
Glioneuronal Tumors: Insights into a Rare Tumor Entity

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Abstract: Glioneuronal tumors are a group of rare neoplasms made up of neural and glial components in heterogenous proportions, generally exhibiting WHO grade I clinical behavior. These tumors affect infants, children and young adults, but are also described in adults and the elderly. They are strongly associated with seizures. Tumor subtypes described under the umbrella of glioneuronal tumors are actively evolving but to date comprise central, extraventricular and lipo- neurocytoma, desmoplastic infantile astrocytoma and ganglioglioma, diffuse leptomeningeal glioneuronal tumor, dysembryoplastic neuroepithelial tumor, papillary glioneuronal tumor, rosette-forming glioneuronal tumor of the fourth ventricle, rosetted glioneuronal tumor with neuropil-like islands, gangliocytoma, ganglioglioma, anaplastic ganglioglioma and paraganglioma. They vary in radiographic appearance, with some exhibiting large heterogenous solid/cystic masses. With large scale genetic and molecular analyses ongoing, classification continues to evolve. Seizure management and surgical resection represent the cornerstones of management, with the use of systemic agents and radiation lacking conclusive results. Optimal management requires multidisciplinary discussion including

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neuro-oncological and neuro-surgical expertise due to both the rarity of these tumors and the lack of evidence with data confined to small retrospective series and reviews.

Keywords: desmoplastic infantile astrocytoma and ganglioglioma; dysembryoplastic neuroepithelial tumor; glioneuronal tumors; neurocytoma; late effects

INTRODUCTION

Glioneuronal tumors are rare tumors comprised of both neural and glial components present in heterogeneous proportions displaying indolent WHO grade I behavior (1–3). More recently, molecular characterization has allowed for more robust classification (4–9). The subtypes falling under the umbrella of glioneuronal tumors are actively evolving but currently include: central, extraventricular and lipo- neurocytoma; desmoplastic infantile astrocytoma and ganglioglioma (DIA/DIG), diffuse leptomeningeal glioneuronal tumor, dysembryoplastic neuroepithelial tumor (DNET), papillary glioneuronal tumor (PGNT), rosette-forming glioneuronal tumor of the fourth ventricle (RGNT), rosetted glioneuronal tumor with neuropil-like islands (GNTNI), gangliocytoma (GC), ganglioglioma (GG) and anaplastic ganglioglioma and paraganglioma (1, 2). Evolving entities including low grade neuroepithelial tumor of the young (9), multinodular and vacuolating neuronal tumor (10), and entities such as paraganglioma (11), are not described in detail in this chapter. Depending on the subtype, glioneuronal tumors can occur in all age groups. Most glioneuronal tumors present with seizures, depending on location and rate of growth. Patients can present with increased intracranial pressure, acute neurological deficits, hydrocephalus, diffuse leptomeningeal spread and symptoms of cord impingement or compression. Overall, the data surrounding glioneuronal tumors remains scant, largely comprised of small retrospective series and reviews of literature (1–3). Management involves seizure and symptom control, including resection when possible (12, 13). In sub-totally resected disease and recurrent or grade II/III tumors, adjuvant treatment in the form of radiation and or chemotherapy may be administered; however, data on improvements in outcome are lacking (14–21). Due to the indolent behavior of these tumors, late effects and survival are increasingly being examined (22–24).

CLINICAL PRESENTATION

Over 50% of patients present with headache (20), hydrocephalus (21, 25) and focal neurological deficits. Glioneuronal tumors are by far the most common histological type of brain tumors requiring surgery for epilepsy management (26) and are therefore part of the “low grade epilepsy associated neuroepithelial tumors” family (26–29). Patients can present with seizures in infancy, childhood or early adulthood and most patients will have a mean duration of epilepsy of approximately 5 years with a range of 0.1 to 35 years (8). A family history of seizures or brain tumors is not typically reported on history and most patients

exhibit multiple seizure types with seizures that tend to be drug-resistant. About 42.9% of patients display two or more types of seizures with more patients presenting with complex partial seizures (dialeptic seizure, with vegetative or affective aura, psycho-sensorial aura and automatisms) or partial seizures evolving to secondarily generalized seizures (8). Temporal location is common, and the seizure presentation can be associated with focal cortical dysplasia (6). Although previous publications indicated a possible predilection for male (8) or female gender (1, 14, 30), more recent data suggests a 1:1 distribution (5, 22). Age at presentation for DIA/DIG is infant to 33 years while for other types such as PGNT, RGNT and GNTNI, it is 12–70 years (7, 8, 20). In addition to seizures, patients can present with hydrocephalus (21, 25), increased intracranial pressure as well as focal neurological deficits depending on tumor location, rate of growth and age. DIA/DIG presents usually, although not exclusively, in infants with increasing head circumference and seizure (31). Most commonly, patients with low-grade tumors present with headache, nausea, vomiting, and seizure; less frequent presentations include neurological deficits, loss of consciousness and chronic intermittent microhemorrhages (32–34) (Table 1).

Pathological, molecular and imaging features

Glioneuronal tumors have been reported since 1910, with the number of publications growing in the last 10 years as the identification of molecular alterations has allowed for better differentiation of glioneuronal tumors from other similar tumors in differential diagnosis (Figure 1, Table 1). Previous limitations in diagnosis were related to limited ability to elicit radiographic differences, scant material for pathological analysis and the overall rarity of glioneuronal tumors. Ganglioglioma, paraganglioma, central neurocytoma and DNET have been reported on for some time (Figure 1) (1–3, 35–44). RGNT (39–41), PGNT (42, 43) and GNTNI (44) were added to the WHO classification in 2007 (1). In 2016, the classification

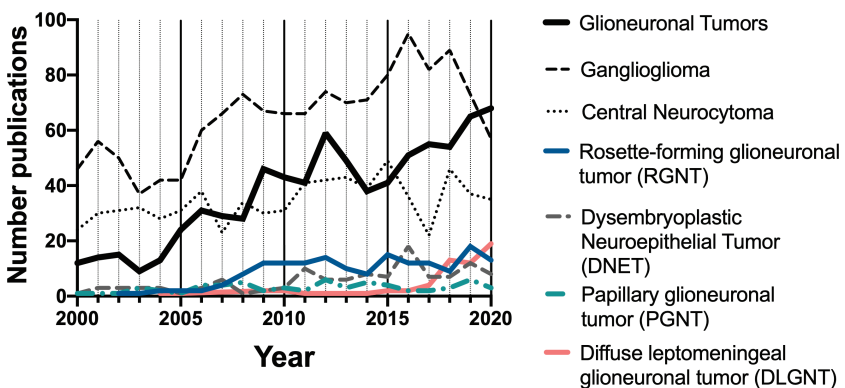


Figure 1. Number of publications from 2000 to 2020 by major glioneuronal tumor histologies. Author's own analysis based on literature search information. Retrieved October to November 2020 from <https://pubmed.ncbi.nlm.nih.gov/?term=glioneuronal+tumors&sort=date> (35).

Summary of glioneuronal tumor features

TABLE 1

| Subtype | Age group | Presentation | Location/Imaging | WHO grade | Genetic/Molecular Features | Management |
|--|--------------------------|---|--|-----------|--|---|
| Central neurocytoma/ Extra-ventricular Neurocytoma | Young adults | Increased intracranial pressure | Lateral ventricle/third ventricle (central neurocytoma) | II | DNA copy alterations | Surgical Resection Radiation (if Subtotal resection) |
| Liponeurocytoma | Young to older | Increased intracranial pressure | Cerebellum | II | TP53 mutation | Surgical Resection (recurrence common) Radiation |
| Desmoplastic infantile astrocytoma and ganglioma (DIA/ DIG) | Infants | Increasing head circumference Seizures | Large Solid/cystic mass | I | RAF V600E NRTK-1 Fusion | Surgical Resection |
| Diffuse leptomeningeal glioneuronal tumor (DLGNT) | Children Young adults | Hydrocephalus Cord compression Seizures | Leptomeningeal tumors/ spinal mass | I | BRAF gene fusion, 1p19q co-deletion (no IDH mutation) H3K27M described | Resection Chemotherapy and Radiation when recurrent |
| Dysembryoplastic neuroepithelial tumor (DNET) | Children Young adults | Epilepsy | Temporal lobe Hyperintense on T2 MRI and FLAIR Multicystic | I | PIK3CA/FGFR1 mutations | Epilepsy management Surgical Resection |
| Gangliocytoma (GC) | Children | Epilepsy | CNS (no specific location) | I | Lhermitte-Duclos Disease (Dysplastic cerebellar gangliocytoma PTEN/SDHB) | Epilepsy management Surgical Resection |

Table continued on following page

Summary of glioneuronal tumor features (Continued)

TABLE 1

| Subtype | Age group | Presentation | Location/Imaging | WHO grade | Genetic/Molecular Features | Management |
|---|------------------------|----------------------------------|--|-----------|---|--|
| Ganglioglioma (GG) | Very young to very old | Epilepsy | Predilection for temporal lobe Cystic and can be contrast enhancing | I | BRAF V600E H3K27M described | Epilepsy management Surgical Resection |
| Anaplastic ganglioglioma | Children and adults | Epilepsy Acute neuro symptoms | Similar to GG Contrast enhancing | III | BRAF V600E | Surgical Resection Chemotherapy and Radiation |
| Papillary glioneuronal tumor (PGNT) | Young adults | Epilepsy | Supratentorial Large Solid/cystic mass | I | SLC44A1-PRKCA NOTCH1-PRKCA | Surgical Resection |
| Rosette-forming glioneuronal tumor of the fourth ventricle (RGNT) | Young adults | Epilepsy | Fourth ventricle | I | PIK3CA/FGFR1 mutations IDH1 mutation | Surgical Resection |
| Rosetted glioneuronal tumor with neuropil-like islands (GNTNI) | Young adults | Epilepsy Acute neuro symptoms | Solid/cystic mass Enhancing | II/III | Evolving | Surgical Resection Chemotherapy and Radiation when possible |

added diffuse leptomeningeal glioneuronal tumors (DLGNT) (1, 2, 45–51) where the number of published case reports, pathological studies and reviews has grown since (Figure 1) (35).

Pathology

The common feature of glioneuronal tumors is the presence of both glial and neuronal tissue as evidenced by glial fibrillary acid protein- positive cells and synaptophysin-positive neuronal cells forming solid areas (Figure 2A (52)). The rarity of PGNT (Figure 2A (52); 68 cases in literature), RGNT (Figure 2B (53); 130 cases in literature), ganglioglioma (Figure 2C (54); 1.3% of all primary brain tumors), neurocytoma (Figure 2D (55); 0.1–0.5% of all brain tumors), makes diagnosis difficult (1–4). While each glioneuronal tumor can display certain distinct features (Figure 2), in some instances a tumor may demonstrate overlapping histologic features with mixed components (36) making diagnosis challenging. With the exception of central neurocytoma (WHO grade II), extraventricular neurocytoma (WHO grade II), liponeurocytoma (WHO grade II), GNTNI (WHO grade II/III) and anaplastic ganglioglioma (WHO grade III), glioneuronal tumors

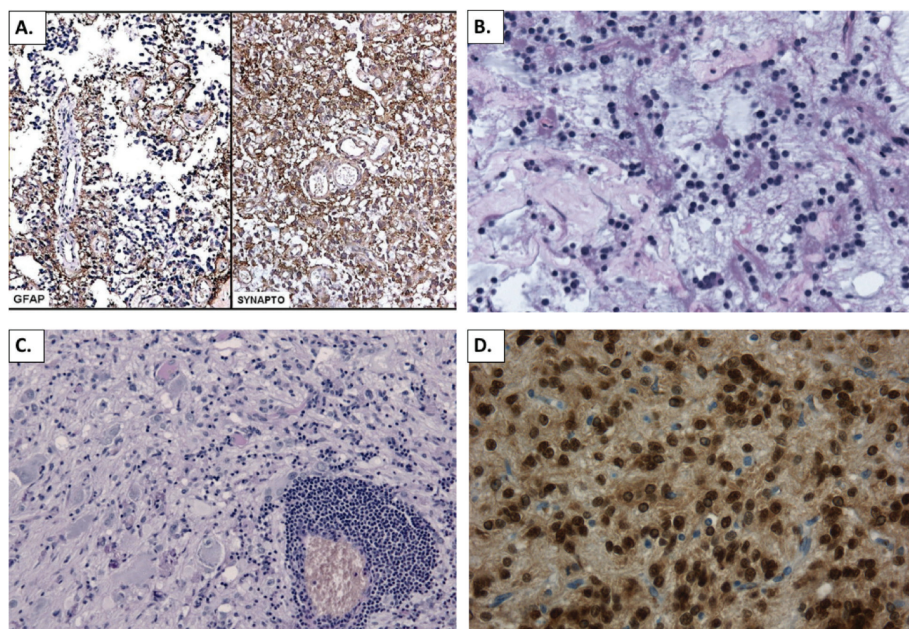


Figure 2. Pathologic features of glioneuronal tumors. A. Histopathology of papillary glioneuronal tumor (PGNT): the pseudopapillae formed by glial fibrillary acid protein (GFAP)-positive cells and synaptophysin (SYNAPTO)-positive neuronal cells forming solid areas. (adapted from 52). B. Histopathology specimen (HE stain) of a RGNT (rosette-forming glioneuronal tumor; adapted from 53). C. PAS stain of a ganglioglioma displaying perivascular lymphocytic infiltrates and weakly PAS-positive eosinophilic granular bodies (x100 magnification; adapted from 54). D. Histopathology of Neurocytoma. Immunohistochemistry for NeuN showing neuronal differentiation of tumor cells adapted from 55).

exhibit WHO grade I behavior (Table 1). The Ki-67 labeling indices of most glioneuronal tumors are low, mostly 1–2% and generally less than 5%; however, in PGNT, 13–14% of total reported cases have shown increased proliferative indices (1, 34, 42) in line with high grade gliomas (56–58). The pathology of glioneuronal tumors is complex, requiring significant neuropathological expertise for interpretation. Notably, unlike most other glioneuronal tumors, GNTNI and WHO grade III variants of GGs, such as anaplastic ganglioglioma and atypical neurocytoma behave more similar to other high-grade gliomas, also carrying a poorer prognosis. DLGNT was introduced in the 2016 WHO classification of central nervous system tumors (1). A number of publications have since focused on this entity (1, 2, 35, 45–51, 59) (Figure 1). DLGNT mainly occurs in children and is mostly characterized by leptomeningeal growth, although Appay *et al.* described cases that are neither diffuse nor leptomeningeal, concluding that DLGNT may represent a “spectrum that has yet to be fully clarified” (45). DNET is a benign, glioneuronal neoplasm also part of the differential for other glial tumors including glioma, ganglioglioma, pilocytic astrocytoma or diffuse astrocytoma (4, 5). DIA/DIG is under-represented in the literature, with fewer than 20 cases, it is present generally in infants less than 24 months and displays prominent desmoplasia (60–64) (Figure 3).

Molecular characterization

While the underlying biology for the different glioneuronal tumor subtypes remains unclear (4), large scale genomic and epigenomic analyses have provided more insight into genetic alterations (4–9). Data is still emerging but the rarity of glioneuronal tumors means it may take some years to fully explore. Stone *et al.* suggest that most glioneuronal tumors fall within two major groups: group 1 containing a higher proportion of tumors with a ganglioglioma-like appearance

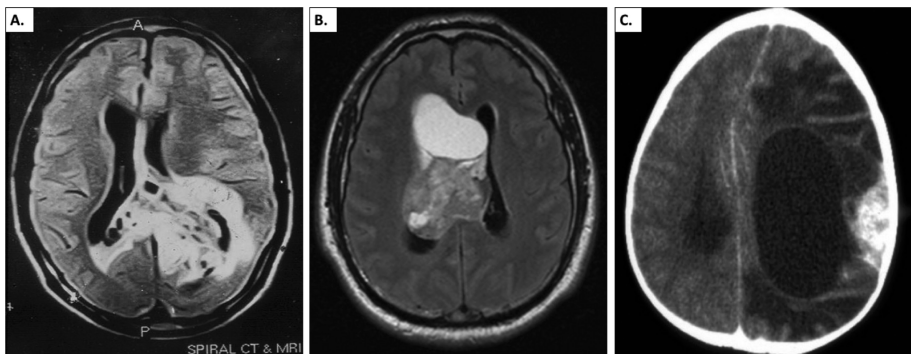


Figure 3. Radiographic appearance of glioneuronal tumors. A. Papillary glioneuronal tumor. Non-contrast magnetic resonance imaging showing hyper-intense lesion involving the left temporal and parieto-occipital regions. The tumor is crossing the midline to the right parietal region (adapted from 62). B. Axial FLAIR (fluid-attenuated inversion recovery) MR image showing a right ventricular mixed solid/cystic mass limited by the septum pellucidum and ventricular walls. With heterogeneous enhancement on post-gadolinium sequences. Provisional diagnosis of central neurocytoma, later confirmed on pathology (adapted from 63). C. Radiologic appearance of desmoplastic infantile ganglioglioma (adapted from 64).

displaying more BRAF-V600E mutations while group 2 tumors are more DNET-like in appearance and display more FGFR1 mutations (4). BRAF is an oncogene mutated in many malignancies and more recently described in one-third of GGs and 20–25% of DNET and DIA/DIG (4, 5, 65, 66). Some gliomas and glioneuronal tumors are characterized by a fusion between the BRAF gene and the locus KIAA1549 (45) (Table 1). The fusion causes a constitutional activation of the tyrosine kinase domain of BRAF and a permanent activation of the MAP kinase (MAPK) pathway (6,66). The detection of a BRAF rearrangement can help distinguish cancers with favorable prognosis such as glioneuronal tumors from those with poorer prognosis, such as diffuse gliomas, including diffuse astrocytomas and oligodendrogliomas. It also has therapeutic implications, as targeted therapies against mutated BRAF-V600 protein are being developed (vemurafenib, dabrafenib) (67). BRAF V600E mutations were identified by DNA sequencing in 33% of GGs and 27% of DNTs (8) and by immunohistochemistry in 29.5% of cases, 61.5% representing GG/GC/anaplastic ganglioglioma (5). Results can be discordant between immunohistochemistry and other molecular tests (5) illustrating the ongoing challenges in harnessing molecular testing for glioneuronal tumors and the as yet limited ability to draw conclusions with respect to diagnosis, prognosis and management. To date, the presence of BRAF mutation has not been associated with clinical presentation, imaging features or resolution of seizures postoperatively, acknowledging the limited data available. This is however evolving with recent descriptions of neuronal/glioneuronal tumors arising from the diencephalic region with a BRAF V600 mutation rate of 75% exhibiting clinically aggressive behavior (68). In pediatric GGs a worse recurrence-free survival of tumors with BRAF V600E mutation was reported by Dahiya *et al.* (69). Other identified mutations include PIK3CA (RGNTs and mixed RGNT/DNET) (69) with implications for targeting the PI3K/AKT/mTOR pathway (70,71), FGFR1 mutations (20, 71–76), H3K27M-mutations (77, 78), SLC44A1-PRKCA and NOTCH1-PRKCA fusion (79), IDH1 mutation (80) and 1p 19q alterations (78, 81) (Table 1).

Imaging Features

The features of glioneuronal tumors on diagnostic imaging are highly variable. Limited data exists, hampering an in-depth analysis of radiographic-pathological correlation. Hybrid features have been noted in many tumors. In general, radiological studies acknowledge overlap of imaging features between glioneuronal tumors and other tumors, which complicates radiographic diagnosis (82). Large tumors demonstrate cystic degeneration and necrosis, hemorrhage, contrast enhancement, and regions of low apparent diffusion coefficient consistent with patterns seen with other high-grade pediatric brain tumors (83). Broadly, glioneuronal tumors are characterized by the presence of a solid/cystic mass in periventricular location with septations and a solid inner component (84) (Figure 3). Attempts have been made to radiographically classify long-term epilepsy-associated tumors, of which glioneuronal tumors form a significant component. A number of small series have described imaging features of PGNT (42, 85), RGNT (40, 41, 86), DLGNT (45–47, 87), GG (56), neurocytomas (16), DNT (8). PGNT, RGNT and GNTNI were added to the WHO classification in 2007 hence imaging reviews are more recent and evolving (2). Most of these tumors are located in the supratentorial region (69%), however, spinal (23%) and

disseminated disease at primary diagnosis (8%) are also described (7). They exhibit variable contrast enhancement with GNTNs appearing mostly as solid tumors in 73% of cases; about 19% appear as cystic with a mural nodule under T2-hyperintensity and T1-hypointensity (7) (Figure 3A (62)). The most common site of glioneuronal tumors is the temporal lobe followed by frontal lobe (8). Tumors with a high Ki-67 index (≥ 5) are more likely to exhibit perilesional edema and ring enhancement on magnetic resonance imaging (MRI) (10). DLGNT was added to the WHO classification in 2016 and publications have increased since (1, 2, 45–50, 55). In DLGNT, MRI is generally consistent with diffuse leptomeningeal enhancement predominantly and multiple cystic-solid lesions along the neural axis (49, 59, 87) but may present more atypically as well (45, 88). GGs appear cystic-solid or solid with long T1 and T2 signals with associated calcification (89). Often there is limited edema, and they may display no or mild contrast enhancement. Neurocytomas can be ventricular or extraventricular. Extraventricular neurocytomas are usually cortically based and infiltrative without peritumoral edema or intratumoral hemorrhage (Figure 3B (63)). DIA/DIG on computed tomography and MRI appear as large superficial large cerebral masses with solid and cystic areas (60). The solid component of the tumor frequently shows contrast enhancement (60) (Figure 3C (64)). Ultimately, the differential diagnosis of these findings includes low-grade glioneuronal tumors and low-grade gliomas.

MANAGEMENT, CLINICAL RESPONSE AND LATE EFFECTS

Generally, surgical resection is the corner stone of seizure management for patients with glioneuronal tumors. The purpose of resection in glioneuronal tumors is twofold: to alleviate symptoms (secondary to CSF flow disruption, seizures and/or increased intracranial pressure) and to achieve debulking in the context of more aggressive tumor subtypes (13, 26, 90).

Symptom control and surgical management

Glioneuronal tumors presenting with hydrocephalus (DLGNT, RGNT) should be considered for urgent ventriculoperitoneal shunting surgery which can result in complete symptom resolution (14, 25, 49). Surgical resection for debulking, and restoration of cerebrospinal fluid (CSF) flow when impeded, is the standard management (12, 25). Often the decision is made in multidisciplinary settings as these tumors are rare and the management is fraught with significant risks for late effects, particularly in patients with tumors that display more benign behavior who generally survive for longer. Several studies suggest that upwards of 70% of patients experience complete resolution of seizures post-operatively (8, 12, 90). Prognosis can be good with a progression-free survival (PFS) in 85 to 95% of patients (12). Gross total resection (GTR) is superior to subtotal resection (STR) and tumors with a lower Ki-67 index and a lower WHO grade have a better prognosis as compared to those with higher index and higher grade (7, 12). Only about 50% of patients undergo GTR prompting the administration of adjuvant radiotherapy and chemotherapy in some patients although due to limited evidence the benefit thereof remains unclear (18, 20, 40).

Systemic Management and Radiation Therapy

Radiation therapy (RT) is generally considered for recurrent and higher-grade tumors such as neurocytoma, anaplastic ganglioglioma and GNTNI. Acharya *et al.* analyzed 150 patients with unresectable pediatric low-grade gliomas and glioneuronal tumors to identify prognostic features in patients treated with RT using clinicopathologic and molecular data (18). RPA (Recursive Partitioning Analysis) yielded low- and high-risk groups with 10-year overall survival (OS) of 95.6% versus 76.4%. High-risk tumors included diffuse astrocytoma or location within thalamus/midbrain while low-risk tumors included pilocytic astrocytoma/ganglioglioma located outside of the thalamus/midbrain (18). The prognosis was independent of BRAF status but within the high-risk group, delayed RT (defined as RT after at least one line of chemotherapy), was associated with a further decrement in OS (18). The administration of chemotherapy is also heterogenous. Johnson *et al.* (16) carried out a comprehensive literature review of central neurocytoma regarding administration of chemotherapy. They identified 18 citations (39 cases of adult and pediatric central neurocytoma treated with chemotherapy) and found that nine patients with recurrent neurocytoma received temozolomide (TMZ) noting significant heterogeneity in chemotherapy administration (16). Chen *et al.* reported on long-term outcomes of 63 neurocytoma patients who received adjuvant radiotherapy after surgical resection (19). With a median follow-up of 69 months the 5-year OS and 5-year PFS were 94.4% and 95% after GTR + RT, 96.4% and 100% after STR + RT, and 100% and 90.9% after PR + RT (19). RT after incomplete resection led to OS and PFS comparable to those for GTR with excellent outcomes and limited late toxicity suggesting that adjuvant RT is a reasonable option for neurocytoma patients with incomplete resection. Radiosurgery as an alternative has also been proposed as an option with 5- and 10-year local tumor control rates 93% and 87%, respectively, and the 5- and 10-year PFS rates 89% and 80%, respectively (91, 92). The use of chemotherapy, targeted agents, and Bevacizumab is only subject of case reports and small studies and benefit remains unclear (93–97). For disseminated, recurrent and high-grade disease, definitive radiotherapy or radiochemotherapy is considered and treatment may overall reflect that of other high-grade gliomas due to the histologic and natural history similarities they share (7, 17). Generally, the outcome in patients with glioneuronal tumors can be broadly discussed in the context of progression of disease, transformation to higher grade tumors and the long-term complications of treatment or late effects. In a series of patients treated at the St. Jude Children's Research Hospital (1986 to 2015), progression of disease and transformation to higher grade glioma accounted for 66% of the mortality (24). Other causes included secondary malignancy, shunt infection/sepsis, suicide and motor vehicle accidents (24). In this series, the median age at death for the cohort was 14.26 years (range, 0.58–32 years), and the median time to death from diagnosis was 4.02 years (range, 0.21–24 years). Overall, our understanding of the optimal management and the outcomes of glioneuronal tumors remains limited due to the rarity of these tumors and the data originating from small series and literature reviews. With ongoing molecular characterization and the paralleled progress of targeted agents, data continues to evolve.

Late effects

Despite more favorable survival outcomes as compared to other more aggressive gliomas, significant late effects are associated with glioneuronal tumors. Late effects are likely multifactorial, stemming from a combination of tumor presence, surgical resection, and adjuvant management including systemic agents and RT. The lack of data surrounding optimal management and outcomes also extends to lack of clarity surrounding the burden of late effects on patients with glioneuronal tumors. Ehrstedt *et al.* carried out a cross-sectional long-term follow-up evaluation on 28 children and adolescents (0–17.99 years), with a mean follow-up period of 12.1 years (23). They identified postoperative gain in cognitive function in seizure-free patients, but at a relatively low level, and high levels of anxiety and depression (23). In a series of 51 patients with low grade glioma and glioneuronal tumors managed at the St. Jude's Children's Research Hospital, USA, (1986 to 2015) with a mean age at diagnosis of 6.47 months (range, 0.17–11.76) and mean duration of follow-up of 11.8 years, 96% of patients experienced at least one long-term deficit, such as endocrinopathy and obesity (51%), neurological deficit and seizure (43%), visual and hearing loss (56%), neurocognitive impairment (49%), cerebrovascular disease and scoliosis (27%) and secondary malignancy (14%) (24). Late effects correlated with tumor location (hypothalamic/optic pathway), administration of radiation therapy and more chemotherapy regimens (24). According to Upadhyaya *et al.*, early psychological intervention should be included as part of the multidisciplinary management approach of children with both glioneuronal tumors and low-grade gliomas to reduce the risk of suicide in vulnerable subjects.

CONCLUSION

Glioneuronal tumors are uncommon tumors comprised of glial and neuronal components. They generally display indolent behavior but can behave aggressively. They are pathologically and radiographically complex, and classification hinges on advancements with respect to molecular analysis to allow for future personalized treatment which may improve outcomes. Currently, cases are best managed in multidisciplinary settings with the role of adjuvant treatment in the form of chemotherapy and radiation therapy beyond surgery remaining unclear. In depth counselling regarding late effects is paramount due to the burden of long-term life altering sequelae in long-term survivors. The creation of robust registries and tumor sequencing is imperative to allow for improvement of outcomes in the long term.

Conflict of Interest: The author declares no potential conflict of interest with respect to research, authorship and/or publication of this chapter.

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