Glioblastoma of pineal region: report of four cases and literature review

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Practice points

- Pineal location is infrequent for glioblastoma location but has similar pathology features than other location.
- Leptomeningeal dissemination is a frequent route for pineal glioblastoma.
- Although median survival is short, some cases have a longer survival.

We report four cases of glioblastoma in the pineal region. The patients presented a severe headache and vomiting. Brain imaging showed a heterogeneously enhanced tumor in the pineal region with obstructive hydrocephalus. Case 3 developed a subependymal dissemination. The patient went to ventricular-peritoneal shunt and subtotal or total resection and radiotherapy with/without chemotherapy. Cases 1 and 2 received radiation and died 8 and 11 later months. Cases 3 and 4 completed radiotherapy and chemotherapy, and survived 28 and 31 months after the initial diagnosis. Glioblastoma in the pineal region carry a poor prognosis and require neurooncology teams.

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Glioblastoma is the most common primary brain tumor at supratentorial level, and although it has a poor prognosis; total surgical resection of the tumor followed by adjuvant treatment with chemotherapy and radiotherapy (RT) has achieved greater survival and disease-free time [1,2].

Tumors of the pineal region represent the 0.1–0.4% of all brain primary tumors and mostly originate in the cells of the pineal parenchyma (pineocytoma, pineoblastoma and pineal tumor of intermediate differentiation) followed by extragonadal germ cell tumors (germinoma and teratoma), from mesenchymal origin, or more infrequently from astrocytic origin (glioblastoma) [3].

Glioblastoma of the pineal region infiltrates the upper portion of the midbrain and both optical thalamus and has a high rate of ependymal and leptomeningeal dissemination [4–6]. Radiographic findings correspond to a mass in the pineal region with poorly defined edges, infiltrative with diffuse contrast enhancement and generally, can be similar to other malignant forms of tumors in this region like the pineoblastoma. Patients usually present with symptoms of intracranial hypertension due to obstructive hydrocephalus and to a deficit in vertical conjugate gaze [7].

Most of the times, it is not possible to perform a wide resection and it is only performed a partial resection or biopsy because of its vicinity to the brainstem. Therefore, the median survival in this location is less than in the supratentorial location [8].

To date, only 22 cases of pineal glioblastoma have been worldwide reported [2–6]. We reviewed 92 pineal region tumors that went to surgery at the Instituto Nacional de Enfermedades Neoplásicas in the last 28 years and found four cases of glioblastoma who are reported in this research.

Table 1. Immunohistochemical study.

Case	GFAP	Neurofilament	KI67	P53	Synaptophysin	Olig2
1	NA	NA	NA	NA	NA	NA
2	Weakly positive in some tumor cells	Highlights focal entrapped axons	Moderate (9%)	NA	Neuropil in tumoral border	Strong positive staining in many tumor nuclei
3	Positive	Positive	High (40%)	Positive	Positive in some cells	NA
4	Strongly positive in a subpopulation	Negative	High (30%)	Negative	Positive in scattered cells	Positive in most of tumor cells

GFAP: Glial fibrillary acidic protein; NA: Not available.

Case report

Case 1

A 48-year-old female patient presented with headache and dizziness from 10 months ago, and nausea and vomiting were added in the last 2 weeks. A CT scan described a hyperdense pineal tumor with poorly defined edges and with a central zone of lower intensity measuring 45 mm larger in diameter that produced cerebral aqueduct obstruction and hydrocephalus that were suggestive of pineoblastoma. The patient was transferred to the Institute where an awake and oriented patient with paresis of vertical conjugate gaze and left hemiparesis 4/5 to crural dominance was found at the initial clinical exam. A ventricular peritoneal shunt and a subtotal resection through supracerebeloso suboccipital approach were performed. Evolution was favorably and the patient was discharged after 15 days. Histopathology report was glioblastoma (Table 1) and patient received adjuvant 5600 cGy (200 cGy per day) of RT into two fields with a good tolerance. Tomographic reevaluation after 3 months of surgery found irregular tumor with heterogeneous contrast enhancement in the pineal region that extended to the midbrain. The patient continued in observation and died 12 months after surgery.

Case 2

A 50-year-old male patient presented with headache from 9 months ago, and nausea and vomiting was added in the last month. An MRI of the brain described a tumor with heterogeneous contrast enhancement in the pineal region that produced obstruction of cerebral aqueduct and severe hydrocephalus. The ventricular peritoneal shunt was performed and tuberculosis treatment for 6 weeks was administered because a pineal tuberculoma was presumed. After an absence of improvement, the patient was transferred to the Institute where an awake and oriented patient with bilateral amaurosis, paralysis of the left sixth cranial nerve, normal motor function in all four limbs and moderate cerebellar incoordination was received. A head MRI revealed a heterogeneous contrast enhancement tumor of 28 × 23 × 17 mm in the pineal gland that infiltrates the left thalamus, midbrain and lateral quadrigeminal sheet. A partial resection of a vascular gray color pineal tumor adhered to adjacent structures was performed. He went to the Intensive Care Unit where underwent a postoperative tracheotomy. The patient was discharged 1 month after surgery with grade 2/5 right hemiparesis and Karnofsky 60%. The pathology report was glioblastoma (Table 1) and the patient began radiation but he decided to leave it after 1800 cGy, and finally died after 6 months of the surgery.

Case 3

A 56-year-old-male patient presented with headache, nausea and vomiting from 1-month before. An MRI describes a tumor with a solid and cystic areas in the pineal region; the solid area is isointense in T1 and intense in T2. Tumor size is 28 × 27 × 31 mm and has subependymal extension into brainstem and left occipital periventricular; it obstructs the cerebral aqueduct producing severe hydrocephalus. The patient is transferred to the institute where he came awake, lucid, decreased visual acuity, bilateral papilledema, without involvement of other cranial nerves, motor function and normal sensitivity and ataxia. A ventricular peritoneal shunt was initially performed and a partial resection through supracerebeloso infratentorial approach of a very vascularized, friable, infiltrative and adhered to adjacent vessels tumor was performed 1 week later. The patient was discharged after 6 days of the surgery. Histopathology report was glioblastoma (Table 1). He received 6000 cGy of radiation in 30 sessions with concurrent temozolomide (TMZ) 125 mg/day. TMZ 250 mg every day for 5 days a week during 28 days was continued during six additional courses. Evolution of the neurological symptoms was favorable for the next 9 months when he developed marked headache and visual impairment. Reassessment of MRI describes a 10-mm residual tumor in the pineal region and several contrasted nodules in the left thalamus and lateral ventricle. Patient

Figure 1. Glioblastoma of pineal region (case 3). (A) Glial tumor with marked nuclear pleomorphism and multinucleated cells (H&E, 40x magnification). (B) Presence of necrotic areas (H&E, 10x magnification). (C) Immunohistochemical study showing a positive reaction for the GFAP. (D) Presence of trapped axons evaluated with neurofilament staining, confirming the nature of the tumor. H&E: Hematoxylin-eosin; GFAP: Glial fibrillary acidic protein.

and his family decided for palliative care and evolution was unfavorable. A brain MRI after 4 weeks describes largest tumor lesion and finally died 29 months after surgery.

Case 4

A 25-year-old-male patient presented with headache, nausea and vomiting 2 weeks ago. A CT and MRI showed a tumor in the pineal region and severe hydrocephalus. A peritoneal shunt ventricle was performed and is transferred to the Institute where an awake, lucid and oriented patient with paresis of vertical conjugate gaze was received. A new MRI describes an hypointense tumor in T1, T2 and Flair bright and heterogeneously capturing contrast located in the pineal region that involves the rear central part of the midbrain and the quadrigeminal sheet (Figure 1). The patient underwent a total removal through a supracerebeloso suboccipital approach of a vascularized, soft consistency, a yellowish gray colored tumor that infiltrates adjacent structures. The patient is released at the 6th day postsurgery. Pathology report informs a glioblastoma (Table 1), and the patient received 2520 cGy axis skull radiation as well as simultaneous TMZ 100 mg/day. During next 6 weeks, the patient developed dizziness, vomiting, ataxia and erythema multiforme related to phenytoin administration, as well as pneumonia and acute herpetic and candida esophagitis that produced TMZ discontinuation. Medical complications improved but MRI describes a 30-mm local recurrence. Patient completed 3960 cGy and 3600 cGy of radiation to skull and column, respectively, with concurrent TMZ. A pulmonary tuberculosis was immediately diagnosed and patient received 6-month treatment. Patient decided for no more chemotherapy. Left-sided motor deficit was found after 19 months of surgery and a new MRI describes the remaining 33-mm local recurrence. Evolution was unfavorable and the patient died 32 months after surgery.

Discussion

We communicate all four cases of pineal operated at the Institute between 1994 and 2012 and increase the number of worldwide reported cases to 26 (Table 2).

In 2008, Moon *et al.* published a 68-year-old case from Korea who underwent resection and ventriculoperitoneal shunt, and died 2 months after diagnosis. They also summarized a total of 18 cases reported until that year in the literature with a median age of 39.4 (5–68-year old). Two of these patients who underwent surgical resection died 2 months later, three patients who received radiation alone lived an average of 3.3 months (range: 2–4 months), and three patients who underwent surgical resection followed by radiation and lived an average of 5.3 months (range:

Table 2. Summary of reported cases of glioblastoma of pineal region.

Study (year)	Country	Age	Sex	Symptoms	Radiological findings	Leptomeningeal dissemination	Treatment	Survival (months)	Ref.
Bradfield <i>et al.</i> (1972)	EEUU	53	F	NA	Hydrocephalus, mass in 3rd ventricle	No on autopsy	Resection	Postoperative death	[9]
Bradfield <i>et al.</i> (1972)	EEUU	5	F	NA	Hydrocephalus, mass in 3rd ventricle	No on autopsy	Shunt	27	[9]
DeGirolami <i>et al.</i> (1973)	EEUU	Three cases	NA	Nausea, vomiting, headache, vertical gaze palsy in one case	NA	NA	RT for all cases, resection for only one case	NA	[10]
Kalyanaraman <i>et al.</i> (1979)	EEUU	68	F	Ataxia, confusion, urinary incontinence, upgaze limitation	CT: hydrocephalus, calcified midline mass	NA	Resection, RT	4	[11]
Norburt <i>et al.</i> (1981)	EEUU	36	M	Headache, blurry vision, Parinaud's syndrome	CT: hydrocephalus, mass in 3rd ventricle	Yes on autopsy (4th ventricle, leptomeninges of cerebral cortex, interpeduncular fossa, brain stem and spinal cord)	Shunt, RT	4	[5]
Frank <i>et al.</i> (1985)	Italy	52	F	Intracranial hypertension, oculomotor disturbances	Hydrocephalus, mass in 3rd ventricle	NA	Stereotactic biopsy, RT	4	[12]
Edwards <i>et al.</i> (1988)	EEUU	12	F	NA	NA	NA	Resection, RT, chemotherapy	18	[13]
Vaquero <i>et al.</i> (1990)	Spain	63	M	Headache, changing of behavior	CT: rounded hyperdense mass with ring enhancement	NA	Shunt, Resection, Whole brain RT	6	[14]
Pople <i>et al.</i> (1993)	UK	6	F	Headache, nausea, vomiting, diplopia, decreased visual acuity, 6th cranial nerve palsy, upgaze limitation	CT and MRI: hydrocephalus, enhanced pineal mass	Yes on follow-up CT (frontal and occipital lobes, scattered leptomeninges)	Shunt, resection, local RT, chemotherapy	4	[15]
Cho <i>et al.</i> (1998)	Republic of Korea	10–15	F	NA	NA	NA	Resection, RT	6	[16]
Gasparetto <i>et al.</i> (2003)	Brazil	29	F	Headache, drowsiness, fever, dizziness, seizure	CT and MRI: heterogeneously enhanced pineal mass with extension to thalamus	No	Shunt, resection	2	[17]
Toyooka <i>et al.</i> (2005)	Japan	49	M	Headache, diplopia, memory disturbance	MRI: irregular heterogeneously enhanced pineal mass	Yes on follow-up MR (lateral ventricle, pons, pontomedullary junction)	Shunt, resection, chemotherapy (ACNU), local RT	11	[6]
Amini <i>et al.</i> (2006)	EEUU	40	M	Headache, nausea, vomiting, diplopia, blurry vision	CT: hydrocephalus, strong enhancement in pineal region, punctuate calcification MRI: heterogeneous pineal enhancement with central necrosis and extension into midbrain	Yes on initial MR (cbl, medulla, temporal lobe)	Endoscopic third ventriculostomy and biopsy, resection, shunt, whole-brain RT, chemotherapy (Temodar)	5	[7]

ACNU: Nimustine; CT: Computed tomography; F: Female; M: Male; MR: Magnetic resonance; NA: Not available; RT: Radiation therapy.

Table 2. Summary of reported cases of glioblastoma of pineal region (cont.).

Study (year)	Country	Age	Sex	Symptoms	Radiological findings	Leptomeningeal dissemination	Treatment	Survival (months)	Ref.
Amini <i>et al.</i> (2006)	EEUU	43	M	Headache, dizziness, decreased level of mental status	MRI: hydrocephalus, heterogeneous pineal enhancement	Yes on follow-up MR (intraventricular)	Third ventriculostomy and biopsy, resection, whole-brain RT, chemotherapy	7	[7]
Amini <i>et al.</i> (2006)	EEUU	52	F	Headache, nausea, vomiting, diplopia, blurry vision, upgaze palsy	MRI: hydrocephalus, heterogeneous enhancement with central necrosis	Yes on follow-up MR (lateral ventricle, leptomeninges of brain and spine)	Endoscopic third ventriculostomy and biopsy, RT	2	[7]
Moon <i>et al.</i> (2008)	Republic of Korea	68	M	Headache, nausea, vomiting, Ataxia	CT: hydrocephalus, hypodense pineal mass MRI: irregular with heterogeneously ring-enhanced pineal mass with central necrosis	Yes on initial MR (4th ventricle)	Resection, shunt	2	[18]
Ozgural <i>et al.</i> (2013)	Turkey	60	M	Headache, Ataxia	CT: periventricular hydrocephalus and isodense rounded mass. MRI: hydrocephalus, regular-edged heterogeneously enhanced tumor	No	Shunt, resection, serial stereotactic biopsies, RT, chemotherapy	24	[19]
Mansour <i>et al.</i> (2014)	EEUU	69	M	Altered mental status, vertigo and fever, forgetfulness. Nausea, vomiting, loss of bowel or bladder function, balance problems, numbness or weakness	CT: heterogeneous mass with obstructive hydrocephalus at the cerebral aqueduct. MRI: a pineal region mass	No	Biopsy, RT, chemotherapy	16	[20]
Suzuki <i>et al.</i> (2014)	Japan	65	M	Sudden-onset disturbance of consciousness	CT: intraventricular hemorrhage and acute hydrocephalus. MRI: heterogeneous enhanced pineal area	NA	Shunt, endoscopic biopsy, resection, RT, chemotherapy	NA	[21]
Matsuda <i>et al.</i> (2015)	Japan	31	F	Headache, nausea, vomiting	MR: hydrocephalus, heterogeneous enhancement in the pineal region	Yes	Shunt, resection, RT, chemotherapy	5	[4]
Present study – Orrego <i>et al.</i> (2017)	Peru	48	F	Headache, dizziness, nausea, vomiting, vertical conjugate gaze paresis and left hemiparesis 4/5 to crural dominance	CT: hyperdense tumor with poorly defined edges, with a central zone of lower density in the pineal region, hydrocephalus	No	Shunt, resection, RT	12	

ACNU: Nimustine; CT: Computed tomography; F: Female; M: Male; MR: Magnetic resonance; NA: Not available; RT: Radiation therapy.

Table 2. Summary of reported cases of glioblastoma of pineal region (cont.).

Study (year)	Country	Age	Sex	Symptoms	Radiological findings	Leptomeningeal dissemination	Treatment	Survival (months)	Ref.
Present study – Orrego <i>et al.</i> (2017)	Peru	50	M	Headache, nausea, vomiting with bilateral amaurosis, paralysis of the sixth cranial nerve left and moderate cerebellar incoordination	MR: heterogeneous tumor enhancement in the pineal region, severe hydrocephalus	No	Resection, RT, chemotherapy	6	
Present study – Orrego <i>et al.</i> (2017)	Peru	56	M	Headache, nausea, vomiting, decreased visual acuity, bilateral papilledema, without involvement of other cranial nerves and slight ataxia	MR: tumor with a solid portion and other cystic in the pineal region, subependymal brainstem and left occipital periventricular extension; severe hydrocephalus	Subependymal in MR	Shunt, resection, RT, chemotherapy	29	
Present study – Orrego <i>et al.</i> (2017)	Peru	25	M	Headache, nausea, vomiting, paresis of vertical conjugate gaze	MR: hypointense tumor in T1, T2 and flair bright and heterogeneously capturing contrast located in the pineal region from the rear central part of the midbrain and encompasses the quadrigeminal sheet	No	Resection, RT, chemotherapy	32	

ACNU: Nimustine; CT: Computed tomography; F: Female; M: Male; MR: Magnetic resonance; NA: Not available; RT: Radiation therapy.

4–6 months). Four patients received only supportive care and lived an average of 9.25 (range: 2–27 months) [18]. In 2013, Ozgural *et al.* reported a 60-year-old case from Turkey who underwent ventriculoperitoneal shunt, serial stereotactic biopsies, and had a 2-year survival [19]. Suzuki *et al.* published in May 2014 a 65-year-old Japanese case who debuted with intraventricular hemorrhage and underwent resection, radiation and chemotherapy [21]. Mansour *et al.* reported in December 2014 a 69-year-old American case who underwent a biopsy and had a survival of 16 months [20]. Matsuda *et al.* published in November 2015 a 35-year-old Japanese patient who developed spinal leptomeningeal dissemination who underwent ventriculoperitoneal shunt and subtotal resection, and had a survival of 5 months [4]. In summary, 12 of the published 22 cases were men and the median age of all previously reported cases was 42.95 (range: 5–69 years) and median survival was 8.16 (range: 0–27 months) [18].

We publish four cases of pineal glioblastoma that were operated between 1994 and 2012 in the Neurosurgery Department at Instituto Nacional de Enfermedades Neoplásicas. Their ages ranged from 25 to 56 years and three were male.

In all cases of our series, patients came to medical evaluation because of symptoms and signs of intracranial hypertension obstructive hydrocephalus that is a symptom previously reported and that reflect obstruction of cerebrospinal fluid flow at aqueduct level [16–18]. Only one of our four patients had evidence of ventricular leptomeningeal dissemination. Moon *et al.* found that seven of the 18 evaluated cases had a leptomeningeal or ventricular extension and it was also found in one case of the lasting four published cases [4–6].

In general, histopathology corresponds to a typical glioblastoma [10–11,14,22–23]. Our case features included marked nuclear pleomorphism, multinucleated cells, some of xanthomatous aspect; presence of atypical mitosis and discrete chronic inflammatory infiltrate, predominantly around thick, proliferating vascular structures. Immunohistochemistry scored positive for glial fibrillary acidic protein and synaptophysin (in the last three cases). Neurofilament in some cells and enhancement of trapped axons confirmed the diffuse nature of the tumor and positive p53 protein

Figure 2. Magnetic resonance image (case 4). (A) Sagittal plane with RM-T1 Gd, pineal tumor with heterogeneous enhancement of contrast that infiltrates upper region of mesencephalon with diffuse borders. **(B)** Axial cut RM-T1 Gd, most of the lesion infiltrates left side of posterior region of mesencephalon as well as lateral and lower areas of both thalamus. Gd: Gadolinium.

was found in one patient, the Ki-67 proliferative index was high in two cases; and epithelial membrane antigen was negative in two cases. No rosettes or small cell features of pineoblastoma were found (Table 1 & Figure 2).

Tomography imaging ($n = 1$) and MRI ($n = 3$) showed an infiltrative brain tumor with heterogeneous contrast enhancement in the pineal region with central area of necrosis. The infiltration of surrounding structures such as midbrain and thalamus that is shown as hyperintensity on T2 and FLAIR can give cancer cells access to the spinal subarachnoid space and produce metastases through leptomeningeal involvement (Figure 1) [9].

Surgical procedures included partial (cases 1, 2 and 3) or total (case 4) resection of tumor and all cases underwent peritoneal shunt ventricle. Survival after partial resection was 12, 6 and 29 months, and after complete resection was 32 months. All cases received adjuvant radiation after surgery and reached a survival from 14 to 32 months. The third and fourth cases received adjuvant chemotherapy along with radiation, and reached an overall survival of 29 and 32 months (despite one case developed pulmonary tuberculosis), respectively. Our four cases developed local progression in the follow-up.

The role of aggressive surgical resection in this rare malignancy is unclear, however, a gross total resection should be performed in those who can be safely performed. Concomitant adjuvant chemotherapy and radiation has demonstrated to increase survival in nonpineal glioblastoma, however, as pathological features do not differ in

pineal location regarding to those observed in more common location, it is expected that no differences will be observed [2].

The review of previously published and our cases find that median survival for the whole cases was 9.27 (range: 0–32 months) [18] that is close to the median survival of primary glioblastoma of more frequent location, and correlates with the poor prognosis of this aggressive malignancy (10–12 months) [22].

Conclusion & future perspective

The pineal glioblastoma is a rare disease. However, in middle-aged patients with brain MRI showing an infiltrative tumor with heterogeneous contrast enhancement in the pineal region and/or leptomeningeal dissemination, you can raise the suspicion of glioblastoma. The treatment is to install a shunt to reduce intracranial pressure and then perform a partial or subtotal resection of the tumor followed by radiation and concurrent chemotherapy [20,22]. Molecular classification will allow to identify patient prognosis and to predict response to target treatment no matter to brain location. However, tumor location will still provide relevant information for decision on local treatment.

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Informed consent disclosure

The authors state that they have obtained verbal and written informed consent from the patient/patients for the inclusion of their medical and treatment history within this case report.

References

Papers of special note have been highlighted as: • of interest; •• of considerable interest

1. Castaneda CA, Casavilca S, Orrego E *et al*. Glioblastoma: molecular analysis and its clinical implications. *Rev. Peru Med. Exp. Salud Publica* 32(2), 316–325 (2015).
2. Stupp R, Hegi ME, Mason WP *et al*. Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised Phase III study: 5-year analysis of the EORTC-NCIC trial. *Lancet Oncol.* 10(5), 459–466 (2009).
3. Hirato J, Nakazato Y. Pathology of pineal region tumors. *J. Neurooncol.* 54(3), 239–249 (2001).
4. Matsuda R, Hironaka Y, Suigimoto T, Nakase H. Glioblastoma multiforme in the pineal region with leptomeningeal dissemination and lumbar metastasis. *J. Korean Neurosurg. Soc.* 58(5), 479–482 (2015).
5. Norbut AM, Mendelow H. Primary glioblastoma multiforme of the pineal region with leptomeningeal metastases: a case report. *Cancer* 47(3), 592–596 (1981).
6. Toyooka T, Miyazawa T, Fukui S, Otani N, Nawashiro H, Shima K. Central neurogenic hyperventilation in a conscious man with CSF dissemination from a pineal glioblastoma. *J. Clin. Neurosci.* 12(7), 834–837 (2005).
7. Amini A, Schmid RH, Salzman KL, Chin SS, Couldwell WT. Glioblastoma multiforme of the pineal region. *J. Neurooncol.* 79(3), 307–314 (2006).
- **Presents a detailed description of symptoms, images and pathology features of three American patients with pineal glioblastoma.**
8. Louis DN, Ohgaki H, Wiestler OD *et al*. The 2007 WHO classification of tumours of the central nervous system. *Acta Neuropathol.* 114(2), 97–109 (2007).
9. Bradfield JS, Perez CA. Pineal tumors and ectopic pinealomas. Analysis of treatment and failures. *Radiology* 103(2), 399–406 (1972).
10. De Girolami U, Schmidek H. Clinicopathological study of 53 tumors of the pineal region. *J. Neurosurg.* 39(4), 455–462 (1973).
11. Kalyanaraman UP. Primary glioblastoma of the pineal gland. *Arch. Neurol.* 36(11), 717–718 (1979).
12. Frank F, Gaist G, Piazza G, Ricci RF, Sturiale C, Galassi E. Stereotaxic biopsy and radioactive implantation for interstitial therapy of tumors of the pineal region. *Surg. Neurol.* 23(3), 275–280 (1985).
13. Edwards MS, Hudgins RJ, Wilson CB, Levin VA, Wara WM. Pineal region tumors in children. *J. Neurosurg.* 68(5), 689–697 (1988).
14. Vaquero J, Ramiro J, Martinez R. Glioblastoma multiforme of the pineal region. *J. Neurosurg. Sci.* 34(2), 149–150 (1990).
15. Pople IK, Arango JC, Scaravilli F. Intrinsic malignant glioma of the pineal gland. *Childs Nerv. Syst.* 9(7), 422–424 (1993).
16. Cho BK, Wang KC, Nam DH *et al*. Pineal tumors: experience with 48 cases over 10 years. *Childs Nerv. Syst.* 14(1–2), 53–58 (1998).

17. Gasparetto EL, Warszawiak D, Adam GP, Bleggi-Torres LF, de Carvalho Neto A. Glioblastoma multiforme of the pineal region: case report. *Arq. Neuropsiquiatr.* 61(2B), 468–472 (2003).
18. Moon KS, Jung S, Jung TY, Kim IY, Lee MC, Lee KH. Primary glioblastoma in the pineal region: a case report and review of the literature. *J. Med. Case Rep.* 2, 288 (2008).
- **Presents a Korean case and an up-to-date of worldwide pineal glioblastoma cases.**
19. Ozgural O, Kahilogullari G, Bozkurt M, Heper AO, Savas A. Primary pineal glioblastoma: a case report. *Turk. Neurosurg.* 23(4), 572–574 (2013).
20. Mansour J, Fields B, Macomson S, Rixe O. Significant anti-tumor effect of bevacizumab in treatment of pineal gland glioblastoma multiforme. *Target Oncol.* 9(4), 395–398 (2014).
21. Suzuki R, Suzuki K, Sugiura Y *et al.* A case of glioblastoma multiforme in the pineal region with intraventricular hemorrhage. *No Shinkei Geka.* 42(5), 429–435 (2014).
- **Presents a Japanese case and the last up-to-date of worldwide pineal glioblastoma cases (most patients were American followed by Japanese and Korean).**
22. Garcia-Corrochano P, Castaneda CA, Orrego E *et al.* Microsurgical resection of glioblastoma guided with intraoperative fluorescein: a retrospective evaluation. *Rev. Peru Med. Exp. Salud Publica.* 32(3), 471–478 (2015).
23. Louis DN, Ohgaki H, Wiestler OD, Cavenee WK. *WHO Classification of Tumours of the Central Nervous System (4th Edition)*. IARC, Lyon, France (2016).