REVIEW

Practical aspects regarding the histopathological grading and anaplastic transformation of gangliogliomas – a literature review

ANTONIA CARMEN LISIEVICI¹⁾, MIHAI GHEORGHE LISIEVICI²⁾, DIANA PAȘOV²⁾,
TIBERIU AUGUSTIN GEORGESCU^{1,3)}, OCTAVIAN MUNTEANU^{4,5)}, CORINA GRIGORIU^{4,6)},
ROXANA ELENA BOHÎLȚEA^{4,6)}, FLORENTINA LIGIA FURTUNESCU⁷⁾, MARIA SAJIN^{1,8)}

¹⁾Discipline of Pathology, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania

²⁾Department of Pathology, Bagdasar-Arseni Emergency Clinical Hospital, Bucharest, Romania

³⁾Department of Pathology, Alessandrescu-Rusescu National Institute for Mother and Child Health, Bucharest, Romania

⁴⁾Discipline of Obstetrics and Gynecology, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania

⁵⁾Discipline of Anatomy, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania

⁶⁾Department of Obstetrics and Gynecology, Emergency University Hospital, Bucharest, Romania

⁷⁾Department of Public Health and Management, Faculty of Medicine, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania

⁸⁾Department of Pathology, Emergency University Hospital, Bucharest, Romania

Abstract

Ganglioglioma represents a benign central nervous tumor, occurring predominantly in the pediatric population and affecting the temporal lobe. It is also renowned for its epileptogenic potential. However, to date, there are numerous uncertain features about this tumor, especially about its grading system. In the former *World Health Organization* (WHO) Classification of central nervous tumors system, gangliogliomas could have been attributed one out of three grades: grade I (benign), grade II (atypical), and grade III (anaplastic). The new classification systems have renounced to atypical ganglioglioma nomenclature, due to the lack of histopathological criteria for this entity. Another controversial aspect of grade I ganglioglioma is its potential to transform into a malignant tumor, namely, most frequently an anaplastic ganglioglioma. Based on our knowledge, there are no literature reviews to date focusing on anaplastic transformation potential. The present paper encompasses all anaplastic transformation of gangliogliomas and has analyzed the time frame between the two events, the age of the patients and its relationship to the complete or subtotal resection and administration of radiotherapy. Thirty-three cases of malignant transformation of ganglioglioma have been reported so far in the literature, with 54.54% of them undergoing progression to anaplastic ganglioglioma and 21.21% to anaplastic ganglioglioma. Median age was 26 years, and the cases were evenly distributed between the two sexes. Only 27.27% of all evaluated cases had been administrated adjuvant radiotherapy, and only 44% of the latter have had an incomplete tumoral resection.

Keywords: ganglioglioma, anaplastic transformation, grading ganglioglioma.

Introduction

Although ganglioglioma is an extremely rare tumor, it is, nonetheless, one of the most common tumors arising in the pediatric population. They are well-differentiated, slowly growing, mixed tumors, often arising in the temporal lobe, in patients with epileptic seizures [1]. Histopathologically, it is made of two intertwining populations: one consisting of dysplastic neurons and one consisting of neoplastic astroglial cells. On the other hand, anaplastic ganglioglioma [*World Health Organization* (WHO) grade III] tends to occur in adults or elderly patients, do not usually arise in the temporal lobe and have increased cellularity and proliferation of the glial component [2, 3]. Classical features suggesting malignancy, like necrosis and microvascular proliferation, can also be encountered.

To this day, little is known about the histopathological (HP) grading of ganglioglioma, although many case reports,

studies, and reviews, were conducted separately, regarding either gangliogliomas or anaplastic gangliogliomas. While the *WHO* Classification has suffered great changes along the past years, the general acceptance of this grouping remains low, due to the lack of consensus and, more importantly, lack of details concerning the HP features of this split. Although it is clear that most tumors can easily be classified as either benign or malignant, there are also rare cases which do not meet either criteria. Therefore, the question remains: should we upgrade them to the anaplastic category and risk overtreatment, or should we put them into the benign category and hope that the follow-up will reveal no tumor progression? Perhaps further studies with thorough correlation between HP features and clinical outcome will eventually lead to the development a software-based scoring system to stratify therapeutic management, as it happened with some pathologies of other organs and systems [4].

Materials and Methods

A thorough search on *PubMed*, *Medline* and *Google* using various combinations of the following headings: “ganglioglioma”, “anaplastic transformation”, and “grading gangliogliomas” revealed a total of 33 cases published in the English literature since 1962, mainly as isolated case reports or short case series.

Results

Table 1 summarizes the main characteristics of the 33 patients with grade I gangliogliomas reported to have suffered anaplastic transformation.

Table 1 – Cases of malignant transformation in ganglioglioma reported in the scientific literature

Case No.	Authors (year) [Ref. No.]	Age [years]	Gender	Complete resection	Age of malignant transformation [years]	Radiotherapy treatment	Histological variant of the malignant transformation
1.	Rusell & Rubinstein (1962) [5]	NA	M	NA	+23	Yes	Glioblastoma
2.	Kalyan-Raman & Olivero (1987) [6]	NA	NA	Yes	+5	Yes	Glioblastoma
3.	Jay <i>et al.</i> (1994) [7]	10	M	No	13	Yes	Malignant transformation of both tumoral components (neuronal and glial)
4.	Sasaki <i>et al.</i> (1996) [8]	26	M	Yes	32	No	Anaplastic ganglioglioma
5.	Kurian <i>et al.</i> (1998) [9]	10	F	Yes	11	No	Anaplastic ganglioglioma
6.	Rumana & Valadka (1998) [10]	32	F	Yes	34	Yes	Anaplastic astrocytoma
7.		24	M	No	36	Yes	Anaplastic ganglioglioma
8.		56	M	No	60	Yes	Anaplastic astrocytoma
9.		30	M	Yes	34	Yes	Glioblastoma
10.	Mittler <i>et al.</i> (1999) [11]	4	NA	Yes	21	No	Glioblastoma
11.	David <i>et al.</i> (2000) [12]	18	F	Yes	25	No	Neuroblastoma
12.	Hayashi <i>et al.</i> (2001) [13]	16	F	No	25	No	Glioblastoma
13.	Wharton <i>et al.</i> (2000) [14]; Whittle <i>et al.</i> (2002) [15]	39	M	No	40	No	Anaplastic ganglioglioma
14.		34	F	No	35	No	Anaplastic ganglioglioma
15.		26	M	No	29	No	Anaplastic ganglioglioma
16.		39	M	Yes	41	No	Anaplastic ganglioglioma
17.	Tarnaris <i>et al.</i> (2006) [16]	45	F	Yes	47	Yes	Neuroblastoma
18.	Mittelbronn <i>et al.</i> (2007) [17]	47	F	NA	49	No	Malignant transformation of both tumoral components (neuronal and glial)
19.	Majores <i>et al.</i> (2008) [18]	NA	NA	No	NA	No	Glioblastoma
20.	Reis <i>et al.</i> (2012) [19]	9	M	No	13	No	Glioblastoma
21.	Lee <i>et al.</i> (2012) [20]	56	M	Yes	57	No	Anaplastic ganglioglioma
22.		61	F	No	61	No	Anaplastic ganglioglioma
23.	Bendersky <i>et al.</i> (2012) [21]	19	M	Yes	22	No	PNET
24.	Morana <i>et al.</i> (2013) [22]	2	F	No	9	No	Anaplastic ganglioglioma
25.	Zanella <i>et al.</i> (2016) [23]	7	M	No	10	No	Anaplastic ganglioglioma
26.		16	F	No	16	No	Anaplastic ganglioglioma with <i>BRAF</i> (V600E) and <i>H3F3A</i> (p.K27M) mutations
27.		8	F	Yes	11	No	Anaplastic ganglioglioma with <i>BRAF</i> V600E mutation
28.	Joyon <i>et al.</i> (2017) [24]	12	F	NA	19	No	Anaplastic ganglioglioma
29.		25	M	NA	25	No	Anaplastic ganglioglioma
30.	Lummus <i>et al.</i> (2014) [25]	27	F	No	32	Yes	Anaplastic ganglioglioma
31.	Qiu <i>et al.</i> (2017) [26]	59	F	No	62	No	Gliosarcoma
32.	Rosselló <i>et al.</i> (2017) [27]	43	F	No	46	No	Anaplastic ganglioglioma
33.	Riesberg <i>et al.</i> (2018) [28]	13	M	Yes	20	No	Anaplastic ganglioglioma

BRAF: B-Raf proto-oncogene, serine/threonine kinase; F: Female; *H3F3A*: H3 histone, family 3A; M: Male; NA: Not available; PNET: Primitive neuroectodermal tumor.

Analyzing the data retrieved from the above-mentioned studies, we quickly observe that most cases underwent malignant transformation into anaplastic ganglioglioma (54.54%), while only 21.21% of patients suffered an upgrade of the HP aspects, leading to glioblastomas. Only a minority featured either malignant transformation of both neuronal and glial components (6.06%) or underwent transformation into an anaplastic astrocytoma (6.06%) or neuroblastoma (6.06%). Exceptional case reports have described malignant transformation of grade I gangliogliomas into gliosarcoma [26] and a primitive neuroectodermal tumor (PNET) [21].

Patients' age varied from two to 61 years old, with an average of 28.9 years and a median of 26 years. The period of time passed between the excision of the primary tumor and the malignant transformation varied between three months and 23 years (average of 5.18 years and median of three years). Gender-wise, the cases were equally distributed between the two genders.

Regarding the controversial radiotherapy treatment [10, 16, 29], 27.27% of patients underwent adjuvant radiotherapy with subsequent malignant transformation. Out of the cases which have received radiotherapy, only 44% of them have had an incomplete/subtotal resection of the primary tumor. No correlations were observed between the incomplete excision of the tumor and the interval between the primary tumor and the malignant transformation, in patients who underwent radiotherapy. The average time passed between the first and the second excision was six years, in patients with incomplete resection who underwent radiotherapy and 7.6% in those with total resection of tumor. Out of all reported cases, 48.48% had a subtotal resection of the first tumor, 39.39% underwent total resection of the tumor, with no imaginistically detectable remaining tumor and 12.12% of the reports did not mention whether the first excision was complete or not.

Discussions

Clinical features

Gangliogliomas usually affect children and young adults, although cases have been reported in patients with a wide age range, from eight months to 70 years [30]. Intracranial tumors are rare in pregnancy and may present a diagnostic and therapeutic challenge. However, anaplastic ganglioglioma is one of the several subtypes of aggressive malignant tumors reported during the third trimester of pregnancy [31, 32]. They are usually located in the temporal lobe (70%), although other anatomic areas can also be involved, especially the cerebellum, the spinal cord, the frontal lobe, the brainstem, or the pineal gland [2]. Studies show a worse prognosis for those situated in the brainstem, compared to those which have a supratentorial location, with a 3.5- to 5-fold increased risk of recurrence [33]. Patients usually present with a long history of epileptic seizures, that do not typically respond to antiepileptic medicine, especially when the tumor involves the neocortex or temporal lobe. Other uncommonly encountered symptoms range from headache, nausea, visual disturbances, and fatigue – if situated in the hypothalamus or third ventricle [34] – to progressive myelopathy, motor and sensory defects, gait abnormalities and bowel or bladder dysfunction – if situated in the spinal cord [33, 35].

Although not currently encompassed in the current *WHO* Classification system due to the lack of consensus regarding its HP features, many authors still believe that grade II gangliogliomas should not be totally removed from the grading system. Regarding the clinical features, they are extremely similar to those of grade I ganglioglioma, namely young adults, presenting with epileptic seizures due to a tumor located in the temporal lobe. One

article even presents a case of a *WHO* grade II ganglioglioma, which has evolved into a glioblastoma, this way questioning the apparently “intermediate” HP grade [36].

Anaplastic gangliogliomas (*WHO* grade III) are much rarer tumors than their benign counterparts, accounting for approximately 3–5% of all gangliogliomas, and although they usually affect patients in the same age range, studies have shown a slight tendency to affect older patients, with a mean age of 35 ± 14.5 years [37, 38]. They are usually supratentorial, with most tumors occurring in the temporal and parietal lobes, but rare cases occurring in the spinal cord have also been reported. Involvement of the temporal lobe is not that frequently encountered, in comparison to *WHO* grade I gangliogliomas [37]. Symptoms are similar to those located in the same anatomic regions as the *WHO* grade I ganglioglioma [39]. Several authors state that grade III gangliogliomas may arise from the malignant transformation of grade I ganglioglioma. One case report even presents a patient where the transformation was into a combined ganglioglioma and pleomorphic xanthoastrocytoma with anaplastic features [25]. The malignant transformation was usually linked to either incomplete therapy, although some authors have claimed in the past, that radiotherapy might also play a role in this degeneration [10, 18]. In a few case reports, malignant transformation was also accompanied by leptomeningeal spread [25, 28].

Imaging aspects

Grade I gangliogliomas (Figure 1) usually appear as a well-circumscribed, low-density enhancing mass, which may associate cystic areas and even calcifications [40] on computed tomography (CT) examination. Clues revealing the slow growing nature of the tumor, like bony remodeling or thinning can sometimes be observed. On magnetic resonance imaging (MRI), the solid component tends to be iso- to hypointense in T1, has pronounced signal increase in proton-density weighted images and less hyperintense in T2 [6]. Also, the content of the cystic mass has a higher signal in T2, than cerebrospinal fluid (CSF), correlating to the gelatinous mass, which can sometimes be found intraoperatively [41]. More than half of the cases have a perilesional edema and tumors occurring in children tend to have larger dimensions [42].

On the other hand, grade II gangliogliomas tend to look more like a true malignant neoplasm: larger dimensions, that appears to extend into the surrounding tissue, with an inhomogeneous aspect. Scant edema and little mass effect can also be observed [43]. Atypical features, like intratumoral hemorrhage or bi-hemispherical extension can occur (Figure 2).

Anaplastic ganglioglioma, although slowly growing, can have extremely aggressive features. Most of them have large dimensions, they can erode the skull and even extend beyond it, sometimes without having even any effect on the median line. They can also have positive mass effect with near complete effacement of the lateral ventricles, especially if located in the temporal lobe [3, 44]. They present as hyperintense or isointense in T1 scans, with more pronounced edema and “ring” Gadolinium enhancement (Figures 3 and 4) [41].

Figure 1 – Typical aspect of a grade I ganglioglioma featuring both a cystic and a solid component, affecting mostly the temporal lobe (T2-weighted MRI image). MRI: Magnetic resonance imaging.

Figure 2 – Malignant ganglioglioma presenting as a diffuse mass affecting both hemispheres (frontal and temporal lobes) and discretely compressing the lateral ventricles (T2-weighted MRI image).

Figure 3 – Recurring ganglioglioma showing a large, irregular temporal mass with a cystic component and mural nodule featuring contrast enhancement (contrast-enhanced T1-weighted MRI image).

Figure 4 – Anaplastic ganglioglioma presenting as a large, irregular temporal mass, with no cystic component. The tumor is compressing the lateral ventricle (contrast-enhanced T1-weighted MRI image).

Practical histopathological aspects

To establish the diagnosis of ganglioglioma, one must identify two types of cellular populations: a neuronal and a glial one, both with clearly benign features. Either one of them can predominate. The glial component can have characteristics of either pilocytic astrocytoma, fibrillary astrocytoma or even oligodendroglioma. This is the component which gives the tumor its HP grade. The glial cells usually do not cluster around the neuronal proliferation [45]. The neuronal component (Figure 5), which is organized in nests, can also have features of atypia (lack of orientation, bizarre shapes, variable sizes, vesicular nuclei, and conspicuous nucleoli) [1]. The cells can have cytomegalic features, binucleation, bizarre nuclei or even ganglioid aspects [2, 46]. A perimembranous condensation of the Nissl substance and the presence of argyrophilic processes are also frequently encountered features. This perimembranous condensation can be highlighted through the Cresyl Violet staining, and the presence of the neuronal processes is identifiable through the modified Bielschowsky, Holmes and Bodian staining.

Regarding the surrounding matrix, one can observe the presence of eosinophilic granular bodies or Rosenthal fibers (mostly accompanying the glial component), suggestive for a long-standing course of progression, and also a fibrillary matrix sustaining the proliferating cells. To illustrate the rich reticulin network, a Reticulin staining can be useful [1]. Desmoplasia (deposition of collagen in the neuropil), a rather prominent capillary network and calcifications are also features of *WHO* grade I ganglioglioma [45, 47]. Surrounding the neoplastic proliferation is a lymphoplasmocytic infiltrate, admixed with activated microglia (Figure 6). Nonetheless, the lack of inflammatory reaction, does not exclude this diagnosis [48].

One should be aware of a diagnostic pitfall, in those exceptional cases, where the neuronal component predominates and where cortical dysplasia or gangliocytoma can be in the differential diagnosis. On the other hand, if the glial component predominates and the neuronal component is inconspicuous, one might be tempted to diagnose the lesion as an astrocytoma [1].

There is not much data concerning the HP diagnosis, or the clinical outcome of atypical ganglioglioma (*WHO* grade II), henceforth the decision to remove this entity from the 2016 *WHO* Classification. In our opinion, the most thorough and accurate paper on this theme is the retrospective study published by Luyken *et al.*, in 2004, in which they analyze cases and evaluate their outcome for a period of eight years. In their study, the threshold for diagnosis of atypical ganglioglioma (Figure 7) was based on the presence of microvascular proliferation, increased cellularity (Figure 8), obvious nuclear pleomorphism of the glial component and increased Ki67 proliferative index (above 5%) [49]. Other authors have considered a proliferative index of 10% as the threshold between low grade (*WHO* grade I and II) and high grade (*WHO* grade III) [41]. Majores *et al.* also included the presence of an increased mitotic rate in their grading system [18]. On the opposite side, Blümcke & Wiestler have regarded the presence of microvascular proliferation and mitotic activity as criteria for anaplastic ganglioglioma [37]. Nevertheless, since many studies, including that of Majores *et al.* [18] have reported more cases of grade II ganglioglioma than anaplastic ganglioglioma, the need of this category should not be doubted.

Regarding the anaplastic ganglioglioma (*WHO* grade III), most authors believe that it consists of a malignant transformation of the glial component. Studies have shown that increased cellularity, increased mitotic activity, presence of necrosis and microvascular proliferation (Figure 9) are elements that aid in making this diagnosis [2]. Mitoses are only rarely observed in the neuronal component, feature also confirmed by the Ki67% proliferative index, which is positive only in the neoplastic astrocytes (Figure 10) [45].

Figure 5 – Grade I ganglioglioma showing a cluster of neuronal cells dispersed in a mixture of glial cells [Hematoxylin–Eosin (HE) staining, ×400].

Figure 6 – Grade I ganglioglioma showing a bland glial proliferation with perivascular lymphocytic cuff, characteristic of neuronal proliferations (HE staining, ×200).

Figure 7 – Atypical ganglioglioma featuring an increased cellularity with rare intermingled dysmorphic neurons (HE staining, ×200).

Figure 8 – Atypical ganglioglioma featuring a hypercellularity of the glial component, which has features of a pilocytic astrocytoma (HE staining, ×200).

Figure 9 – Anaplastic ganglioglioma showing marked cellular pleomorphism of the glial proliferation, which encompasses rare dysmorphic neurons. Increased vascularization, suggestive for aspects of microvascular proliferation can also be observed (HE staining, ×200).

Figure 10 – High-power field of an anaplastic ganglioglioma showing marked hypercellularity, pleomorphism and atypical mitosis (HE staining, ×400).

Practical immunohistochemical aspects

There are multiple aspects regarding the immunohistochemical approach of these neoplasms. First of all, it is necessary to confirm the presence of a mixed glioneuronal proliferation and exclude a gangliocytoma or an astrocytoma. To achieve this goal, one must demonstrate the presence of the neuronal component through microtubule-associated protein 2 (MAP2), synaptophysin, chromogranin A, neuronal nuclei (NeuN), and neurofilaments [2, 50], respectively of the glial component through glial fibrillary acidic protein (GFAP) [2].

Second of all, once the histogenesis is established, one should try to establish the grading. Probably, Ki67 is the most useful immunomarker for this decision. It is unanimous in the literature that a low proliferative index, namely less than 5% is characteristic for a clearly benign ganglioglioma, while an index higher than 10% is typical for an anaplastic ganglioglioma [41]. The literature features many opinions regarding a proliferative index ranging between 5% and 10%. Some authors believe that a Ki67% proliferative index of ~5% is fairly high for a benign neoplastic process and acknowledge that it probably should be interpreted as a *WHO* grade II neoplasm [37, 41]. The current *WHO* Classification reports that the mean Ki67 proliferative index should range between 1.1% and 2.7%, although no range has been given for the anaplastic variant. Nonetheless, there are also authors who believe a Ki67 proliferative index of 5–7% can be enough to establish that the lesion is indeed anaplastic [39]. Others believe that one should only diagnose a ganglioglioma if the proliferative index is less than 1% [45, 46, 51, 52].

Another controversial immunomarker is the cluster of differentiation 34 (CD34) expression, which stains both the perikarya and the subdividing processes. The normal nervous tissue does not usually express CD34, nor do most of the central nervous system tumors (exception: pleomorphic xanthoastrocytoma). This expression, encountered in almost 80% of all gangliogliomas, is particular to this diagnosis [37, 53]. However, this expression tends to be limited to *WHO* grade I ganglioglioma, with most of the anaplastic gangliogliomas featuring a lack of CD34 immunoreexpression [2]. This expression of the stem cell epitope might be suggestive of a malformative origin of gangliogliomas. Blümcke & Wiestler even noticed that most of the ganglioglioma tumors which were positive for CD34 were actually located in the temporal lobe, and half of those situated in other anatomic regions lacked this expression [37]. Also, gangliogliomas with multiple dysplastic neurons, are also negative for CD34 [37]. However, the absence of this staining should not exclude the diagnosis of ganglioglioma. Majores *et al.* observed that grade II gangliogliomas and also glioblastoma stemming from gangliogliomas, may express CD34 only focally, in the cellular processes, giving the tumor an adverse outcome, or it may be lost altogether [18, 36]. Intriguingly, although focal cortical dysplasia does not usually express CD34, dual lesions composed of both focal cortical dysplasia and gangliogliomas express almost invariably CD34 [37, 53].

In the literature, there are three patterns of CD34 immunostaining: the solitary pattern, where only single cells with prominent immunoreactive processes can be

identified; the bushy pattern, where cells were arranged in clusters or nests, occasionally featuring satellitosis; and the diffuse pattern, which was the most frequently encountered (55%) [53, 54].

Worth mentioning for differential diagnosis is the absence of the MAP2 immunoreexpression in the glial component, which differs from the usual diffuse expression seen in gliomas [2].

Prognostic and therapeutic aspects

For *WHO* grade I gangliogliomas, surgical resection is the “gold standard”. Usually, the tumor is totally resected and symptoms improve, especially the seizures [1]. A better response to therapy may be seen in younger patients, although not all studies have confirmed this hypothesis [1, 55]. Literature data shows that after 7.5 years, patients have 97% recurrence free survival rate. Complete removal of the tumor, as well as tumors situated in the temporal lobe seems to have a better prognosis [2]. These tumors do not usually respond to radiation and some studies claim that this approach might favor a malignant transformation of the tumor [48]. This alternative should only be taken into consideration when the tumor has an unfortunate localization and the complete resection is improbable. Authors have proved that radiotherapy following subtotal surgical resection gives better local control but does not usually improve the survival rate [56, 57].

If the tumor was completely resected, studies have shown that the patients either cease to have any epileptic seizures (66%), or they decrease in frequency (33%) [58]. In rare occasions, if some residual tumor still exists, recurrences can occur, either presenting with the same HP grade, or by having a higher grade, and therefore being malignant in behavior. Some authors report cases where the recurrence happened only few months after the first intervention and the tumor featured a higher grade [48]. This data can actually endorse the idea of a three-tier grading system, but to this date, no reliable HP information predicting this outcome has been discovered.

An interesting approach of the definition of “atypical” was presented in a fairly recent study, where tumors received this label if they had an imagistic atypical aspect, *i.e.*, which were poorly circumscribed, had a more infiltrative aspect, or an unusual location. Curiously enough, in this study, the great majority of the typical gangliogliomas were totally resected, without any adjuvant therapy, and without requiring a second surgical intervention. On the other hand, most of those interpreted as atypical, required either adjuvant chemotherapy alone, or chemotherapy combined with radiotherapy, or even a second intervention. Moreover, three of 19 cases of the clinically appearing atypical ganglioglioma, on HP examination, were either *WHO* grade III anaplastic ganglioglioma, or had anaplastic features [59].

Majores *et al.* observed a higher survival rate in the *WHO* grade II ganglioglioma (79%) compared to anaplastic ganglioglioma (53%), but recurrences were noted in 33% and malignant transformation to secondary glioblastoma in 14% of all atypical gangliogliomas, thus justifying this grading system. Interestingly, focal immunostaining

of the cellular processes for CD34, correlated with a shorter overall survival [18]. The authors also concluded that some clinical data also influence the prognosis (male gender, age beyond 40 years, atypical localization), along with the incomplete resection and the presence of a gemistocytic component [18, 38, 39]. Other authors have observed that an unfortunate position of the tumor, and therefore an incomplete resection, correlates best with a poor outcome and did not report any correlation with the HP grade [56].

Regarding anaplastic gangliogliomas, to this moment there is insufficient data concerning the “gold standard” treatment. It is unanimously accepted that surgical removal of the entire tumor is desirable, but studies opine that adjuvant therapy can also be an option [38]. An argued point of view is that of Rades *et al.*, who has proposed the following therapeutic approach for high-grade tumors: if gross total resection was achieved, radiotherapy should not be taken into consideration, since the local control does not improve; if gross total resection was not achieved, then radiotherapy will give a better local control, but the overall survival will not improve [56]. Other study reports that a frontal location of the tumor, along with a fluid-attenuated inversion recovery (FLAIR) crossing the midline correlates with shorter overall survival. Intriguingly, they have observed that patients who have undergone subtotal resection and combined chemotherapy have a shorter progression free survival and the best overall survival was observed in cases where the tumor was totally resected, and the patient underwent adjuvant therapy with combined standard chemotherapy [60].

✉ Conclusions

Although no HP criteria have been established for the diagnosis of *WHO* grade II gangliogliomas, increased cellularity, microvascular proliferation and some cellular pleomorphism have been used to define this category. Further studies concerning the immunoeexpression of CD34 and Ki67 proliferation rate might offer some insight in this direction. Studies have shown that an atypical imaging aspect correlates with a higher local recurrence rate and, secondary with further reinterventions or adjuvant therapy. This aspect might have an impact on the definition of *WHO* grade II ganglioglioma. Regarding the therapy, it is desirable to achieve complete gross resection, in both low- and high-grade tumors, but if this goal cannot be achieved, due to an unfortunate tumor localization, then adjuvant radiotherapy can be taken into consideration. Since there have been many reports of a malignant transformation of a grade I ganglioglioma, it is imperiously necessary to follow-up the patient closely.

Conflict of interests

The authors declare that they have no conflict of interests.

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Corresponding authors

Tiberiu Augustin Georgescu, Assistant Professor, MD, PhD, Discipline of Pathology, Carol Davila University of Medicine and Pharmacy, 8 Eroilor Sanitari Avenue, Sector 5, 050474 Bucharest, Romania; Phone +40721–468 622, e-mail: tiberiuaugustin.georgescu@gmail.com

Roxana Elena Bohlîtea, Associate Professor, MD, PhD, Discipline of Obstetrics and Gynecology, Carol Davila University of Medicine and Pharmacy, 8 Eroilor Sanitari Avenue, Sector 5, 050474 Bucharest, Romania; Phone +40722–383 060, e-mail: r.bohiltea@yahoo.com

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