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Five-year Review of Pineal Region Tumors at the Philippine General Hospital

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Rationale: Pineal region tumors are rare neoplasms with a reportedly higher incidence in Asian countries; however, local Philippine data is lacking.

Methods: A retrospective chart review was conducted on all newly diagnosed adult and pediatric patients with pineal region tumors admitted at the Philippine General Hospital between 2011 and 2015. Data about demographic profile, biochemical markers, imaging findings, histopathology, and treatment were collected.

Results: Forty-two patients (36 males, 6 females; Sex Ratio = 6:1) were included in the study, with a mean age of 16.5 years. On imaging, solitary pineal area tumors were seen in 34 (81%) patients, while 8 (19%) presented with synchronous tumors in the pineal and suprasellar areas. Hydrocephalus was present in 41 (98%). Tumor marker (serum +/- CSF αFP and βhCG) determination was performed in 33(79%) patients. Thirty-eight (90%) patients underwent surgical intervention for tumor biopsy and/or CSF diversion. Combining the tumor marker levels and histopathology results, there were 20(48%) germ cell tumors, 4(9%) pineal parenchymal tumors, 1(2%) meningioma, 1(2%) epidermoid tumor, and 16(38%) tumors with incomplete diagnosis. Regarding adjuvant treatment, 5 patients underwent chemotherapy, 6 underwent radiotherapy, and 1 patient received both. Follow-up data were available in only 16 patients, with a mean follow-up of 12 months (range: 1-33 months).

Conclusion: The demographic profile and histologic subtypes of patients with pineal region tumors in this series were comparable with other series in the literature. However, due to limited resources leading to suboptimal medical care and poor follow-up, a reliable treatment outcome could not be determined.

Key words: pineal gland, brain neoplasms, germinoma, biomarkers-tumor

Pineal region tumors are rare neoplasms accounting for approximately 0.4% to 1% of tumors of the central nervous system. They have a predilection for the pediatric population, representing 2.8%-9% of all childhood malignancies.[1]

It has been reported that the incidence of pineal region tumors is higher in Asian countries where they constitute 2.2% to 8% of all brain tumors in adults and approximately 12% in children.[2] However, there is a paucity of local data about the incidence, demographic profile, tumor histopathology, and treatment outcomes of pineal region tumors. This study was conducted to collect local data on pineal region tumors to gain a better understanding of the disease in the local setting and eventually help improve outcomes. A secondary goal was to contribute to the current pool of data on pineal region tumors in Asian countries.

Methods

Study Population

A retrospective chart review was conducted on all newly diagnosed adult and pediatric patients with pineal region tumors admitted at the Philippine General Hospital from January 2011 to December 2015.

The list of patients was generated using the databases of the Neurosurgery, Neuro-oncology, Pediatric Neurology, Pediatric Hematology-Oncology, and Radiation Oncology sections. Medical records as well as radiology and histopathology reports were reviewed. Data on patient demographics, clinical symptomatology, biochemical markers, imaging findings, histologic

diagnosis, treatment modalities, and treatment outcome were gathered.

Diagnosis

The diagnosis of pineal region tumor was based on radiologic imaging (CT or MRI) since an anatomic classification method was employed. The different subtypes of germ cell tumors were initially determined using biochemical parameters (Figure 1), i.e., serum and/or cerebrospinal fluid (CSF) levels of alpha-feto protein (αFP) and beta-human chorionic gonadotropin (βhCG).[3,4,5] In cases where it was deemed safe to do so, tumor biopsy to obtain specimens for histopathologic diagnosis was performed, usually through an endoscopic route, in the same sitting as the CSF diversion procedure should the latter be indicated. In the presence of significantly elevated tumor markers with suggestive radiologic findings, tumor biopsy was deferred (Figure 2).[6,7] When there is discordance between the histopathology and tumor marker levels, the more malignant diagnosis is used as the basis for treatment and prognostication.[8]

The diagnosis of germinoma was established by the presence of normal αFP, normal or slightly elevated βhCG (βhCG <50 IU/L), and histologic conformation. To establish a diagnosis of non-germinomatous germ cell tumor (NGGCT), either tumor marker testing (αFP with values above the normal range and/or βhCG>50 IU/L) or histologic confirmation would suffice. For pineal parenchymal tumors and other types of tumors, histopathology alone can establish the diagnosis. The following tumors were classified as an "incomplete diagnosis": 1) histologically proven germinoma but with no or incomplete tumor markers, 2) tumors with normal serum αFP and βhCG but without histologic diagnosis, and 3) tumors diagnosed using radiologic imaging only.

Figure 1. Serum and CSF tumor markers used in the diagnosis of pineal region tumors.[5]

GCT Subtype	αFP	β-hCG
Germinoma	-	+
Teratoma	+	-
Yolk sac tumor	+++	-
Embryonal carcinoma	++	++
Choriocarcinoma	-	+++
Pineocytoma	-	-
Pineoblastoma	-	-
Papillary tumor of the pineal region	-	-

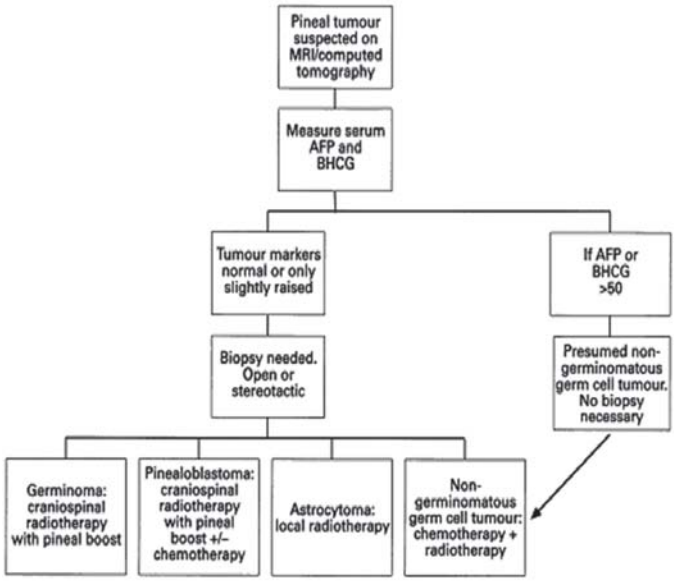

Figure 2. Flow chart describing the management of pineal region tumors.[12]

Staging

Staging of the disease was performed using lumbar CSF cytology to detect the presence of malignant cells and/or craniospinal MRI to check for evidence of disseminated disease.[7,9,10]

Adjuvant Treatment

Platinum-based chemotherapy was administered to selected patients. Various doses of radiation were administered to the neuroaxis depending on the degree of tumor dissemination.[7,9,10]

Data Analysis

Demographic variables were summarized using mean, range, frequency, and percentage.

Ethics Approval

This study was approved by the University of the Philippines Manila (UPM) Research Ethics Board. All patient information were kept confidential, and each case was assigned a numerical code to maintain patient anonymity.

Results

Fifty-three patients with newly diagnosed pineal region tumors were identified between 2011-2015. Eleven (21%) cases were not included in the analysis due to missing charts. The final cohort consisted of 42 patients, 36 males (86%) and 6 females (14%). The mean age at diagnosis was 16.5 years (range: 7-36 years). The incidence was highest in the second decade of life (55%), followed by the first decade (21%) and third decade (19%), with only a few cases being diagnosed after age 30 (5%). (Figures 3 & 4).

Majority complained of headache (95%), vomiting (60%), blurring of vision (50%), and diplopia (45%) as the presenting symptoms. The average time between onset of symptoms to initial consult was 30 weeks, with a range of 2 to 144 weeks. Ten patients (24%) were documented to have at least one type of endocrinopathy, with the following diagnoses: central diabetes insipidus in 8 patients (19%), hypothyroidism in 5 (12%), and hypocortisolism in 3 (7%).

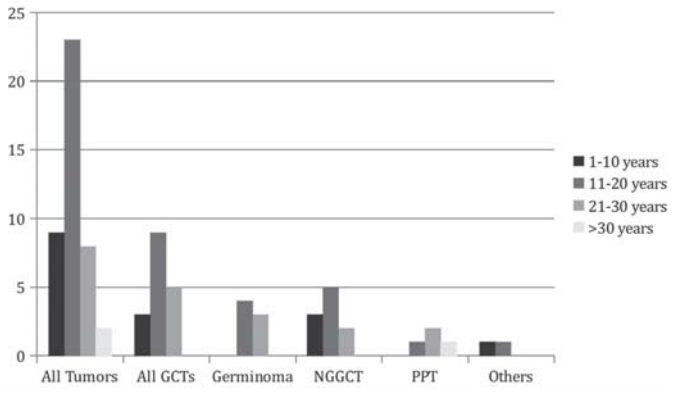

Figure 3. Age of patients with pineal region tumors according to histologic subtype. (X axis: Number of Patients, GCT: Germ Cell Tumor, NGGCT: Non-Germinomatous Germ Cell Tumor, PPT: Pineal Parenchymal Tumor)

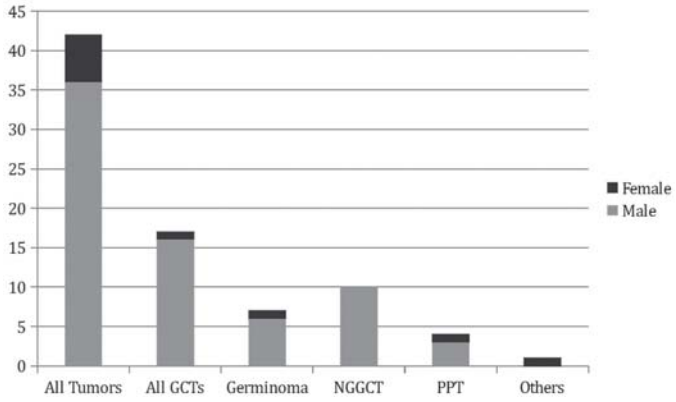

Figure 4. Sex of patients with pineal region tumors according to histologic subtype. (X axis:Number of Patients, GCT: Germ Cell Tumor, NGGCT: Non-Germinomatous Germ Cell Tumor, PPT:Pineal Parenchymal Tumor)

Radiologic diagnosis was established using contrast-enhanced cranial imaging. Cranial CT scan was performed in 18 patients (43%), cranial MRI in 10 (24%), and both modalities in 14 (33%). Tumors were solitary (pineal) in 34 patients (81%), while bifocal (pineal and suprasellar) in 8 (19%). Obstructive hydrocephalus at the level of the third ventricle was documented in 41 patients (98%).

Levels of serum tumor markers αFP and βhCG were recorded in 24 patients (57%). Incomplete tumor makers were recorded in 9 patients (21%), wherein 5 had determination of αFP only and 4 had βhCG only. The results of the remaining 9 patients (21%) were not available. Of the 33 patients with tumor markers, a presumptive diagnosis of a secretory tumor can be made in 10(24%) patients, non-secretory in 15(36%), and non-diagnostic in 8(19%). Two patients had CSF βhCG testing and one patient had both CSF αFP and βhCG testing (Table 1).

Thirty-eight patients (90%) underwent surgical intervention (Table 2), while 4 did not consent to surgery. Because of the concomitant hydrocephalus, majority of patients underwent a CSF diversion procedure with or without tumor biopsy. The initial CSF diversion procedure was an endoscopic third ventriculostomy (ETV) in

23(55%) patients and ventriculoperitoneal shunt (VPS) insertion in 13. Twenty-two patients (52%) had a tumor biopsy, 20(48%) of which underwent endoscopic biopsy of the pineal area tumor while 2(5%) patients underwent pterional craniotomy and biopsy of the concurrent suprasellar tumor.

Twenty patients (48%) did not undergo a biopsy. The reasons for deferral of biopsy were the presence of elevated tumor markers in 7 patients, lack of consent in 3, depressed sensorium (necessitating emergency CSF diversion) in 2, metastatic disease in 2, intraoperative decision to defer biopsy (due to perceived tumor vascularity) in 2, unavailability of endoscopic equipment in 1, pre-operative decision to treat with radiation therapy outright in 1, and undocumented in 2. Of these 20 patients, 16 underwent CSF diversion alone: 11 had a VPS inserted and 5 underwent ETV.

Seven patients (18%) underwent at least one reoperation for persistent hydrocephalus and/or infection. Four patients underwent VPS insertion due to failure of ETV, 2 patients underwent shunt removal and tube ventriculostomy for shunt infection, and one patient underwent Ommaya reservoir insertion for post-meningitic hydrocephalus. There were 8 peri-operative mortalities reported, as well as 7 cases with a surgical morbidity (Table 3). All surgical procedures were performed in this institution except for two cases, one tumor biopsy and one VPS insertion.

Table 1. Tumor markers of patients with pineal region tumors.

Procedure	Number of Patients
Complete markers	n = 24
Elevated αFP, normal βhCG	4
Elevated βhCG (>50 IU/L), normal αFP	2
Slightly elevated βhCG (<50 IU/L), normal αFP	6
Elevated αFP and elevated βhCG (>50 IU/L)	2
Elevated αFP and slightly elevated βhCG (<50 IU/L)	1
Normal αFP and βhCG	9
Incomplete markers	n = 9
αFP only (n = 5)	
Elevated αFP	1
Normal αFP	4
βhCG only (n = 4)	
Elevated βhCG (>50 IU/L)	0
Slightly elevated βhCG (<50 IU/L)	1
Normal βhCG	3
Total	33

Table 2. Initial surgical intervention performed on patients with pineal region tumors. (ETV: Endoscopic Third Ventriculostomy, VPS: Ventriculoperitoneal Shunt).

Procedure	Number of Patients
ETV and endoscopic biopsy	18
VPS insertion and endoscopic biopsy	2
Craniotomy, biopsy	2
ETV only	5
VPS insertion only	11
Total	38

Table 3. Peri-operative mortality and morbidity after surgery for pineal area tumors.

Cause of Death	Number of Cases
Septic shock	3
Brain herniation	2
Multiple organ dysfunction syndrome	2
Hypothalamic injury	1
Morbidity	
Failure of ETV	4
Ventriculitis	2
Post-meningitic hydrocephalus	1

Of the 22 patients who underwent tumor biopsy, only 19 (86%) yielded a histopathologic diagnosis. The diagnosis could not be determined in 3 patients due to inadequacy of the tumor specimen. The histopathology results are as follows: 13 germ cell tumors (10 germinoma, 3 NGGCT), 4 pineal parenchymal tumors, 1 meningioma, and 1 epidermoid tumor (Table 4).

Combining the results of tumor markers and histopathology, a final diagnosis can be made in 26 cases (Table 5). There were 10 patients with germinoma, 7 of whom satisfactorily met the criteria for diagnosis (histology and tumor marker levels) while 3 were incompletely diagnosed because they lacked complete tumor marker testing despite histologic findings of

germinoma. Ten patients met the criteria for a final diagnosis of NGGCT, 3 by histology and 7 by elevated tumor markers alone.

Table 4. Histopathology results of patients with pineal area tumors who underwent biopsy.

Histopathology	Number of Cases
Germinoma	10
Pineoblastoma	2
Pineal parenchymal tumor of intermediate differentiation	2
Yolk sac tumor	1
Mixed germ cell tumor	1
Immature teratoma	1
Epidermoid tumor	1
Meningioma	1
Non-diagnostic	3
Total	22

Table 5. Final diagnosis of patients with pineal area tumors.

Diagnosis	Number of Cases
Pure germinoma	4
βhCG-secreting germinoma	3
Incompletely diagnosed germinoma	3
NGGCT	10
Pineoblastoma	2
Pineal parenchymal tumor of intermediate differentiation	2
Epidermoid tumor	1
Meningioma	1
Incomplete diagnosis (non-diagnostic tumor markers and no histology)	16
Total	42

Staging was performed using craniospinal MRI in 2 patients (5%), lumbar puncture in 5 (12%), and both procedures in 3 (7%). Evidence of metastatic disease was identified in 2 patients (5%). One patient showed evidence of ventricular and leptomeningeal spread on the initial cranial MRI, while another showed spinal metastasis on MRI after he developed quadriparesis.

Thirty-four patients were discharged home. Of these, 16 patients had at least one follow-up visit at the outpatient department, with a mean follow-up of 12 months (range: 1-33 months). The remaining 18 did not follow up after discharge.

Twelve patients received adjuvant treatment. Five patients underwent chemotherapy, 6 underwent radiotherapy, and one patient received both treatment modalities. In this subgroup, there were 4 cases of germ cell tumors (2 βhCG-secreting germinomas and 2 NGGCTs), 3 cases of pineal parenchymal tumors (2 pineoblastomas and 1 pineal parenchymal tumor (PPT) of intermediate differentiation), 1 case of incompletely diagnosed germinoma, and 4 cases of unknown histology. Both patients with βhCG-secreting germinomas were alive at last follow-up (5 and 9 months). One patient with NGGCT died after 1 month while the other was lost to follow-up after treatment. One pinealoblastoma patient died after 4 months and the other was lost to follow-up. The patient with PPT of intermediate differentiation died of tumor progression after 15 months. Three patients with unknown histology were alive at last follow-up (2, 16, and 24 months) and one did not follow up after radiotherapy.

Discussion

The three main types of pineal region tumors are germ cell tumors, pineal parenchymal tumors, and other tumors (Figure 5).[3,11] Patients usually present with symptoms of increased intracranial pressure from obstructive hydrocephalus, mass effect from brainstem and cerebellar compression, endocrine dysfunction (e.g., diabetes insipidus), or a combination of the above. In patients with synchronous tumors at the suprasellar area, hypothalamic and pituitary disorders as well as chiasmatic compression symptoms may also be seen.

In the present study population, majority presented with signs and symptoms from obstructive hydrocephalus. Ten patients manifested with endocrinologic dysfunction such as diabetes insipidus, hypothyroidism, and hypocortisolism, and among them six had synchronous (pineal and suprasellar) tumors while four had purely pineal tumors. There was no report of precocious puberty in this series, as can sometimes be seen in βhCG-secreting tumors.

Table 6. Histological classification of pineal region tumors.[5,6]

Germ Cell Tumors (GCT)
Germinoma
Mature Teratoma
Immature Teratoma
Teratoma with Malignant Transformation
Yolk sac tumor (endodermal sinus tumor)
Embryonal carcinoma
Choriocarcinoma
Pineal Parenchymal Tumors (PPT)
Pineocytoma - WHO Grade I
Pineal parenchymal tumor of intermediate differentiation - WHO Grade II or III
Pineoblastoma - Grade IV
Papillary tumor of the pineal region - Grade II or III
Other Tumors
Astrocytoma
Glioma (glioblastoma or oligodendroglioma)
Medulloepithelioma
Ependymoma
Choroid plexus papilloma
Meningioma
Hemangioma
Hemangiopericytoma or blastoma
Chemodectoma
Craniopharyngioma
Metastases

In the local institutional series described in this paper, germ cell tumors, both germinoma and non-germinomatous subtypes, comprised the majority of tumors in the pineal region. They were mainly seen in young males with a mean age of 17.5 years (range: 9-27 years). The male-to-female ratio is 6:1 which is comparable to other series in Japan and the US. Germ cell tumors were the most common subtype, and exhibiting similar age and sex predilection as the literature.[13,14] The second most common tumor type was pineal parenchymal tumors, which included pineoblastoma and the intermediate subtype. These tumors were seen in relatively older patients with a mean age of 25 years (range: 16-36 years) and a male-to-female ratio of 3:1. These findings are similar to those in the US.[14] Other tumors of the pineal region were rare, and in this series, only two were seen: meningioma and epidermoid tumor.

Multiplicity of tumors is characteristic of germ cell tumors.[12,15] Approximately 5%-25% of patients with intracranial germ cell tumors will present with synchronous or bifocal lesions, and in a fairly large series of 71 patients with intracranial germ cell tumors, 19.7% were synchronous.[16] In the present study, 4 (24%) of the 17 patients who satisfactorily met the criteria for a diagnosis of either germinoma or NGGCT, were bifocal. There were four other bifocal tumors in this series that had no histologic confirmation and incomplete or no tumor marker testing.

Serum and/or cerebrospinal fluid (CSF) determination of αFP and βhCG is a standard of practice.[3,14,17] The biologic basis of these assays is the ability of germ cell tumors to reactivate their developmental state. A presumptive diagnosis of NGGCT can be made in cases wherein the level of serum and/or CSF αFP is elevated and/or βhCG is >50 IU/L, thus obviating the need for tissue diagnosis. In their review, Parker, et al.[17] advocated the use of tumor markers not only for the diagnosis and classification of germ cell tumors, but also for prognostication. Increasing levels of either αFP or βhCG, especially those that are 10-fold above normal, are associated with a worse prognosis and higher incidence of metastatic spread.

Tumor biopsy is indicated in patients with normal serum and/or CSF αFP and βhCG, because the treatment varies according to tumor pathology. The same is recommended for patients with βhCG <50 IU/L and normal αFP, to differentiate βhCG-secreting germinoma from choriocarcinoma or immature teratoma. Some germinomas may secrete moderate amounts of βhCG (<50 IU/L) that do not reach the levels seen in choriocarcinoma or immature teratoma (βhCG >50 IU/L). Immunohistochemical studies (Placental alkaline phosphatase, cytokeratin, synaptophysin, glial fibrillary acidic protein, neurofilament, and others) are helpful especially if there is a limited specimen available for histopathologic examination.[3,14,17]

A comprehensive staging approach is essential to avoid treatment failure. Foo, et al.[10] defined metastasis as the presence of more than one focus within the

cranium (excluding bifocal lesions in the pineal and suprasellar areas), spinal spread, or tumor cells identified in the CSF. Currently, however, there is no universally accepted staging system for germ cell tumors, although craniospinal MRI and/or lumbar CSF cytology are routinely used to detect metastatic spread. Some authors say that either craniospinal MRI or CSF cytology would be sufficient, whereas other authors advocate that both should be done.[7,10,12] Reddy, et al.[18] recommended an additional step in the staging evaluation of pineal region germinomas with the use of neuroendoscopy to visualize metastatic nodules along the ventricular floor or wall.

In the present series, only 24 patients had a complete determination of serum tumor markers αFP and βhCG, 19 had histologic confirmation, and 8 had immunohistochemical studies done. Complete staging was performed in only three patients.

The adjuvant treatment protocol instituted on the patients was adopted from international guidelines, namely, the National Health Services of the United Kingdom and the National Institutes of Health of the United States.[7,19]

Limitations

The main limitations of this study are its retrospective nature, the small sample size, and the poor follow-up of the patients. Complete diagnostic and staging work-up were not performed in most of the patients due to financial constraints. Likewise, these patients did not receive the recommended standard-of-care treatment in a timely fashion for the same reason. Organizational limitations include the absence of a central registry or database, missing charts, and lack of standardized recording of patient information. There are also logistic issues such as the unavailability of tumor marker reagents in the laboratory leading to incomplete diagnosis and occasional malfunction of the neuroendoscope which precludes endoscopic biopsy.

Conclusion

Pineal region tumors are rare but challenging tumors that affect children and adolescents, with a distinct male predilection. The most common subtype is germ cell tumor followed by pineal parenchymal tumor. Due to the diversity of tumors in this location, treatment options and prognoses vary according to histopathology.

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