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Original Research Article

Outcomes for pediatric patients with central nervous system germ cell tumors treated with proton therapy

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ABSTRACT

Purpose: We assessed outcomes after proton therapy (PT) for central nervous system germinomas or non-germinomatous germ cell tumors (NGGCTs) in children.
Patients and methods: We identified children with germ cell tumors of the central nervous system who received proton therapy in 2006–2009 and extracted information on tumor response, treatment failures, and toxicity.
Results: Of the 20 identified patients (median age 12 years [range 3–16]), 9 had germinoma and 11 NGGCTs; 19 patients received three-dimensional conformal PT and 1 scanning-beam PT. Fourteen patients had craniospinal irradiation (CSI), 4 had ventricular irradiation that excluded the 4th ventricle, and 2 had whole-ventricle irradiation. All received involved-field boosts. At a median follow-up interval of 5.6 years (range, 0.3–8.2 years), 1 patient with germinoma had an out-of-field failure in the 4th ventricle and 2 with NGGCT died from disease progression after CSI. Rates of local control, progression-free survival, and overall survival at 5 years were 89%, 89%, and 100% for patients with germinoma; corresponding rates for NGGCTs were 82%, 82%, and 82%. The most common late toxicity (9 patients [45%]) was endocrinopathy.
Conclusions: PT for CNS germ cell tumors is associated with acceptable disease control rates and toxicity profiles.

Introduction

Central nervous system (CNS) germ cell tumors (GCTs) include two general types—germinomatous and nongerminomatous germ cell tumors (NGGCTs). Although treatment has evolved for these tumors over the past 3 decades, significant controversy remains. Radiation therapy, whether photons or protons, is a key component of treatment for either tumor type. Historically, germinomas were treated with craniospinal irradiation (CSI); however, concern for late effects has resulted in CSI being gradually replaced with whole-ventricular radiation therapy (WVRT). The addition of chemotherapy may allow further reductions in radiation field size and dose [1,2]. Given the relatively unfavorable treatment outcomes for NGGCTs, irradiation of the craniospinal axis is considered standard by many practitioners. However, new studies are exploring more limited radiation fields for this type of tumor as well [3].

Relative to photon-based radiation, particle therapy such as proton beam therapy (PBT) can improve sparing of normal tissues [4–6]. Dosimetric comparisons suggest that PBT should reduce adverse effects for both germinomas and NGGCTs. However, clinical experience with PBT for such tumors is limited. We sought to assess tumor response, treatment failures, and toxicity among children treated for CNS GCTs at The University of Texas MD Anderson Cancer Center Proton Therapy Center (Houston, TX).

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Patients and methods

Patient eligibility

Inclusion criteria were (1) a diagnosis of isolated CNS GCT based on imaging findings, tumor markers, or histologic confirmation; (2) age ⩽18 years at time of PBT; and (3) receipt of definitive PBT at the Proton Therapy Center from 2006 through 2009. All patients were enrolled in a prospective study of proton therapy for pediatric malignancies approved by the institutional review board. Of the 24 patients initially identified, 4 were excluded who were treated for recurrent disease after previous photon therapy at other facilities. The remaining 20 patients comprise the subject of this report.

Tumor classification and staging

CNS GCTs were classified according to the World Health Organization system [7,8]. Briefly, elevated levels of tumor markers in serum or cerebrospinal fluid (CSF; alpha-fetoprotein [AFP] level >10 ng/dL or institutional norm, or beta-human chorionic gonadotropin [β-HCG] level >100 mIU/mL) indicated NGGCTs. Extent of disease was evaluated with brain and spine magnetic resonance imaging [MRI] and CSF cytology. When more than 1 lesion, only the diameter of the single largest primary lesion was recorded as the baseline target lesion size. Primary lesion location was recorded as pineal, suprasellar, bifocal, or disseminated. Disseminated disease was defined by imaging or surgical evaluation (or both) as the presence of: more than 1 intracranial tumor focus (excluding bifocal disease alone); leptomeningeal spread; spinal metastases; or tumor cells in the CSF. Surgical interventions were assessed by reviewing operative and radiology reports and categorized as gross total resection (GTR; complete excision without residual disease); subtotal resection (STR; residual disease evident after resection attempt); or biopsy/shunt placement (resection not attempted).

PBT treatment planning

Treatment plans were based on computed tomography (CT) simulation with subsequent registration to volumetric MRI scans to facilitate target volume delineation. Two patients received WVRT to the entire ventricular system (right and left lateral, third, and fourth ventricles, with or without prepontine cistern); 4 received WVRT excluding the fourth ventricle (WVRT− [minus] 4th); and 14 patients received CSI encompassing the entire cranium, treated by right posterior oblique and left posterior oblique beams, and multiple spinal fields defined by posterior–anterior beams [9]. Proton beam energies ranged from 160 MeV to 200 MeV. CSI field junctions were shifted to minimize the risk of potential overlap. All patients received sequential involved-field boosts. Gross tumor volume (GTV) was defined as the tumor bed and residual disease, contoured from the pre-chemotherapy images with adjustment for shifts after surgery or chemotherapy. A 0.5–1.0-cm margin for microscopic disease was added, as determined by the treating physician or per protocol, to form the clinical tumor volume (CTV), with adjustment for anatomic boundaries. The total prescribed dose was in Gy(RBE), using a relative biologic effectiveness (RBE) value of 1.1 [10].

Diagnosis and response to treatment

Date of diagnosis was defined as the date of definitive biopsy or, if no biopsy performed, the date of the first diagnostic MRI and tumor marker measurement. Follow-up interval was calculated from date of PBT completion until last known contact. Measurable target lesions (⩾10 mm) at baseline and their subsequent response to treatment were assessed with the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines, version 1.1 [11].

Toxicity

Information on tumor- and treatment-related morbidity was extracted from multidisciplinary clinical evaluations, laboratory values, and imaging. Treatment-induced toxicity was evaluated prospectively with the Common Toxicity Criteria for Adverse Events, version 4.0. Acute toxicity was that appearing <90 days from the initiation of treatment; ⩾90 days was considered late. Endocrinopathies were defined as deficiencies confirmed by laboratory screening and requiring supplementary medication. Panhypopituitarism was diagnosed by the primary clinician as a deficiency of >3 anterior pituitary hormones. Visual field and visual acuity deficits were recorded if physical or ophthalmologic exams showed declines from baseline. Vascular toxicity was reported if symptoms correlated with vasculopathy on cranial imaging. Hypothalamic dysfunction was diagnosed by the primary clinician on the basis of several related comorbidities, such as thermoregulation dysfunction, behavior disorders, emotional lability, hyperphagia, morbid obesity, sleep disturbances, autonomic instability, and metabolic syndrome.

Statistical analysis

Patient, tumor, and treatment characteristics were evaluated with descriptive statistics. Categorical data were analyzed for nonrandom associations with Pearson's χ^2 test (Fisher's exact test used if <5 values per cell). Wilcoxon's rank-sum tests were used to compare outcomes between two independent groups with continuous data. Overall survival (OS) was calculated from date of diagnosis until date of last known contact or death. Progression-free survival (PFS) was calculated from date of completion of PBT until date of tumor progression or recurrence, last known contact, or death. The Kaplan–Meier method was used to calculate OS and PFS times. Two-sided P values of <0.05 were considered statistically significant. Analyses were performed with JMP software (version 10.0.2; SAS Institute Inc.).

Results

Patient and treatment characteristics

Twenty patients met criteria for this analysis; patient, disease, and treatment characteristics are summarized in Table 1. Median age at initial diagnosis was 12.0 years (range, 3.4–16.1 years). Seven patients (35%) initially had evidence of disseminated disease (4 with gross intracranial seeding, 4 with positive CSF cytologic findings, and 1 with infiltrating intra-axial extension >1 cm beyond tumor). No patients had initial gross seeding of the spinal canal.

Seventeen patients (85%) had surgical intervention at diagnosis. Of these, 3 had initial STR to relieve compressive symptoms before definitive chemoradiotherapy; 1 with a solitary pineal mixed NGGCT (patient 10) developed asymptomatic cyst growth during chemotherapy and underwent cyst decompression to reduce the boost volume before PBT was begun; and 1 had growing teratoma syndrome (patient 18), once during chemotherapy and once during radiation therapy, both requiring emergent debulking procedures. Second emergent surgery was a GTR followed by completion of the planned chemoradiotherapy regimen, with no evidence of recurrence at 5.2 years follow-up.

Four patients with germinoma received definitive PBT, and the other 5 received induction chemotherapy followed by PBT. Two patients (10%) were ⩽5 years old at the time of PBT. PBT was