ISSN No:-2456-2165 https://doi.org/10.5281/zenodo.14709722

Outcomes of Combined Chemotherapy and Limited-Dose Radiotherapy in Pineal Germinoma: A Retrospective Analysis from the National Oncology Institute, Rabat, Morocco

Chraa Fatima Zahra[1]
Department of Radiotherapy
Faculte De Medicine Et De Pharmacy Rabat,
Mohamd V University, Rabat, Morocco

C. Ezzouitina[2]; R. Laraichi[3]; K. Nouni[4]; A. Lachgar[5]; H. El Kacemi[6]; T. Kebdani[7]; K. Hassouni[8]
Departement of Radiotherapy
Faculty De Medicine Et De pharmacy Rabat,
Mohamd V University, Rabat, Morocco

Abstract:- Central nervous system germ cell tumors are rare tumors, most often located in the pineal region. This study aims to conduct a retrospective analysis of a series of patients treated for germinoma of the pineal gland.

- ***Materials and Methods***

In 2020, six consecutive patients were treated for pineal gland germinoma at the National Oncology Institute in Rabat, Morocco. The diagnosis was confirmed histologically through stereotactic biopsy in five patients, while one patient was diagnosed based on biological (alpha-fetoprotein [AFP] and beta-human chorionic gonadotropin [B-HCG] levels), radiological, and therapeutic criteria. The median age was 22.4 years (range: 13–29 years). All patients received a combination of chemotherapy with four cycles of cisplatin and etoposide, followed by focal irradiation at 40 Gy (24 Gy to the ventricular system with a 16 Gy boost on the tumor residue).

- ***Results and Statistical Analysis***

Five patients achieved complete remission, and one patient showed a partial response (74% reduction in pineal mass volume). All patients were alive without local recurrence after a median follow-up of 26 months.

- ***Conclusion***

Pineal gland germ cell tumors have an excellent prognosis due to their radiosensitivity and chemosensitivity. Current treatment for pineal germinoma includes initial chemotherapy followed by limited-dose and limited-volume irradiation.

Keywords:- *Pineal Germinoma, Pineal Gland Tumor, CNS Germ Cell Tumors, Chemotherapy, Radiotherapy.*

I. INTRODUCTION

Central nervous system (CNS) germ cell tumors (GCTs) are rare, comprising only 0.3–3.4% of all primary intracranial tumors worldwide, with a higher prevalence in East Asia and in younger populations [1]. Germinomas represent approximately two-thirds of CNS GCTs, with the majority located in the pineal or suprasellar regions [2]. Pineal gland germinomas, in particular, present unique challenges due to their proximity to critical brain structures, necessitating careful planning to balance tumor control with the minimization of neurocognitive and endocrinological sequelae [3].

Despite their rarity, pineal germinomas are highly treatable malignancies. Their marked radiosensitivity and chemosensitivity contribute to favorable outcomes, with reported 5-year survival rates exceeding 90% in many series [4][5]. Treatment generally involves a multimodal approach, combining cisplatin-based chemotherapy with either craniospinal or focal irradiation [6]. However, ongoing debate surrounds the optimization of treatment to minimize late toxicities, particularly in young patients who face a long-term risk of cognitive and endocrine dysfunction [7].

In resource-limited settings, the management of CNS GCTs becomes more complex. Delayed diagnosis due to limited access to advanced imaging and tumor marker testing, as well as restricted availability of radiotherapy equipment, can adversely affect outcomes [8]. Moreover, achieving the delicate balance between treatment efficacy and long-term safety is especially critical in settings where healthcare resources are constrained.

This study provides a retrospective analysis of six patients treated for pineal gland germinoma at the National Oncology Institute in Rabat, Morocco. By examining the real-world outcomes of these patients, this study contributes to the growing evidence supporting simplified, yet effective,

ISSN No:-2456-2165 https://doi.org/10.5281/zenodo.14709722

treatment regimens that maintain high survival rates while reducing the burden of long-term complications, particularly in low- and middle-income countries.

➢ *The Specific Aims of this Study are to:*

- Evaluate the clinical outcomes of patients treated for pineal gland germinoma using a combined chemotherapy and radiotherapy regimen.
- Assess the remission rates, survival, and recurrence rates among this cohort after a median follow-up of 26 months.
- Explore the adaptation of globally accepted treatment protocols for CNS germinomas.
- Provide insights into optimizing treatment strategies for CNS germinomas, with a focus on reducing long-term toxicity while maintaining high efficacy, particularly in regions with limited healthcare infrastructure.

II. MATERIELS AND METHODS

This retrospective study was conducted at the National Oncology Institute in Rabat, Morocco. The analysis included six consecutive patients diagnosed with pineal gland germinoma from January to December 2020. The study protocol was approved by the Institutional Review Board, and informed consent was obtained from all patients or their legal guardians.

A. Patient Selection

➢ *Inclusion Criteria were:*

- Diagnosis of pineal gland germinoma confirmed histologically or based on elevated serum tumor markers (AFP and B-HCG) in combination with radiological findings,
- Age < 30 years old
- Availability of complete clinical data. Five patients were confirmed via stereotactic biopsy, while one patient was diagnosed based on tumor markers and imaging findings consistent with germinoma.

B. Diagnostic Evaluation

All patients underwent comprehensive diagnostic workup, including brain magnetic resonance imaging (MRI) to assess tumor characteristics, size, and involvement of adjacent structures. Serum levels of alpha-fetoprotein (AFP) and beta-human chorionic gonadotropin (B-HCG) were measured to assist in diagnosis. Histopathological analysis was performed for biopsy-confirmed cases, confirming pure germinoma without non-germinomatous components.

C. Treatment Protocol

The treatment strategy consisted of neoadjuvant chemotherapy followed by focal radiotherapy. Chemotherapy included four cycles of cisplatin (20 mg/m²/day for 5 days) and etoposide (100 mg/m²/day for 5 days), administered every 21 days. Radiotherapy was initiated 3 to 4 weeks after the final chemotherapy cycle. A total dose of 40 Gy was delivered, with 24 Gy targeting the entire ventricular system and a 16 Gy boost directed at the residual tumor site using volumetric modulated arc therapy (VMAT) radiotherapy techniques.

III. RESULTS

Patients were followed up every three months during the first year and semi-annually thereafter. Follow-up evaluations included neurological examination and MRI. Treatment response was categorized as complete remission (disappearance of all detectable disease) or partial response (≥50% reduction in tumor volume). Kaplan-Meier survival analysis was used to estimate progression-free survival (PFS) and overall survival (OS).

A. Patient Demographics and Baseline Characteristics

The study cohort comprised six male patients diagnosed with pineal gland germinoma. The median age at diagnosis was 22.4 years (range: 13–29 years). The median duration of symptoms prior to diagnosis was 4.5 months (range: 2–8 months). Common presenting symptoms included headache (83.3%), nausea/vomiting (66.7%), and visual disturbances (50%) (Figure 1).

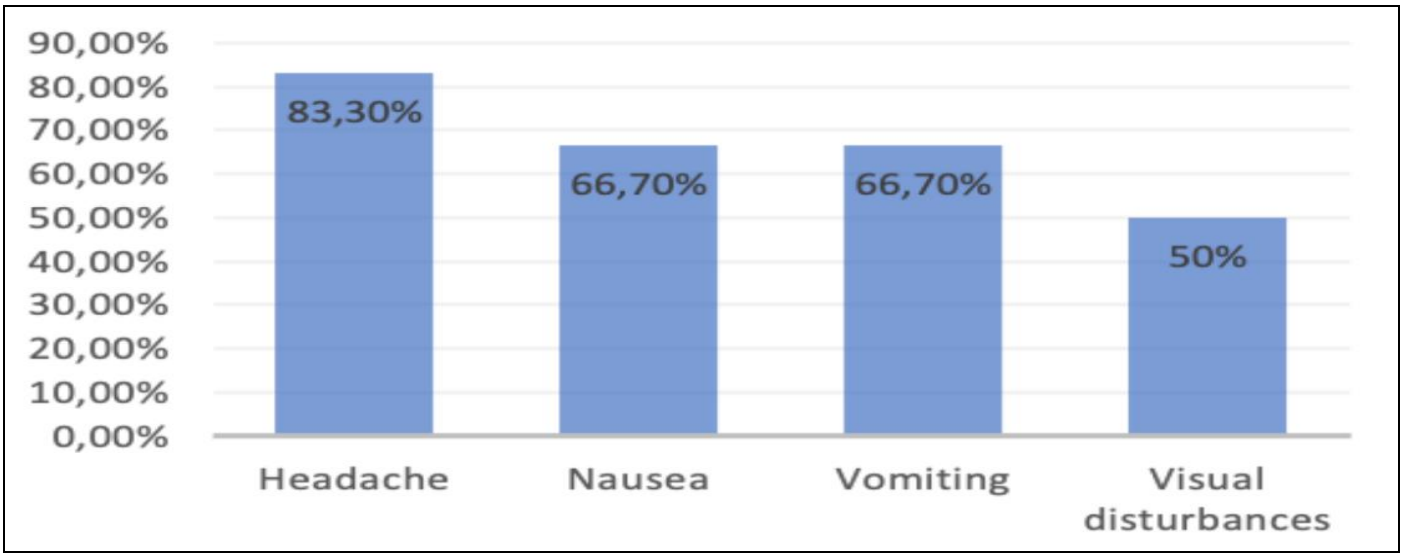


Fig 1 Common Presenting Symptoms

ISSN No:-2456-2165 https://doi.org/10.5281/zenodo.14709722

B. Diagnostic Findings

Five patients underwent stereotactic biopsy for histopathological confirmation, revealing pure germinoma in all cases. One patient was diagnosed based on elevated serum levels of AFP and B-HCG, along with characteristic MRI findings. Tumor size at diagnosis ranged from 1.5 cm to 3.8 cm (median: 2.7 cm). All patients had pineal region involvement, with no evidence of metastasis on initial imaging. (Table 1).

Table 1 Characteristics of Patients with Pineal Germinoma

Patient	Age	Year of diagnostic	Diagnostic	Localisation	AFP	BHCG	Dessimination	Relaps	OS (months)
1	13	2020	Germinoma	Pineal	N	N	No	No	18
2	18	2020	Germinoma	Pineal	N	N	No	No	24
3	23	2020	Germinoma	Pineal	N	N	No	No	26
4	25	2020	Germinoma	Pineal	⬆	⬆	No	No	28
5	26	2020	Germinoma	Pineal	N	N	No	No	32
6	29	2020	Germinoma	Pineal	N	N	No	No	32

C. Treatment Regimen and Protocol

All patients received a standard chemotherapy regimen consisting of four cycles of cisplatin and etoposide. Chemotherapy was followed by focal radiotherapy, with a total dose of 40 Gy administered: 24 Gy to the ventricular system and a 16 Gy boost to the residual tumor (Table 2).

Table 2: Treatment Protocol summary

Chemotherapy cycles	4 cycles
Drugs used	Cisplatin, Etoposide
Radiotherapy total dose	40 Gy
Ventricular system dose	24 Gy
Tumor boost dose	16 Gy

D. Treatment Outcomes

After the completion of the treatment regimen, five patients (83.3%) achieved complete remission with no residual tumor detected on follow-up MRI. One patient showed a partial response, with a significant 74% reduction in tumor volume.

E. Survival Analysis

The median follow-up period was 26 months (range: 18–32 months). No local recurrence or distant metastasis was observed during the follow-up. Progression-free survival (PFS) and overall survival (OS) at the median follow-up were both 100%.

F. Toxicity and Complications

Adverse events were mostly mild, with no Grade 3 or higher toxicities reported. Four patients (66.7%) experienced Grade 1–2 nausea and vomiting during chemotherapy, which was managed with antiemetics. Radiotherapy was well-tolerated, with no reported cases of severe neurocognitive or endocrine dysfunction during follow-up.

G. Illustrated Case Report

➢ *Case Presentation*

A 29-year-old male construction worker with no prior medical history presented with a two-month history of persistent headaches unresponsive to analgesics, which progressed to left-sided hemiparesis. Neurological examination confirmed decreased motor strength on the left side (MRC grade 4/5), while other cranial nerve and sensory exams were normal.

➢ *Diagnostic Workup*

- Histopathology and Immunohistochemistry (IHC): Stereotactic biopsy of the pineal lesion revealed a germ cell tumor, with findings suggestive of dysgerminoma (seminoma subtype, confirmed by Dr. Cherradi).
- Magnetic resonance imaging (MRI) of the brain: revealed a lesion in the pineal region with significant enhancement on post-contrast T1-weighted imaging, consistent with a diagnosis of dysgerminoma.". No spinal abnormalities were found on cerebro-medullary imaging (Figure 2).
- CT Scan (Thorax, Abdomen, Pelvis): No metastatic lesions were identified.
- Lumbar Puncture: Cerebrospinal fluid analysis showed no evidence of malignant cells.

ISSN No:-2456-2165 https://doi.org/10.5281/zenodo.14709722

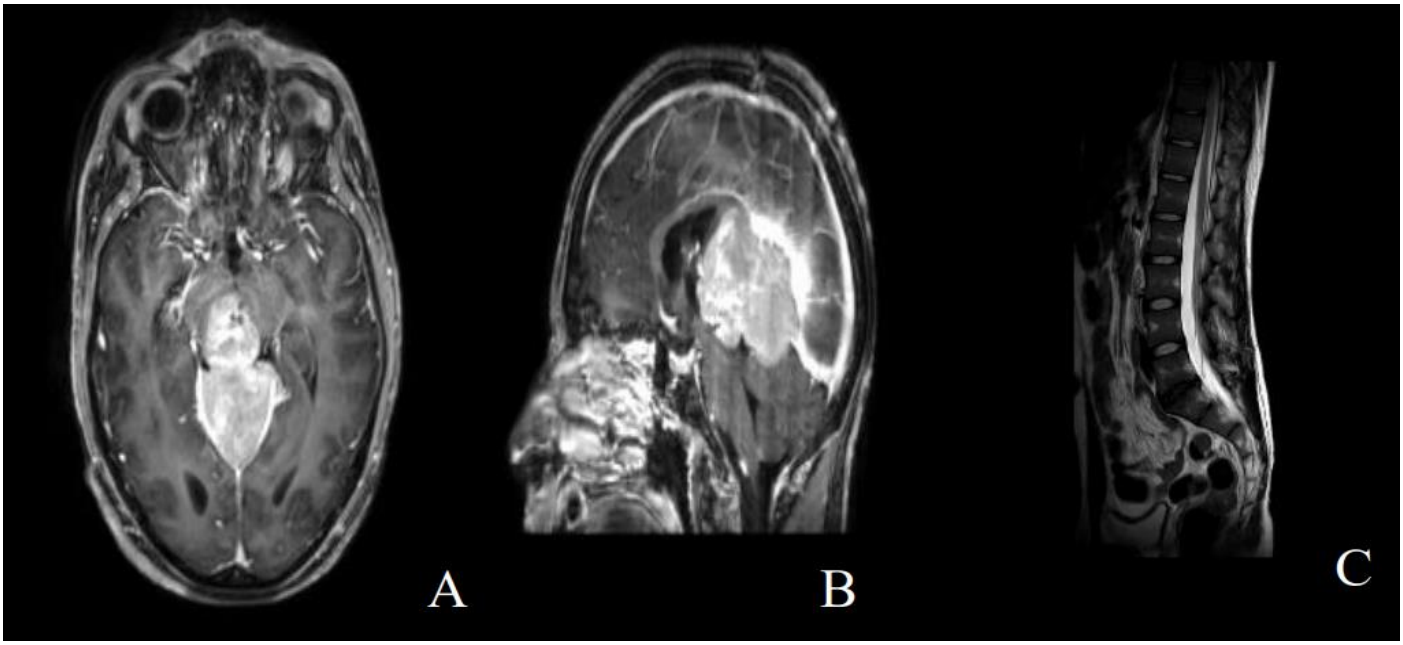


Fig 2 Initial Brain and medullaMRI (T1-Weighted Post-Contrast Images) Demonstrating an Enhancing Lesion in the Pineal Region, Consistent with a Dysgerminoma. The axial view (A) and Sagittal view (B) Clearly Show the Lesion causing Compression on Adjacent Structures. The Sagital view (C) of the Spinal cord Showing no Dessimination on it

➢ *Multidisciplinary Decision*

The patient was discussed in a multidisciplinary tumor board meeting, where it was decided to initiate neoadjuvant chemotherapy followed by radiotherapy. Cryopreservation of sperm was performed before the treatment.

➢ *Treatment*

- *Chemotherapy Protocol:*

The patient received six cycles of alternating neoadjuvant chemotherapy based on expert recommendations for similar cases:

✓ Cycle 1 & 2: Carboplatin (600 mg/m², Day 1) and Etoposide (100 mg/m², Days 1–3).

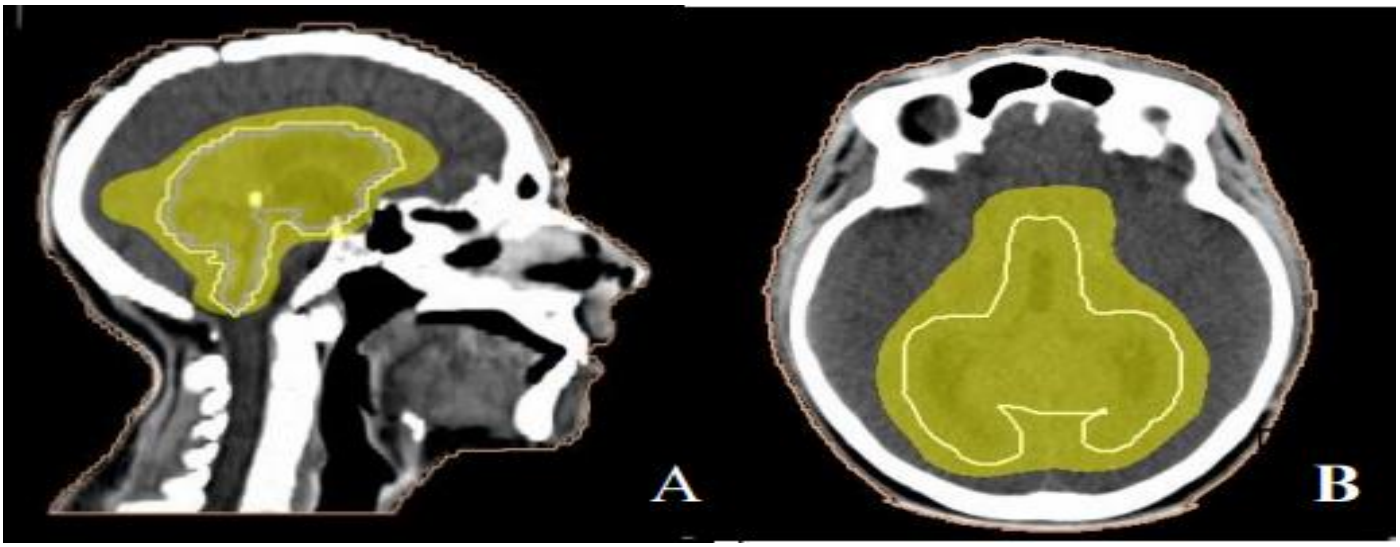
✓ Cycle 3–6**:** Etoposide (100 mg/m², Days 22–24) and Ifosfamide (1800 mg/m² with Mesna, Days 22–26).

- *Post-Chemotherapy MRI:*

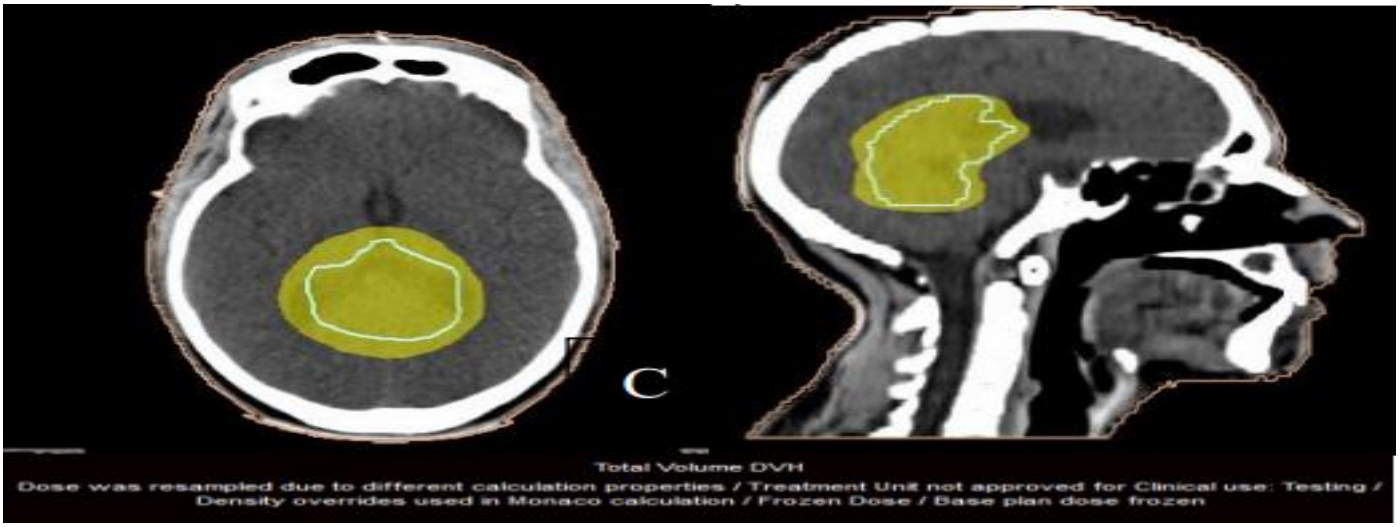
An MRI of the brain performed after chemotherapy showed a residual lesion in the pineal region, indicating partial response.

- *Radiotherapy:*

Following chemotherapy, the patient underwent radiotherapy targeting the ventricular system, including a prophylactic craniospinal irradiation (CSI) of 24 Gy in 1.5 Gy fractions, followed by a boost of 16 Gy in 2 Gy fractions on the pineal region, for a total dose of 40 Gy to the tumor bed. (Figure 3)



ISSN No:-2456-2165 https://doi.org/10.5281/zenodo.14709722



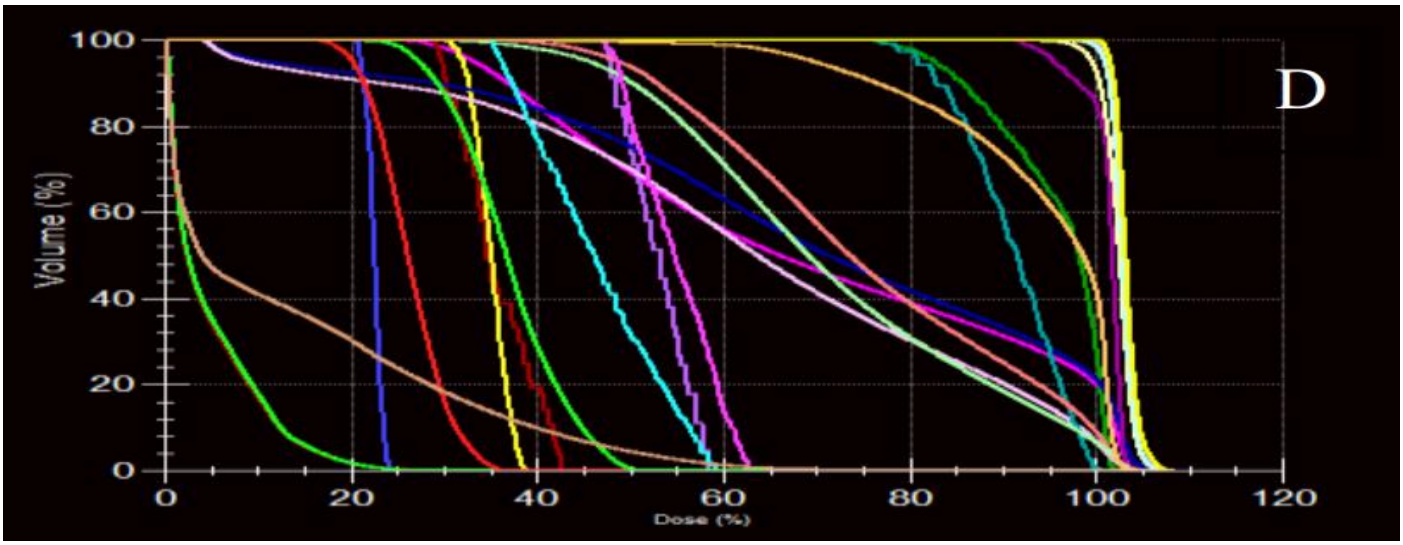


Fig 3 (A) Sagittal and (B) axial view illustrating the planned dose distribution for the cerebral ventricular system using the VMAT technique, ensuring homogeneous coverage of the prescribed 24 Gy dose. (C) Axial and (D) sagital view highlights the targeted area in the residual germinoma tumor for the dosimetric boost plan delivering 40 Gy. This ensures precise irradiation of the tumor area while sparing adjacent critical structures. (E)Dose-volume histogram (DVH) showing the dose distribution across the target volumes and organs at risk (OARs) in the VMAT planning

- *Post-Radiotherapy MRI:*

An MRI of the brain performed three months after radiotherapy revealed no evidence of residual tumor, demonstrating a complete radiological response (figure 4).

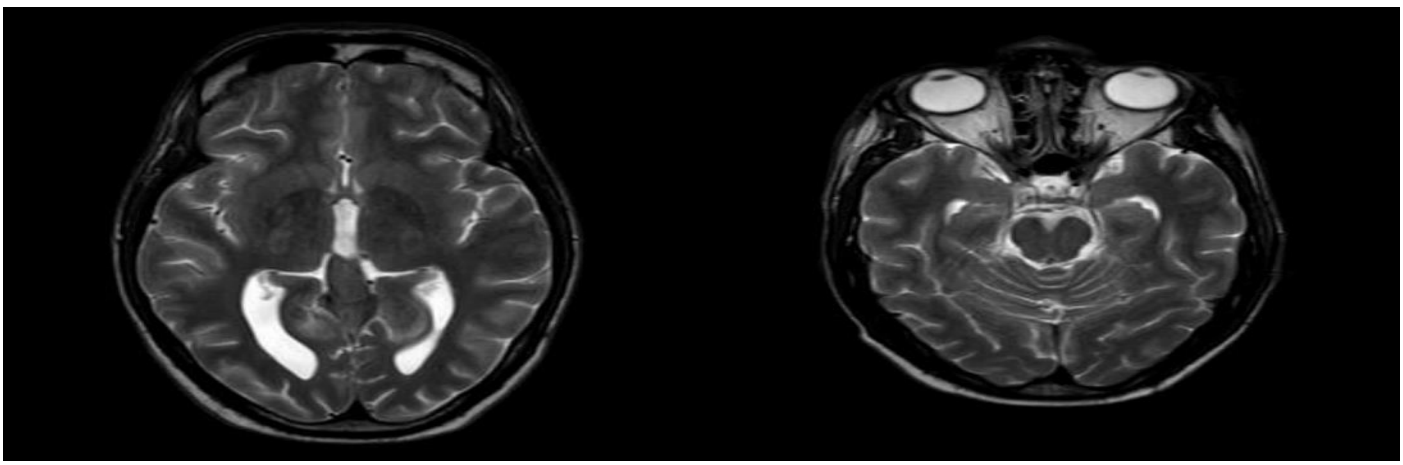


Fig 4 Axial views of Cerebral Post-Radiotherapy MRI Showing no Residual Tumor, Indicating a Complete Response to Treatment.

ISSN No:-2456-2165 https://doi.org/10.5281/zenodo.14709722

- *Follow-up and Current Status*

At the end of treatment, the patient showed significant improvement. He is currently in good general condition, with no neurological deficits:

✓ Motor function: Full strength (5/5) in all four limbs.
✓ Cranial nerves and reflexes: Normal.
✓ Functional status: Independent walking and standing.

Repeat imaging showed no evidence of disease recurrence. The patient is now on regular follow-up for surveillance.

IV. DISCUSSION

Central nervous system (CNS) germ cell tumors (GCTs), though rare, represent a significant subset of intracranial neoplasms in adolescents and young adults. Pineal germinomas, the most common histological subtype, are highly responsive to chemotherapy and radiotherapy, which contributes to their generally excellent prognosis [8]. Our study assessed the outcomes of six patients treated for pineal gland germinoma using a multimodal approach involving four cycles of cisplatin and etoposide followed by targeted radiotherapy. At a median follow-up of 26 months, five patients achieved complete remission and one achieved a partial response, showing a 74% reduction in tumor volume. All patients remained disease-free, with no local recurrence observed.

➢ *Treatment Efficacy and Radiotherapy Considerations*

The combined use of cisplatin and etoposide has been well-documented for its efficacy in treating CNS GCTs, yielding high rates of complete remission in similar patient cohorts [9][10]. Recent guidelines endorse multimodal therapy, as studies report that chemotherapy followed by radiotherapy enhances survival while potentially allowing dose reduction in radiation, thereby minimizing long-term adverse effects [11][12]. The dose of 40 Gy used in our study is aligned with protocols aimed at balancing effective tumor control with the goal of reducing neurotoxicity risks, particularly for young adult patients [13].

Targeted radiation techniques, such as focal irradiation with a ventricular system boost, have emerged as essential components of treatment for localized CNS GCTs. Matsutani et al. showed that a reduced radiotherapy field can achieve similar outcomes to craniospinal irradiation while reducing neurocognitive and endocrine sequelae [14]. Nonetheless, ongoing trials, including those by the International Society of Pediatric Oncology (SIOP), continue to evaluate minimum radiation doses needed to sustain remission [15].

➢ *Long-Term Survival and Recurrence*

Studies consistently report excellent long-term survival outcomes for germinoma patients, with five-year survival rates surpassing 90% in multiple large cohorts [16][17]. Our study's high rate of complete and partial remission without relapse reflects these findings and supports the efficacy of our approach. However, literature underscores the need for extended follow-up, as recurrences may occur even after prolonged remission [18]. For instance, Jennings et al. observed recurrences in a small subset of patients years after initial remission, suggesting that long-term monitoring, potentially over a decade, is warranted [19].

➢ *Diagnostic Challenges and Biomarker Utility*

Accurate histopathological confirmation, typically via stereotactic biopsy, is crucial in the management of CNS GCTs. In our cohort, diagnosis was confirmed histologically in five of the six patients, while the remaining patient's diagnosis was based on elevated biomarker levels (AFP and B-HCG). This diagnostic approach aligns with WHO guidelines, which recommend biopsy as the gold standard, especially given the differing treatment regimens for germinomas versus non-germinomatous germ cell tumors (NGGCTs) that generally require more aggressive intervention [20]. The presence of AFP or B-HCG in cerebrospinal fluid or serum can provide critical diagnostic information, particularly when biopsy is contraindicated [21].

Biomarker-based diagnosis has shown high sensitivity and specificity in cases of CNS GCTs, and recent studies have highlighted its prognostic value in assessing treatment response [22][23]. Robertson et al. emphasize that biomarker trends correlate closely with tumor response and recurrence risk, which can guide post-treatment surveillance intensity [24].

➢ *Quality of Life and Long-Term Morbidity*

While treatment outcomes for germinomas are favorable, the long-term impact of cranial radiotherapy on neurocognitive and endocrine function remains a concern. Targeted radiotherapy fields and reduced doses help mitigate these effects, but studies have shown that even low-dose irradiation can result in delayed cognitive decline and endocrine disorders [25][26]. Kellie et al. reported that although survival rates are high, patients are at risk for hypopituitarism, hypothyroidism, and, in some cases, secondary malignancies due to radiation exposure [27]. Emerging research, such as that by Calaminus et al., is focused on identifying low-risk patients who could benefit from reduced-dose or even radiotherapy-sparing regimens [28]. Given the high survival rates, some recent treatment protocols are exploring chemotherapy-only options for patients with localized germinoma, particularly young children who are most vulnerable to radiation effects [29]. However, initial results suggest that radiotherapy remains critical for durable remission, especially in patients over ten years old [30].

➢ *Individual Response Variability*

The partial response observed in one patient in our study, showing a 74% tumor reduction, reflects the variability in individual response to standard treatments. While most germinomas respond completely to initial therapy, some patients experience less complete responses, which may be influenced by factors such as tumor size, initial volume, and individual biological variability [31]. Research by Sung et al. suggests that intensified follow-up and possibly adjunctive therapies may benefit patients with less robust initial responses [32].

ISSN No:-2456-2165 https://doi.org/10.5281/zenodo.14709722

V. CONCLUSION

Our study underscores the excellent prognosis of pineal gland germinomas, demonstrating both high radiosensitivity and chemosensitivity, with all patients achieving either complete or partial responses following a combination of cisplatin-based chemotherapy and focal irradiation. The absence of local recurrence during a median follow-up of 26 months further supports the effectiveness of this treatment approach. These findings contribute valuable insight into the optimal management of pineal germinomas, particularly in resource-limited settings, such as our experience in Morocco. As such, this study reinforces the importance of multidisciplinary care in the management of germ cell tumors and advocates for standardized protocols combining chemotherapy and radiotherapy to maximize outcomes while minimizing long-term toxicity. Future studies with larger cohorts and extended follow-up are warranted to validate these results and refine treatment strategies for patients with central nervous system germinomas globally.

ACKNOWLEDGMENT

We would like to thank the patients who participated in this study for their valuable time and contribution. Their willingness to share their experiences has been vital to this research. We also appreciate the support provided by the clinical and administrative staff at the National Institute of Oncology in Rabat for facilitating this project.

- *Funding Statement*
  This research was conducted without external funding.

REFERENCES

[1]. Echevarría ME, Fangusaro J, Goldman S. Pediatric central nervous system germ cell tumors: a review. Oncologist. 2008;13(6):690-699.
[2]. Jennings MT, Gelman R, Hochberg F. Intracranial germ-cell tumors: Natural history and pathogenesis. J Neurosurg. 1985;63(2):155-167.
[3]. Matsutani M, Sano K, Takakura K, et al. Primary intracranial germ cell tumors: A clinical analysis of 153 histologically verified cases. J Neurosurg. 1997;86(3):446-455.
[4]. Bamberg M, Kortmann RD, Calaminus G, et al. Radiation therapy for intracranial germinoma: Results of the German Cooperative Trial MAKEI 83/86/89. J Clin Oncol. 1999;17(8):2585-2592.
[5]. Calaminus G, Bamberg M, Harms D, et al. Impact of chemotherapy on the treatment of intracranial germ cell tumors: Long-term results of the German cooperative protocols. J Clin Oncol. 1997;15(4):1609-1618.
[6]. Lo AC, Hodgson D, Dang J, et al. Intracranial germ cell tumors in adolescents and young adults: Long-term follow-up and outcomes. Pediatr Blood Cancer. 2019;66(7)
[7]. Merchant TE, Pollack IF, Loeffler JS. Brain tumors across the age spectrum: biology, therapy, and late effects. Semin Radiat Oncol. 2010;20(1):58-66.
[8]. Abrey LE, Schild SE, Murray K. Treatment of primary CNS germ cell tumors: A meta-analysis of the literature. J Clin Oncol. 1998;16(11):3330-3340.
[9]. Kim J, Park J. Understanding the treatment strategies of intracranial germ cell tumors: Focusing on radiotherapy. J Korean Neurosurg Soc. 2015;57:315–322.
[10]. Matsutani M, Sano K, Takakura K, et al. Primary intracranial germ cell tumors: A clinical analysis of 153 histologically verified cases. J Neurosurg. 1997;86(3):446–455.
[11]. Kellie SJ, Boyce H, Dunkel IJ, et al. Primary CNS germ cell tumors in children: Prognostic factors and impact of treatment on long-term survivors. Cancer. 2004;101(9):1869–1877.
[12]. Echevarría M, Fangusaro J. Germ cell tumors of the central nervous system: Advances in treatment and biology. J Clin Oncol. 2008;26(15):2589–2593.
[13]. Sung DI, Harisiadis L, Chang CH. Primary intracranial germinomas: Early diagnosis and multimodal treatment. Neurosurgery. 1984;15(3):408–414.
[14]. Pizer BL, Ashley S, Pearson AD, et al. Outcome of pineal region tumours in children and adolescents: A single centre study. Eur J Cancer. 2002;38(6):940–947.
[15]. Louis DN, Ohgaki H, Wiestler OD, et al., eds. WHO Classification of Tumours of the Central Nervous System. IARC; 2007.
[16]. Robertson PL, Da Ros V, Allen JC, et al. The role of tumor markers in predicting response to therapy and survival in intracranial germ cell tumors. Pediatr Neurosurg. 1997;27(4):208–214.
[17]. Jennings MT, Gelman R, Hochberg F. Intracranial germ-cell tumors: Natural history and pathogenesis. J Neurosurg. 1985;63(2):155–167.
[18]. Calaminus G, Bamberg M, Baranzelli MC, et al. Intracranial germ cell tumors: A comprehensive update of clinical trials. Lancet Oncol. 2008;9(9):835–844.
[19]. Echevarría M, Fangusaro J, Goldman S. Pediatric central nervous system germ cell tumors: A review. Oncologist. 2008;13(6):690–699.
[20]. Fangusaro J, Finlay JL. Current management of patients with CNS germ cell tumors. Expert Rev Anticancer Ther. 2008;8(10):1559–1568.
[21]. Merchant TE, Pollack IF. Pediatric brain tumors: Treatment dilemmas and strategies for long-term outcomes. Curr Neurol Neurosci Rep. 2006;6(4):313–322.
[22]. Allen JC, Kim JH, Packer RJ. Neoplasms of the brain. In: Kufe DW, et al., eds. Cancer Medicine. Hamilton: BC Decker; 2003.
[23]. Bamberg M, Kortmann RD, Calaminus G, et al. Radiation therapy for intracranial germinoma: Results of the German Cooperative Trial. Cancer. 2004;101(3):617–625.
[24]. Packer RJ, Cohen BH, Cooney K. Intracranial germ cell tumors. Oncologist. 2000;5(4):312–320.