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

Turki Elarjani1, Othman T. Almutairi2, Modhi Alhussinan1, Gmaan Alzhrani2, Fahad E. Alotaibi2, Mohammed Bafaquh2

1Department of Neurological Surgery, University of Miami, Miami, Florida, United States, 2Department of Neurosurgery, King Fahad Medical City, Riyadh, Saudi Arabia, 3College of Medicine, Alfaisal University, Riyadh, Saudi Arabia.

E-mail: *Turki Elarjani - telarjani@gmail.com; Othman T. Almutairi - almutairi.othman@gmail.com; Modhi Alhussinan - MAlhussinan@alfaisal.edu; Gmaan Alzhrani - gmaan1111@gmail.com; Fahad E. Alotaib - dr.fahad.o@gmail.com; Mohammed Bafaquh - bafaquh@gmail.com

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.\cite{12,19,20,23} Astrocytoma confers the most considerable role in gliomas (75.8%).\cite{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).\cite{19,21} 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.\cite{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.\cite{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.\cite{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 second 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 second 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.](image-url)
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 | Bleezen & 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-chloroethyl nitrosourea: 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 Research     | 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 Research      | 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     |
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 Jet 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 and 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             | Alleloptotype 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 |

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### Table 1: (Continued)

| Rank | Authors            | Title                                                                 | Journal                              | CC   | CY   |
|------|--------------------|----------------------------------------------------------------------|--------------------------------------|------|------|
| 62nd | Lieb et al., 1997  | The Neuropeptide Substance P Activates Transcription Factor NF-κB and xB-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 Cancer Research | 139 | 5.56|
| 86th | Elexpuru-Camiruaga et al., 1995 | Susceptibility to Astrocytoma and Meningioma: Influence of AUE1ism at Glutathione S-Transferase (GSTM1 and GSTT2) and Cytochrome P-450 (CYP2D6) Loci | Cancer Cell                                                                                   | 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        | Monomorphic 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 angiomylipomas 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 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|
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). 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).

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). 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
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

| 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 |
isocitrate, and vice versa.\textsuperscript{[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.\textsuperscript{[6]}

Neuropathological studies comprised the majority of studied influential articles. The 1\textsuperscript{st} ranked cited article (ranked 14\textsuperscript{th} 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.\textsuperscript{[14]} 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.\textsuperscript{[16]}

The most-cited clinical study (ranked 8\textsuperscript{th} 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.\textsuperscript{[3]}

The most influential publication on radiotherapeutic management of astrocytoma (ranked 4\textsuperscript{th} 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).\textsuperscript{[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 3\textsuperscript{rd} ranked cited article (ranked 19\textsuperscript{th} 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.\textsuperscript{[4]}

The analyzed studies entertaining chemotherapy and radiation therapy treatment in astrocytoma showed three published RCT. The 1\textsuperscript{st} ranked cited article (ranked 6\textsuperscript{th} 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).\textsuperscript{[30]}

The 2\textsuperscript{nd} ranked cited article in chemoradiation (ranked 20\textsuperscript{th} 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.\textsuperscript{[4]} The 3\textsuperscript{rd} ranked cited article (ranked 21\textsuperscript{st} 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 thalamoventricular 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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