

# To the editor: Is it possible to achieve long-term survival in relapsed Intracranial Non-Germinomatous Germ Cell Tumours?

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**To the editor: Is it possible to achieve long-term survival in relapsed Intracranial Non-Germinomatous Germ Cell Tumours?**

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**To the editor:**

We report a case of an adolescent with relapsed metastatic yolk sac tumour (YST) of the pineal region who received multimodal treatment and remains alive and progression-free at 5 years from his last end of treatment. This encouraging case contributes to the limited existing body of literature on the management of relapsed non-germinomatous germ cell tumours of the central nervous system (CNS NG-GCT).

A 12-year-old male presented with a 2-week history of headache, nausea, vomiting, ataxia and drowsiness. Head CT scan showed a pineal lesion, subsequently confirmed on Magnetic Resonance (MR) (Supplemental figure S1). No leptomeningeal spread on MRI. Serum alpha-fetoprotein (AFP) 1,832 ng/ml. Serum beta-human chorionic gonadotropin ( $\beta$ -HCG) 16 IU/L. Cerebrospinal fluid (CSF) cytology: no malignant cells. AFP in CSF 34.9 ng/ml ( $\beta$ -HCG not available).

An endoscopic third ventriculostomy, stereotactic biopsy of the pineal lesion, and insertion of a Rickham reservoir were undertaken. The initial biopsy was inconclusive. A second biopsy was consistent with a malignant GCT with predominant features of YST.

The child was treated as per SIOP CNS GCT 96 protocol off-trial with 4 cycles of cisplatin, etoposide and ifosfamide (PEI) with partial response according to Response Evaluation Criteria in Solid Tumors v1.1<sup>1</sup>. Serum tumour markers normalized. Subsequently, he received radical volumetric modulated arc therapy (VMAT) to the residual tumour (54 Gy in 30 fractions). End of treatment MR scan revealed a stable subcentimetre tumour residuum with negative serum tumour markers.

Two years after the end of treatment, routine serum tumour markers showed AFP 56.6 ng/ml and  $\beta$ -HCG <2 IU/L. MR brain and spine demonstrated stable intracranial appearances, with a new solitary plaque of enhancing tissue over the surface of the spinal cord posteriorly at the level of T10 disc space (Supplemental figure S1). The child received alternating carboplatin/etoposide and ifosfamide/etoposide for a total of 4 cycles as per SIOP CNS GCT II trial (NCT01424839). After 4 cycles of chemotherapy, the T10 meningeal spinal metastasis shrunk and serum AFP decreased to 4.8 ng/ml. He then received high dose thiotepa and etoposide followed by autologous stem cell transplant (ASCT) followed by craniospinal irradiation -CSI- (30 Gy in 16 fractions) with a boost to the spinal recurrence (20.8 Gy in 13 fractions). The end of treatment MRI showed ongoing response and serum AFP was normal. This young man is currently alive, with normal serum tumour markers and free of recurrence 5 years after treatment.

Whilst most relapsed CNS germinomas can be salvaged, relapsed CNS NG-GCTs have a much worse prognosis<sup>2-4</sup>. There is no international consensus on salvage therapy for relapsed CNS NG-GCT and there are relatively few published case series with limited and heterogeneous cases<sup>5</sup>. Murray et al.<sup>6</sup> reported a cohort of 32 relapsed CNS NG-GCT patients with a 5-year overall survival (OS) of 9% (95%CI: 2-26). Of the 16 patients who received high dose chemotherapy (HDC) and ASCT, 2 of 3 long term survivors had received irradiation after HDC and ASCT. Similarly, Callec et al.<sup>5</sup> reported a retrospective multicenter study of 25 patients with relapsed CNS NG-GCT showing a 5-year OS of 72% (95%CI: 46-87) for patients who received HDC versus 29% (95%CI: 4-61) for those who didn't (p=0.006). These studies and others have led the Third International CNS Germ Cell Tumor Symposium to recommend HDC, surgery, and irradiation, if feasible, for the management of relapsed CNS NG-GCTs<sup>7</sup>.

Elevated serum AFP at initial diagnosis (>1000 ng/ml) was incorporated as a poor prognostic factor in the SIOP CNS GCT II trial (NCT01424839), following results of the SIOP CNS GCT 96<sup>8</sup>. This case could receive CSI because he had only had focal radiotherapy at initial diagnosis. However, cases with metastatic disease at initial diagnosis who receive CSI upfront would not have this choice in case of metastatic relapse. Although relapsed CNS NG-GCTs have a dismal prognosis, this case illustrates the importance of close surveillance with tumour markers and that long-term survival is achievable with multimodal treatment, including induction chemotherapy, high dose chemotherapy with ASCT, and radiotherapy.

### Conflict of Interest statement

The Authors declare that there is no conflict of interest.

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**Supplemental figure S1:** Series of head (axial T2-weighted turbo spin echo sequences) and spine (sagittal post-gadolinium T1-weighted turbo echo sequences) MR examinations. A 12 year-old male presented with a lobulated neoplastic pineal mass (A1; arrow), biopsy-proven to be a yolk sac tumour, approximately measuring 4 x 2.5 x 4 cm (ap tr cc/ob), markedly vascularised but non-high-cellular, and containing a couple of subcentimetric central cystic foci. This lesion compressed and distorted the third ventricle causing moderate obstructive hydrocephalus and exerted mass effect also onto the right dorsal medial thalamic nuclei and onto the ipsilateral dorsal midbrain along its aqueduct. No intracranial or spinal metastases at baseline (A2). Favourable response to chemotherapy and radical VMAT therapy was achieved 7 months after diagnosis with a minimal cystic residuum (B1; arrow) which has remained stable over time (C1, D1; arrow). However, 23 months after end of treatment a millimetric faintly enhancing leptomeningeal deposit overlying the cord at the level of T10-11 (B2; circle) developed. This resolved (C2) the following year, after completion of further chemotherapy, autologous stem cell transplant, and craniospinal irradiation and has not reoccurred (D2) to date, 5 years off treatment.