Papillary Tumor of the Pineal Region: Systematic Review and Analysis of Prognostic Factors

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BACKGROUND: Clinical outcomes and biological behavior of papillary tumors of the pineal region (PTPR) are still under investigation. The best therapeutic strategy has not been defined.

OBJECTIVE: To perform a comprehensive patient-level analysis of all PTPR cases and identify their clinical features, treatment options, and prognostic factors.

METHODS: A search of the medical databases for case series and reports on PTPRs from January 2003 to June 2017 was performed. Data addressing PTPR's clinical presentation, imaging, treatment, and histological features were. Variables associated with the primary outcome of 36-mo survival were identified through Cox regression models.

RESULTS: The initial search yielded 1164 studies, of which 71 were included (60 case reports and 11 case series), containing 177 patients (mean age 33.0 ± 15.3 yr and 53.2% male). Intracranial hypertension and hydrocephalus prevailed as the clinical picture. Surgery was performed on 82.0% and gross total resection (GTR) was achieved on 71.4%. A total of 56.8% recurred after a median 29 mo (quartiles 10.5-45.5). The 36-mo survival rate was 83.5% (95% confidence interval [CI] 76.2-89.2%). Good functional outcomes (Glasgow Outcome Scale 4/5) were observed in 60.0%. The variables of interest were inconsistently reported and the multivariable analysis final sample was 133 patients. After adjustment for age, tumor size (each additional centimeter, hazard ratio [HR] 1.99, 95% CI 1.12-3.53, $P = .019$) and surgical treatment (HR 0.16, 95% CI 0.05-0.45, $P = .001$) were associated with 36-mo survival.

CONCLUSION: Tumor size and surgery are associated with improvement in 36-mo survival. We did not observe any significant benefits from GTR or adjuvant treatments.

KEY WORDS: Brain neoplasms, Pineal gland, Papillary tumor of the pineal region, Systematic review, Meta-analysis

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Tumors in the pineal region are rare, representing less than 1% of all intracranial tumors in adults.[1-3] Nearly 17 histological tumor types have been described for pineal tumors, each with different oncologic behaviors.[2] The papillary tumor of the pineal region (PTPR) is the most recently identified type of pineal tumor. It was described in 2003 by Jouvet et al[4] and included in the 2007 World Health Organization (WHO) classification of central nervous system tumors.[5,6] Its origin is from the ependymal cells of the subcommissural organ with epithelial-like growth patterns and fibrovascular papillae associated with a well-defined secretory function.[4,7,8] Immunoreactions against cytokeratin, vimentin, and S100 proteins, and variable reactivity with glial fibrillary acid protein (GFAP) and epithelial membrane antigen (EMA)[4] represent typical characteristics of the PTPR through immunohistochemical evaluation.

Noncommunicating acute hydrocephalous due to the obliteration of the cerebral aqueduct is a common clinical presentation of PTPR.[9,10] Radiologically, this is depicted as a heterogeneously enhancing mass with cystic

ABBREVIATIONS: CI, confidence interval; **EMA,** epithelial membrane antigen; **GOS,** Glasgow Outcome Scale; **GFAP,** glial fibrillary acid protein; **GTR,** gross total resection; **HR,** hazard ratio; **MRI,** magnetic resonance imaging; **NSE,** neuron-specific enolase; **PTPR,** papillary tumors of the pineal region; **QTx,** chemotherapy; **RTx,** radiotherapy; **SRS,** stereotactic radiosurgery; **WHO,** World Health Organization

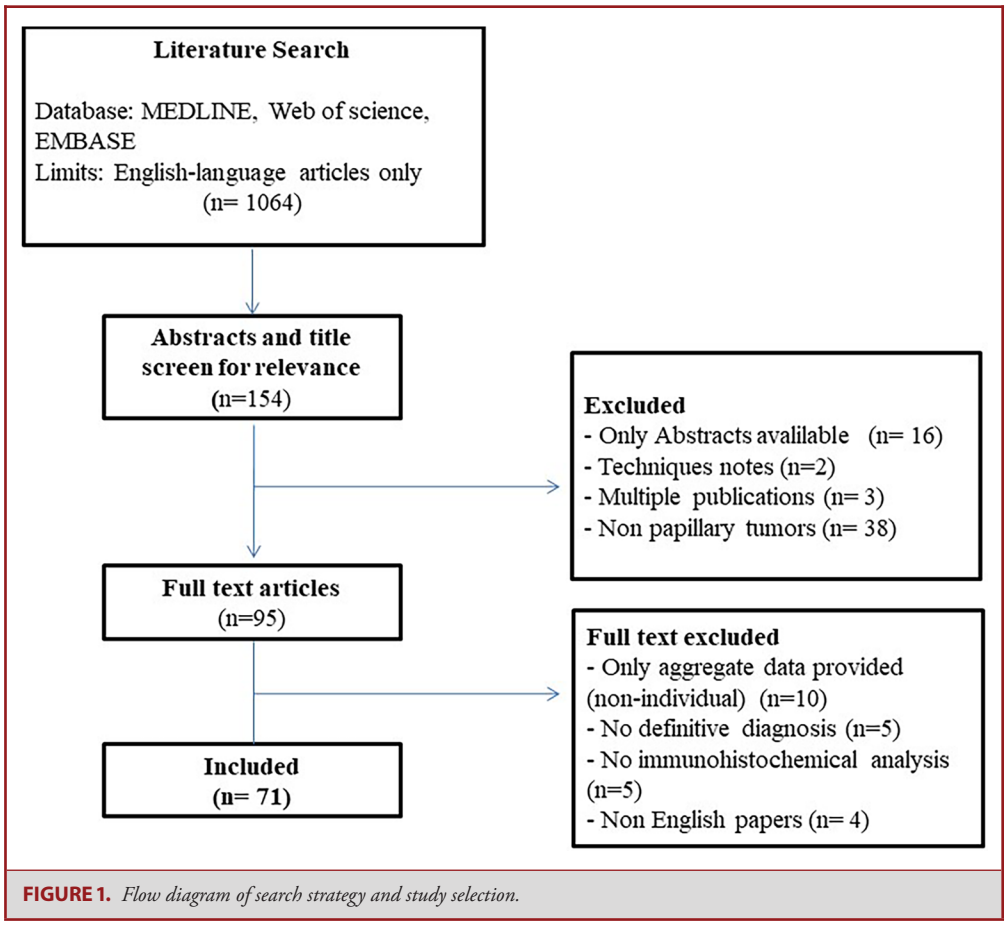

FIGURE 1. *Flow diagram of search strategy and study selection.*

components.[11-13] Due to the recent identification of PTPRs, no valid histologic grading system or standard treatment options exist for this type of tumor. In previous series, only gross total resection (GTR) resulted in longer overall survival.[9,14] In addition, the role of adjuvant treatments has not yet been determined.[9,10]

To study the factors associated with better survival, we performed a comprehensive patient-level analysis of all PTPR cases reported in the last 15 yr.

METHODS

Literature Search

We performed a search in the Web of Sciences, Medline, and EMBASE databases for case series or case reports on PTPRs published between January 2003 and June 2017, using the following keywords in both AND and OR combinations: "papillary," "tumor," "pineal," "gland," "treatment," "surgery," "outcome," and "follow-up." The keywords were searched in "all fields" modality. Studies were independently evaluated for inclusion criteria by 2 authors (Vitor Nagai Yamaki and Davi Jorge Fontoura Solla). In cases of disagreement, a third author (Eberval Gadelha Figueiredo) made the final decision.

Study Selection

Case series or case reports with histologically-proven PTPR cases that met the 2007 WHO classification criteria were included in our review. Individuals of any age were included. Studies without individual patient-level data were excluded. Papers were carefully scanned for duplications. If duplications occurred, the most recent description was selected (Figure 1). Papers were stratified into 5-yr intervals for descriptive purposes.

Data Abstraction

We collected data regarding the clinical presentation, imaging, treatment, and histologic features of PTPRs, including (1) clinical pictures, (2) magnetic resonance imaging (MRI) characteristics and tumor extensions, (3) procedures prior to treatment (such as ventriculoperitoneal shunts, ventriculostomies, and biopsies), (4) treatment modalities (such as surgery, radiosurgery, radiotherapy [RTx], and chemotherapy [QTx]), (5) the Glasgow Outcome Scale (GOS) at final follow-ups, (6) survival, (7) histologic features (such as mitosis rates and presence or absence of necrosis), and (8) immunohistochemical markers (such as cytokeratin, vimentin, S100 proteins, synaptophysin, GFAP, and EMA). The median follow-up was 36 mo and, therefore, we defined a 36-mo survival as the primary outcome. The GOS was selected as the standard functional outcome score.

If original papers did not report the GOS, reported functional scales were used to obtain these data according to the respective degree of dependency.

Statistical Analysis

For descriptive purposes, categorical variables were presented through relative and absolute frequencies. Normally distributed continuous data were presented as mean and standard deviations and, otherwise, by median and quartiles.

Potential predictors of 36-mo survival were identified through the Kaplan-Meier method, using the Log-rank (Mantel-Cox) test to compare the survival functions. Continuous variables were analyzed through a univariate Cox regression. The variables considered for inclusion on the multivariable Cox regression model were patient's age (predetermined, due to biological plausibility) and those variables significant at the univariate analysis at $P < .10$. Hydrocephalus and preoperative biopsies fulfilled the criteria based on the univariate results, but their incidences were too low to permit inclusion on the multivariable model without creating relevant instability. Results were presented through hazard ratios (HR) and 95% confidence intervals (CI). The proportionality and linearity assumptions were verified using graphical methods and the Schoenfeld and Martingale residuals, respectively.

All tests were 2-sided and final *P* values under .05 were considered to be statistically significant. All analyses were conducted with the Statistical Package for Social Sciences (IBM SPSS Statistics for Windows, version 24.0.; IBM, Armonk, New York) software.

RESULTS

A systematic search yielded 1164 studies, 71 of which were included (60 case reports and 11 case series). These studies contained 177 total patients. The study selection process is summarized in Figure 1. Although 15 yr have passed since the first description of PTPRs, meaningful changes in histopathological features and treatment have not been observed (Table 1).[15-76] The variables of interest were inconsistently reported and these are the amount of missing information: clinical picture 77 (43.5%), hydrocephalus 62 (35.0%), symptoms duration 125 (70.6%), tumor size 31 (17.5%), surgical treatment 10 (5.6%), RTx 4 (2.3%), QTx 4 (2.3%), recurrence 57 (32.2%), functional outcome 99 (55.9%), and survival 38 (21.5%). Age and gender had no missing information.

Our analysis found PTPR predominantly in young adults (33.0 ± 15.3 yr), with a slightly higher proportion of male patients (53.2%). Headache with intracranial hypertension was the most common warning sign (82.9%), followed by visual disturbance (45.7%). Computed tomography scan diagnosed hydrocephalus in 88.6% of the cases and half underwent urgent shunt derivation or ventriculostomy. On MRI, PTPR was characterized by a partially cystic pineal region mass with heterogeneous enhancement, measuring approximately 3 cm (2.9 ± 1.0 cm). Extension to the third ventricle associated with cerebral aqueduct obstruction was present in 67.6% of cases. Extension to the lateral ventricles was present in 13.3% and to the fourth ventricle in 3.0%.

TABLE 1. Included Studies Stratified in 15 yrs Interval

Year	No. of studies	Type of study	No. of patients	Gender (female)	Age (mean, yr)	Tumor Size (mean, cm)	Clinical onset	Treatment modalities		Disease free-interval (mean, mo)	Follow-up (mean, mo)
2003-2007	7	Case reports [1,15-18]	45	25/45 (55.5%)	34.0 ± 14.5	2.8 ± 1.0	Headache 6/7 (85.7%)	Surgery	38/45 (84.4%)	33.7 ± 22.2	61.0 ± 49.3
								SRS	4/45 (8.8%)		
		Case series [17,19]					Visual disturb 2/7 (28.5%)	RTx	26/45 (57.5%)		
							Ataxia 1/7 (14.2%)	QTx	6/45 (13.3%)		
2008-2012	38	Case reports [8,12,13,20-49]	58	25/58 (43.1%)	34.0 ± 14.7	2.8 ± 1.0	Headache 44/54 (81.4%)	Surgery	43/56 (76.7%)	34.0 ± 33.2	57.0 ± 69.5
								SRS	3/56 (5.3%)		
		Case series [50-52]					Visual disturb 27/54 (50%)	RTx	29/56 (51.7%)		
							Ataxia 13/54 (24%)	QTx	6/56 (10.7%)		
2013-2017	26	Case reports [53-75]	74	37/74 (50.0%)	33.1 ± 16.5	2.9 ± 1.0	Headache 28/39 (71.7%)	Surgery	57/66 (86.3%)	33.0 ± 29.7	54.8 ± 47.7
								SRS	9/66 (13.6%)		
		Case series [9,10,76]					Visual disturb 5/39 (12.8%)	RTx	25/66 (37.8%)		
							Ataxia 12/39 (30.7%)	QTx	6/66 (9.0%%)		
Total	71		177								

TABLE 2. Clinical and Imaging Characteristics and Procedures Before Definitive Treatment According to 36-mo Survival

Variables	General (139)	36-mo survival		*P* value[a]
		Dead (16)	Alive (123)	
Gender				.385
Female	65/139 (46.8%)	9/16 (56.3%)	56/123 (45.5%)	
Male	74/139 (53.2%)	7/16 (43.8%)	67/123 (54.5%)	
Age (mean ± SD, yr)	33.4 ± 15.4	35.9 ± 13.7	33.4 ± 15.9	.510
Clinical onset				
Headache	58/70 (82.9%)	2/2 (100%)	56/68 (82.3%)	.542
Ataxia	15/70 (21.4%)	1/2 (50.0%)	14/68 (20.5%)	.441
Visual disturbances	32/70 (45.7%)	2/2 (100%)	30/68 (44.1%)	.183
Parinaud's syndrome	8/70 (11.4%)	0/2 (0.0%)	8/68 (11.7%)	.629
Symptoms duration (median and quartiles, mo)	2.0 (1.0-6.0)	2.5 (1.0-4.0)	2.0 (1.0-8.0)	.749
Imaging characteristics				
Cystic component	52/65 (80.0%)	2/2 (100%)	50/63 (79.3%)	.549
Gadolinium enhancement	63/65 (96.9%)	2/2 (100%)	61/63 (96.8%)	.778
Lateral ventricle extension	8/60 (13.3%)	0/2 (0.0%)	8/58 (13.8%)	.566
III Ventricle extension	44/65 (67.6%)	2/2 (100%)	42/63 (66.6%)	.387
IV Ventricle extension	2/65 (3.0%)	0/2 (0.0%)	2/63 (3.1%)	.769
Hydrocephalous	70/79 (88.6%)	2/4 (50.0%)	68/75 (90.6%)	.012
Tumor size (mean ± SD, cm)	2.8 ± 1.0	3.4 ± 1.0	2.7 ± 1.0	.018
Tumor volume (mean ± SD, cm^3)	8.3 ± 7.1	14.0 ± 11.2	7.8 ± 7.2	.580
Procedures before treatment				
Ventriculoperitoneal shunt	29/69 (42.0%)	1/4 (25.0%)	28/65 (43.1%)	.385
Ventriculostomy	18/62 (29.0%)	1/4 (25.0%)	17/58 (29.3%)	.956
Biopsy	38/78 (48.7%)	6/6 (100%)	32/72 (44.4%)	.018

Data presented as valid n (%), except if otherwise specified.
SD: Standard deviation.
[a]Survival analysis by the log-rank test (categorical variables) or Cox regression (continuous variables).

Three yr after diagnosis, 83.5% (95% CI 76.2-89.2%) of the patients were alive and good functional outcomes (GOS 4 or 5) were observed in 60.0% at the last follow-up available. On univariate survival analysis, no demographic or clinical characteristic was associated with 36-mo survival. The median time delay for treatment following detection of the first symptoms was 2 mo (quartiles 1-6), without significant implications for the outcome. Larger tumors were associated with decreased 36-mo survival (3.4 ± 1.0 vs 2.7 ± 1.0 cm, $P = .018$; Table 2).

Most patients underwent surgical resection (82.0%), which was associated with increased survival at 36 mo ($P < .001$) in univariate analysis (Table 3 and Figures 2 and 3). However, the extent of resection did not affect outcomes; GTR did not increase survival compared to nontotal resection. Other treatment modalities, such as RTx (44%), QTx (10.3%), and radiosurgery (10.8%) did not improve survival. Patients submitted to GTR were as likely to receive adjuvant therapy as those who underwent nontotal resection (QTx 13.6% vs 15.2%, $P = .778$; RTx 53.4% vs 42.4%, $P = .282$; radiosurgery 3.4% vs 9.1%, $P = .342$; brachytherapy 0.0% vs 3.1%, $P = .267$). Due to the limited sample size and heterogeneous definitions used, patients submitted to "partial," "subtotal," or "incomplete" resection were analyzed as part of the nontotal resection group. Individual analysis for each treatment modality, such as adjuvant or isolated RTx, stereotactic radiosurgery (SRS), and adjuvant or isolated QTx, was not reliable due to inherent features of the sample.

The median follow-up was 36 mo (quartiles 15-84). Although the tumor's biological behavior has not been well defined, local recurrence has marked PTPR follow-up. Our study demonstrated local recurrence in 57.6%. Survival was not influenced by recurrence. Tumor size was the only independent variable associated with recurrence. Tumors that did not recur had a mean size of 2.5 ± 1.0 cm, while those that recurred had a mean size of 3.1 ± 1.0 cm ($P = .003$; Table 4). We could not evaluate histologic features on risk of recurrence due to the amount of missing information on this regard. We have not included details of the immunohistochemical markers due to the limited amount and heterogeneity of the information.

After multivariable analysis, tumor size (each additional centimeter, HR 1.98, 95% CI 1.11-3.53, $P = .019$) and surgical treatment (HR 0.16, 95% CI 0.05-0.45, $P = .001$) were shown to be associated with 36-mo survival (Table 5 and Figure 3). Older patients demonstrated a tendency to worse prognosis but

TABLE 3. Treatment of PTPR

Variables	General (139)	36-mo survival		*P* value[a]
		Dead (16)	Alive (123)	
Treatment				
Surgery	114/139 (82.0%)	8/16 (50.0%)	106/123 (86.1%)	<.001
RTx	69/138 (44.0%)	11/16 (68.7%)	58/122 (47.5%)	.456
QTx	18/138 (10.3%)	3/16 (18.7%)	15/122 (12.2%)	.661
Radiosurgery	15/139 (10.8%)	1/16 (6.2%)	14/123 (11.4%)	.211
Extent of resection				.186
GTR	75/105 (71.4%)	4/8 (50.0%)	71/97 (73.2%)	
Non-total resection[b]	30/105 (28.6%)	4/8 (50.0%)	26/97 (26.8%)	

Data presented as valid n(%).
[a]Survival analysis by the log-rank test.
[b]Includes subtotal, partial or incomplete resections.

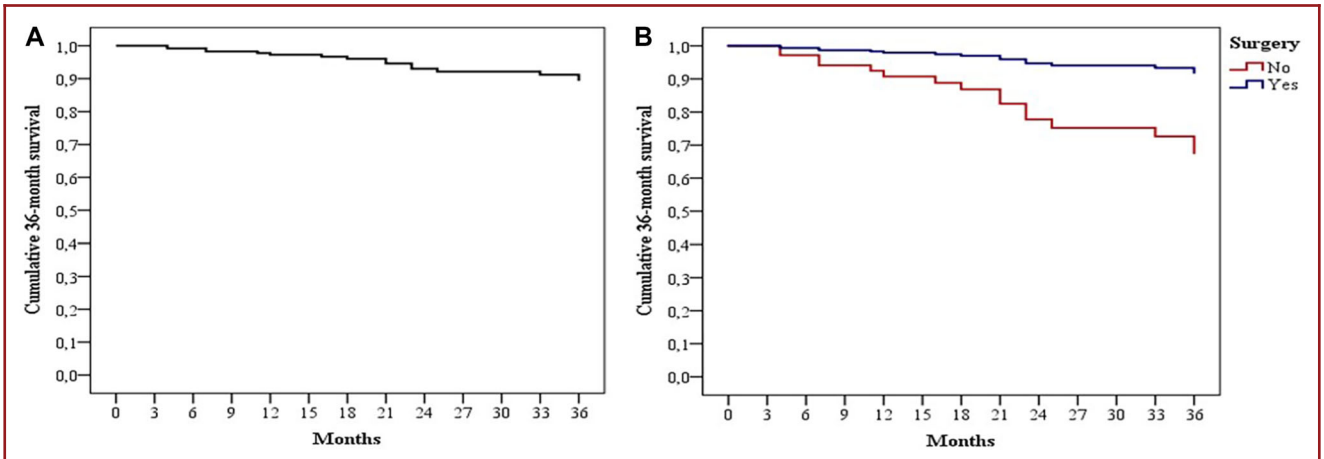

FIGURE 2. **A**, *Overall survival.* **B**, *Influence of the surgical treatment on overall survival.*

this association was not statistically significant (each additional year, HR 1.03, 95% CI 0.99-1.07, $P = .065$). The multivariable analysis was restricted to the cases with survival outcome data and since the number of patients that also lacked tumor size was low (6 patients), we decided not to perform any imputation of missing data. There was no missing age. Therefore, the final sample for the multivariable analysis was 133 patients.

DISCUSSION

The PTPR originates from a distinct ependymal cell of the subcommissural organ, which has a unique papillary architecture associated with particular histological and immunohistochemical features.[1,7,9,57,76] Although rare, a crescent number of cases have been registered over time since PTPR was first described by Jouvet et al[4] and included in the 2007 WHO classification of central nervous system tumors.[5,6] Thus, a refined histologic diagnosis criteria has been developed since its first report.[6] However, the standard of care for PTPR and its biological behavior have not yet been well established.

This systematic review evidenced an increasing number of PTPR cases over the years, with an increase of nearly 30% of cases in 5 yr (Table 1). We opted for a patient-level analysis, since case reports represented the majority of studies. As previously stated, PTPR is most prevalent in young adults with clinical presentation of a headache with signs of intracranial hypertension due to an obstructive hydrocephalus. MRI findings are nonspecific. However, they permit appreciation of the tumor size, which is shown by the multivariable analysis to be related to the survival rate at 36 mo. Surgical treatment is mandatory, as it is the only treatment modality effective for reducing mortality at 3 yr. GTR was not shown to improve outcomes in our series, as had been previously postulated. Local recurrence was a hallmark of the PTPR clinical course, and disease-free interval might have prognostic value.

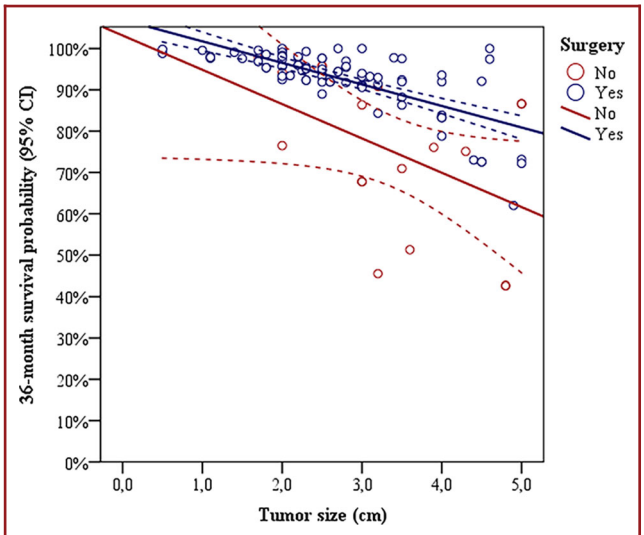

FIGURE 3. *Survival probability at 36 mo according to tumor size and surgical treatment.*

TABLE 4. Outcomes for PTPR

Variables	Total
Follow-up (median and quartiles, months)	36.0 (15.0-84.0)
Survival rate (36-mo)	116/139 (83.5%)
Functional outcome (GOS)[a]	
1	24/76 (31.6%)
2	1/76 (1.3%)
3	7/76 (9.2%)
4	23/76 (30.3%)
5	21/76 (27.6%)
Recurrence	68/118 (57.6%)
Time to recurrence (median and quartiles, months)	29.0 (10.5-45.5)

Data presented as valid n (%), except if otherwise specified.
SD: Standard deviation; GOS: Glasgow outcome scale.
[a]Functional outcome at the end of each original study follow-up.

TABLE 5. Multivariable Analysis for Predictors of 36-mo Survival

Variable	Coefficient ± SE	Wald	HR	95% CI	*P* value
Age (each yr)	0.03 ± 0.02	3.39	1.03	0.99-1.07	.065
Tumor size (each cm)	0.68 ± 0.29	5.49	1.98	1.11-3.53	.019
Surgical treatment	−1.83 ± 0.53	11.74	0.16	0.05-0.45	.001

SE: Standard error; HR: Hazard ratio; CI: Confidence interval.

Clinical and Imaging Characteristics

The PTPR has a marked clinical onset: a headache associated with clinical signs of intracranial hypertension, such as vomiting without nausea, early morning headache, and bilateral papilledema, followed by visual disturbance, characterized by diplopia and visual blurriness. These first symptoms represent warning signs that require radiological investigation. Our results showed a 2-mo median delay for tumor diagnosis after the appearance of the first symptoms. Radiological assessment depicted hydrocephalus in 88.6% of patients. An emergency procedure, such as a ventriculostomy or ventriculoperitoneal shunt, was required in nearly half of the cases. The PTPR is located deep in the brain's topography, near the mesencephalic tectal area (anteriorly-inferiorly) and the cerebral aqueduct/third ventricle (posteriorly). Even a small pineal mass can become symptomatic due to compression of these adjacent structures.

Tumor size at diagnosis had prognostic implication for PTPR in the multivariable analysis. Hydrocephalus at clinical presentation did not affect outcomes. Symptoms of increased intracranial pressure were the main reason for early diagnosis; diagnosis of this type may lead to early treatment and possibly to better outcomes. However, we did not have access to functional outcomes or cognitive evaluations at discharge, so we were unable to evaluate the implications of sudden neurologic deterioration due to acute hydrocephalus in those patients. We believe that tumor size might influence treatment response, as demonstrated in our results.

PTPR present as well-circumscribed masses and tend to be larger than other pineal tumors. On MRI, it has variable T1 and T2 signal intensities with heterogeneous contrast enhancement. A cystic component or the presence of multiple cysts was described, as well as hyperintense foci in T1-weighted images representing inclusions of proteins. Our results found those features in more than 80% of PTPRs. However, few papers reported MRI features, and those that reported these features did not show them to influence overall survival. Image patterns on diffusion-weighted image and spectroscopy have not been established in the literature on PTPRs yet.[11] In 2 case reports, spectroscopy showed increased choline and N-acetyl-aspartate and a discrete lactate peak for PTPR.[9,32,43] Differentials include teratomas, meningiomas, metastatic carcinomas, and parenchymal pineal tumors.[1,11,77]

Histopathology

Histologic examination of PTPRs reveal epithelial-like neoplasm arranged in 2 major architectural patterns, papillary and solid. Papillary areas exhibit broad fibrovascular cores, sometimes containing multiple capillaries that impart a pseudoangiomatous aspect to the tumor. These vessels are lined by a multilayered cuboidal or columnar epithelium with pale eosinophilic cytoplasm, arranged in perivascular pseudorosettes.[78,79] In solid regions of the tumor, clearing or vacuolation of the cytoplasm may occur, often containing an acidophilic intracytoplasmic structure that is periodic acid-Schiff positive. True rosettes, tubules, and canals have also been reported, and tend to be more prominent in solid areas.[19,78]

High-power examination reveals round-to-oval nuclei situated toward the basal pole of the cells. Finely mottled chromatin

and small nucleoli may be present. Occasional nuclear features include hyperchromasia, multinucleation, and anisonucleosis, which seem to be reactive in nature.

Immunohistochemistry is an essential tool in the diagnosis of pineal region neoplasms. The expression of a wide array of low molecular weight cytokeratins appears to be the trademark of PTPR, with particularly strong reactivity to CK18. Staining for S100, NCAM, neuron-specific enolase (NSE), and transthyretin is frequent. PTPR is usually negative for GFAP, synaptophysin, chromogranin, and neural antigens, although focal, weak staining may be observed.[4,76,78,80] Mitotic rates and Ki67 immunolabeling vary widely, and correlation with biological behavior is yet to be determined. Some authors advocate that higher proliferative activity is found in younger patients.[19] Heim et al[79] have reported an association between increased mitotic/proliferative activity and higher recurrence rates in a series of 21 patients.[79] Further studies remain necessary to corroborate this data.

Electron microscopy analysis of PTPR suggests its origin is in specialized ependymal cells of the subcommissural organ. Tumor cells exhibit features of ependymal, secretory, and neuroendocrine cells. Copious cytoplasm containing zonated organelles is found in both dark and clear cells, held together by intercellular junctional complexes. A rough endoplasmic reticulum containing secretory products is a common finding, and so are numerous clear and coated vesicles, mitochondria, and microvilli.[14,76,78]

All pineal region tumors with papillary architecture and/or epithelioid cell morphology are included in the differential diagnosis of PTPR. The diffuse positivity for cytokeratins is the major difference between PTPR and other primary central nervous system lesions, except for choroid plexus papillary lesions. The latter often exhibit single-layered epithelium, Kir7.1, and stanniocalcin-1 staining, whereas PTPRs do not. Ependymomas are typically negative for CK18 and Cam5.2, although AE1/AE3 expression caused by cross-reactivity with GFAP has been reported. Papillary meningiomas may have characteristic EMA expression and should not exhibit diffuse positivity for cytokeratins. Germ cell tumors boast a distinctive morphology and immunophenotype, which includes reactivity for PLAP, AFP, CD30, and β-HCG.[7,76,78]

Detection of a pineal neoplasm with papillary architecture in an adult patient should warrant a differential with metastatic tumors. Careful review of the clinical history, morphology, and the absence of vimentin, NSE, and S100 immunoreactivity favors the diagnosis of metastatic carcinoma. Primary site markers such as TTF-1 are also helpful.[4,8,20]

This paper focused on the clinical course and treatment of PTPR to provide concise results; further studies are necessary to detail the histopathological findings of this particular tumor.

Treatment

Resection of a pineal lesion is the primary therapeutic intervention to improve outcomes and survival rate.[9,78] Resection is effective for both benign and malignant lesions. Several authors believe that gross total tumor resection is critical for preventing local recurrence.[1,9,10,19] Multivariable analysis confirmed that patients who underwent surgery presented better survival rates at 36 mo. However, GTR did not improve outcomes over other resections. The pineal region is in a deep location, surrounded by important structures of the brainstem. We encourage maximum safe surgical resection to ameliorate response to adjuvant treatments and improve survival rate. GTR might be achieved, but it entails risks that should be considered.

The infratentorial supracerebellar approach is classically employed to access the pineal region.[81,60] This approach is optimal for small or medium-sized tumors confined to the quadrigeminal cistern or third ventricle (types A, B, and C). Type D or E tumors, with large extensions to supra- and infratentorial compartments, are better treated through an occipital transtentorial approach. A combined approach has been considered in cases featuring giant tumors.[82] The infratentorial supracerebellar approach was employed most often in our series. Nevertheless, very few papers addressed the surgical approach to the PTPR in detail, and those that addressed it did not provide enough data for statistical analysis.

Other treatment modalities for PTPR include isolated or adjuvant RTx, QTx, or SRS. Brain-local radiation is a well-established treatment to avoid local recurrence of intracranial ependymomas. Although the method has been adopted by most authors in these case reports, our large series did not find better outcomes with adjuvant RTx (whole-brain or fractioned 3-dimensional conformal RTx). The use of QTx (adjuvant temozolomide and cisplatin) was reported as an alternative, especially for recurrence or evidence of cerebral spinal fluid dissemination. However, there is no evidence of better outcomes after QTx. Fauchon et al[9] studied the effectiveness of RTx and QTx in treatment of the PTPR. There was no improvement in overall survival or performance status after these treatments.

The SRS is another treatment modality that should be explored for relatively small brain tumors in deep locations. Kim et al[36] reported the first use of the gamma knife surgery for a PTPR. Although the surgery controlled the disease in the pineal region, it did not avoid leptomeningeal seeding, and the patient experienced a progressive decline in neurological status months later. Fauchon et al[9] promoted SRS as the primary and adjuvant treatments for PTPR. In this series, the patients who underwent SRS without tumor debulking developed several local recurrences. SRS employed in addition to surgical resection led to better control of local disease. Local recurrence was not considered a prognostic factor for the survival rate at 36 mo.

Univariate analysis did not show significant results for alternative treatment modalities, such as QTx, RTx, and SRS. Our nonsignificant results might be explained by the limited sample available for individual analysis of each treatment modality, heterogeneous protocols of QTx, RTx, and SRS, and bias due to the retrospective design of the study. Prospective studies with well-defined methodology are necessary to draw further conclusions, yet these may be unpractical due to the rarity of the disease.

Biologic Behavior

The PTPR can be classified as WHO grade II or III, with a high propensity for local recurrence, such as ependymal or choroid plexus carcinomas.[58,79] A moderate mitosis rate was evidenced, with a mean Ki67 of approximately 6%. Surgical resection is the current standard of care, while PTPR's sensitivity to RTx and QTx need more convincing evidence. Studies registered long-term follow-up with relatively good functional outcomes. We found a median follow-up period of 36 mo with satisfactory GOS. More than 50% of patients had GOS 4 or 5 at the last available follow-up.

Of PTPRs, 56% showed local recurrence in follow-up. Tumor relapse did not determine a worse prognosis. However, a longer disease-free interval correlated to better overall survival results at 36 mo, according to the univariate analysis. Distant dissemination was described by Kim et al[36] in a patient with a rare leptomeningeal seeding into the internal acoustic canals, anterior clinoid process, cavernous sinuses, pituitary stalk, and optic chiasm. These lesions did not respond to SRS, and the patient had an unfavorable outcome with death 11 mo after the first symptoms were detected. Hong et al[30] reported spinal metastasis as an intradural mass at the level of L3. They assumed dissemination through cerebral spinal fluid, based on the tumor's location. This patient underwent surgery, followed by local radiation, but the patient experienced rapid neurologic deterioration and died 8 mo after detection of the spinal tumor. A complete cerebrospinal imaging investigation must be performed at the time of diagnosis and during follow-up. Distant metastatic lesions represent aggressive behavior of tumors and can lead to worse outcomes.

Limitations

Our paper is the first comprehensive multivariable analysis published with patient-level data on PTPR. Most available reports were single case descriptions or case series with small samples, but individual information could be gathered from each patient and analyzed using refined statistical tools. This retrospective design may have influenced the results presented, as it could introduce publication bias related to this type of paper. Some data have been missed due to different methodologies employed among the studies. Therefore, we have included a variable number of studies according to the topic analyzed in order to reunite the best information available. The time interval between interventions (surgery, QTx, RTx, or other) was not analyzed because this information was not available in most studies. Functional outcomes represented by the GOS were not included as endpoints because they were mostly described at the last follow-up instead of at hospital discharge immediately after treatment.

Despite these limitations, our patient-level analysis is the largest PTPR's sample in the literature, with 177 patients studied. Our results provide reasonable data for the rational management of PTPR and constitute the best evidence available thus far related to this uncommon and poorly understood neoplasm.

CONCLUSION

Our results provide consistent information related to the clinical outcomes and management of PTPR. Tumor size and surgical resection are associated with 36-mo survival. Surgical resection remains the current standard of care, as it provides the best prognosis at 36 mo. We did not find additional benefit to GTR or adjuvant treatment.

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COMMENTS

Initially described in 2003, papillary tumors of the pineal region (PTPR) are one of the most recent additions to the histopathologic milieu of lesions seen in this location. They present a significant clinical challenge as they are locally aggressive and frequently recur. While the literature is replete with case reports and small case series on these lesions, their rarity has precluded the establishment of the treatment algorithms often applied to other pineal region tumors. In this meta-analysis – the largest for PTPRs – the authors evaluate how current surgical and clinical management patterns impact patient outcomes. Most interestingly, and in contrast to several other smaller studies, the authors report that while surgical resection improved patient outcomes, gross total resection did not confer a survival benefit. Given the difficulty in obtaining a definitive diagnosis at the time of surgical resection, this result underscores the importance of maximal safe resection of pineal lesions while ensuring that enough tissue for diagnostic workup is obtained. Performing an open surgical resection and biopsy upfront certainly achieves this goal. The authors' result suggests that this may be the optimal initial surgical strategy in these patients, as opposed to a needle biopsy which may be complicated by sampling errors, low diagnostic yield, and the need for an additional surgical procedure.

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The authors should be commended for having completed the first comprehensive study regarding the presentation, treatment, and management of patients with papillary tumors of the pineal region (PTPR), a rare and poorly understood neoplasm that has only recently been classified by the WHO. Due to the rarity of the pathology, the authors were forced to rely on case reports and case series of varying quality; however, they were able to use multivariate analysis to study individual factors related to patient outcomes. Ultimately, they have determined that tumor size and surgical resection are the only two factors associated with survival at 36 months. By providing a comprehensive review of the literature for PTPR and addressing clinical presentation, surgery, the role of gross total resection, adjuvant therapy, imaging, and histopathology, the authors conclusions can be translated into reasonable recommendations that can help guide clinical decision making.

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