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Tailor-made treatment combined with proton beam therapy for children with genitourinary/pelvic rhabdomyosarcoma

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ABSTRACT

Background: Rhabdomyosarcoma (RMS) is one of the most common soft tissue sarcomas among children. Patients who developed genitourinary/pelvic rhabdomyosarcoma (GU/P-RMS) have a higher complication ratio and relatively poorer event free survival, with local therapy being very important. While proton beam therapy (PBT) is expected to reduce co-morbidity, especially for children, this lacks firm evidence and analysis. We analyzed GU/P-RMS children who had undergone multimodal therapy combined with PBT at a single institution.

Method: We retrospectively reviewed charts of children with GU/P-RMS treated from January 2007 to May 2013 at the University of Tsukuba Hospital who had undergone multimodal therapy with PBT.

Results: There were 5 children and their median age at diagnosis was 2.8 years (0.6–4.4 years). Primary sites were the bladder (2) and the prostate (3). All received neo-adjuvant chemotherapy and 3 underwent chemotherapy during PBT (Group Cx). All patients of Group Cx developed leukocytopenia (WBC <1000/μL). The median dose of PBT was 47.7 GyE (41.4–50.4 GyE). All patients survived by their last hospital visit (median, 36 months).

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Conclusions: We analyzed multimodal treatment combined with PBT applied for GU/P-RMS. PBT was well tolerated and could be a plausible choice instead of photon therapy for this population.

1. Background

Rhabdomyosarcoma (RMS) is one of the most common soft tissue sarcomas among children.[1] Cure rates for RMS have reached up to 60–80% with multimodal treatment consisting of chemotherapy, surgery and radiotherapy.[1–3] While patients with genitourinary/pelvic rhabdomyosarcoma (GU/P-RMS) account for around 25% of all patients with RMS, they have a higher complication ratio and relatively poorer event free survival.[4–6] Local control, particularly complete surgical resection and adequate radiotherapy, is very important among this population.[7,8] While photon therapy has been used for this population for decades, adverse effects around the genitourinary pelvic regions are of much concern due to the closely-packed vital organs such as the colon, hip joints, ovary and urinary tract.

Proton beam therapy (PBT) is a novel method of particle radiotherapy that is optimized to spare normal organs beyond the treatment target volume due to its sharp and narrow dose peak,[9] but lacks firm evidence as a treatment of malignancy, particularly among children.[10] Cotter et al. reported that PBT for prostate/bladder RMS spared doses to the normal structure of reproduction or skeleton and provided doses equally to target volumes compared with volumes generated for Intensity Modulated Radiation Therapy (IMRT).[11]

Since the feasibility of PBT concurrent with multimodal treatment had not been well explored, particularly for children, we analyzed feasibility and early outcome among GU/P-RMS children who had undergone multimodal treatment with chemotherapy, surgery and PBT.

2. Method

2.1. Patients

Included in our study were pathologically proven GU/P-RMS patients treated with multimodal treatment, including multimodal chemotherapy and surgery combined with PBT at the University of Tsukuba Hospital between January 2007 and May 2013.

2.2. Chart review

Charts were reviewed retrospectively. Neo-adjuvant chemotherapy, chemotherapy during PBT and high-dose chemotherapy with autologous hematopoietic transplantation were reviewed. Adverse events during PBT, including the lowest white blood cell count, blood transfusions, infections, cessation of PBT, or any other events related to multimodal therapy combined with PBT were assessed. Patients' conditions and time at last follow-up were recorded as patients or their primary physicians contacted our institution.

2.3. Proton beam therapy

Before treatment, CT images for PBT planning were obtained at intervals of 2–5 mm in the treatment position. The interval was determined based on the patient's age, height and treatment site. Proton beams from 155 to 250 MeV generated through a linear accelerator and synchrotron were spread out and shaped with ridge filters, double-scattering sheets, multicollimators, and a custom-made bolus to ensure that the beams conformed to the treatment planning data. The clinical target volume was defined as the area of residual tumor. The margin for clinical target volume was 10–15 mm at first. After 41.4–45 GyE, clinical target volume was reduced to the area of macroscopically residual tumor. The margin for clinical target volume was then reduced to 5–10 mm. The dose for the whole bladder was limited to 41.4 GyE. After 41.4 GyE, we minimized the irradiated volume of the small bowel. The treatment was provided 5 days a week. The photon equivalent dose (GyE) was defined as the physical dose (Gy) × relative biological effectiveness of the proton beam assigned the value of 1.1. Before each treatment, correct placement of the patient relative to the radiation field was confirmed fluoroscopically for all cases. Ultrasonography was conducted to confirm the bladder volume for selected sedated cases. A sedative was administered for 4 patients aged 1.3–3.7 years old for planning CT and treatment. Patients underwent physical examination every day and laboratory tests were conducted more than once a week.

3. Results

We reviewed charts of children who had been treated at our hospital. There were 5 patients with GU/P-RMS who had undergone multimodal treatment combined with PBT between January 2007 and May 2013. Patient characteristics are shown in Table 1 and treatment summary and patient outcome are in Table 2. The median age at diagnosis was 2.8 (0.6–4.4) years and the median age at PBT was 2.9 (1.3–6.4) years. There were 1 female and 4 males. The tumor was located in the bladder in 2 patients and in the prostate in 3 patients. All were diagnosed as having embryonal RMS, except for one patient whose histologic subtype was unknown.

All patients underwent VAC treatment, which consisted of Vincristine, Actinomycine-D and Cyclophosphamide according to the intergroup rhabdomyosarcoma study-IV with minor institutional changes, as their first line therapy.[3] Then treatment protocol was changed for Cases 1, 2, 4 and 5 due to refractory clinical course.