocytoma is integrated with oligodendroglioma in a more extensive nomenclature termed "glioma."[17] Conversely, astrocytoma contains astrocytic tumor entities independent of the glioma classification, such as pilocytic astrocytoma (World Health Organization [WHO] Grade I; ICD: 9421/1) and subependymal giant cell astrocytoma (SEGA; WHO Grade I; ICD: 9384/1).[17] Astrocytoma is categorized into low- and high-grade tumors. In general, glioma forms 26% of primary CNS tumors with an incidence of 6.57/100,000; low-grade glioma contributes to 15% of

primary CNS tumors.[12,19,20,23] Astrocytoma confers the most considerable role in gliomas (75.8%).[19]

The preferred astrocytoma site of origin is the supratentorial compartment, mainly the frontal (25.6%) followed by temporal (19.6%) lobes, apart from pilocytic astrocytoma (infratentorial compartment) and primary glioblastoma (temporal lobe predilection in 31% of patients).[7,19] Low-grade astrocytoma has a 5-year progression-free survival (PFS) of 37–55% and overall survival (OS) of 58–72%. Despite the rapidly evolving multimodal management paradigm, high-grade astrocytoma's outcome remains dismal, with anaplastic astrocytoma patients' median survival of 3–5 years and glioblastoma with 14–16 months.[15,24]

Bibliometric analysis studies the impact of specific articles in their respective field. Since its inception in 1969, bibliometric analysis has gained popularity and approval among the scientific community, as it introduces junior physicians and others in different specialties to the subject analyzed in the article.[21] Furthermore, it explores the chronological trend in the searched topic, especially in subjects with a vast publication rate. Citation analysis can act as a supplementary tool to the peer-review of articles, with its objective ranking and analysis of individual studies. Multiple bibliometric analyses were published in the field of neurosurgery, such as in vestibular schwannoma, low-grade glioma, meningioma, and pituitary adenoma.[1,2,3,13] Of the published bibliometric analyses, no article has focused on astrocytoma.

MATERIALS AND METHODS

Search strategy

A title specific nontime restricted search using the Scopus database was performed in May 2020 utilizing the following keywords "astrocytoma, diffuse astrocytoma, anaplastic astrocytoma, pilocytic astrocytoma, subependymal giant cell astrocytoma, pleomorphic astrocytoma, and xanthoastrocytoma." The outcome of the search was rearranged based on the citation count (CC), and the top 100 most-cited articles were collected for the authors' review.

Data

The critical data of importance were collected and included the following: article title, authors, first authors specialty, institute of contribution, publishing journal, country of origin, year of publication, and CC. Critical appraisal of the top 100 articles from abstract to full articles was performed to categorize the studied titles into the following 10 categories: clinical, clinicopathological, clinicosurgical, medical management, surgical management, radiotherapy, chemotherapy, chemoradiotherapy, neuropathology, and neuroradiology.

Bibliometric parameters

Article-based cytometrics like CC were obtained from the Scopus database, and the citation per year (CY) was calculated based on the total number of citations divided by the number of years since their publication. Journal-based cytometric identifiers such as the Source Normalized Impact per Paper (SNIP), SCImago Journal Rank (SJR), and impact factor were obtained from the Scopus base.

RESULTS

Article, author, and journal analysis

The search outcome showed 4303 articles that were published on astrocytoma. The top 100 most-cited articles received a total of 23,720 citations with an average CC of 237 cites per paper with an overall 9.2% rate of self-citations. The list of the most influential articles is listed in [Table 1]. The top 100 articles were published between 1975 and 2015, with approximately 50% of published articles that were produced between 1995 and 2005, which marks the most prolific era on the influential publication on astrocytoma [Figure 1].

Subcategorical critical appraisal showed that approximately 50% of publications were discussing neuropathological studies, and clinical studies halted the 2nd most studied category by 17 articles in the list [Figure 2].

The USA was the most active in studying astrocytoma by collaborating in producing 67 articles in the top 100 most-cited articles [Figure 3]. Almost 150 institutes contributed the most influential work; institutes with more than 5 articles of contribution showed that the University of California San Francisco was the most fertile by producing 11 articles, while the German Cancer Research Center headed the 2nd position by producing 9 articles [Figure 4].

A quantified review of the 32 contributing journals showed that 8 journals contributed to at least 4 or more articles in the

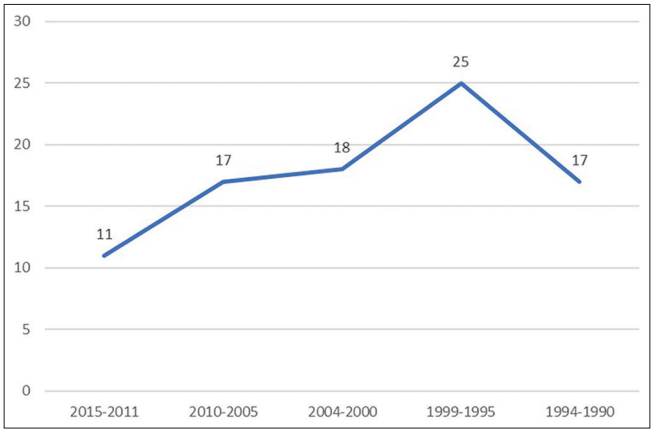

Figure 1: Publication trends.

Table 1: Top 100 most cited articles on astrocytoma.

Rank	Authors	Title	Journal	CC	CY
1st	Smith *et al*., 2000	Alterations of chromosome arms 1p and 19q as predictors of survival in oligodendrogliomas, astrocytomas, and mixed oligoastrocytomas	Journal of Clinical Oncology	682	34.1
2nd	Watanabe *et al*., 2009	IDH1 mutations are early events in the development of astrocytomas and oligodendrogliomas	American Journal of Pathology	666	60.5
3rd	Yung *et al*., 1999	Multicenter phase II trial of temozolomide in patients with anaplastic astrocytoma or anaplastic oligoastrocytoma at first relapse	Journal of Clinical Oncology	658	31.3
4th	Van Den Bent *et al*., 2005	Long-term efficacy of early versus delayed radiotherapy for low-grade astrocytoma and oligodendroglioma in adults: The EORTC 22845 randomised trial	Lancet	625	41
5th	Schindler *et al*., 2011	Analysis of BRAF V600E mutation in 1,320 nervous system tumors reveals high mutation frequencies in pleomorphic xanthoastrocytoma, ganglioglioma and extra-cerebellar pilocytic astrocytoma	Acta Neuropathologica	617	68.5
6th	Wick *et al*., 2012	Temozolomide chemotherapy alone versus radiotherapy alone for malignant astrocytoma in the elderly: The NOA-08 randomised, phase 3 trial	The Lancet Oncology	609	76.1
7th	Wallner *et al*., 1989	Patterns of failure following treatment for glioblastoma multiforme and anaplastic astrocytoma	International Journal of Radiation Oncology, Biology, Physics	572	18.45
8th	Burger *et al*., 1985	Glioblastoma multiforme and anaplastic astrocytoma pathologic criteria and prognostic implications	Cancer	525	15
9th	Smith *et al*., 2001	PTEN mutation, EGFR amplification, and outcome in patients with anaplastic astrocytoma and glioblastoma multiforme	Journal of the National Cancer Institute	478	25.1
10th	Franz *et al*., 2006	Rapamycin causes regression of astrocytomas in tuberous sclerosis complex	Annals of Neurology	465	33
11th	Franz *et al*., 2013	Efficacy and safety of everolimus for subependymal giant cell astrocytomas associated with tuberous sclerosis complex (EXIST-1): A multicentre, randomised, placebo-controlled phase 3 trial	The Lancet	453	64.7
12th	McGirt *et al*., 2009	Independent association of extent of resection with survival in patients with malignant brain astrocytoma: Clinical article	Journal of Neurosurgery	446	40.5
13th	Laws Jr. *et al*., 1984	Neurosurgical management of low-grade astrocytoma of the cerebral hemispheres	Journal of Neurosurgery	392	11
14th	Jones *et al*., 2013	Recurrent somatic alterations of FGFR1 and NTRK2 in pilocytic astrocytoma	Nature Genetics	386	55
15th	Saas *et al*., 1997	Fas ligand expression by astrocytoma in vivo: Maintaining immune privilege in the brain?	Journal of Clinical Investigation	372	16.17
16th	Zhu *et al*., 2005	Early inactivation of p53 tumor suppressor gene cooperating with NF1 loss induces malignant astrocytoma	Cancer Cell	350	23.3
17th	Thomas *et al*., 2001	Randomized trial of procarbazine, lomustine, and vincristine in the adjuvant treatment of high-grade astrocytoma: A Medical Research Council Trial	Journal of Clinical Oncology	313	16.4
18th	Fults *et al*., 1992	p53 Mutation and Loss of Heterozygosity on Chromosomes 17 and 10 during Human Astrocytoma Progression	Cancer Research	301	10.7
19th	Bleehen & Stenning, 1991	A medical research council trial of two radiotherapy doses in the treatment of grades 3 and 4 astrocytoma	British Journal of Cancer	299	10.3
20th	Finlay *et al*., 1995	Randomized phase III trial in childhood high-grade astrocytoma comparing vincristine, lomustine, and prednisone with the eight-drugs-in-1-day regimen	Journal of Clinical Oncology	279	11.16

(Contd...)

Table 1: (*Continued*).

Rank	Authors	Title	Journal	CC	CY
21st	Spostol *et al*., 1989	The effectiveness of chemotherapy for treatment of high grade astrocytoma in children: Results of a randomized trial - A report from the Childrens Cancer Study Group	Journal of Neuro-Oncology	279	9
22nd	Jaeckle *et al*., 1998	Correlation of tumor O6 methylguanine-DNA methyltransferase levels with survival of malignant astrocytoma patients treated with bis-chloroethylnitrosourea: A Southwest Oncology Group study	Journal of Clinical Oncology	278	12.6
23rd	Broderick *et al*., 2004	Mutations of PIK3CA in anaplastic oligodendrogliomas, high-grade astrocytomas, and medulloblastomas	Cancer Research	277	15.3
24th	Von Deimling *et al*., 1992	P53 Mutations Are Associated with 17p Allelic Loss in Grade II and Grade III Astrocytoma	Cancer Research	268	9.5
25th	Shaw *et al*., 1989	Radiation therapy in the management of low-grade supratentorial astrocytomas	Journal of Neurosurgery	264	8.5
26th	Tishler *et al*., 1992	Taxol Sensitizes Human Astrocytoma Cells to Radiation	Cancer Research	263	9.39
27th	Giese *et al*., 1996	Dichotomy of astrocytoma migration and proliferation	International Journal of Cancer	250	10.4
28th	Okamoto *et al*., 2004	Population-based study on incidence, survival rates, and genetic alterations of low-grade diffuse astrocytomas and oligodendrogliomas	Acta Neuropathologica	246	15.3
29th	Reardon *et al*., 2006	Recent advances in the treatment of malignant astrocytoma	Journal of Clinical Oncology	243	17.3
30th	Guha *et al*., 1995	Expression of PDGF and PDGF receptors in human astrocytoma operation specimens supports the existence of an autocrine loop	International Journal of Cancer	228	9.12
31st	Reuss *et al*., 2015	ATRX and IDH1-R132H immunohistochemistry with subsequent copy number analysis and IDH sequencing as a basis for an "integrated" diagnostic approach for adult astrocytoma, oligodendroglioma and glioblastoma	Acta Neuropathologica	227	45.4
32nd	McCormack *et al*., 1992	Treatment and survival of low-grade astrocytoma in adults--1977–1988	Neurosurgery	217	7.75
33rd	Bajenaru *et al*., 2002	Astrocyte-specific inactivation of the neurofibromatosis 1 gene (NF1) is insufficient for astrocytoma formation	Molecular and Cellular Biology	216	12
34th	Laperriere *et al*., 1998	Randomized study of brachytherapy in the initial management of patients with malignant astrocytoma	International Journal of Radiation Oncology Biology Physics	214	9.72
35th	Sathornsumetee *et al*., 2008	Tumor angiogenic and hypoxic profiles predict radiographic response and survival in malignant astrocytoma patients treated with bevacizumab and irinotecan	Journal of Clinical Oncology	211	17.58
36th	Jones *et al*., 2009	Oncogenic RAF1 rearrangement and a novel BRAF mutation as alternatives to KIAA1549:BRAF fusion in activating the MAPK pathway in pilocytic astrocytoma	Oncogene	210	19
37th	Korshunov *et al*., 2009	Combined molecular analysis of BRAF and IDH1 distinguishes pilocytic astrocytoma from diffuse astrocytoma	Acta Neuropathologica	208	18.9
38th	Pasquier *et al*., 1980	Extraneural metastases of astrocytomas and glioblastomas clinicopathological study of two cases and review of literature	Cancer	208	5.2
39th	Watanabe *et al*., 1997	Incidence and timing of p53 mutations during astrocytoma progression in patients with multiple biopsies	Clinical Cancer Research	207	9

(Contd...)

Table 1: (*Continued*).

Rank	Authors	Title	Journal	CC	CY
40th	Konnikova *et al*., 2003	Knockdown of STAT3 expression by RNAi induces apoptosis in astrocytoma cells	BMC Cancer	206	12.11
41st	Ding *et al*., 2001	Astrocyte-specific expression of activated p21-ras results in malignant astrocytoma formation in a transgenic mouse model of human gliomas	Cancer Research	206	10.84
42nd	Harsh IV *et al*., 1987	Reoperation for recurrent glioblastoma and anaplastic astrocytoma	Neurosurgery	205	6.12
43rd	Fontebasso *et al*., 2014	Recurrent somatic mutations in ACVR1 in pediatric midline high-grade astrocytoma	Nature Genetics	202	33.6
44th	Aldape *et al*., 2004	Immunohistochemical detection of EGFRvIII in high malignancy grade astrocytomas and evaluation of prognostic significance	Journal of Neuropathology and Experimental Neurology	195	12.18
45th	Giese *et al*., 1994	Determinants of Human Astrocytoma Migration	Cancer Research	195	7.5
46th	Henson *et al*., 1994	The retinoblastoma gene is involved in malignant progression of astrocytomas	Annals of Neurology	195	7.5
47th	Sonoda *et al*., 2001	Akt pathway activation converts anaplastic astrocytoma to glioblastoma multiforme in a human astrocyte model of glioma	Cancer Research	194	10.2
48th	Abdulrauf *et al*., 1998	Vascular endothelial growth factor expression and vascular density as prognostic markers of survival in patients with low-grade astrocytoma	Journal of Neurosurgery	194	8.81
49th	Chan J*et al*., 2004	Pathogenesis of tuberous sclerosis subependymal giant cell astrocytomas: Biallelic inactivation of TSC1 or TSC2 leads to mTOR activation	Journal of Neuropathology and Experimental Neurology	193	12.06
50th	Sonoda *et al*., 2001	Formation of intracranial tumors by genetically modified human astrocytes defines four pathways critical in the development of human anaplastic astrocytoma	Cancer Research	193	10.15
51st	Van Veelen *et al*., 1998	Supratentorial low grade astrocytoma: Prognostic factors, dedifferentiation, and the issue of early versus late surgery	Journal of Neurology Neurosurgery and Psychiatry	192	8.7
52nd	Kondziolka *et al*., 1993	Unreliability of contemporary neurodiagnostic imaging in evaluating suspected adult supratentorial (low-grade) astrocytoma	Journal of Neurosurgery	188	6.96
53rd	Louis, 1997	A molecular genetic model of astrocytoma histopathology	Brain Pathology	187	8.13
54th	Bar *et al*., 2008	Frequent gains at chromosome 7q34 involving BRAF in pilocytic astrocytoma	Journal of Neuropathology and Experimental Neurology	178	14.83
55th	Orellana *et al*., 1985	Phorbol ester inhibits phosphoinositide hydrolysis and calcium mobilization in cultured astrocytoma cells	Journal of Biological Chemistry	172	6.88
56th	Sallinen *et al*., 1994	Prognostication of astrocytoma patient survival by Ki-67 (MIB-1), PCNA, and S-phase fraction using archival paraffin-embedded samples	The Journal of Pathology	167	6.42
57th	Sahm *et al*., 2014	Farewell to oligoastrocytoma: in situ molecular genetics favor classification as either oligodendroglioma or astrocytoma	Acta Neuropathologica	166	27.6
58th	Chow *et al*., 2011	Cooperativity within and among Pten, p53, and Rb Pathways Induces High-Grade Astrocytoma in Adult Brain	Cancer Cell	166	18.4
59th	Fults *et al*., 1990	Allelotype of Human Malignant Astrocytoma	Cancer Research	166	5.53
60th	Gajjar *et al*., 1997	Low-grade astrocytoma: A decade of experience at St. Jude Children's Research Hospital	Journal of Clinical Oncology	164	7.13
61st	Burkhard *et al*., 2003	A population-based study of the incidence and survival rates in patients with pilocytic astrocytoma	Journal of Neurosurgery	163	9.5

(Contd...)

Table 1: (*Continued*).

Rank	Authors	Title	Journal	CC	CY
62nd	Lieb *et al*., 1997	The Neuropeptide Substance P Activates Transcription Factor NF-κB and κB-Dependent Gene Expression in Human Astrocytoma Cells	Journal of Immunology	163	7.08
63rd	Duprex *et al*., 1999	Observation of measles virus cell-to-cell spread in astrocytoma cells by using a green fluorescent protein-expressing recombinant virus	Journal of Virology	162	7.71
64th	Wakimoto *et al*., 1996	Prognostic significance of Ki-67 labeling indices obtained using MIB-1 monoclonal antibody in patients with supratentorial astrocytomas	Cancer	162	6.75
65th	Ransom *et al*., 1992	Cytogenetic and loss of heterozygosity studies in ependymomas, pilocytic astrocytomas, and oligodendrogliomas	Genes, Chromosomes and Cancer	160	5.7
66th	Bouaboula *et al*., 1995	Stimulation of cannabinoid receptor CB1 induces krox-24 expression in human astrocytoma cells	Journal of Biological Chemistry	159	6.36
67th	Taratuto *et al*., 1984	Superficial cerebral astrocytoma attached to dura: Report of six cases in infants	Cancer	155	4.3
68th	Berger *et al*., 1990	Neurophysiological monitoring during astrocytoma surgery.	Neurosurgery clinics of North America	153	5.1
69th	Keles *et al*., 2006	Volumetric extent of resection and residual contrast enhancement on initial surgery as predictors of outcome in adult patients with hemispheric anaplastic astrocytoma	Journal of Neurosurgery	152	10.8
70th	Chan *et al*., 1998	Expression of vascular endothelial growth factor and its receptors in the anaplastic progression of astrocytoma, oligodendroglioma, and ependymoma	American Journal of Surgical Pathology	152	6.9
71st	Mocchetti *et al*., 1989	Regulation of nerve growth factor biosynthesis by β-adrenergic receptor activation in astrocytoma cells: A potential role of c-Fos protein	Proceedings of the National Academy of Sciences of the United States of America	150	4.83
72nd	Bunin *et al*., 1990	Gestational and Familial Risk Factors for Childhood Astrocytoma: Results of a Case-Control Study	Cancer Research	149	4.96
73rd	Guizzetti *et al*., 1996	Acetylcholine as a mitogen: Muscarinic receptor-mediated proliferation of rat astrocytes and human astrocytoma cells	European Journal of Pharmacology	148	6.16
74th	Guan *et al*., 2010	MiRNA-196 is upregulated in glioblastoma but not in anaplastic astrocytoma and has prognostic significance	Clinical Cancer Research	147	14.7
75th	Kasahara *et al*., 1991	IL-1 and TNF-α induction of IL-8 and monocyte chemotactic and activating factor (MCAF) mRNA expression in a human astrocytoma cell line	Immunology	147	5.06
76th	Butowski *et al*., 2006	Diagnosis and treatment of recurrent high-grade astrocytoma	Journal of Clinical Oncology	146	10.41
77th	Broniscer & Gajjar, 2004	Supratentorial High-Grade Astrocytoma and Diffuse Brainstem Glioma: Two Challenges for the Pediatric Oncologist	Oncologist	145	9.06
78th	Leibel *et al*., 1975	The role of radiation therapy in the treatment of astrocytomas	Cancer	144	3.2
79th	Hawkins *et al*., 2011	BRAF-KIAA1549 fusion predicts better clinical outcome in pediatric low-grade astrocytoma	Clinical Cancer Research	143	15.8
80th	Cin *et al*., 2011	Oncogenic FAM131B-BRAF fusion resulting from 7q34 deletion comprises an alternative mechanism of MAPK pathway activation in pilocytic astrocytoma	Acta Neuropathologica	142	15.7
81st	Komotar *et al*., 2004	Pilocytic and Pilomyxoid Hypothalamic/Chiasmatic Astrocytomas	Neurosurgery	142	8.875

(Contd...)

Table 1: (*Continued*).

Rank	Authors	Title	Journal	CC	CY
82nd	Larner *et al*., 1998	A phase I-II trial of lovastatin for anaplastic astrocytoma and glioblastoma multiforme	American Journal of Clinical Oncology: Cancer Clinical Trials	142	6.45
83rd	Minehan *et al*., 1995	Spinal cord astrocytoma: Pathological and treatment considerations	Journal of Neurosurgery	142	5.68
84th	Lachman *et al*., 1987	Growth-promoting effect of recombinant interleukin 1 and tumor necrosis factor for a human astrocytoma cell line	Journal of Immunology	142	4.3
85th	Gitter *et al*., 1995	Amyloid β peptide potentiates cytokine secretion by interleukin-1β-activated human astrocytoma cells	Proceedings of the National Academy of Sciences of the United States of America	139	5.56
86th	Elexpuru-Camiruaga *et al*., 1995	Susceptibility to Astrocytoma and Meningioma: Influence of AUelism at Glutathione 5-Transferase (GSTT1 and GSTM1) and Cytochrome P-450 (CYP2D6) Loci	Cancer Research	139	5.56
87th	Xiao *et al*., 2002	Astrocyte inactivation of the pRb pathway predisposes mice to malignant astrocytoma development that is accelerated by PTEN mutation	Cancer Cell	138	7.6
88th	Salhia *et al*., 2005	Inhibition of Rho-kinase affects astrocytoma morphology, motility, and invasion through activation of Rac1	Cancer Research	137	9.13
89th	Hernández *et al*., 1998	Secretory phospholipase A2 activates the cascade of mitogen-activated protein kinases and cytosolic phospholipase A2 in the human astrocytoma cell line 1321N1	Journal of Biological Chemistry	136	6.18
90th	Aarsen *et al*., 2004	Long-term sequelae in children after cerebellar astrocytoma surgery	Neurology	135	8.43
91st	Shamah *et al*., 1993	Dominant-negative mutants of platelet-derived growth factor revert the transformed phenotype of human astrocytoma cells	Molecular and Cellular Biology	135	5
92nd	Rao *et al*., 2010	Genome-wide expression profiling identifies deregulated miRNAs in malignant astrocytoma	Modern Pathology	134	13.4
93rd	Wang *et al*., 2005	Monomorphous angiocentric glioma: A distinctive epileptogenic neoplasm with features of infiltrating astrocytoma and ependymoma	Journal of Neuropathology and Experimental Neurology	134	8.93
94th	Fisher *et al*., 2000	A clinicopathologic reappraisal brain stem tumor classification: Identification of pilocytic astrocytoma and fibrillary astrocytoma as distinct entities	Cancer	134	6.7
95th	Henske *et al*., 1997	Loss of tuberin in both subependymal giant cell astrocytomas and angiomyolipomas supports a two-hit model for the pathogenesis of tuberous sclerosis tumors	American Journal of Pathology	133	5.7
96th	Carbonara *et al*., 1994	9q34 loss of heterozygosity in a tuberous sclerosis astrocytoma suggests a growth suppressor-like activity also for the TSC1 gene	Human Molecular Genetics	133	5.11
97th	Krueger *et al*. 2013	Everolimus long-term safety and efficacy in subependymal giant cell astrocytoma	Neurology	132	18.85
98th	Shepherd *et al*., 1991	Subependymal giant cell astrocytoma: A clinical, pathological, and flow cytometric study	Neurosurgery	132	4.55
99th	Cenci *et al*., 2008	Down-regulation of RNA editing in pediatric astrocytomas: ADAR2 editing activity inhibits cell migration and proliferation	Journal of Biological Chemistry	131	10.91
100th	Weissenberger *et al*., 1997	Development and malignant progression of astrocytomas in GFAP-v-src transgenic mice	Oncogene	128	5.56

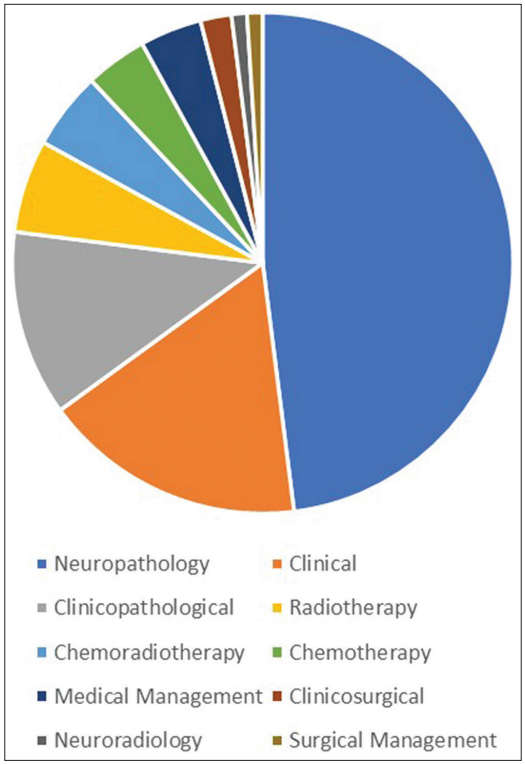

Figure 2: Studied categories.

list. The Cancer Research Journal was the most productive by publishing 12 articles. The Journal of Clinical Oncology is the 2nd most prolific journal and had the highest impact (26), highest SNIP score (5.2), and highest SJR score (11.7) among the journals of contribution [Figure 5]. Around 160 authors have contributed to the most influential publications with 11 authors contributing to at least 5 articles in the list; Scheithauer, B.W., a neuropathologist, has the highest number of contributing articles (8) and the highest H-index (118) when compared to the top authors [Figure 6].

A summary of the eight identified clinical trials showed the most-cited clinical trial on astrocytoma was "Long-term Efficacy of early versus delayed radiotherapy for low-grade astrocytoma and oligodendroglioma in adults: The European Organization for Research and Treatment of Cancer (EORTC) 22,845 Randomized trial" that received a total of 625 citations and 41 citations/year which was published in The *Lancet* journal and authored by Van Den Bent *et al*. in 2005 [Table 2].

The top most-cited article in the field of astrocytoma was published in 2000 by Smith *et al*. in the *Journal of Clinical Oncology* titled "Alterations of chromosome arms 1p and 19q as predictors of survival in oligodendrogliomas, astrocytomas, and mixed oligoastrocytomas" where it received a total of 682 citations and 34.1 citations/year.

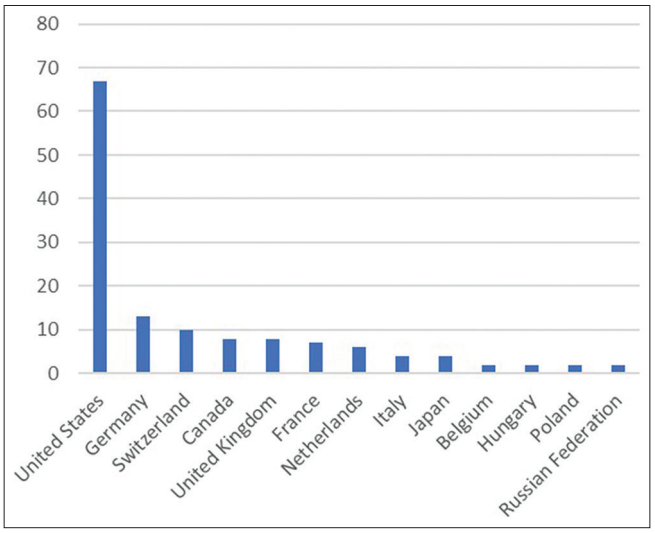

Figure 3: Countries with a contribution of two or more articles.

DISCUSSION

The highest cited article in our top 100 list with 682 CC is "Alterations of chromosome arms 1p and 19q as predictors of survival in oligodendrogliomas, astrocytomas, and mixed oligoastrocytomas" by Smith *et al*. published in 2000 in the Journal of Clinical Oncology. However, it is ranked 9th in terms of CY (34.1). The large CC of the article stems from the novel finding of positive outcomes in 1p/19q co-deleted tumors. Of the 162 glioma samples collected, 79 were astrocytomas, 52 oligodendrogliomas, and 31 mixed oligoastrocytomas. There was a significant finding of high 1p/19q codeletion associated oligodendroglioma ($P < 0.0001$) and that it confers positive chemosensitivity ($P = 0.03$).[26] The positive finding was not found in astrocytoma. After the publication of this article, the approach in diagnosing oligodendroglioma depended on the presence of 1p/19q codeletion instead of only histological diagnosis, and the prognosis improved with a 5-year OS of 74.9% in oligodendroglioma and 51.1% in anaplastic oligodendroglioma (WHO Grade III; ICD: 9451/3).[18]

The 2nd highest cited article with 666 citations is "Isocitrate dehydrogenase 1(IDH1) mutations are early events in the development of astrocytomas and oligodendrogliomas" by Watanabe *et al*. in 2009 in the *American Journal of Pathology*. It is ranked 4th in terms of CY (60.5). Of the 321 gliomas collected in the study, 130 showed IDH1 mutation. Diffuse astrocytoma showed the highest rate of having IDH mutation (88%) followed by secondary glioblastoma (82%). Primary glioblastoma and pilocytic astrocytoma were found to have low IDH mutation (5 and 10%, respectively).[29] IDH mutation was found to be the 1st molecular pathway mutated, then other mutations occur afterward, such as P53 and 1p/19q codeletion. They concluded that as IDH mutation is the earliest marker of astrocytoma, it may play

Table 2: List of the most cited clinical trials on astrocytoma.

Rank	Authors	Title	Journal	Citation count	Citation per year
1st	Van Den Bent *et al*., 2005	Long-term efficacy of early versus delayed radiotherapy for low-grade astrocytoma and oligodendroglioma in adults: The EORTC 22,845 randomized trial	Lancet	625	41
2nd	Wick *et al*., 2012	Temozolomide chemotherapy alone versus radiotherapy alone for malignant astrocytoma in the elderly: The NOA-08 randomized, Phase 3 trial	Lancet Oncology	609	76.1
3rd	Franz *et al*., 2013	Efficacy and safety of everolimus for subependymal giant cell astrocytomas associated with tuberous sclerosis complex (EXIST-1): A multicenter, randomized, placebo-controlled Phase 3 trial	Lancet	453	64.7
4th	Thomas *et al*., 2001	Randomized trial of procarbazine, lomustine, and vincristine in the adjuvant treatment of high-grade astrocytoma: A Medical Research Council Trial	Journal of Clinical Oncology	313	16.4
5th	Bleehen and Stenning, 1991	A medical research council trial of two radiotherapy doses in the treatment of Grades 3 and 4 astrocytoma	British Journal of Cancer	299	10.3
6th	Finlay *et al*., 1995	Randomized Phase III trial in childhood high-grade astrocytoma comparing vincristine, lomustine, and prednisone with the eight-drugs-in-1-day regimen	Journal of Clinical Oncology	279	11.1
7th	Sposto *et al*., 1989	The effectiveness of chemotherapy for the treatment of high-grade astrocytoma in children: Results of a randomized trial – A report from the Children's Cancer Study Group	Journal of Neuro-Oncology	279	9
8th	Larner *et al*., 1998	A Phase I-II trial of lovastatin for anaplastic astrocytoma and glioblastoma multiforme	American Journal of Clinical Oncology: Cancer Clinical Trials	142	6.45

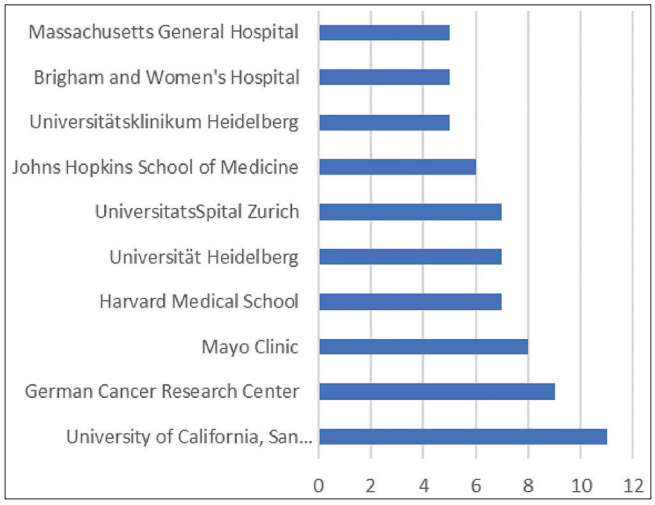

Figure 4: Institutions with a contribution of five or more articles.

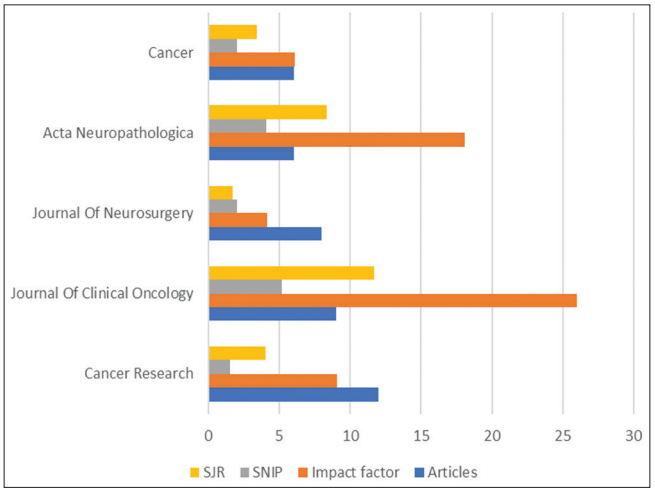

Figure 5: Journals with a contribution of four or more articles.

a role in tumorigenesis. This study sparked more authors to research the area of IDH mutation associated with glioma. It was found that mutant-type IDH astrocytomas have a better prognosis than their wild-type counterparts with better chemosensitivity to temozolomide (TMZ).[6,14,25] The response, stable, and progression rates in mutant-type IDH low-grade glioma receiving TMZ were 33%, 59%, 8%, respectively. In contrast, wild-type IDH low-grade glioma who received TMZ had a response, stable, and progression rates of 16%, 25%, and 59%, respectively.[14]

Further published articles have studied the physiology of IDH mutations concerning gliomas.[6] IDH is an integral enzyme in the citric acid cycle and facilitates the bilateral conversion of NADPH-dependent alpha-ketoglutarate to

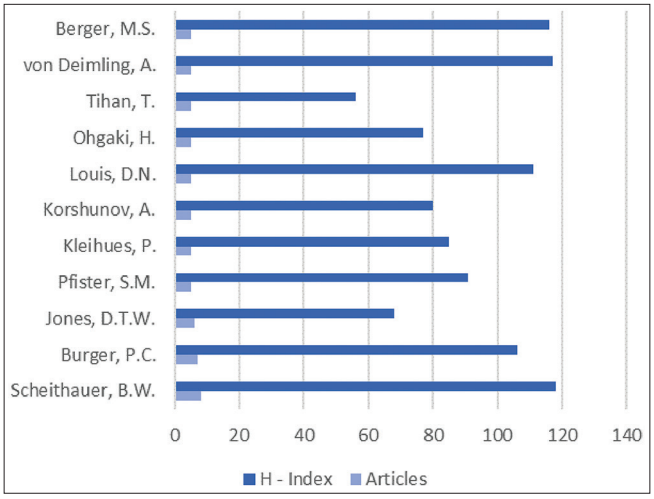

Figure 6: Authors with a contribution of five or more articles.

isocitrate, and vice versa.[6] Mutation in IDH is a concomitant loss and gain of function, with a new conversion pathway of alpha-ketoglutarate to 2-hydroxyglutarate. When excess 2-hydroxyglutarate accumulates in the cytosol, multiple enzymes relevant for nucleic and amino acids are inhibited; the combined effects of direct cell toxicity and enzymatic inhibition are thought to play a role in glioma formation.[6]

Neuropathological studies comprised the majority of studied influential articles. The 1st ranked cited article (ranked 14th overall) with 386 CC and 55 CY is "Recurrent somatic alterations of FGFR1 and NTRK2 in pilocytic astrocytoma" by Jones *et al*. in 2013 in *Nature Genetics* journal. The authors found that pilocytic astrocytoma is a single pathway tumor with over activation of mitogen-activated protein kinase due to mutations in FGFR1, NTRK2, and PTPN11 genes.[16] They concluded that specific drug agents targeting the mutated genes might play a role in the management; furthermore, FGFR1 mutation may have an impact in midline/brainstem glioblastoma formation.[16]

The most-cited clinical study (ranked 8th overall) in the list accounted for 525 CC, and 15 CY is "Glioblastoma multiforme and anaplastic astrocytoma pathologic criteria and prognostic implications" by Burger *et al*. in 1985 in the Cancer journal. In this article, two groups of patients with high-grade glioma (known as malignant astrocytic gliomas at the time) were studied to define histologic variants based on three-tiered systems and its associated outcome. They concluded that malignant astrocytic gliomas could be classified into anaplastic astrocytoma and glioblastoma multiforme, with the latter conferring a more unfortunate outcome than the former.[5]

The most influential publication on radiotherapeutic management of astrocytoma (ranked 4th overall) was "Long-term efficacy of early versus delayed radiotherapy for low-grade astrocytoma and oligodendroglioma in adults: The EORTC 22845 randomized trial" by Van Den Bent *et al*. in 2005 in the Lancet journal with 525 CC and 41 CY. The randomized controlled trial (RCT) segregated patients into an early radiotherapy group (n = 157) and late radiotherapy group (n = 157) and found that early radiotherapy group had a better PFS with a median of 5.3 years than late radiotherapy group with a median of 3.4 years ($P < 0.0001$).[28] However, there was no effect on OS (7.2 years vs. 7.1 years, $P = 0.87$). Seizures were better controlled at 1-year postradiation.

Another RCT on radiotherapy for astrocytoma was the 3rd ranked cited article (ranked 19th overall) with 299 CC and 10.3 CY is "A medical research council trial of two radiotherapy doses in the treatment of Grades 3 and 4 astrocytoma" by Bleehen and Stenning in 1992 in the *British Journal of Cancer*. Of the 474 patients with high-grade astrocytoma, 318 were allocated to high-dose radiation course (60 Gy in 30 fractions over 6 weeks) and 156 to low-dose course (45 Gy in 20 fractions over 4 weeks). The trial showed modest improvement and statistical significance in median survival from 9 months to 12 months in the high-dose receiving group.[4]

The analyzed studies entertaining chemotherapy and radiation therapy treatment in astrocytoma showed three published RCT. The 1st ranked cited article (ranked 6th overall) with 609 CC and 76.1 CY is "TMZ chemotherapy alone versus radiotherapy alone for malignant astrocytoma in the elderly: The NOA-08 randomized, Phase 3 trial" by Wick *et al*. in 2012 in the *Lancet Oncology* journal. The trial allocated 373 patients with high-grade astrocytoma into TMZ group (n = 195) and radiotherapy group (n = 178), with median OS of 9.6 months in radiotherapy (95% CI 8.2–10.8) versus 8.6 months in TMZ (7.3–10.2) (P [noninferiority] = 0.033). The MGMT promoter methylated high-grade astrocytoma patients had a longer OS than nonmethylated group (median 11.9 vs. 8.2 months, $P = 0.014$). The event-free survival was higher in the methylated group receiving TMZ (median of 8.4 months vs. 4.6), and the nonmethylated group had a higher event-free survival when receiving radiotherapy (median 4.6 months vs. 3.3).[30]

The 2nd ranked cited article in chemoradiation (ranked 20th overall) with 279 CC and 11.16 CY is "Randomized Phase III trial in childhood high-grade astrocytoma comparing vincristine, lomustine, and prednisone with the eight-drugs-in-1-day regimen" by Finlay *et al*. in 1995 in *Journal of Clinical Oncology*. They concluded that no difference in PFS and OS in the eight-drugs-in-1-day group versus vincristine, lomustine, and prednisone group; however, PFS improved in the extent of resection (>90%) and nonmidline astrocytoma.[8] The 3rd ranked cited article (ranked 21st overall) with 279 CC and 9 CY is "The effectiveness of chemotherapy for treatment of high-grade astrocytoma in children: Results of a randomized trial – A

report from the Children's Cancer Study Group" by Sposto *et al*. in 1989 in the *Journal of Neuro-oncology*. The conclusion was that patients who received adjuvant nitrosourea, vincristine, and prednisone regimen with radiotherapy had higher event-free survival than radiotherapy alone (46% vs. 18%, $P = 0.026$). The OS was not statistically significant (43% vs. 17%, $P = 0.067$).[27]

The assessment of articles discussing medical management used in astrocytoma signified two published RCT. The 1st ranked cited article (ranked 11th overall) with 453 CC and 64.7 CY is "Efficacy and safety of everolimus for subependymal giant cell astrocytomas associated with tuberous sclerosis complex (EXIST-1): A multicenter, randomized, placebo-controlled Phase 3 trial" by Franz *et al*. in 2013 in the *Lancet* journal. Patients with SEGA ($n = 78$) who received everolimus had 35% reduction of at least 50% tumor volume than patients who did not receive everolimus ($n = 39$).[9] SEGA is a benign tumor representing 1.4% of all pediatric CNS tumors and is associated with tuberous sclerosis (5–20%).[11,22] They originate in the lateral ventricle at the thalamocaudate groove, with 50% mortality due to acute hydrocephalus and intraventricular hemorrhage.[11] A 10th ranked cited article of the top 100 list with 465 CC and 33 CY is "Rapamycin causes regression of astrocytomas in tuberous sclerosis complex" by Franz *et al*. in 2006 in the *Annals of Neurology*. Five patients (4 SEGA and 1 pilocytic astrocytoma) with tuberous sclerosis were treated with sirolimus, and all showed regression in size; lesions grew bigger when treatment was suspended.[10] A recommended management for SEGA is surgery coupled with a mammalian target of rapamycin drug.

A top 50 low-grade glioma bibliometric analysis was published by Atci *et al*. in 2019.[3] Their search yielded a total of 2226 articles; the publication dates were in 1992–2013. The average CC is 195 (571–81), with the Journal of Neurosurgery ranked 1st in publishing articles among the top 50 (10/50), followed by the Journal of Clinical Oncology (9/50). Most articles were written by 1st authors with a neurosurgery background (44%) followed by neurologists (26%). The 1st ranked study category was "natural history" (38%) then nonoperative management (26%). Approximately 26% of articles in their list were focused on molecular analysis of gliomas. Only 4/50 articles were solely assessing astrocytomas. Six articles were RCTs; however, none of the RCTs listed in our top 100 astrocytoma articles were found in their study.

Our data showed that 50% of the top 100 articles were published between 1995 and 2005, with the majority between 1995 and 1999. Earlier publications were focused on surgical and radiation management, and over 20 years, the goal was directed on studying molecular pathways that play a significant role in prognosis and their clinical significance in directing a new gene-targeted therapy for astrocytoma.

Limitations

Bibliometric studies have their inherent limitations, such as over signifying old studies by CC accumulation and under signifying recently published impactful articles; this disadvantage can be rectified by utilizing the CY for articles. In addition, articles with high CC do not necessarily signify major impact, as some studies are cited to demonstrate a weakness or error in that study. The source of citation, such as authors self-citing their publications and in-house citation, reflects inherent bibliometric study limitations. We used one search engine, that is, Scopus, and may have missed other impactful studies. A topic-specific limitation to astrocytoma is that some significant articles studying astrocytoma are titled glioma, which is overlooked in our review, but focusing on astrocytoma alone makes our bibliometric representation of the impactful articles more specific.

CONCLUSION

We performed a comprehensive review of astrocytoma citations and collected the top 100 articles. Most articles were published between 1995 and 2005, with 8 RCTs. The highest ranked authors were neuropathologists followed by neuro-oncologists. The highest ranked journal was Cancer Research, followed by the Journal of Clinical Oncology. Most articles were focused on the neuropathology category, with great emphasis on molecular diagnosis and its potential related outcome. This article is to serve as a guide and introduction for medical specialties related to neuro-oncology interested in astrocytoma; it highlights the most impactful studies, the chronological trend, and to govern future studies in neuro-oncology.

Declaration of patient consent

Patients consent not required as patients identity is not disclosed or compromised.

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Conflicts of interest

There are no conflicts of interest.

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