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Original article

Use of proton therapy for re-irradiation in pediatric intracranial ependymoma

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ABSTRACT

Background and purpose: To report disease control, survival and treatment-associated toxicity with the use of proton therapy (PRT) for re-irradiation of intracranial ependymoma.
Materials and methods: Twenty patients underwent 33 PRT re-irradiation courses for recurrent or metastatic lesions between June 2004 and February 2015 at Massachusetts General Hospital.
Results: The majority of patients were female (60%), with infratentorial tumors (90%), anaplastic histology (55%), and initially received 55.8 GyRBE (52.2–59.4) involved field (IF) PRT. First failure was local (55%), distant (30%) or both (15%) at a median time of 23.9 months (9.9–98.5) from first treatment. Salvage therapy included re-resection (75%), chemotherapy (60%) and IFPRT (70%) to a median dose 50.4 GyRBE (35–55.8) in the majority of patients. The median follow-up was 37.8 months (5.5–138.0). Three year OS and PFS are 78.6% (95% CI 67.6–89.6) and 28.1% (95% CI 15.6–40.6), respectively. Longer OS was significantly associated with surgical resection of recurrent disease (HR 9.19, 95% CI 1.27–66.44, $p = 0.028$). The pattern of second failure after re-irradiation was directly related to the pattern of first failure ($p < 0.01$). Three of 14 patients (21.4%) locally re-treated experienced grade 2 radiation-associated treatment change.
Conclusions: Proton therapy appears safe and efficacious for the re-treatment of recurrent intracranial ependymoma.

Ependymoma is the third most common pediatric brain tumor, comprising approximately 8–10% of intracranial tumors diagnosed annually among children and adolescents in the Unites States [1,2]. With maximal safe resection and involved field radiotherapy, event free survival ranges from 40–85% and varies with the extent of surgical resection, tumor grade, and other prognostic features [3]. Tumor recurrence is most often located at the site of the original tumor, although neuroaxis dissemination may also be seen [3–5].

The outcome for patients with relapsed ependymoma historically has been dismal, with only 25% of patients achieving long-term disease control [4,5]. In the last decade, multiple retrospective series employing re-irradiation in the form of stereotactic radiosurgery, fractionated involved field RT, or craniospinal irradiation have established a role for re-irradiation [6–9] and demonstrated improved disease control and survival among patients receiving retreatment [10,11].

Proton therapy (PRT) is now increasingly utilized in the initial management of children with ependymoma [12]. PRT has a dosimetric advantage over conventional photon therapy which allows for equivalent target volume coverage with reduced dose delivered to normal tissues, which is expected to reduce the long-term morbidity associated with cranial radiotherapy is young patients [13]. Likewise, PRT may be advantageous for cases of re-irradiation by reducing the cumulative dose received to normal tissues with subsequent treatments. However, there have been concerns about the toxicity of high dose PRT when treating targets adjacent to the brainstem [14], and data demonstrating the safety of proton therapy re-irradiation are lacking. Herein, we report the first study of clinical outcomes among patients treated with proton therapy re-irradiation for intracranial ependymoma.

Materials and methods

Patient selection

Following institutional review board approval, the pediatric database at Massachusetts General Hospital was searched to identify children with a diagnosis of ependymoma who had received

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multiple courses of radiotherapy (RT). Twenty-five children treated from 1996 to 2013 were identified. Five patients were excluded because of spinal ependymoma ($n = 3$), incorrect pathologic diagnosis ($n = 1$) or no available records for review ($n = 1$).

Treatment

All patients were initially treated with maximal safe resection followed by involved field RT with or without the use of pre-RT chemotherapy. Details of initial PRT delivery have previously been described [15]. After definitive treatment, patients were followed with routine physical exams and serial magnetic resonance imaging (MRI). Tumor recurrence was diagnosed by MRI defined new or progressive enhancing tumor within the brain or spine. Additional work-up with CSF analysis and full MRI neuroaxis imaging to characterize the extent of disease was performed. Patients were presented at a multi-disciplinary pediatric neuro-oncology tumor board and maximal safe resection was recommended whenever feasible. Sequential or concurrent chemotherapy was also used in the majority of cases and included etoposide alone or in combination with other agents such as cyclophosphamide, vincristine and/or carboplatin in most cases.

All patients received re-irradiation to one or more sites of recurrent disease. Re-irradiation consisted of conventionally fractionated involved field PRT in the majority of cases. Craniospinal irradiation (CSI), hypofractionated or single fraction radiosurgery, or iodine-131 brachytherapy were used in select cases at the discretion of the treating radiation oncologist in light of the patient's unique clinical situation and after discussion with the family. Radiosurgery was primarily reserved for the setting of repeated tumor progression following re-irradiation or among patients with multiple distant metastases.

Prior to treatment planning and daily treatment, patients received IV sedation under the care of a pediatric anesthesiologist [16]. Patients underwent a high-resolution treatment planning MRI with and without IV contrast and CT simulation with IV contrast in the supine position. Heterogeneity corrections were used for treatment planning. A custom Aquaplast (Qfix, Avondale, PA) mask and neck cradle was used for immobilization. The gross tumor volume (GTV) and/or recurrent tumor bed were defined on MRI co-registered to the CT scan. The clinical tumor volume (CTV) for patients treated with involved field PRT consisted of the GTV and/or recurrent tumor bed, when present according to the surgical resection status, with an additional 3–5 mm margin. For single fraction or hypofractionated proton radiosurgery, the GTV was expanded by 0–1 mm margin to create the CTV. CSI was prescribed using a modified technique as described by Merchant et al. to limit the previously irradiated portion of the upper cervical spine and brainstem to 16.2 Gy [6]. When used, I-131 brachytherapy seeds were placed in the periphery of the tumor bed on the day of re-resection.

PRT was delivered with three-dimensional conformal (3DC) double scatter proton technique and dose was prescribed in gray relative biological equivalents (Gy(RBE)) using the RBE value of 1.1. At the time of both initial and re-irradiation, PRT was delivered with every effort to minimize dose to the brainstem and spinal cord given that these are dose limiting structures for the treatment of posterior fossa ependymoma and typically has significant dose overlap in local retreatment. In the initial PRT course, the upper cervical cord was typically restricted to 50.4 Gy, or 52 Gy in the setting of adjacent GTV, and boost fields were used to bring the CTV above the foramen magnum to full prescription dose. At the time of re-irradiation, the upper cervical spinal cord was generally allowed to receive up to an additional 50% of the previous dose received when the interval between RT treatments was $\geqslant 1$ year. The optic nerves and chiasm were constrained to a maximum dose of 50.4–54 Gy when located near the initial or re-treatment irradiation field.

After re-treatment, patients were recommended to undergo routine follow-up including physical exam and MRI surveillance imaging of the brain and/or spine every 3 months for the first 1–2 years and every 4–6 months thereafter, or earlier in the event of clinical symptoms. If the patient has no known disease in the spine, surveillance screening MRI of the spine was recommended at alternating follow-up examinations. Follow-up MRIs were reviewed at a multi-disciplinary conference in evaluation for disease progression and radiation associated treatment change.

Outcome variables

The primary outcome variables include overall survival (OS), progression free survival (PFS), patterns of failure, and treatment related toxicity. OS was defined from the time of first disease progression until death from any cause or was censored at last follow-up. PFS was defined from the time of re-irradiation until subsequent disease progression or was censored at last follow-up. The location of tumor recurrence was categorized as local if occurring at the site of the original tumor and within the previous high dose radiation field, distant if occurring within the brain ($distant_B$) or spine ($distant_S$) at sites distant from the original tumor, or local plus distant if tumor progression was found to be local and distant simultaneously. Radiographic post-treatment imaging changes associated with clinical symptoms (grade $\geqslant 2$) and considered at least possibly related to re-irradiation therapy were recorded as re-irradiation associated toxicity. Treatment toxicity was graded according to the CTCAE version 4.03.

To evaluate cumulative dosimetry for normal tissues in patients locally re-treated, the DICOM dose files for each RT plan were fused through rigid registration using Mim (MIM Software Inc., Cleveland, OH) when available, and cumulative dose–volume statistics for the brainstem, spinal cord and normal brain are presented. Maximum dose represents the maximum point dose for that structure. The brainstem and spinal cord were drawn by the treating physician such that the inferior border of the brainstem and the superior border of the cervical spinal cord are located at the opening of the foramen magnum. A sum RT dose plan could not be created if one RT dose file was unavailable due to early time period of RT ($n = 1$), initial RT being performed at an outside institution ($n = 2$), or brachytherapy use and lack of post-implant dosimetry ($n = 1$).

Statistical analysis

Demographic, tumor and treatment characteristics are described for the patient population. OS and PFS are calculated by the Kaplan–Meier method. The effect of covariables, such as patient gender, histology, surgical resection at the time of first relapse, use of salvage chemotherapy, failure pattern (local vs. distant), re-irradiation dose, re-irradiation timing (up front vs. delayed after chemotherapy or second progression), and re-irradiation technique (IFRT vs. SRS vs. CSI) were analyzed for their relationship to the outcome variables using Cox-regression analysis. Statistical analyses were performed using SPSS software version 21 (IBM, Armonk, NY).

Results

Patient population

The patient population includes 20 patients initially treated for intracranial ependymoma between 1996 and 2012, who underwent 33 courses of re-irradiation for recurrent or metastatic

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