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# Clinical and molecular features of disseminated pediatric low-grade glioma and glioneuronal tumors: a systematic review and survival analysis

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**Abstract**

**Background.** Disseminated pediatric low-grade gliomas and glioneuronal tumors (dpLGG/GNTs) are associated with a poorer prognosis than nondisseminated pLGG/GNTs. To date there is no comprehensive report characterizing the genome profile of dpLGG/GNTs and their relative survival. This systematic review aims to identify the pattern of genetic alterations and long-term outcomes described for dpLGG/GNT.

**Methods.** A systematic review of the literature was performed to identify relevant articles. A quality and risk of bias assessment of articles was done using the GRADE framework and ROBINS-I tool, respectively.

**Results.** Fifty studies published from 1994 to 2020 were included in this review with 366 cases reported. There was sporadic reporting of genetic alterations. The most common molecular alterations observed among subjects were 1p deletion (75%) and *BRAF-KIAA1549* fusion (55%). BRAF p.V600E mutation was found in 7% of subjects. A higher proportion of subjects demonstrated primary dissemination compared to secondary dissemination (65% vs 25%). First-line chemotherapy consisted of an alkylation-based regimen and vinca alkaloids. Surgical intervention ranged from biopsy alone (59%) to surgical resection (41%) and CSF diversion (28%). Overall, 73% of cases were alive at last follow-up. Survival did not vary by tumor type or timing of dissemination. All studies reviewed either ranked low or moderate for both quality and risk of bias assessments.

**Conclusions.** Chromosome 1p deletion and *BRAF-KIAA1549* fusion were the most common alterations identified in dpLGG/GNT cases reviewed. The relative molecular heterogeneity between DLGG and DLGNT, however, deserves further exploration and ultimately correlation with their biologic behavior to better understand the pathogenesis of dpLGG/GNT.

## Key Points

- Disseminated pediatric low-grade gliomas and glioneuronal tumors express heterogeneous biological behavior and molecular characteristics with chromosome 1p deletion and *BRAF-KIAA1549* fusion representing the most common molecular alterations.
- Overall survival might not be influenced by timing of dissemination, histologic subtype, or age at diagnosis; other factors including unidentified molecular features, may carry greater prognostic value.

## Importance of the Study

There has been an increased reporting of cases of disseminated pediatric low-grade gliomas and glioneuronal tumors (dpLGG/GNTs) over time, a phenomenon which was previously thought to be rare. There is however no existing comprehensive report collating the molecular landscape of dpLGG/GNTs. In this systematic review we describe the pattern of molecular alterations found in reported cases of dpLGG/GNTs, as well as outcomes in relation to adjuvant therapy. This manuscript will serve as a comprehensive background resource for clinicians caring for dpLGG/GNT patients, as well as for researchers exploring the molecular and therapeutic nuances of this heterogeneous disease.

Central nervous system (CNS) tumors are the most frequent solid tumors in children, with a prevalence of ~5.6 diagnoses per 100,000.[1] Gliomas of the brain and spinal cord are the most frequent subtype, accounting for ~45.7% of all pediatric CNS tumors.[2] Classified as World Health Organization (WHO) grade 1 or grade 2 malignancies, pediatric-type low-grade gliomas and glioneuronal tumors (pLGG/GNT) occur more commonly in early childhood compared to high-grade gliomas which are more common in older children.[1] While adult LGGs have a predilection for the cerebral hemispheres and often undergo a malignant transformation, pLGG/GNTs can arise throughout the neuro-axis and are less likely to transform.[3–7]

The ubiquity of magnetic resonance imaging (MRI) has resulted in an increased detection rate with increased reporting of dissemination of pLGG/GNTs (dpLGG/GNTs) throughout the leptomeninges or at multifocal sites, a phenomenon previously thought to be rare.[8–12] Dissemination can be present at the time of initial diagnosis with or without an identifiable primary CNS lesion (primary dpLGG/GNT) or at the time of disease progression (secondary dpLGG/GNT).[8,9,11,13–15] Recent advances in genetic sequencing and molecular alteration profiling have led to a better understanding of genetic alterations in pLGG/GNTs and has also demonstrated fundamental molecular differences between pediatric and adult low-grade gliomas. These 2 tumor groups have been found to be heterogeneous entities despite overlapping morphologies found in some tumor types.[16,17] Commonly identified alterations in pLGG include BRAF p.V600E, *BRAF* fusion with tandem duplication, and *FGFR* alterations.[5,7,18] While isocitrate dehydrogenase (*IDH 1/2*) mutation and 1p deletion with or without 19q deletions are the most common drivers in adult low-grade glioma, these mutations are rare in pLGG/GNTs.[19–21] Neurofibromatosis type 1 (NF1) tumor predisposition syndrome increases risk of pLGG.[16] In the 5th Edition of the World Health Organization (WHO) Classification of Tumors of CNS pLGG/GNTs, diffuse leptomeningeal glioneuronal tumor (DLGNT) is a newly recognized tumor entity under glioneuronal tumors and have been found to express *BRAF-KIAA1549* fusion and chromosome 1p deletion in a few studies conducted.[15,22,23]

Management of pLGG/GNTs typically begins with surgical resection or biopsy, depending upon the location and nature of the disease at diagnosis. When possible, gross total resection (GTR) of pLGG/GNTs offers the most favorable predictor of long-term outcome with 10-year overall survival of >90%.[10,24,25] When total resection is not possible or safe, the survival rate is predictably lower (50%–85%).[10,14,24,25] Disseminated pLGG/GNTs demonstrates a variable prognosis as some tumors run an indolent clinical course with prolonged progression free survival while others exhibit a very aggressive behavior.[10,12,18,26,27] Overall, a 5-year progression free survival of 15% and 17% has been reported in literature.[11,12] Optimum therapy for dpLGG/GNTs including the role of expectant management is unknown. In most cases, radiotherapy and alkylating-agent-based chemotherapy is used and the utility of targeted molecular therapies remains investigational.[5,9,18,27,28]

Currently, however there is no comprehensive report collating the molecular landscape of dpLGG/GNTs. This systematic review aims to identify the pattern of genetic alterations found in reported cases of dpLGG/GNTs, common adjuvant therapies, and overall survival.

## Methods

A systematic review of the literature was performed in accordance with the Preferred Reporting Items of Systematic Reviews and Meta-analyses (PRISMA) guidelines.[29] The search was conducted in OVID Medline/Embase, Web of Science, and PubMed electronic databases in January 2021 to identify relevant articles published between 1990 and 2020. Medical Subject Headings (MeSH) and non-MeSH terms used included "low-grade glioma," "disseminated low-grade glioma," "DLGNT," "disseminated leptomeningeal tumor," and "leptomeningeal dissemination." After title and abstract review, the articles were exported and managed using EndNote 20. Searches in the databases were supplemented by manual search to retrieve additional articles identified via reference list review of the initial set of articles. Article inclusion and exclusion were deliberated among 2 authors (J.H.-C. and M.C.D.). We included only articles that examined the molecular characteristics, surgical and adjuvant therapy, and treatment outcomes of disseminated pediatric low-grade glioma and/or leptomeningeal glioneuronal tumors among the pediatric population (<19 years). Articles which discussed only the adult population or nondisseminated pediatric low-grade glioma, pediatric high-grade glioma, or that were unavailable as English language text were excluded.

The quality assessment for each article reviewed was conducted using the GRADE framework[30,31] and risk of bias assessment for cohort studies using ROBINS-I tool

respectively.[32,33] Authors reached a consensus on the critical appraisal of study quality and risk of bias.

Data extracted from articles included author, year of publication, study design, sample size, tumor group [disseminated low-grade glioma (DLGG) and DLGNT as classified and reported in the articles reviewed], timing and status of dissemination, molecular characteristics of tumors, surgical and adjuvant therapy, patient-specific survival outcome, and follow-up duration. Molecular alterations were reported as a percentage of specimens for which the given alteration was interrogated. Survival data were reported as percentage of patients alive at the time (mean/median in months) of last follow-up. Kaplan–Meier curves were plotted for tumor groups (DLGG and DLGNT) and timing of dissemination (primary and secondary) for subjects with the available individual survival outcome, which is defined as data time from diagnosis to death with those alive censored at the last follow-up. The log-rank test was used to estimate compare the differences in survival between the groups. A multivariable Cox proportional hazard regression model with robust standard errors survival analysis was conducted using fitted Cox proportional hazard regression model to ascertain the effect of multiple factors on survival. Covariates considered for this analysis were age at diagnosis, tumor type, and timing of dissemination. Statistical analysis was performed using the survival analysis package in R version 4.1.1.

## Results

The database search yielded a total of 708 publications: 339 from OVID Medline/Embase, 295 from Web of Science, and 369 from PubMed. Twelve additional articles identified from examining the reference list of articles were assessed for eligibility. An initial review of identified articles was done based on title and type of article leading to the exclusion of abstract reviews, letters to the editor, conference abstracts, and duplicates. The full text of the remaining articles ($N = 208$) was screened for eligibility using the criteria described above. To avoid double counting of study subjects, studies conducted by Gnekow et al.,[34] Gajjar et al.,[9] and Hukin et al.,[11] were excluded due to their data overlapping with that of von Hornstein et al.,[35] Chamdine et al.,[36] and Hukin et al.,[12] respectively.

Fifty full-text manuscripts published from 1994 to 2020 were included in this review (Figure 1). A majority of studies reviewed was case series and reports (72%), followed by retrospective cohort studies (26%) and a single prospective cohort study (2%) (Table 1). Using the GRADE framework, 56% of the reviewed articles were classified as having low quality and 44% with moderate quality. Based on the ROBINS-I tool, 57% of articles assessed had a low risk of bias and 43% had a moderate risk of bias.

Overall, there were 366 pediatric subjects with disseminated disease. The 2 main tumor groups observed were DLGG (61.7%, $n = 226$) and DLGNT (37.9% $n = 139$) (Figure 2A). One subject had desmoplastic infantile ganglioglioma with diffuse leptomeningeal seeding. Out of the 366 pediatric subjects, 65% ($n = 239$) had a primarily disseminated disease while 25% ($n = 91$) were localized on initial presentation and later found to be secondarily disseminated; 10% ($n = 36$) were unspecified (Figure 2B). Average time to secondary dissemination was 21.9 months from original tumor diagnosis. Dissemination was confirmed on MRI for all subjects with majority of subjects (74%) having both a cranial and spinal MRI; 65% of subjects had craniospinal dissemination, 19% had an intracranial dissemination only, and 16% had an intraspinal dissemination only (Figure 2C). Eighty-four percent had leptomeningeal dissemination, 13% had multifocal disease, and 3% had both multifocal disease and leptomeningeal dissemination (Figure 2D). No case of metastasis outside the CNS was described in the studies reviewed. There was sporadic testing and reporting of molecular alterations. Thirty studies conducted some genetic analysis of tumors including interrogation for BRAF p.V600E, *BRAF-KIAA1549* fusion, *TP53* mutation, *IDH* mutation, 1p deletion, 19q deletion, 1p/19q co-deletion, *FGFR* mutation, and *CDKN2A* deletion (Table 2). The remaining 20 studies did not report on molecular alterations. Of the studies which did not report on molecular alterations, 50% were published within the last 10 years. Forty-one percent of subjects (149/366) were interrogated for some genetic alterations (Figure 3A) out of which 31% (47/149) were DLGG and 69% (103/149) were DLGNT (Figure 3B).

Overall, 58% ($n = 87/149$) were found to harbor at least 1 identifiable genetic alteration. The most common genetic alteration observed among all study subjects tested was 1p deletion (75%, $n = 63/84$) and *BRAF-KIAA1549* fusion (55%, $n = 52/95$) (Figure 3C). BRAF p.V600E was found in 7% ($n = 5/70$) of subjects tested (Figure 3C). There was no *IDH1* R132H mutation by immunohistochemical staining all 36 subjects examined. One subject was tested for mutations in *IDH1* R132H and *IDH2* R140 and R172 by next generation sequencing analysis and was found to be absent. *FGFR1* and *CDKN2A* analysis was reported by only 2 studies and found to be wild-type in all 8 subjects. Reporting molecular alterations tested and identified by tumor groups, 67% (2/3) of DLGG expressed 1p deletion, 42% (15/36) *BRAF-KIAA1549* fusion, and 10% (4/41) BRAF p.V600E (Figure 3D). In the DLGNT group, 75% (61/81) expressed 1p deletion, 63% (37/59) *BRAF-KIAA1549* fusion, and 3% (1/29) BRAF p.V600E (Figure 3E). Few studies reported genetic alterations specifically for secondarily disseminated tumors. In this group, 3 subjects were tested for BRAF p.V600E, with 67% ($n = 2/3$) being positive. None of these subjects was tested for *CDKN2A* deletion. Only 1 patient with secondary disseminated tumor was tested for 1p deletion and was found positive. All remaining genetic testing among secondarily disseminated tumors was noncontributory (Table 2). Fourteen study subjects had a diagnosis of NF1 with 1 subject diagnosed solely based on NIH criteria based on authors' report. None of these 14 subjects was interrogated for additional genetic alterations. Two subjects were excluded from this review because they had H3K27M alteration even though they had been described as pLGG based on histology.

Rates of tumor biopsy and resection varied widely and depended largely upon location of tumor and timing of dissemination. Out of 109 cases with primary tumor dissemination who received surgical intervention, 72% ($n = 78/109$) had biopsy and 28% ($n = 31/109$) underwent resection of

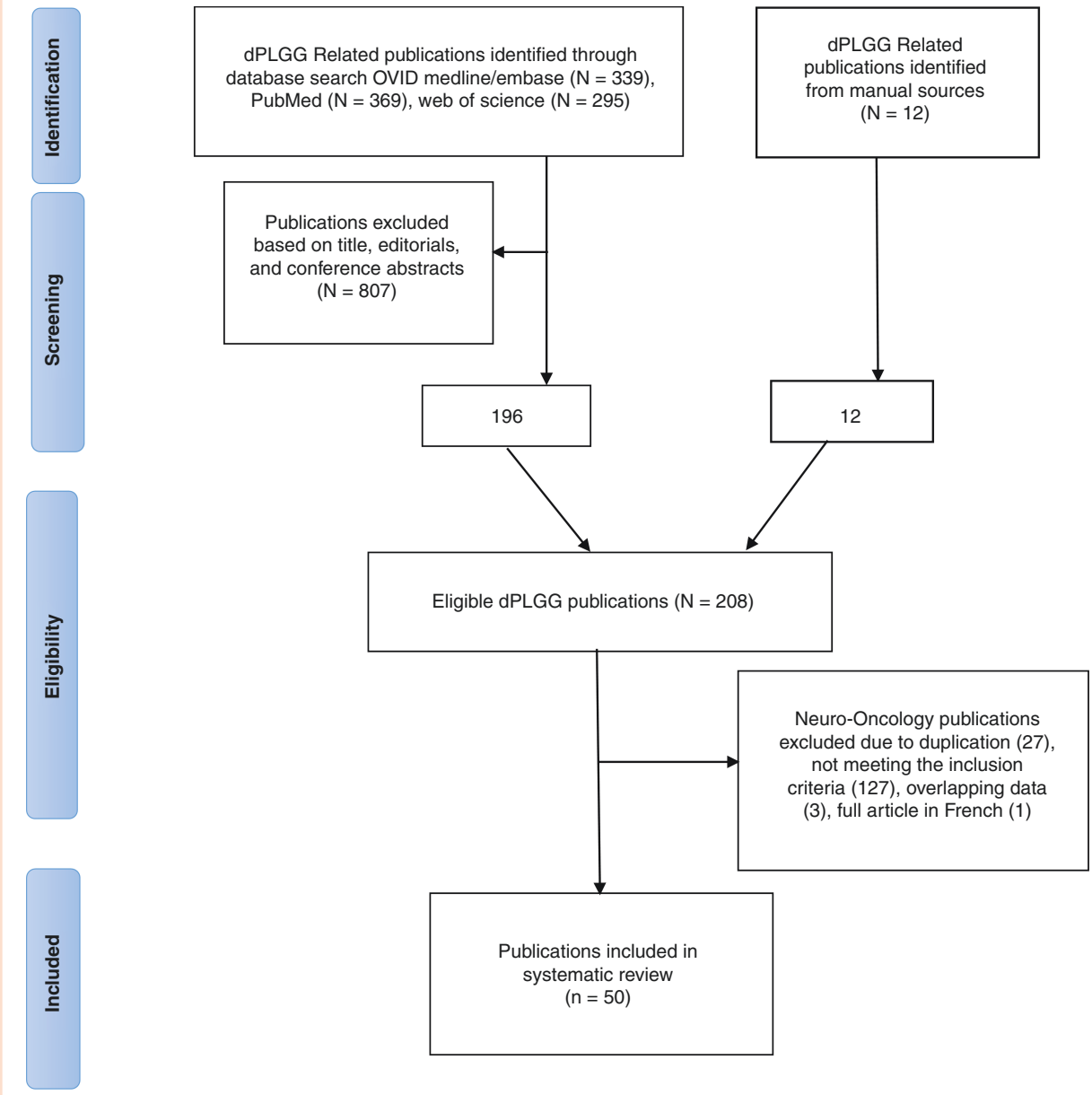


**Figure 1.** PRISMA flow diagram for the literature search to identify disseminated pediatric low-grade glioma and glioneuronal tumor publications.

primary tumor focus. Among the cohort with secondary tumor dissemination who received surgical intervention, 35% ($n$ = 19/55) had undergone biopsy and 65% ($n$ = 36/55) received an upfront tumor resection (before dissemination). Seven cases had an upfront GTR and 30 cases had either a subtotal resection (STR) or partial resection. One-hundred and three out of 366 (28%) patients required CSF diversion via shunt or ventriculostomy. Adjuvant therapy was reported for 248 cases. Two hundred and eight cases (84%) received chemotherapy and 65 cases (26%) received radiation therapy. First-line chemotherapy consisted primarily of an alkylation-based regimen and vinca alkaloids, with 98 cases (47%) receiving vincristine and carboplatin as first-line chemotherapy. More heterogeneous second-line regimens were reported (see Supplementary Table S1). Three out of 208 cases (1.4%) were reported to have received targeted therapies: BRAF or MEK 1/2 inhibitors. Among those who received radiation therapy, 71% ($n$ = 46/65) received craniospinal radiation and 29% ($n$ = 19/65) received focal radiation.

Based on follow-up data available for 199 cases with primarily and secondarily disseminated disease, the aggregate mean and median follow-up duration was 22.0 and 40.2 months, respectively (range 0.5–290.4 months). Among cases with secondarily disseminated tumor, 67% of those who had biopsy only and 68% of those who had tumor resection were alive at last follow-up. Forty-four percent of primarily disseminated tumor cases and 31% of

**Table 1.** Reported Cases of Disseminated PLGG From 1994 to 2020

| Author | Year | Study Design | Total Number of Cases | Risk of Bias | Grade |
|---|---|---|---|---|---|
| Abongwa et al.[37] | 2020 | Case report | 3 | N/A | Low |
| Bell et al.[38] | 2020 | Retrospective cohort study | 36 | Moderate | Low |
| Chen et al.[39] | 2020 | Case report | 1 | N/A | Moderate |
| Finch et al.[40] | 2020 | Case report | 1 | N/A | Low |
| Lakhani et al.[41] | 2020 | Case report | 7 | N/A | Low |
| Saez-Alegre et al.[42] | 2020 | Case report | 1 | N/A | Moderate |
| Ryall et al.[7] | 2020 | Retrospective cohort study | 13 | Low | Moderate |
| Tiwari et al.[43] | 2020 | Case report | 1 | N/A | Moderate |
| Lu et al.[44] | 2019 | Case report | 1 | N/A | Low |
| Tan et al.[45] | 2019 | Case report | 1 | N/A | Moderate |
| Tiwari et al.[46] | 2019 | Case report | 1 | N/A | Moderate |
| Deng et al.[23] | 2018 | Retrospective cohort study | 24 | Moderate | Low |
| Guillén et al.[47] | 2018 | Case report | 1 | N/A | Low |
| Aguilera et al.[48] | 2017 | Case report | 7 | N/A | Moderate |
| Bavle et al.[49] | 2017 | Case report | 1 | N/A | Low |
| Schwetye et al.[50] | 2017 | Case report | 2 | N/A | Low |
| Sublett et al.[51] | 2017 | Case report | 1 | N/A | Low |
| Tsang et al.[52] | 2017 | Retrospective cohort study | 12 | Low | Moderate |
| Chamdine et al.[36] | 2016 | Retrospective cohort study | 38 | Moderate | Low |
| Dodgshun et al.[18] | 2016 | Retrospective cohort study | 10 | Low | Moderate |
| Gessi et al.[53] | 2016 | Retrospective cohort study | 17 | Low | Moderate |
| Cho et al.[54] | 2015 | Case report | 1 | N/A | Low |
| Lyle et al.[55] | 2015 | Case report | 1 | N/A | Moderate |
| Preuss et al.[56] | 2015 | Retrospective cohort study | 4 | Low | Moderate |
| Rodriguez et al.[57] | 2015 | Retrospective cohort study | 23 | Low | Moderate |
| Kosker et al.[58] | 2014 | Case report | 1 | N/A | Low |
| Legault et al.[59] | 2014 | Case report | 1 | N/A | Low |
| Bian et al.[60] | 2013 | Case report | 6 | N/A | Low |
| Schniederjan et al.[61] | 2013 | Case report | 9 | N/A | Moderate |
| Rodriguez et al.[27] | 2012 | Retrospective cohort study | 33 | Moderate | Low |
| Agamanolis et al.[62] | 2012 | Case report | 3 | N/A | Moderate |
| Moon et al.[26] | 2012 | Case report | 1 | N/A | Low |
| Demir et al.[63] | 2011 | Case report | 1 | N/A | Moderate |
| von Hornstein et al.[35] | 2011 | Prospective cohort study | 61 | Low | Moderate |
| Shaikh et al.[64] | 2011 | Case report | 3 | N/A | Low |
| Gardiman et al.[65] | 2010 | Retrospective cohort study | 4 | Moderate | Low |
| Rhiew et al.[66] | 2010 | Case report | 1 | N/A | Low |
| Poliani et al.[67] | 2009 | Case report | 1 | N/A | Moderate |
| Sherman et al.[68] | 2009 | Case report | 1 | N/A | Moderate |
| Bourne et al.[69] | 2006 | Case report | 1 | N/A | Low |
| Distelmaier et al.[70] | 2006 | Case report | 1 | N/A | Low |
| Meléndez et al.[71] | 2006 | Case report | 1 | N/A | Low |
| Milanaccio et al.[72] | 2005 | Case report | 1 | N/A | Low |
| Tabori et al.[73] | 2005 | Retrospective cohort study | 6 | Low | Moderate |
| Kageji et al.[74] | 2003 | Case report | 1 | N/A | Low |
| Hukin et al.[12] | 2003 | Retrospective cohort study | 13 | Moderate | Low |
| Perilongo et al.[28] | 2002 | Case report | 3 | N/A | Low |
| Jamjoom et al.[75] | 1998 | Case report | 1 | N/A | Low |
| Morikawa et al.[76] | 1997 | Case report | 1 | N/A | Low |
| Pollack et al.[10] | 1994 | Case report | 3 | N/A | Moderate |

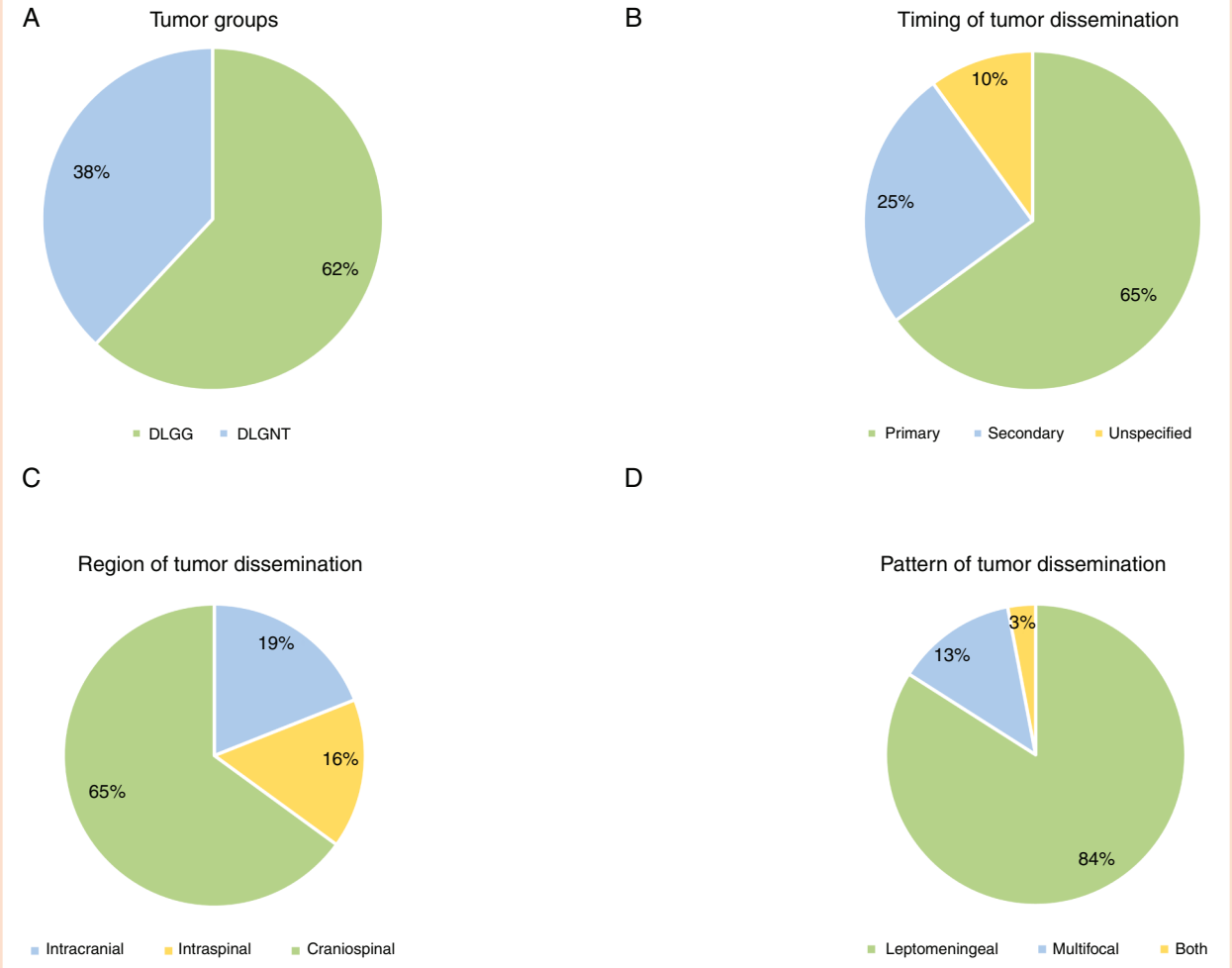


**Figure 2.** Pie chart describing tumor groups and dissemination pattern in study cohort. (A) Tumor groups identified in the study cohort. (B) Timing of tumor dissemination. (C) Region of tumor dissemination. (D) Pattern of tumor dissemination. ** One case of desmoplastic infantile ganglioglioma with diffuse leptomeningeal seeding was not shown on graph.

secondarily disseminated tumor had no data on survival outcomes. Overall, 73% (146 out of 199) of cases were alive at last follow-up. Seventy-four percent of cases with primary disseminated tumor and 71% of cases with secondary disseminated tumor were alive at last follow-up. Kaplan–Meier analysis (Figure 4) demonstrated similar survival between cases with primary disseminated tumor and those with secondary dissemination ($P = .7$) (Figure 4A). There was no statistically significant difference in survival between cases with DLGG and DLGNT ($P = 1.00$) (Figure 4B). Survival of primary and secondary disseminated tumor cases by tumor type (DLGG and DLGNT) showed secondary disseminated DLGNT had the poorest survival ($P = .02$). However, there were only 3 patients in the secondary DLGNT group (Figure 4C). The Cox proportional hazard regression model using completed data from 171 patients (37 deaths) indicated little evidence of effects of age at diagnosis {adjusted Hazard Ratio [HR (95% confidence interval, CI)] for every 6 years increase = 1.3[0.8–2.1], $P = .29$}, tumor type [HR of DLGNT vs DLGG = 0.9(0.4–2.2), $P = .84$], and timing of dissemination [HR of secondary vs primary = 0.8(0.3–1.8), $P = 0.58$] did not affect survival significantly ($P = .29$, $P = .83$, and $P = .58$, respectively).

## Discussion

Despite increasing awareness of dpLGG/GNTs, there is limited knowledge on their molecular profile and long-term response to adjuvant therapy. In this systematic review, we report the molecular alterations, treatment offered and survival experience of 366 children with dpLGG/GNTs reported in literature out of which 31% (47/149) were DLGG and 69% (103/149) were DLGNT. Sixty-five percent of cases had primary dissemination, 25% had secondary dissemination at an average time of 21.9 months from solitary tumor diagnosis, and 10% were unspecified. The most common molecular alterations in all dpLGG/GNT cases identified were chromosome 1p deletion (75%) and *BRAF-KIAA1549*

**Table 2.** Molecular Characteristics of Primary and Secondary dPLGG

| Author | Tumor Type | Average Time to Dissemi-nation (Months) | Overall Number of Cases | Molecular Characteristics | | | | | | | Follow-up Period Mean/Median (months) | % Alive at Last Fol-low-up |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | BRAF V600E Mutation | BRAF KIAA Fusion | P53 Mutation | IDH Mutation | 1p Deletion | 19q Deletion | 1p/19q Co-deletion | | |
| **Primary dPLGGw** | | | | | | | | | | | | |
| Chen et al.[39] | DLGNT | — | 1 | / | / | 0/1 | / | / | / | / | 16/16 | 0 |
| *Bell et al.[38] | DLGG | — | 36 | 1/10 | 5/10 | / | / | / | / | / | -/72 | 75 |
| Finch et al.[40] | DLGG | — | 1 | 1/1 | / | / | / | / | / | / | 30/30 | 100 |
| Lakhani et al.[41] | DLGNT | — | 7 | / | 2/7 | / | / | 2/7 | 0/7 | 0/7 | -/- | - |
| Saez-Alegre et al.[42] | DLGNT | — | 1 | 0/1 | / | / | 0/1 | 1/1 | 0/1 | 0/1 | 5/5 | 100 |
| Tan et al.[45] | DLGNT | — | 1 | 0/1 | 1/1 | 1/1 | 0/1 | 1/1 | 0/1 | 0/1 | -/- | 100 |
| Tiwari et al.[46] | DLGNT | — | 1 | / | 1/1 | / | 0/1 | 1/1 | 1/1 | 1/1 | 18/18 | 100 |
| Deng et al.[23] | DLGNT | — | 24 | 0/6 | 17/24 | / | 0/9 | 24/24 | 8/24 | 8/24 | -/- | 80 |
| Guillén et al.[47] | DLGNT | — | 1 | 0/1 | 0/1 | / | 0/1 | 0/1 | / | / | 7/7 | 50 |
| Aguilera et al.[48] | DLGNT | — | 7 | 0/7 | / | / | 0/7 | / | / | / | -/- | 100 |
| Schwetye et al.[50] | DLGNT | — | 2 | 0/1 | 0/2 | / | 0/1 | 1/2 | 0/2 | 0/2 | 30/30 | 50 |
| Tsang et al.[52] | DLGG | — | 9 | 0/9 | 1/9 | / | / | / | / | / | 89/62.4 | 67 |
| Dodgshun et al.[18] | DLGNT | — | 9 | 0/4 | 4/6 | / | / | / | / | / | 31/24 | 78 |
| *Gessi et al.[53] | DLGG | — | 17 | 1/17 | 9/15 | / | / | / | / | / | 127.4/147 | 65 |
| Cho et al.[54] | DLGNT | — | 1 | / | / | / | 0/1 | / | / | / | 23/23 | 100 |
| Lyle et al.[55] | DLGNT | — | 1 | / | / | 0/1 | 0/1 | / | / | / | 24/24 | 100 |
| Preuss et al.[56] | DLGNT | — | 4 | / | / | / | 0/4 | 0/3 | 0/3 | 0/3 | 54/50 | 75 |
| Rodriguez et al.[57] | DLGNT | — | 23 | 0/9 | 12/16 | / | / | 10/17 | 3/17 | 3/17 | -/- | 100 |
| Legault et al.[59] | DLGG | — | 1 | 0/1 | 0/1 | / | / | / | / | / | 19/19 | 100 |
| Schnieder-jan et al.[61] | DLGNT | — | 9 | / | / | / | 0/8 | 6/8 | 2/8 | 1/8 | 137/137 | 100 |
| Rodriguez et al.[27] | DLGNT | — | 33 | / | / | / | 0/10 | 11/15 | 3/15 | 3/15 | -/5 | 76 |
| Agamano-lis et al.[62] | DLGG | — | 3 | / | / | / | / | 2/3 | 0/3 | 0/3 | 36/36 | 66 |
| Demir et al.[63] | DLGG | — | 1 | / | / | 0/1 | / | / | / | / | 19/19 | 100 |
| Gardiman et al.[65] | DLGNT | — | 4 | / | / | / | / | 1/1 | 0/1 | 0/1 | 47/48 | 75 |
| Rhiew et al.[66] | DLGNT | — | 1 | / | / | / | / | 1/1 | 1/1 | 1/1 | 16/16 | 100 |
| Bourne et al.[69] | DLGNT | — | 1 | / | / | / | / | 1/1 | 0/1 | 0/1 | -/- | 100 |
| Perilongo et al.[28] | DLGG | — | 2 | / | / | 0/2 | / | / | / | / | 47/24 | 50 |
| **Secondary dPLGG** | | | | | | | | | | | | |
| Lu et al.[44] | DLGNT | 24 | 1 | 0/1 | 0/1 | 0/1 | 0/1 | 1/1 | 0/1 | 0/1 | 3/3 | 0 |
| Bavle et al.[49] | DLGG | 28 | 1 | 1/1 | 0/1 | / | / | / | / | / | 70/70 | 0 |
| Dodgshun et al.[18] | DLGNT | — | 1 | 1/1 | / | / | / | / | / | / | 31/24 | 100 |
| Poliani et al.[67] | DLGNT | 14 | 1 | / | / | 0/1 | / | / | / | / | 30/30 | 0 |
| Perilongo et al.[28] | DLGG | 3 | 1 | / | / | 0/1 | / | / | / | / | 47/24 | 0 |

Studies with no molecular analysis were not included in this table.
/ indicates unable to perform
*Timing of dissemination was not specified

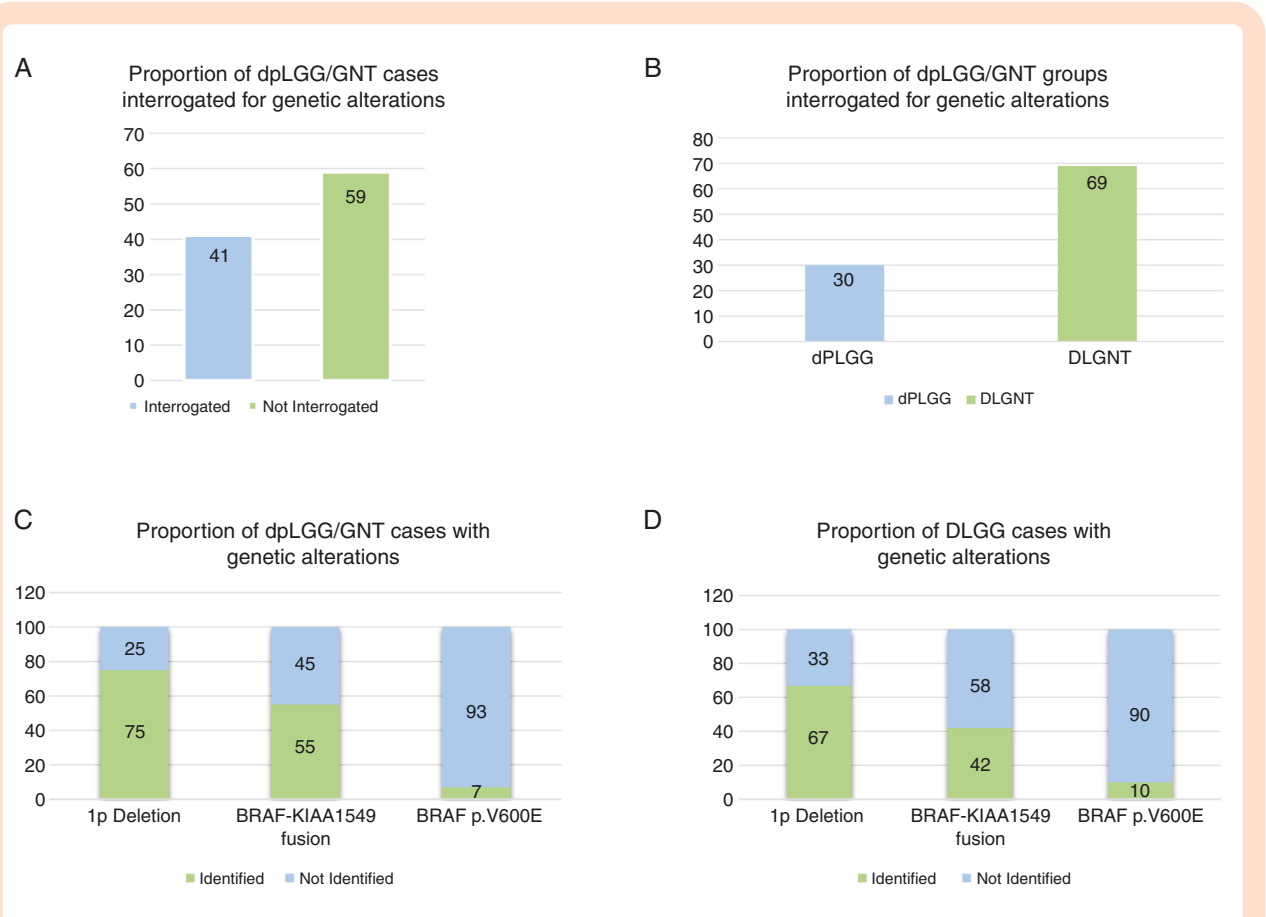


**Figure 3.** Bar graph demonstrating percentage of genetic alterations in dpLGG/GNTs. (A) dpLGG/GNT cases interrogated for genetic alterations. (B) Proportion of dpLGG/GNT groups interrogated for genetic alterations. (C) Proportion of all dpLGG/GNT cases with genetic alterations. (D) Proportion of DLGG cases with genetic alterations. (E) Proportion of DLGNT cases with genetic alterations.

fusion (55%). A higher proportion of DLGNT cases tested had chromosome 1p deletion and *BRAF-KIAA1549* fusion compared to DLGG cases similar to reports in previous studies.[15,23] It is however worth noting that only 3 cases of DLGG were tested for chromosome 1p deletion. Alterations encountered less frequently were 19q deletion (21%), 1p/19q co-deletion (20%), and BRAF p.V600E (7%).

While the frequency of *BRAF-KIAA1549* fusion in nondisseminated pLGGs is high (34%–73%), chromosome 1p deletion, either with or without 19q co-deletion, is uncommon (3%–15%).[7,77–80] *BRAF-KIAA1549* fusion, chromosome 1p deletion, and gain of chromosome 1q has been described in some glioneuronal tumors.[15,23] One study has examined methylation patterns in DLGNT. Two clusters were studied showing 1p deletion in both, with 19q co-deletion occurring in 1 group and 1q gain seen in the other.[23] As copy number analysis may not routinely be done in dpLGG/GNT, this has given some insight into recurrent copy number changes. There is limited literature documenting chromosome1p deletion in nondisseminated pLGG/GNT, however, there seems to be a relationship between1p deletion and both DLGGs and DLGNTs potentially suggesting a mechanistic role in dissemination. Further research is needed to ascertain the prevalence of 1p deletion in both DLGGs and DLGNTs and the specific mechanism by which 1p deletion could contribute to tumor spread. Identifying the biological and molecular similarities and differences between these 2 groups will help better understand the mechanisms of dissemination.

The frequency of BRAF p.V600E in pLGG/GNT differs by histology.[81–83] A high rate of this mutation is found in pleomorphic xanthoastrocytoma (50%–78%) with moderate rates in gangliogliomas (13%–49%) and lower rates in pilocytic astrocytoma and other glioma subtypes (0%–14.3%).[83–85] Fukuoka et al. identified a unique *IDH* wild-type oligodendroglioma-like tumors harboring BRAF p.V600E with no 1p/19q co-deletion in a small subset of adolescents and young adults.[86] BRAF p.V600E seems to be rare in dpLGG/GNT.[87]

The biologic features which permit pLGG/GNT to disseminate throughout the craniospinal axis and the role of specific molecular alterations in this process remain unclear. Previous studies have suggested tumor dissemination occurs via the CSF pathway with tumor cells penetrating ependymal lining and interstitial spaces and adhering to leptomeninges at near and distant sites.[9,10,8] A study

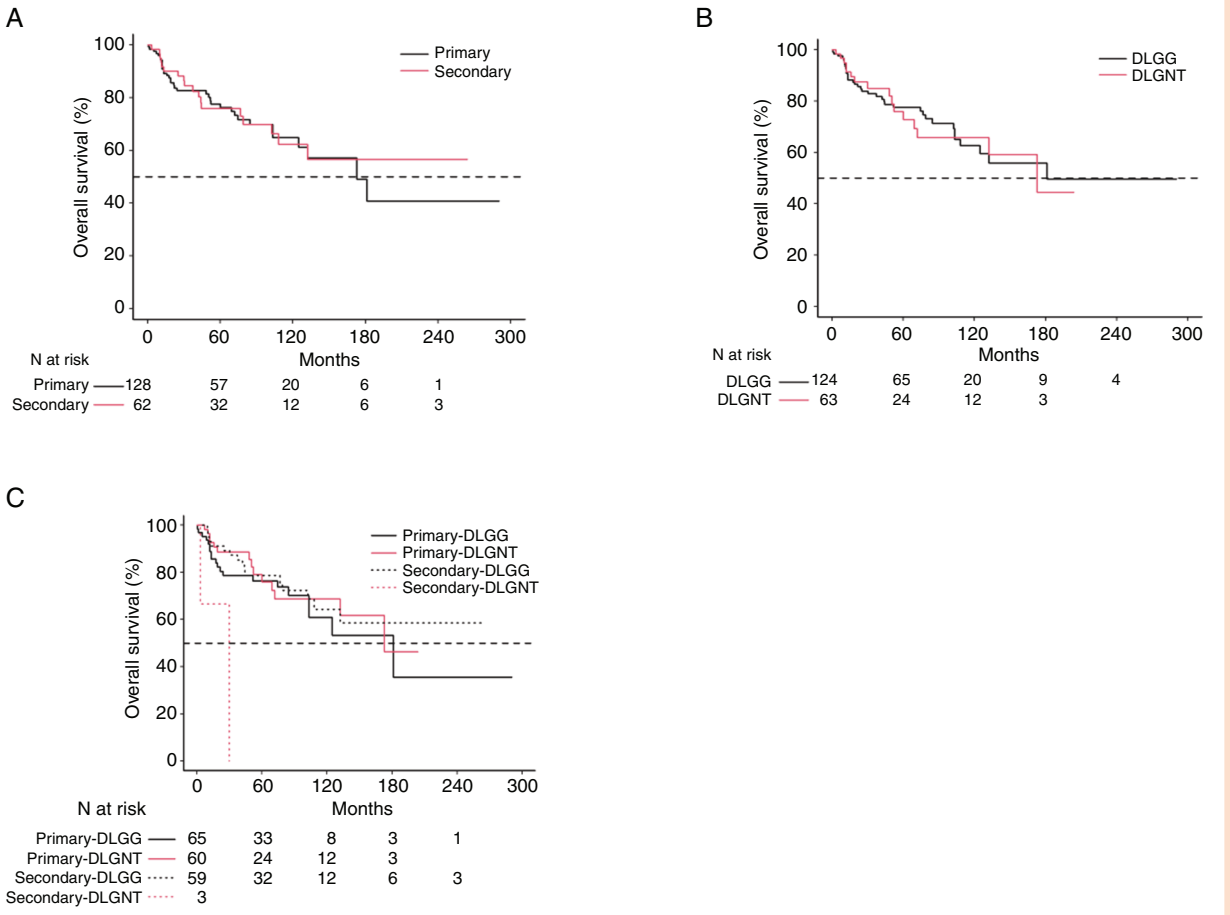


**Figure 4.** Kaplan–Meier survival curves with log-rank test for dpLGG/GNTs stratified by timing of dissemination (primary and secondary), tumor type (DLGG and DLGNT) and timing of dissemination and tumor type combined (primary/secondary and DLGG/DLGNT). (A) There was no difference in long-term survival between primary and secondary tumor cases ($P = .7$). (B) There was no difference in long-term survival between DLGG and DLGNT cases ($P = 1.0$). (C) Cases with secondary disseminated DLGNT were observed to have the poorest survival ($P = .02$).

conducted by Tabori et al. identified an increased rate of epidermal growth factor receptor amplification known to promote growth and the invasive potential of tumor cells in dpLGG/GNTs compared to nondisseminated pLGG/GNTs.[73,88,89] Other biomarkers which have been identified to promote tumor metastasis include overexpression of *ERBB2* (also known as HER2) leading to activation of the *PI3K/AKT* signaling pathway and *ERK1/2* pathway resulting in the up-regulation of *S100A4*, have been found in metastatic medulloblastoma.[90,91] *S100A4* has also been found to be up-regulated more often in ependymoma and glioblastoma than in low-grade astrocytoma.[92,93] Increased expression of *PDGFR*, a tyrosine kinase which promotes glioma stem cell migration and invasion through increasing MMP-2 activity has been found in low-grade gliomas and glioneuronal tumors.[15,17,94–96] The possible connection of these drivers of metastasis with pLGG/GNT dissemination and the molecular alterations which characterize dpLGG/GNT is an intriguing prospect that warrants attention.

Treatment approach for dpLGG/GNTs was observed to be similar to that of nondisseminated pLGG/GNTs for all treatment modalities. Neurosurgical intervention was largely influenced by the timing of dissemination and the location of primary lesion if identified. A less invasive surgical approach is typically favored in patients with primary dissemination wherein the primary goal is to obtain diagnostic tissue rather than attempt curative excision of lesions. An exception is when a dominant lesion is causing symptoms related to mass effect, edema, or cortical irritation, and surgical resection or debulking facilitates symptom resolution and/or adjuvant therapy initiation.

The clinical course of dpLGG/GNTs tends to be protracted and may require multiple interventions including salvage therapy for disease progression, as well as CSF diversion. Compared to nondisseminated pLGG/GNT, dpLGG/GNTs is associated with worse outcomes.[5,10,11,26,48] Hukin et al. reported a 5-year survival rate of 68% and 87% in a cohort of DLGG and nondisseminated pLGG, respectively.[11] Based on the limited survival data available,

there were no statistically significant differences in survival by tumor group or timing of dissemination. Age at diagnosis, tumor type, or timing of dissemination did not affect survival. This implies that survival may possibly be influenced by other factors including the biologic ramifications of molecular alterations specific to each tumor. Nondisseminated pLGG/GNT is well known to be influenced by the presence of molecular alterations including BRAF p.V600E and CDKN2A; whether a similar phenomenon exists for dpLGG/GNT remains undefined and demands further study.[5,6,77,81,83]

There are several limitations to be considered in the interpretation of results presented in this review. The clinical use of variable terminologies to describe dpLGG/GNTs may have influenced our search results. Beyond including the most common descriptors, we address this by reviewing the reference lists of articles initially identified to find additional articles which may not have been captured by the original search terms. Authors relied on publication information for the diagnosis of dpLGG/GNT and half of the studies reviewed were published >10 years ago predating current molecular testing and the recent edition of the WHO classification of CNS tumors published in 2021. The review involved studies published >30 years which spans multiple iterations of the WHO CNS tumor classification which were not specified. There was lack of comprehensive reporting on the genomic profile of tumors limiting broad conclusions on the pattern of molecular alterations found in dpLGG/GNTs. Most manuscripts did not report on the staging done for secondary dpLGG/GNTs at first diagnosis to confirm nondissemination on initial presentation. Finally, studies reviewed carried a measurable risk of bias as determined by the ROBINS-I tool. Based on GRADE assessment of quality of evidence, all studies reviewed either ranked low or moderate. This underscores the need for larger and prospective dpLGG/GNT cohorts to characterize the molecular alterations and drivers of tumor dissemination in dpLGG/GNTs using advanced genomic techniques. A better understanding of the pattern of molecular alterations will help evaluate the efficacy of standard therapy and potential targeted therapies in the management of disseminate disease specifically.

## Conclusion

Chromosome 1p deletion and *BRAF-KIAA1549* fusion in dpLGG/GNTs were the most common alterations identified in dpLGG/GNT cases reviewed. The relative molecular heterogeneity between DLGG and DLGNT, however, deserves further exploration and ultimately correlation with their biologic behavior. This review suggests that the presence of disseminated disease may not necessarily confer a poor prognosis for all patients as previously noted in earlier reports and that other factors may influence survival outcomes. There is however, a lack of comprehensive and quality studies characterizing the molecular makeup of dpLGG/GNTs and how treatment approaches including the use of targeted therapy impact survival outcome. Additional studies on the molecular and biological features of these tumors are needed to better understand the pathogenesis of dissemination of pLGG/GNT and inform the development of additional targeted regimens to further improve outcomes.

## Supplementary Material

Supplementary material is available at *Neuro-Oncology Advances* online.


## Keywords

dissemination | glioneuronal tumor | low-grade glioma | molecular alteration | pediatric.

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