Teaching Case

Pineal Parenchymal Tumors of Intermediate Differentiation Treated With Ventricular Radiation and Temozolomide

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Introduction

The pineal gland is a small, pinecone-shaped midline circumventricular organ that produces melatonin. It is located posterior to the third ventricle and is embryologically derived from an outpouching of its ependyma. Tumors of the pineal region are rare, composing less than 1% of intracranial neoplasms.1 They typically present with symptoms secondary to mass effect on nearby structures. Compression of the cerebral aqueduct results in cerebrospinal fluid (CSF) obstruction and hydrocephalus. Involvement of the tectum results in diplopia and Pari- naud syndrome. Larger lesions may involve the cerebel- lum and its peduncles, resulting in nystagmus and ataxia.

Neoplasms in the pineal region may arise from pineal parenchymal cells or residual stem cells and neighboring glia. Approximately 27% of pineal region tumors arise from pineal parenchymal cells and are termed pineal parenchymal tumors.7 Historically, these tumors have been divided into the well-differentiated pineocytoma (World Health Organization [WHO] grade 1) and the much more aggressive, poorly differentiated pineoblastoma (WHO grade 4). Pineocytomas are more common in adults and are more prevalent in females. Pineocytomas may grow locally but rarely exhibit craniospinal spread.3 They are treated with surgery alone, and the prognosis is generally excellent.4,5 At the other end of the spectrum of pineal parenchymal tumors are poorly differ- entiated pineoblastomas. These highly aggressive neo- plasms have a high risk of craniospinal metastases, with a metastasis rate at diagnosis of 25% to 33%. Pineoblasto- mas are most common in children. Age at diagnosis is inversely related to prognosis, and 5-year survival is only 15% for children who are 5 years old or younger at diag- nosis compared with 57% for those older than 5 years. The treatment of these poorly differentiated neoplasms involves surgery, craniospinal radiation, and multimodal chemotherapy with consideration of myeloablative chemotherapy with stem cell rescue.6,7

Pineal parenchymal tumors of intermediate malignancy between pineocytomas and pineoblastomas have been recognized for some time under a variety of names such as malignant pineocytoma, pineocytoma with anaplasia, and atypical pineocytoma.8 The term pineal paren- chymal tumors of intermediate differentiation (PPTID) was introduced in the 1990s and was recognized by the WHO in 2000.9 Formal histologic grading criteria have yet to be established, but PPTIDs are generally considered tumors of grade 2 or 3. Some schemes for distinguishing lower risk from higher risk PPTID have been proposed. One such system10 uses mitoses and antineurofilament staining, whereby rare or absent antineurofilament staining or 6 or more mitoses per high-power field characterize high-grade PPTID, whereas positive neurofilament staining with fewer than 6 mitoses characterize low-grade tumors.
Whereas surgery is typically curative for pineocytomas, aggressive chemoradiation (and often, stem cell transplantation) are required for pineoblastomas. However, there is no consensus on the treatment of PPTID, and treatment paradigms have been reported that span the wide range of aggressiveness between these 2 extremes. After maximal safe surgical resection, a decision must be made to use chemotherapy and radiation. This decision is often influenced by the degree of resection and the presence of spinal or CSF metastases. Systemic chemotherapy and more comprehensive ventricular radiation plans are aimed at reducing the risk of craniospinal recurrence. On the other hand, long-term toxic effects from chemotherapy and radiation must be taken into consideration. These considerations are balanced against the risk of recurrence and survival, which is highly variable in PPTID. Low-grade PPTID carries an estimated 5-year overall survival of 74% versus 39% for high-grade PPTID.3

Methods

Using an institutional review board—approved retrospective protocol, we identified adult patients with PPTID who were treated with whole-ventricle irradiation and concurrent temozolomide. Diagnosis of PPTID was made by histopathologic evaluation of the tumor tissue. All data were analyzed per the ethical standards and approval of the institutional review board. The year of diagnosis for identified patients ranged from 2009 to 2017, and follow-up extended to September 2020, yielding a minimum of 3 years of follow-up.

Ventricle irradiation and temozolomide

We sought to balance the risk of craniospinal dissemination with the adverse effects of cerebral and spinal irradiation. After maximal safe resection, patients were treated with an image-guided intensity modulated technique with sequential boosts to the volumes at increased risk for residual tumor. In this scheme, the whole ventricles plus a 1.5-cm margin are initially treated to a modest 25.2-Gy dose in 1.8-Gy daily fractions (Fig 1, cyan isodose line). This radiation course is followed by a stereotactic boost (an additional 25.2 Gy) to the resection bed plus a 1.5-cm margin (Fig. 1, red isodose line), then a second boost of 5.4 to 9 Gy to the residual tumor plus a 3-mm margin (Fig. 1, orange isodose line). All of the patients were treated using daily image guidance and a relocatable, semirigid face mask, and thus, no additional margin was applied to account for setup error. Therefore, the total dose delivered was 55.8 to 59.4 Gy, all in 1.8-Gy fractions, and the total dose selected was driven by the key dose constraints of <54 Gy to the anterior visual pathways and <5% and <1% of the brain stem receiving doses in excess of 54 Gy and 59 Gy, respectively. All patients were treated with highly conformal fields, with the current practice of treating with intensity modulated techniques exclusively for the whole-ventricle and boost courses. Our premise was that ventricular radiation would reduce the risk of spinal metastases while avoiding the toxic effects associated with craniospinal and high-dose ventricular radiation. Patients were concurrently treated with daily oral temozolomide (75 mg/m²) for 6 weeks. We then treated with adjuvant daily temozolomide (150-200 mg/m²) for 5 days in 28-day cycles, for 6 to 12 cycles.

Results

Case Series

We treated 5 patients since 2009 using the low-dose ventricular radiation therapy approach plus temozolomide, as described (Table 1). All patients completed 6.5 weeks of radiation therapy with concurrent temozolomide and adjuvant 5-day temozolomide, except for case 5, for whom concurrent temozolomide was discontinued early owing to hyponatremia. Three patients suffered progressive disease, of whom 2 died (cases 1 and 2).

Case 1

A 38-year-old woman presented in November 2009 with syncope after 6 months of progressively worsening headaches. Magnetic resonance imaging (MRI) showed a 5-cm mass in the pineal region and resulting hydrocephalus. A ventriculoperitoneal shunt was placed, and she underwent subtotal resection of the mass, with pathology showing grade-3 PPTID. She underwent radiation therapy, receiving a total of 55.8 Gy as earlier described, with concurrent temozolomide. Toxic effects during chemoradiation were mild fatigue and nausea. She began adjuvant 5-day temozolomide and completed approximately 3 to 4 cycles. Her chemotherapy course was stopped owing to cost and then resumed after approximately 3 months at an 80% reduced dose owing to a misunderstanding until progressive disease was noted on MRI in March 2011. She resumed an appropriate dose of 5-day temozolomide (200 mg/m²) and completed 12 cycles. During her course of 5-day temozolomide, MRI scans began showing leptome ningeal enhancement involving the pituitary infundibulum and sellar regions. She experienced further progression despite salvage therapy with daily metronomic temozolomide (50 mg/m²) and then single-agent bevacizumab. Her clinical course was complicated by panhypopituitarism and central diabetes insipidus. She was admitted to the hospital with severe hypernatremia in March 2012 and was ultimately discharged to hospice.
**Case 2**

A 55-year-old woman presented with hydrocephalus in 2011. She underwent subtotal resection, and pathology showed grade-3 PPTID. She underwent radiation therapy, receiving a total of 59.4 Gy, with concurrent temozolomide, followed by 18 months of 5-day temozolomide. Toxic effects experienced during chemoradiation were remarkable only for manageable fatigue. Radiographic progression was noted at the pineal gland in October 2014, and she resumed 5-day temozolomide dosed at 200 mg/m². However, she progressed further after 2 cycles of temozolomide. A repeat resection was performed, and the pathology now showed a glioneuronal tumor. She was subsequently treated with multiple salvage regimens, including postoperative stereotactic radiation surgery followed by bevacizumab plus daily metronomic temozolomide, then etoposide, carboplatin, and finally, CCNU (lomustine). She transitioned to hospice in 2017 and died shortly thereafter.

**Case 3**

A 38-year-old man presented with hydrocephalus in 2012. After an endoscopic third ventriculostomy, he underwent gross total resection with pathology showing grade-3 PPTID. He was then treated with chemoradiation, receiving a total of 59.4 Gy as described earlier, and 12 cycles of 5-day temozolomide. Toxic effects for this course of chemoradiation were fatigue and patchy alopecia. He experienced thrombocytopenia (grade 1) during adjuvant temozolomide (cycles 1 and 2) dosed at 200 mg/m² with 5 days on and 23 days off. This grade-1 toxic effect resolved, and treatment continued at 150 mg/m² for 5 days on and 23 days off for 10 additional cycles. Toxic effects experienced during chemoradiation were remarkable only for manageable fatigue. He was monitored off therapy and was clinically and radiographically stable until May 2019, when an MRI scan showed disease progression at the tectal plate. Clinically, he had no new neurologic symptoms, and he opted for surveillance MRI scans until he developed worsening diplopia and left-sided clumsiness in December 2019. He was treated with stereotactic radiation surgery and bevacizumab. At the last follow-up in September 2020, he had a favorable radiographic response, although diplopia persisted. In follow-up, the patient required testosterone supplementation for resultant pituitary dysfunction.

**Case 4**

A 44-year-old woman presented in December 2016 with hydrocephalus, which was treated with an endoscopic third ventriculostomy followed by subtotal surgical resection, with pathology showing PPTID. A repeat surgery to achieve a gross total resection was then performed. She was treated with chemoradiation, receiving a total dose of 59.4 Gy as described earlier, followed by 12 cycles of 5-day temozolomide. Noted toxic effects for this course of chemoradiation were fatigue and patchy alopecia. She remained clinically and radiographically stable as of the last follow-up MRI scan in September 2020.
| Case | Age in y/sex | Presentation | Surgery | Pathology (grade) | Adjuvant 5-day TMZ | Progression, months since initial resection: Treatment | Complications since last MRI (months since initial resection) |
|------|--------------|--------------|---------|------------------|-------------------|---------------------------------------------------|-----------------------------------------------------------|
| 1    | 38/F         | Hydrocephalus, syncope | VPS, STR | PPTID (3)        | 12 cycles (started after a delay of 8-9 mo) | 14 mo: 5-day TMZ at correct dose (200 mg/m²) 22 mo: Leptomeningeal enhancement, continue 5-day TMZ 27 mo: Metronomic TMZ (50 mg/m²) 29 mo: BEV | Panhypopituitarism, DI, admitted for hyponatremia 38 mo after surgery, discharged to hospice |
| 2    | 55/F         | Hydrocephalus | STR, STR | PPTID (3), glioneuronal tumor | 18 cycles | 40 mo: 5-day TMZ 42 mo: Craniotomy (glioneuronal tumor), SRS 51 mo: Metronomic TMZ + BEV 60 mo: ETO + BEV, ETO discontinued owing to poor tolerance after 2 mo 64 mo: Carboplatin + BEV 68 mo: CCNU + BEV | Hospice 69 mo after initial surgery |
| 3    | 38/M         | Hydrocephalus | ETV, GTR | PPTID (3)        | 12 cycles | 85 mo: Asymptomatic, monitored off therapy 72 mo: SRS, BEV | 96 mo: MRI stable, persistent diplopia, low testosterone requiring supplementation |
| 4    | 44/F         | Hydrocephalus | ETV, STR, GTR | PPTID (3) | 12 cycles | No progression | 39 mo: MRI stable |
| 5    | 69/F         | Hydrocephalus, tinnitus, gait instability, cognitive impairment | GTR, GTR | PC (1) | PPTID (3) | None, owing to hyponatremia 18 mo: Craniotomy (PPTID), radiation therapy with concurrent TMZ; TMZ stopped after 3 wk owing to severe hyponatremia | 34 mo since PC, 16 mo since PPTID diagnosis; MRI stable |

**Abbreviations:** BEV = bevacizumab; CCNU = lomustine; DI = diabetes insipidus; ETO = etoposide; ETV = endoscopic third ventriculostomy; GTR = gross total resection; MRI = magnetic resonance imaging; PC = pineocytoma; PPTID = pineal parenchymal tumor of intermediate differentiation; SRS = stereotactic radiosurgery; STR = subtotal resection; TMZ = temozolomide; VPS = ventriculoperitoneal shunt.
Case 5
A 69-year-old woman presented in March 2017 with pulsatile tinnitus, gait instability, and mild cognitive impairments. An MRI scan showed a mass in the pineal region and hydrocephalus. Gross total resection was performed, and pathology showed pineocytoma of WHO grade 1. She was monitored off therapy until 2018, when a surveillance MRI scan showed recurrence. A repeat gross total resection was performed, and this time, the pathology showed grade-3 PPTID. She began receiving chemoradiation but developed severe hyponatremia requiring hospitalization after 3 weeks. Temozolomide was discontinued per the patient’s request after 3 weeks of temozolomide therapy, although she did complete her radiation therapy course, receiving the prescribed dose of 59.4 Gy. Noted toxic effects during this chemoradiation course included hyponatremia and fatigue. Adjuvant 5-day temozolomide was not initiated. The patient had no further treatment, and based on the most recent MRI scan from January 2020, her condition remained stable.

Discussion
These 5 cases suggest the feasibility of reduced-dose ventricular irradiation and temozolomide for the treatment of high-grade PPTID. The small number of patients in the cohort precludes definitive generalizable conclusions regarding this approach. The favorable outcomes in 3 of the 5 patients are roughly comparable with the 39% 5-year survival reported by Fauchon et al for the 18 grade-3 pineal parenchymal tumors analyzed in their series. In designing this regimen, we sought to balance the toxic effects of chemoradiation therapy against the known risks of spinal metastasis. Only 1 of the patients (case 1) developed evidence for leptomeningeal disease. It is encouraging that all of the surviving patients maintained reasonable cognitive status, and MRI scans showed no new periventricular white matter disease at 2, 3, and 8 years after radiation therapy. The time interval since treatment has been relatively short, and thus further follow-up of these patients will be essential to assess their long-term disease control and cognitive outcomes.

In selecting this ventricular radiation therapy strategy, we were informed by the successful use of this approach to treat germinomatous germ cell tumors. Owing to their propensity for craniospinal metastases, germ cell tumors have historically been treated with craniospinal radiation. However, concerns regarding the long-term neurocognitive and systemic sequelae of such aggressive therapy coupled with the high long-term survival of patients with germinomatous germ cell tumors have led to the use of progressively more localized radiation therapy regimens. Although determining the optimal radiation and chemotherapy regimen for these tumors remains an active clinical research area, current protocols generally include focused radiation to the tumor bed, lower-dose ventricular radiation, and chemotherapy. Attempts to exclude radiation therapy entirely have resulted in significantly higher relapse rates, whereas focal radiation and chemotherapy without ventricular irradiation have resulted in risks for ventricular recurrence. Moreover, in a phase 2 study on response-based radiation therapy for nongerminomatous germ cell tumors in children (ACNS1123), pediatric patients received reduced radiation therapy (30.6 Gy to the whole ventricular field and a 54-Gy tumor-bed boost) for complete or partial response, and results showed that despite initial positive radiographic response, there was a trend of recurrence, particularly to the leptomeninges involving the spine. Therefore, concerns remain that disease control must be balanced by sparing the entire neuroaxis in favor of causing less neurologic toxicity. Children and adolescents with CNS germinomas treated with reduced-dose ventricular irradiation in addition to chemotherapy showed preservation of neurocognitive, social, and emotional function.

In our experience, adult patients often experience more severe acute toxicity, particularly bone marrow suppression, compared with pediatric patients, lending further justification to avoiding craniospinal irradiation in adults when appropriate. Notwithstanding the significant biological differences between germinomatous germ cell tumors and PPTID, we feel that these germinomatous germ cell tumor experiences provide a reasonable rationale for the use of ventricular irradiation in combination with chemotherapy in PPTID.

A great diversity of treatment paradigms has been reported in the literature, ranging from surgery alone to approaches that add craniospinal radiation and systemic chemotherapy. Das et al treated 5 patients with PPTID who were unable to undergo gross total resections with localized external beam radiation therapy. They reported no disease recurrence, white matter abnormalities on brain MRI, or neurocognitive disorders after a median follow-up of 21.4 months. In a single-institution review of 5 patients with PPTID, Watanabe et al reported treating 3 patients who had local disease by using local radiation (dose of 54 Gy; 2 patients) or whole-ventricular radiation (dose of 34.2 Gy; 1 patient) with or without systemic chemotherapy; the 2 patients with evidence of cerebrospinal dissemination received craniospinal (36 Gy) and whole-ventricular (18 Gy) radiation and chemotherapy. Patients who received whole-ventricular radiation developed white-matter abnormalities on MRI, and the 2 patients who additionally received craniospinal radiation developed neurocognitive disorders 4 and 6 years after radiation therapy, respectively.

In Helsinki, Finland, 15 patients first underwent surgical resection. Of these, 3 were subtotal resections and underwent subsequent local radiation. For patients on whom a gross total resection was achieved, radiation therapy was reserved for disease recurrence or concerning...
histology (pineoblastoma features or elevated MIB-1 index). Chemotherapy was not used.

An alternative protocol was devised by Mallick et al.\(^23\) after a systematic review of 29 studies involving 127 patients with PPTID: after maximal safe resection, the decision on local radiation, craniospinal radiation, and surveillance is made based on the presence of spinal metastases or CSF positivity and the degree of resection. For gross total resections without spinal and/or CSF spread, Mallick et al propose surveillance with radiation reserved for recurrence. In cases of subtotal resections without spinal and/or CSF spread, local radiation is pursued. If there is evidence of spinal and/or CSF spread, Mallick et al propose craniospinal radiation followed by chemotherapy.

We opted to incorporate systemic chemotherapy in all patients because of the risk of craniospinal spread, especially in the setting of reduced-dose ventricular radiation. We chose temozolomide owing to its side-effect profile, CNS penetration, and our experience with its use in diffuse glioma. Given the rarity of PPTID, however, we acknowledge that there is little literature guidance on the optimal chemotherapeutic choice. The degree of surgical resection is a key determinant of prognosis in pineal parenchymal tumors,\(^24\) and it is notable that the 3 patients who are still alive all underwent gross total resections. All of our patients thus far have had high-grade PPTID without initial evidence for craniospinal metastases. An alternative approach will be necessary for patients with craniospinal metastases, for which we would consider craniospinal radiation. Given that this article reflects a retrospective case series treated at a single institution, we are limited in the fact that this was not a formal clinical trial. Therefore, specific guidance on the timing of interval imaging, evaluation of specific toxic effects of radiation therapy and chemotherapy, and interdisciplinary involvement are limited in this retrospective analysis. Patients with rare tumors such as PPTID will benefit from larger, multi-institutional clinical trials. Moreover, given that our treatment regimen includes ventricular radiation therapy that could compromise cognition, a formal clinical trial could provide more information regarding toxic effects if routine and longitudinal neurocognitive testing was performed. It is notable that survivors of childhood germ-cell tumors have been shown to have less cognitive dysfunction when they were treated with ventricular radiation therapy rather than craniospinal radiation therapy.\(^25\)

Lack of serial neurocognitive testing is a limitation of the current study, but it would be a critical component of future clinical trials. It is also essential to recognize that our technique evolved during the course of this study, and our current practice is to always treat the whole ventricles and the successive boost volumes using an intensity modulated technique, typically volumetric modulated arc therapy, with daily image guidance, yielding improved conformality and a reduced dose to the normal brain parenchyma.

Two of this study’s cases showed a diagnostic change on recurrence. In case 2, initial resection showed PPTID, whereas subsequent resection at recurrence 3 years later revealed a glioneuronal tumor. This second sample appeared to be ganglioglioma with a pilocytic astrocytoma-like component, although BRAF:KIAA1549 and BRAFV600E testing did not show gene rearrangement or mutation. Of interest, a case of gangliogliomatous differentiation in a pineocytoma has been reported in the pathology literature.\(^26\) These cases suggest the ability of neoplastic pineal parenchymal cells to exhibit multipotential differentiation.

In case 5, a pineocytoma recurred as PPTID only 1 year after gross total resection. To our knowledge, there are only a few case reports of such malignant transformation from pineocytomas to PPTID. In 1 reported case, a 63-year-old woman developed PPTID with diffuse leptomeningeal spread 6 years after gross total resection for a pineocytoma.\(^27\) In another case, a 39-year-old woman was diagnosed with pineocytoma via endoscopic biopsy.\(^28\) The patient was treated with stereotactic radiation surgery and did well until 10 years later, when MRI showed diffuse leptomeningeal enhancement and nodular enhancement along the trigeminal nerve. Dural biopsy showed PPTID. Although pineocytomas are generally clinically indolent, these cases suggest that in rare instances, pineocytomas may undergo malignant transformation to the more aggressive PPTID.

In summary, this study suggests that maximal safe surgical resection followed by local radiation and reduced-dose ventricular irradiation combined with temozolomide is a feasible approach to treating PPTID. We hope that this approach will avoid the significant toxic effects associated with more aggressive therapies while reducing the risks of recurrence and craniospinal metastases.

References

1. Ostrom QT, Gittleman H, Truitt G, Boscia A, Kruchko C, Barnholtz-Sloan JS. CBTRUS statistical report: Primary brain and other central nervous system tumors diagnosed in the United States in 2011–2015. Neuro Oncol. 2018;20:iv1–iv86.
2. Konовалov AN, Pittkhaelauri DI. Principles of treatment of the pineal region tumors. Surg Neurol. 2003;59:250–268.
3. Fauchon F, Jouvet A, Paquis P, et al. Parenchymal pineal tumors: A clinicopathological study of 76 cases. Int J Radiat Oncol Biol Phys. 2000;46:959–968.
4. Sato K, Kubota T. Pathology of pineal parenchymal tumors. Prog Neurol Surg. 2009;23:12–25.
5. Schild SE, Scheithauer BW, Haddock MG, et al. Histologically confirmed pineal tumors and other germ cell tumors of the brain. Cancer. 1996;78:2564–2571.
6. Fanguuso J, Finlay J, Sposto R, et al. Intensive chemotherapy followed by consolidative myeloablative chemotherapy with autologous hematopoietic cell rescue (AuHCR) in young children with newly diagnosed supratentorial primitive neuroectodermal tumors

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6. J.T. Low et al Advances in Radiation Oncology: XXX 2021
7. Tate MC, Rutkowski MJ, Parsa AT. Contemporary management of pineoblastoma. *Pediatr Blood Cancer*. 2008;50:312–318.

8. Schild SE, Scheithauer BW, Schomberg PJ, et al. Pineal parenchymal tumors: Clinical, pathologic, and therapeutic aspects. *Cancer*. 1993;72:870–880.

9. Kleihues P, Louis DN, Scheithauer BW, et al. The WHO classification of tumors of the nervous system. *J Neuropathol Exp Neurol*. 2002;61:215–225. discussion 226-219.

10. Jouvet A, Saint-Pierre G, Fauchon F, et al. Pineal parenchymal tumor treatment paradigm. *Advances in Radiation Oncology: XX 2021 Pineal parenchymal tumor treatment paradigm*. 2021;7.

11. Sands SA, Kellie SJ, Davidow AL, et al. Long-term quality of life and neuropsychologic functioning for patients with CNS germ-cell tumors: From the First International CNS Germ-Cell Tumor Study. *Neuro Oncol*. 2001;3:174–183.

12. Rogers SJ, Mosleh-Shirazi MA, Saran FH. Radiotherapy of localised intracranial germinoma: Time to sever historical ties? *Lancet Oncol*. 2005;6:509–519.

13. Khatua S, Dhall G, O'Neil S, et al. Treatment of primary CNS germinomatous cell tumors with chemotherapy prior to reduced dose whole ventricular and local boost irradiation. *Pediatr Blood Cancer*. 2010;55:42–46.

14. de Rezende ACP, Weltman E, Chen MJ, et al. Intensity-modulated ventricular irradation for intracranial germ-cell tumors: Survival analysis and impact of salvage re-irradiation. *PLoS One*. 2019;14:e0226350.

15. Balmaceda C, Heller G, Rosenblum M, et al. Chemotherapy without irradiation—A novel approach for newly diagnosed CNS germ cell tumors: Results of an international cooperative trial. The First International Central Nervous System Germ Cell Tumor Study. *J Clin Oncol*. 1996;14:2908–2915.

16. da Silva NS, Cappellano AM, Diez B, et al. Primary chemotherapy for intracranial germ cell tumors: Results of the third international CNS germ cell tumor study. *Pediatr Blood Cancer*. 2010;54:377–383.

17. Eom KY, Kim IH, Park CI, et al. Upfront chemotherapy and involved-field radiotherapy results in more relapses than extended radiotherapy for intracranial germinoma: Modification in radiotherapy volume might be needed. *Int J Radiat Oncol Biol Phys*. 2008;71:667–671.

18. Fangusaro J, Wu S, MacDonald S, et al. Phase II trial of response-based radiation therapy for patients with localized CNS nongerminomatous germ cell tumors: A Children’s Oncology Group study. *J Clin Oncol*. 2019;37:3283–3290.

19. O’Neil S, Ji L, Buranahirun C, Azoff J, et al. Neurocognitive outcomes in pediatric and adolescent patients with central nervous system germinoma treated with a strategy of chemotherapy followed by reduced-dose and volume irradiation. *Pediatr Blood Cancer*. 2011;57:669–673.

20. Das P, McKinstry S, Devadass A, Herron B, Conkey DS. Are we over treating pineal parenchymal tumour with intermediate differentiation? Assessing the role of localised radiation therapy and literature review. *Springerplus*. 2016;5:26.

21. Watanabe T, Mizowaki T, Arakawa Y, et al. Pineal parenchymal tumor of intermediate differentiation: Treatment outcomes of five cases. *Mol Clin Oncol*. 2014;2:197–202.

22. Choque-Velasquez J, Resendiz-Nieves JC, Jahromi BR, et al. Pineal parenchymal tumors of intermediate differentiation: A long-term follow-up study in Helsinki Neurosurgery. *World Neurosurg*. 2019;122:e729–e739.

23. Mallick S, Benson R, Rath GK. Patterns of care and survival outcomes in patients with pineal parenchymal tumor of intermediate differentiation: An individual patient data analysis. *Radiother Oncol*. 2016;121:204–208.

24. Raleigh DR, Solomon DA, Lloyd SA, et al. Histopathologic review of pineal parenchymal tumors identifies novel morphologic subtypes and prognostic factors for outcome. *Neuro Oncol*. 2017;19:78–88.

25. Mabbott DJ, Monsalves E, Spiegler BJ, et al. Longitudinal evaluation of neurocognitive function after treatment for central nervous system germ cell tumors in childhood. *Cancer*. 2011;117:5402–5411.

26. Rubinstein LJ, Okazaki H. Gangliogliomatous differentiation of pineocytoma. *J Pathol*. 1970;102:27–32.

27. Bando T, Ueno Y, Shinoda N, et al. Therapeutic strategy for pineal parenchymal tumor of intermediate differentiation (PPTID): Case report of PPTID with malignant transformation to pineocytoma with leptomeningeal dissemination 6 years after surgery. *J Neurosurg*. 2018;Jul 1:1–7.

28. Gomez C, Wu J, Pope W, Vinters H, Desalles A, Selch M. Pineocytoma with diffuse dissemination to the leptomeninges. *Rare Tumors*. 2011;3:e53.