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CLINICAL STUDY

Utility of MRI versus tumor markers for post-treatment surveillance of marker-positive CNS germ cell tumors

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Abstract Patients with marker-positive central nervous system (CNS) germ cell tumors are typically monitored for tumor recurrence with both tumor markers (AFP and b-hCG) and MRI. We hypothesize that the recurrence of these tumors will always be accompanied by an elevation in tumor markers, and that surveillance MRI may not be necessary. We retrospectively identified 28 patients with CNS germ cell tumors treated at our institution that presented with an elevated serum or cerebrospinal fluid (CSF) tumor marker at the time of diagnosis. We then identified those who had a tumor recurrence after having been in remission and whether each recurrence was detected via MRI changes, elevated tumor markers, or both. Four patients suffered a tumor recurrence. Only one patient had simultaneously elevated tumor markers and MRI evidence of recurrence. Two patients had evidence of recurrence on MRI without corresponding elevations in serum or CSF tumor markers. One patient had abnormal tumor markers with no evidence of recurrence on MRI until 6 months later. We conclude that in patients with marker-positive CNS germ cell tumors who achieve complete remission, continued surveillance imaging in addition to measurement of tumor markers is indicated to detect recurrences.

Keywords CNS tumors · Germ cell tumors · Surveillance MRI · Tumor markers

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Introduction

Central nervous system (CNS) germ cell tumors represent 3–5 % of all intracranial childhood malignancies in the United States [1]. They typically arise in midline CNS structures, most commonly in the pineal or suprasellar region, and can be divided into two main categories. Germinomas comprise 60–65 % of all CNS germ cell tumors and are the most sensitive to radiation and chemotherapy. Non-germinomatous germ cell tumors (NGGCT) are less radiosensitive and include embryonal cell carcinomas, immature teratomas, endodermal sinus tumors, and choriocarcinomas [2]. If a germ cell tumor is composed of more than one type of these histological elements, it is classified as a mixed malignant germ cell tumor (MMGCT).

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After treatment with surgery, radiation, and/or chemotherapy, patients are monitored for tumor recurrence with the tumor markers alpha-fetoprotein (AFP) and beta-human chorionic gonadotropin (b-hCG) and surveillance MRIs. In a retrospective review of 31 patients with marker-positive CNS germ cell tumors, Martinez et al. [3] found that all nine patients who had a recurrence following initial remission had elevated serum tumor markers at recurrence, while only eight patients had MRI evidence of recurrence. They concluded that the use of MRI might not be necessary in the long-term surveillance of patients with marker-positive CNS germ cell tumors. Therefore, we hypothesized that patients with elevated serum tumor markers at diagnosis who achieve biochemical and radiological remission may not need surveillance MRI scans to detect recurrence.

Methods

From our institutional patient database, we retrospectively identified those patients with CNS germ cell tumors who presented with an elevated serum or cerebrospinal fluid (CSF) AFP or b-hCG at diagnosis who were treated at NYU Langone Medical Center between 1990 and 2014 and followed for at least 1 year post diagnosis. An elevated serum or CSF tumor marker was defined as a value above our laboratory's reported upper limit of normal.

We then identified those patients who suffered a tumor recurrence after having achieved biochemical and radiographic stability. Our surveillance schedule followed those outlined in Children's Oncology Group protocols: after completion of treatment, patients were monitored every 3 months during the first year, every 4 months during the second year, and yearly starting the third year. Monitoring included brain and spine MRI surveillance and serum tumor markers. CSF markers were not monitored unless there was a specific reason for concern. We then determined whether each recurrence was detected by elevated serum or CSF tumor markers, MRI, or via both modalities.

Results

Patient demographics

Of the 90 reviewed charts, a cohort of 28 patients fulfilled the inclusion criteria above. Demographic characteristics are shown in Table 1. The median age was 14.5 years at diagnosis. Our cohort included three times as many males (n = 21) as females (n = 7). This is expected given the higher prevalence of primary CNS germ cell tumors in males. The median follow-up period, defined as months from diagnosis to the last MRI performed, was 59 months. Tumor sites included the pineal region only (n = 10), the sellar/suprasellar region only (n = 9), both regions (n = 3), disseminated disease (n = 5), and the left hypothalamus and basal ganglia (n = 1). Diagnoses included germinoma (n = 12), NGGCT (n = 10), and MMGCT (n = 6) established either by tumor marker level alone, or by biopsy and histology.

Table 1 Marker-positive CNS germ cell tumor patient demographics

	Marker-positive CNS germ cell tumor patients (n = 28)
Median age at diagnosis (range)	14.5 years (7–25)
Sex	21 male, 7 female
Median follow-up (range)	59 months (12–176)
Tumor location	Pineal (n = 10)
	Sellar/suprasellar (n = 9)
	Pineal and sellar/suprasellar (n = 3)
	Disseminated (n = 5)
	Hypothalamus and basal ganglia (n = 1)
Diagnosis	Germinomas (n = 12)
	Non-germinomatous germ cell tumors (n = 10)
	Mixed malignant germ cell tumors (n = 6)

Marker-positive CNS germ cell tumor patients with recurrence

Four of the 28 patients suffered a tumor recurrence (Table 2). Two patients presented with mixed malignant germ cell tumors, one with a pure germinoma, and the other with a non-germinomatous germ cell tumor that was demonstrated to be a yolk sac tumor. Contrary to our original hypothesis, only one patient had elevated tumor markers and simultaneous MRI evidence of tumor recurrence. Two patients had evidence of recurrence on MRI without corresponding elevations in serum or CSF AFP or b-hCG. One patient had abnormal tumor markers without evidence of recurrence on MRI until 6 months later.

Patient 1 presented at 12 years of age with panhypopituitarism, right hemiparesis, and elevated serum AFP and b-hCG markers secondary to a left hypothalamic and basal ganglia MMGCT. No CSF studies were available for review. After treatment, he remained in continuous remission for 5 years until he complained of anorexia, and intermittent nausea and vomiting at his scheduled follow-up. At this time, MRI showed metastatic lesions in the medulla and on the floor of fourth ventricle near the obex, with corresponding elevations in serum and CSF b-hCG. He was subsequently treated with multi-agent oral antiangiogenic (metronomic) chemotherapy [4] and craniospinal radiation with boost to the involved field. He has now been in remission for 7 years.

Table 2 Patients with tumor recurrence

Patient	1	2	3	4
Pathological diagnosis	MMGCT	Germinoma	MMGCT	NGGCT
AFP at diagnosis				
Serum (ng/mL)	18.5	wnl	Elevated*	27400
CSF (ng/mL)	Not available	wnl	Elevated*	14000
b-hCG at diagnosis				
Serum (IU/L)	52.7	wnl	>100*	wnl
CSF (IU/L)	Not available	30	>100*	wnl
Initial treatment				
Surgery	Resection	None	Resection	None
Chemotherapy	Carboplatin etoposide	Ifosfamide cisplatin etoposide	Cyclophosphamide carboplatin etoposide	Ifosfamide carboplatin etoposide
Radiation	Craniospinal irradiation with protons: 36 Gy to the craniospinal axis plus 5.4 Gy boost to the pineal gland	Whole ventricular irradiation with photons: 24 Gy to whole ventricles plus boost to 45 Gy to suprasellar region	None	Whole ventricular irradiation with photons: 50.4 Gy
MRI at recurrence	Abnormal	Abnormal	Abnormal	Normal
AFP at recurrence				
Serum (ng/mL)	wnl	wnl	wnl	10.4
CSF (ng/mL)	wnl	wnl	wnl	30
b-hCG at recurrence				
Serum (IU/L)	49	wnl	wnl	wnl
CSF (IU/L)	474	wnl	wnl	wnl

NGGCT nongerminomatous germ cell tumor, *MMGCT* mixed malignant germ cell tumor, *AFP* alpha-fetoprotein, *b-hCG* the beta subunit of human chorionic gonadotropin, *wnl* within normal limits, *MRI* magnetic resonance imaging

*Exact numerical values for patient 3 were not recorded in the chart

Patient 2 presented at 10 years of age with headaches, visual changes, and diabetes insipidus secondary to a large suprasellar germinoma. Only her CSF b-hCG was elevated. After treatment, she remained stable for 11 years until surveillance MRI showed abnormal ependymal and subependymal enhancement involving the lateral, third, and fourth ventricles. At this time, she was asymptomatic and her serum and CSF tumor markers were within normal limits. She underwent treatment with gemcitabine, paclitaxel, oxaliplatin, high dose carboplatin/thiotepa, and whole ventricular radiation therapy with a boost to the suprasellar region. She has remained stable with no evidence of disease for 1 year.

Patient 3 presented at 8 years of age with headaches, progressive diabetes insipidus, and elevated serum and CSF tumor markers secondary to a suprasellar MMGCT with periventricular dissemination. She remained in remission for 4 years after treatment, until she developed a new visual field deficit and increasing right-sided weakness. MRI showed enhancement in the left corona radiata and basal ganglia with an increase in the size of her pineal gland. However, serum and CSF AFP and b-hCG were within normal limits. Thus, a biopsy was performed and was consistent with a pure germinoma. The patient was subsequently treated with two cycles of oral etoposide, taxol, and cyclophosphamide, and craniospinal irradiation. She has remained in continuous remission since 2006.

Patient 4 presented at 25 years of age with diplopia, a frontal headache, papilledema, and elevated serum and CSF AFP secondary to an enhancing pineal region yolk sac tumor. After treatment, he was in biochemical and radiographic remission for about 1 year, until he was found to have an increase in serum AFP to 10.4 ng/mL and CSF AFP to 30 ng/mL. At this time, he was asymptomatic and had no evidence of recurrence on brain or spine MRI or testicular ultrasound. Serum AFP continued to rise with no radiographic changes until MRI 6 months later showed a new pineal lesion, consistent with tumor recurrence. At that time, the patient had complained of persistent nausea and vomiting, and serum AFP had risen to 779 ng/mL. He was

subsequently treated with chemotherapy including gemcitabine, oxaliplatin, and everolimus. About 7 months later, spine MRI revealed multifocal leptomeningeal metastasis. He underwent spinal irradiation and treatment with Lapatinib and Herceptin, but he nevertheless died of his disease.

Discussion

While Martinez et al. identified nine recurrences in 31 patients, our study only identified four recurrences in 28 patients. One possible explanation for this discrepancy is that the patients in the Martinez cohort were referred at all stages of therapy, suggesting a possible selection bias towards higher risk patients. In addition, while all nine patients in the Martinez cohort had elevated serum tumor markers at recurrence, two patients in this cohort actually had evidence of recurrence solely on MRI [3]. Only one patient's relapse was identified by tumor markers alone, and in this individual's case, treatment did not commence until MRI showed a pineal lesion. This highlights the important role of MRI imaging in not only identifying recurrences, but also in guiding treatment decisions and patient outcomes. Therefore, the results of this study suggest that both serum and CSF tumor markers and MRI imaging continue to be necessary in monitoring for recurrence of marker-positive CNS germ cell tumors after patients achieve complete biochemical and radiographic remission.

This conclusion is consistent with results found in adults with extraneural marker-positive germ cell tumors. In a retrospective study of 96 patients with first relapses of advanced germ cell tumors, Flechon et al. [5] found that 35 patients (36.4%) had normal serum tumor markers at relapse and concluded that systematic screening needs to include both serum tumor markers and total-body CT scan. Similarly, in a retrospective study of 138 patients with relapses of non-seminomatous, poor-prognosis germ cell tumors, Oechsle et al. found that 36 patients (26%) presented with isolated radiologic evidence of relapse without tumor marker elevation, and concluded that radiologic imaging is warranted in follow-up [6].

There are several important limitations to this study. This was a single institution retrospective cohort study, so we cannot comment on the absolute incidence of recurrence in patients with germ cell tumors. In addition, the sample size was limited due to the rarity of marker-positive CNS germ cell tumors. However, despite these limitations, the high incidence of patients whose tumor recurrence was detected solely by imaging supports the recommendation for comprehensive monitoring with both MRI and tumor markers.

Compliance with ethical standards

The study protocol was approved by the Institutional Review Board of NYU Langone Medical Center and was performed in accordance with institutional policies.

Conflict of interest The authors declare that they have no conflict of interest.

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