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CLINICAL STUDY

Gliomas of the pineal region

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Abstract Although several series of pineal region tumors are available, the issue of pineal gliomas has been scarcely faced in the literature. Gliomas are usually included in largest series of pineal neoplasms. Therefore, whether pineal gliomas share the biological behavior of either hemispheric gliomas or other midline lesions is not yet defined. The aim of this retrospective study is to analyze long-term morbidity and mortality of these lesions. In English published literature gliomas account for about 14–22 % of all pineal region tumors. Most of these tumors are pilocytic astrocytomas, while glioblastoma multiforme is rare. We retrospectively analyzed all pineal region tumors operated on in our department in the last 28 years, and identified eight pineal astrocytomas, accounting for 14.03 % of all pineal tumors. The series includes four pilocytic astrocytomas, two grade II diffuse astrocytomas, and two anaplastic astrocytomas. A comprehensive review of the available literature data shows that the mean survival time of WHO grade II gliomas is shorter when tumor grows in the pineal region than for hemispheric locations, although the limited amount of available data prevents a rigorous statistical analysis. This difference might be due to the peculiar infiltrating behavior of pineal tumors, which often can't be satisfactorily resected from vital structures.

Keywords Glioma · Pineal region · Pilocytic astrocytoma · Diffuse astrocytoma · Anaplastic astrocytoma

Salima Magrini and Alberto Feletti contributed equally to this study

S. Magrini · A. Feletti (✉) · E. Marton · P. Longatti
Department of Neurosurgery, Treviso Regional Hospital, University of Padova, Piazzale Ospedale 1, 31100 Treviso, Italy
e-mail: alberto.feletti@gmail.com

Introduction

The pineal region is anatomically located posteriorly in the midline between the roof of the third ventricle dorsally and the tectum of the midbrain caudally [1]. A wide collection of tumors can grow in this area, with different natural histories. Although several pineal region tumor series have been published, the specific issue of pineal gliomas has been scarcely discussed. Gliomas are uncommon in the pineal region, and are usually either included in larger series along with other neoplasms, or reported as small series or case reports. Therefore, there is a lack of studies focusing on the peculiar characteristics, treatment, and prognosis of these tumors. Moreover, in some cases the tumors are so large that it is not possible to precisely determine their origin within the pineal region, which is very small. We thoroughly reviewed the English-language literature about this topic, adding our series of eight pineal gliomas in order to describe their clinical pattern, treatment options, and outcome.

Methods

Article selection

A comprehensive PubMed search of the English-language literature was performed with key words "pineal" alone and in combination with "glioma," and "tumor". Inclusion criteria were the following: follow-up data for patients treated for pineal region gliomas were presented in a useable fashion, articles contained disaggregated individual patient data (age, sex, treatment modality, and follow-up survival data) for each patient, a clear origin of the tumor from the pineal region was proved, and articles were

published after 1985 in order to restrict the analysis to recent literature. Pineal cysts were excluded. After reviewing these articles, a thorough review of all referenced sources was also performed.

Our search resulted in 84 publications reporting on 683 patients treated for pineal region glioma. Epidemiological data were then collected. Further analysis was possible considering only the 349 patients for which a defined histotype was available. A defined treatment strategy was available for 159 patients.

Literature review

Basing on the available disaggregated data [2–85], gliomas occurring in the pineal region usually affect young patients, with a mean age of 26.24 years (range 1–81 years). The male:female ratio is 5:4. The histotype distribution, according to the World Health Organization Classification (WHO) is summarized in Table 1. The histotype was available in 349 cases. Diffuse astrocytoma (grade II WHO) is the most common histotype, accounting for 24.6 % of all pineal gliomas, followed by glioblastoma (grade IV WHO, 18.6 %), ependymoma (grade II WHO, 15.5 %), pilocytic astrocytoma (grade I WHO, 14 %), anaplastic astrocytoma (grade III WHO, 9.2 %), anaplastic ependymoma (grade III WHO, 8.3 %), and oligodendroglioma (grade II WHO, 5.7 %). Symptoms are shown in Table 2.

The treatment strategies are reported for 159 patients. In most cases (59.7 %) a partial or total craniotomic surgical resection was performed. Surgical approach has been reported in 43 cases. Infratentorial supracerebellar is the most commonly used approach (53.5 %), followed by occipital interhemispheric transtentorial approach (44.2 %) and transcallosal interhemispheric approach (2.3 %). Entity of removal has been reported in 45 cases. Gross total removal has been achieved in 24 cases (5 pilocytic astrocytomas, 4 pleomorphic xanthoastrocytomas, 4 glioblastomas, 4 astrocytomas not otherwise specified (NOS), 1 oligodendroglioma grade II, 1 anaplastic oligodendrogliomas, 1 subependymal giant cell astrocytoma, 1 juvenile astrocytoma, 1 fibrillary astrocytoma, 1 diffuse astrocytoma, 1 papillary ependymoma). Subtotal removal was possible in 10 cases (2 diffuse astrocytomas, 2 glioblastomas, 2 astrocytomas NOS, 1 pilomyxoid astrocytoma, 1 malignant glioma, 1 malignant astrocytoma, 1 anaplastic ependymoma). In 11 patients only a partial removal was

Table 2 Signs and symptoms—review of the literature [2–85]

Symptoms	Prevalence (%)
Headache	52.3
Nausea/vomiting	37.6
Decreased visual acuity	12.8
Parinaud's syndrome	11.9
Diplopia/coordination extraocular movements	11
Ataxic gait	8.3
Behavioral (memory/concentration/ irritability/food aversion)	8.3
Dizziness/somnolence/drowsiness	4.6
Vertigo/balance	3.7
Hemiparesis	3.7
Postural tremors/extrapyramidal disorders	2.7
Seizures	1.8

Table 1 Histotype distribution—review of the literature [2–85]

WHO grade	Histopathology	Number of cases	%	References
I (53)	Pilocytic astrocytoma	49	14	[10, 12–15, 18, 23, 27, 29, 42, 49, 52, 57, 59, 75, 77, 83]
	Juvenile pilocytic astrocytoma	2	0.6	[47, 58]
	Subependymal giant cell astrocytoma	2	0.6	[24, 26]
II (167)	Diffuse astrocytoma	86	24.6	[11, 12, 14, 17, 19, 23, 28, 30, 31, 34, 35, 41, 49, 52, 56, 60, 64, 67, 68, 75, 83]
	Ependymoma	54	15.5	[21, 23, 34, 37, 43, 46, 48, 53, 57, 67, 70, 72, 80, 83]
	Oligodendroglioma	20	5.7	[6, 23, 37, 38, 46, 53, 57, 72, 85]
	Pilomyxoid astrocytoma	1	0.3	[7]
	Pleomorphic xanthoastrocytoma	6	1.7	[2, 8, 9, 36, 63]
III (64)	Anaplastic astrocytoma	32	9.2	[3, 12, 17, 21, 23, 29, 34, 37, 43, 49, 50, 57, 83]
	Anaplastic ependymoma	29	8.3	[14, 34, 45, 76]
	Anaplastic oligodendroglioma	3	0.8	[14, 20]
IV (65)	Glioblastoma multiforme	65	18.6	[5, 12, 16, 22, 23, 25, 32, 37, 38, 40, 43, 44, 51–54, 61, 66, 68, 70, 74, 75, 77, 83]

Table 3 Radiotherapy—review of the literature [2–85]

Histotype	Fractionated radiotherapy	Gamma knife	Interstitial therapy	References
Pilomyxoid astrocitoma	1 pt: 31 + 21 Gy			[7]
Pilocytic astrocytoma			1 pt: I125 10.000–12.000 rads (periphery); 30.000–40.000 rads (central) 3 pts: 60 Gy	[49, 83]
Low grade glioma	1 pt: 60 Gy 1 pt: 20 Gy 1 pt 18 Gy	1 pt: 28 Gy	3 pts: I125 10.000–12.000 rads (periphery); 30.000–40.000 rads (central)1pt: 60 Gy	[17, 28, 49, 56, 83]
Anaplastic astrocytoma III	2 pts: 60 Gy	1 pt: 24 Gy	1 pt: I125 10.000–12.000 rads (periphery); 30.000–40.000 rads (central)1 pt: 36 + 50 Gy	[17, 49, 50, 83]
Ependymoma II	1 pt: 30 + 20 Gy 1 pt: 56 Gy		1 pt: I125 10.000–12.000 rads (periphery); 30.000–40.000 rads (central)	[57, 80, 83]
Astrocytoma NOS	1 pt: 20 1 pt: 41 1 pt: 54	1 pt: 45 3 pts: 50		[55, 56, 68, 80]
Glioblastoma	1 pt: 20 Gy 1 pt: 60 + 20 Gy 1 pt: 4000 + 4500 rads 1 pt: 5940 cGy 1 pt: 7200 rads			[22, 25, 68, 74, 77]
High grade glioma	2 pt: 60 Gy			[49]
Fibrillary astrocytoma	6 pt: 40 Gy or >			[60]
Malignant glioma	1 60 Gy			[62]
Pleomorphic xanthoastrocytoma		1 pt: 56 Gy 1 pt: 45 Gy		[63]

Pt patient, *pts* patients, *Gy* grey

obtained (7 fibrillary astrocytomas, 1 malignant astrocytoma, 1 pleomorphic giant cell astrocytoma, 1 glioblastoma, 1 pilocytic astrocytoma). A biopsy was performed in 39 patients (24.5 %); afterwards, 12 of them underwent a craniotomic procedure for tumor removal (30 % of patients who underwent biopsy). Preoperative liquor diversion is reported in 25.8 % of patients (27 ventriculo-peritoneal shunts, 1 ventriculo-atrial shunt, 13 ventriculostomies); postoperative VP-shunt was necessary in 15 patients (9.4 %). Ocular motor disfunction (3 cases of diplopia and 2 cases of Parinaud's syndrome) and visual field impairment (2 cases of hemianopsy) are the most frequent postoperative complications. Ischemic or hemorrhagic infarction (3 cases), tumor dissemination (3 cases), transient lethargy, seizure, and cerebellum swelling (1 case each) have also been reported.

Adjuvant therapy is mainly based on radiotherapy. Conventional radiotherapy is described in 51 out of 159 patients, interstitial radiotherapy was offered to 20 patients, Gamma-knife was used in 25 cases. The details of radiotherapeutic plans are available in a limited number of cases, which are summarized in Table 3. The use of chemotherapy is reported for only 17 patients (Table 4). In one case vincristine and cisplatin were administered in combination with radiotherapy. The use of vincristine is reported in 3 cases, temozolomide, lomustine, dibromodulcitol, procarbazine, and 6-thioguanine in two cases, ACNU in one case.

A progression of disease has been reported in 11 patients (2 pilocytic astrocytomas, 5 fibrillary astrocytomas, 2 glioblastomas, 1 pilomyxoid astrocytoma, 1 pleomorphic xanthoastrocytoma). The reported recurrences seem to be

Table 4 Chemotherapy—review of the literature [2–85]

Histotype	Chemotherapy	References
1 pilocytic astrocytoma	Cisplatin + vincristine	[27]
1 anaplastic oligodedroglioma	Temozolomide	[20]
1 glioblastoma	Temozolomide	[22]
2 glioblastomas	Intravenous ACNU 6-TG, CCNU, PCB, DBD, VCR	[25, 77]
3 glioblastomas	Not reported	[22, 40, 61]
3 gliomas grade III NOS	Not reported	[44, 49]
1 pilocytic astrocytoma	Not reported	[77]
1 astrocytoma NOS	6-TG, CCNU, PCB, DBD, VCR	[77]
1 astrocytoma NOS	Not reported	[16]
1 astrocytoma grade II	Not reported	[64]
2 astrocytomas grade III	Not reported	[21]

ACNU nimustine, *CCNU* lomustine, *DBD* dibromodulcitol, *NOS* not otherwise specified, *PCB* procarbazine, *VCR* vincristine, *6-TG* 6-thioguanine

Table 5 Mortality per histotype—review of the literature [2–85]

Histotype (no. reported cases)	WHO	Dead	Survival after diagnosis (months)	Alive	Follow up (months)	References
Subependymal giant cell astrocytoma (2)	I			1	18	[26]
Juvenile pilocytic astrocytoma (2)	I			1	12	[58]
Pilocytic astrocytoma (49)	I	1	12	12	41	[13, 27, 49, 77]
Diffuse astrocytoma (86)	II	2	12; 45	6	30.3	[17, 19, 30, 49, 56, 58, 64]
Fibrillary (11)				1	24	
Gemistocytic (1)						
Pleomorphic xanthoastrocytoma (6)	II			5	32.4	[2, 8, 9, 36, 63]
Pl. Xant. with anapl. feat. (1)				1	114	
Oligodendroglioma (20)	II			1	6	[6]
Ependymoma (54)	II			3	34	[38, 48, 57]
Papillary (1)				1	18	
Anaplastic astrocytoma (32)	III	8	11.7	2	3; 4	[17, 43, 50]
Anaplastic oligodendroglioma (3)	III			1	9	[20]
Glioblastoma (65)	IV	12	5.8			[22, 25, 32, 40, 43, 61, 68, 74, 77]

Follow up time is given as average when $n > 3$

Table 6 Mortality per grading–review of the literature

Grade	No. of reported cases	Alive	Follow up (months)	Dead	Follow up (months)	References
I	14	13	13.8 (12–96)	1	12	[13, 26, 27, 49, 58, 77]
II	37	35	26 (12–96)	2	12; 45	[2, 6, 8, 9, 17, 19, 30, 36, 38, 48, 49, 56–58, 63, 64]
III	11	3	3; 4; 114	8	14.25 (1–27)	[17, 20, 36, 43, 45, 49, 50]
IV	12	/	/	12	5.8 (2–12)	[22, 25, 32, 40, 43, 61, 68, 74, 77]

Follow up time is given as average when n > 3

related to the entity of resection that was below 75 % in all cases. In Tables 5 and 6 we collected the available disaggregated data about outcome and mortality in relation with both histotype and grading.

Personal series

57 patients affected by pineal tumors were treated in our department between 1985 and 2010. Among them eight

patients (14 %) were affected by pineal glioma. Four patients were affected by pilocytic astrocytomas (Fig. 1), 2 patients by diffuse astrocytomas grade II, 2 patients by diffuse anaplastic astrocytomas. None of our patients were diagnosed with glioblastoma multiforme (GBM) (Tables 7, 8). Glial lesions presenting with a wide macroscopical infiltration of the surrounding regions were excluded because of the uncertain origin of the tumor. The male–female ratio was 1:3; the median age of affected patients was 22 years (range 16–61 years). Symptoms generally appeared 2–3 weeks before the radiological diagnosis (12 ± 5.21 days) and progressively worsened in relation to hydrocephalus (5 cases). Main symptoms were referred to intracranial hypertension due to obstructive hydrocephalus: headache, nausea and vomiting were reported by the 87.5 % of patients (7 patients). Secondary hydrocephalus may explain cognitive impairment (50 %), gait disturbances (37.5 %), vertigo (25 %) and urinary incontinence (25 %). Compression of the tectum of mesencephalus by a mass or hydrocephalus gives explanation for ocular motility impairment as Parinaud's syndrome, and III or VI cranial nerves palsy. Papilledema was found in only 62.5 % of patients. We also observed a peculiar association between pineal pilocytic astrocytoma and Neurofibromatosis type I in 2 female patients.

The first aim of the management of our patients was the resolution of acute/subacute hydrocephalus. Neuroendoscopy offers the opportunity not only for a third ventriculostomy, but also for tumor biopsy. We use a flexible scope, which allows performing both ETV and biopsy through the same burr hole and trajectory. According to the histological examination and the tumor extent at neuroradiological imaging, a craniotomic removal of the tumor was scheduled. Adjuvant therapy was not proposed for patients with pilocytic astrocytoma, which represents a very different disease compared to infiltrating gliomas. Conversely, patients with non-pilocytic histological diagnosis underwent chemotherapy or radiotherapy. Two patients with grade II and III gliomas experienced such a dramatic progression that adjuvant therapy could not be administered. Outcome and survival time are summarized in Table 7.

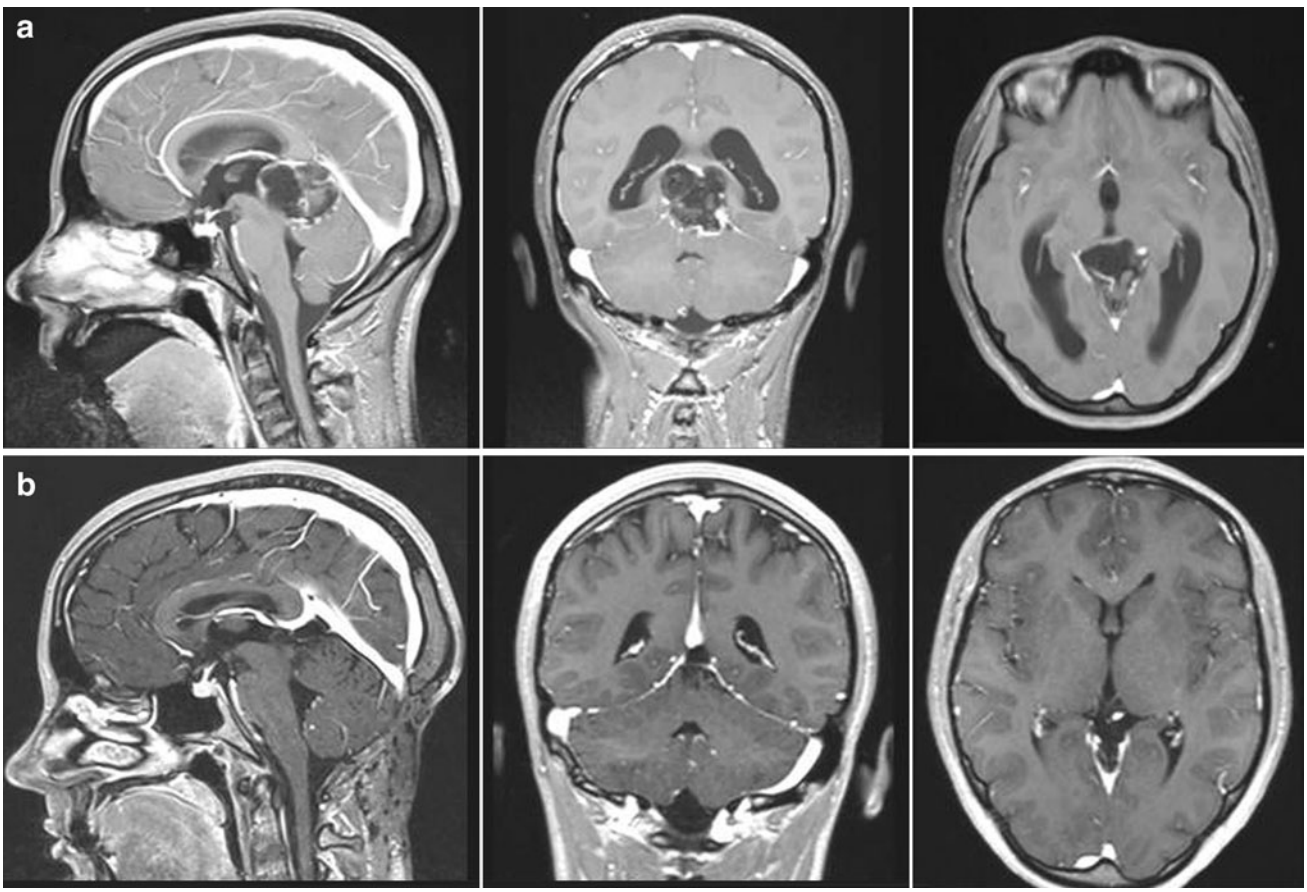

Fig. 1 Preoperative **a** sagittal, coronal and axial contrast-enhanced T1-weighted MRI showing a pineal pilocytic astrocytoma. The follow-up contrast-enhanced T1-weighted MRI **b** shows no residual or recurrence 3 years later

Table 7 Summary of patients treated for pineal glioma at Treviso hospital

Patient	Age, sex	Grade	Surgical treatment	Surgical approach	Adjuvant therapy	Survival	Cause of death	Comorbidity
B.S.	17, F	III	VP-shunt; stereotactic biopsy; partial removal	Infratentorial supracerebellar		4 months, dead	Progression of disease	
M.A.	54, M	III	Stereotactic biopsy		Radiotherapy	17 months, dead	Progression of disease	
B.L.	16, M	II	VP-shunt; endoscopic biopsy		TCT-therapy; chemotherapy	12 months, dead	Progression of disease	
B.L.	17, F	II	Debulking	Infratentorial supracerebellar		1 months, dead	Progression of disease	
C.L.	61, F	I	VP-shunt; total removal	Infratentorial supracerebellar		13 years, dead	Other	PD
P.C.S.	52, F	I	ETV; endoscopic biopsy; total removal	Infratentorial supracerebellar		7 months, dead	Other	NF1 AMI
Z.L.	24, F	I	Total removal	Infratentorial supracerebellar		10 years, alive		NF1
C.A.	20, F	I	ETV; endoscopic biopsy; total removal	Infratentorial supracerebellar		3 years, alive		

VPshunt ventriculo-peritoneal shunt, *TCT-therapy* telecobalt therapy, *PD* Parkinson disease, *ETV* endoscopic third ventriculostomy, *NF1* neurofibromatosis type 1, *AMI* acute myocardial infarction

Table 8 Signs and symptoms - Our series

Signs and symptoms	No. patients	Prevalence (%)
Intracranial hypertension	7 pts	87.5
Cognitive impairment	4 pts	50
Gait disturbances	3 pts	37.5
Ocular movement impairment	2 pts	25
Vertigo	2 pts	25
Hyperthermia	1 pt	12.5
Urinary incontinence	1 pt	12.5
Papilledema	5 pts	62.5

pt patient

Discussion

Pineal region tumors represent 0.4–1 % of adult brain tumors in Europe and in the United States. In Northeast Asia the corresponding rate is 2.2–8 %. They are more common in children and young adults, accounting for 3–11 % of pediatric brain tumors in the United States and 12.5 % in Northeast Asia [77, 86–90]. Tumors arising from this region belong to three major categories: germ cell tumors, pineal cell tumors, and glial tumors. Germinoma and pineal cell tumor are the most common histological type, comprising 78–86 % of all pineal tumors. Other lesions, including gliomas, account for 14–22 % of pineal neoplasms. Pineal cysts are common benign lesions of this region. Although clinically undistinguishable from pineal gliomas, they are different pathological entities. For this reason we excluded them from our series and literature review.

While the anatomical definition of pineal region is clear, it is sometimes very difficult to assess whether a tumor has originated from the pineal region or from adjacent structures, particularly from the tectum mesencephali. For this reason, we excluded all the cases when the tectum mesencephali was not clearly distinguishable in the sagittal MRI.

Most gliomas arising in this region are low-grade astrocytomas [47, 77, 91]. Glioma in the pineal region can develop from a small population of astrocytes within the pineal gland or from glial cells in the median-posterior aspect of the thalamus or midbrain [1].

Aim of this retrospective study is to analyze long-term morbidity and mortality of pineal gliomas, and to compare their prognosis with that of gliomas arising in different locations. Limits of this retrospective study are the small number of cases, and the long observation time. However, this can still be acceptable, considering the rarity of the disease.

Considering both the literature and our series, average onset-age of non-pilocytic pineal gliomas is lower compared to hemispheric gliomas [92, 93]. Not surprisingly, symptoms are often related to hydrocephalus, and have a subacute onset (few days). The interval between the onset of symptoms and diagnosis is actually shorter than for hemispheric gliomas [77].

We also noticed an association between pineal pilocytic astrocytoma and neurofibromatosis type I in two female patients. Ogura et al. [27] described for the first time a 12 year-old female presenting this association in 2004.

As the data about outcome and survival are available only in a limited number of patients, a reliable statistical analysis is not possible. However, considering both the literature and our series, it is possible to make some descriptive observations. Besides the well-known poor prognosis of high-grade glioma (Grade III, WHO) [94], we noticed a survival difference between patients with low-grade glioma of pineal region and other intracerebral locations. In particular, while pilocytic glioma showed a prognosis similar to that of other locations, non-pilocytic low-grade pineal glioma (grade II WHO) showed a dramatically short survival time [95]. This can be due to the peculiar anatomical location of the pineal region, which makes it challenging to completely remove an infiltrating tumor without damaging adjacent structures.

The role of adjuvant therapy is not clear. Chemotherapy has been explicitly reported only in 17 cases in the literature. This is mainly due to the fact that these patients are included in larger series and data are aggregated with those of other tumors growing in the pineal region. Although data about radiotherapy are also limited due to the same reason, radiotherapy has been more frequently reported. However, fragmentation of data point out the need for new studies focusing on adjuvant therapy for pineal gliomas. We decided to use either chemotherapy or radiotherapy in two of our patients because of the large volume of the tumor, in order to shrink it. Chemotherapy was not administered in patients with grade I glioma. In two patients with grade II and III glioma progression was so dramatic that adjuvant therapy could not be administered.

There are data suggesting that surgery has a role in the treatment of pineal glioma because it can improve patients' outcome. The usual poor prognosis is likely related to a very limited resection of infiltrative disease localized in such a ticklish area [94].

Conclusions

Many series of pineal lesions are described in the literature, but there are very few works concerning specifically with glioma of this region [47, 60, 77, 91, 96]. GBM are well documented by the literature and show an average survival of 7 months [97]. The prognosis of pineal pilocytic astrocytoma seems to be quite good. Conversely, grade II and III gliomas have a dismal outcome: because of their tendency to infiltrate eloquent surrounding tissues, gross-total resective surgery is not feasible and consequently the response to radio and chemotherapy is reduced. Moreover, deep location represents a negative prognostic factor, not only because it is difficult to reach, but mainly due to the presence of unresectable structures. Particularly glioma grade II (WHO) shows a dramatically reduced survival compared to its hemispheric counterpart, although the amount of data are not enough for a statistical study. For this reasons the traditional distinction between low grade and high-grade glioma is likely to be not appropriate for pineal gliomas. A distinction between pilocytic and non-pilocytic pineal gliomas would better reveal the prognostic value of diagnosis.

Conflict of interest None.

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