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Clinical Investigation: Central Nervous System Tumor

Patterns of Failure After Proton Therapy in Medulloblastoma: Linear Energy Transfer Distributions and Relative Biological Effectiveness Associations for Relapses

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Summary

The pattern of failure associated with medulloblastoma patients treated with proton radiation therapy is similar to the pattern of failure in patients treated with photon radiation therapy. Monte Carlo-calculated linear energy transfer (LET) distributions were performed, and demonstrated no clear correlation between recurrence and low LET.

Purpose: The pattern of failure in medulloblastoma patients treated with proton radiation therapy is unknown. For this increasingly used modality, it is important to ensure that outcomes are comparable to those in modern photon series. It has been suggested this pattern may differ from photons because of variations in linear energy transfer (LET) and relative biological effectiveness (RBE). In addition, the use of matching fields for delivery of craniospinal irradiation (CSI) may influence patterns of relapse. Here we report the patterns of failure after the use of protons, compare it to that in the available photon literature, and determine the LET and RBE values in areas of recurrence.

Methods and Materials: Retrospective review of patients with medulloblastoma treated with proton radiation therapy at Massachusetts General Hospital (MGH) between 2002 and 2011. We documented the locations of first relapse. Discrete failures were contoured on the original planning computed tomography scan. Monte Carlo calculation methods were used to estimate the proton LET distribution. Models were used to estimate RBE values based on the LET distributions.

Results: A total of 109 patients were followed for a median of 38.8 months (range, 1.4-119.2 months). Of the patients, 16 experienced relapse. Relapse involved the supratentorial compartment (n = 8), spinal compartment (n = 11), and posterior fossa (n = 5). Eleven failures were isolated to a single compartment; 6 failures in the spine, 4 failures in the supratentorium, and 1 failure in the posterior fossa. The remaining patients had multiple sites of disease. One isolated spinal failure occurred at the spinal junction of 2 fields. None of the 70 patients treated with an involved-field-only boost failed in the posterior fossa outside of the tumor bed. We found no correlation between Monte Carlo-calculated LET distribution and regions of recurrence.

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Conclusions: The most common site of failure in patients treated with protons for medulloblastoma was outside of the posterior fossa. The most common site for isolated local failure was the spine. We recommend consideration of spinal imaging in follow-up and careful attention to dose distribution in the spinal junction regions. Development of techniques that do not require field matching may be of benefit. We did not identify a direct correlation between lower LET values and recurrence in medulloblastoma patients treated with proton therapy. Patterns of failure do not appear to differ from those in patients treated with photon therapy.

Introduction

Medulloblastoma is a pediatric brain tumor that arises in the posterior fossa, and has a high propensity for spread to the brain and spine through the cerebrospinal fluid (CSF). Standard treatment for children over the age of 3 years includes maximal safe resection followed by radiation to the entire neuro-axis. Patients are classified as standard- and high-risk depending on age, extent of residual disease, and presence of disseminated disease at presentation. High-risk patients undergo craniospinal irradiation (CSI) at a dose of 36 Gy, whereas standard-risk patients receive CSI at a dose of 23.4 Gy or 18 Gy on trial (1, 2).

Medulloblastoma is a highly radiosensitive disease. As a result, the technical quality of radiation delivery significantly influences the risk of recurrence (3-5). Carrie et al found that patients experience a stepwise increase in the risk of relapse according to the number of targeting deviations (3). These failures are ominous, as recurrent medulloblastoma has a dismal prognosis; the vast majority of patients do not survive. Frequent review of institutional patterns of failure is therefore an important quality assurance measure.

At our institution, CSI proton radiation therapy (PRT) has been used to treat patients with medulloblastoma since 2002. PRT delivers significantly less radiation to healthy tissue than conventional photon treatment, in large part because of the absence of exit dose. However, the pattern of failure associated with the relatively new application of this technique is unknown. It is important to ensure that patterns of failure do not differ because of steeper dose gradients in this more precise modality. It has also been speculated that the risk of recurrence may be slightly increased in the areas of field matching for any modality (photons or protons). Although the cold spot introduced by this technique is greater with photons than with protons, there is still potential for increased failures at match sites for both techniques. We examined all spinal recurrences to see if any occurred at the match sites for fields. In addition, Jones et al have raised concerns of an elevated risk of peripheral or subdural brain recurrences due to differences in the homogeneity of photon versus proton treatment plans. Whereas photon plans generally deliver a dose that is higher than the prescription dose in the peripheral areas (~1.4 cm depth for 6-MV photons), proton plans deliver a relatively homogenous physical dose. Finally, Jones et al also speculate on the effect of the high linear energy transfer (LET) nature of PRT compared to the low LET nature of photon radiation therapy (RT). While this is an area that requires further research, variations in LET distribution may influence RBE-weighted dose and thus the risk of tumor recurrence, particularly for rapidly dividing cells with a high α/β value (6).

In this study, we review the location of recurrences in the largest existing cohort of patients with medulloblastoma who have received PRT. In addition, to assess the possible influence of LET variation on the risk of treatment failure, we calculated the proton LET at the site of recurrences and compared these values to the LET in the whole target volume.

Methods and Materials

Patients and clinical data

Between May 2002 and December 2011, a total of 109 pediatric patients with medulloblastoma were treated with CSI PRT at the Massachusetts General Hospital (MGH). We excluded any patients who underwent involved-field-only or posterior fossa-only irradiation. Clinical data obtained from a retrospective review of charts included the patient's sex, ethnicity, date of birth, date of pathological diagnosis, histological grade (based on review by MGH pathologists), risk status (standard vs high; high risk was defined as residual disease greater than 1.5 cm^2, presence of metastatic disease at presentation, and age less than 3 years), dates of surgical procedures, extent of surgical resection, radiation dose, field arrangement, dates of start and completion of radiation treatment, location of relapse, date of relapse, treatment of relapse, disease status at last follow-up, and date of last follow-up.

Radiation therapy

Computed tomography (CT)-based 3-dimensional planning was used. All patients received passively scattered protons with brass apertures and Lucite blocks custom-made for each field. All patients received CSI in the prone position. The clinical target volume (CTV) for the whole brain followed conventional anatomical definition of this structure. The CTV for the spine included the thecal sac (defined as dura surrounding the spinal cord, cauda equine, and cerebrospinal fluid) and excluded bony anatomy. Exiting nerves were included only until their emergence from the spinal foramina. Brain and spine fields were matched in a similar manner to the technique used for photon CSI, using a feathered junction that alternated every day across 3 locations. Fields were matched anterior to the spinal cord, introducing an area slightly colder than prescription dose but less cold than with photon techniques because of decreased beam divergence at this depth for proton beams. Patients received either an involved field boost or whole posterior fossa boost. Sites of metastatic disease were also boosted. Most patients received the boost portion of this treatment in the supine position. Anesthesia was administered for most children for CSI (typically aged <11 years) and for some children for the boost portion of treatment (typically aged <8 years).

LET and RBE-Weighted dose distribution

We calculated the LET distribution for 9 discrete recurrences. These patients were selected because they experienced discrete