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Long-term follow-up after proton beam therapy for pediatric tumors: a Japanese national survey

Masashi Mizumoto,[1] Shigeyuki Murayama,[2] Tetsuo Akimoto,[3] Yusuke Demizu,[4] Takashi Fukushima,[5] Yuji Ishida,[6] Yoshiko Oshiro,[1] Haruko Numajiri,[1] Hiroshi Fuji,[7] Toshiyuki Okumura,[1] Hiroki Shirato[8] and Hideyuki Sakurai[1]

[1]Department of Radiation Oncology, University of Tsukuba, Tsukuba; [2]Division of Proton Therapy, Shizuoka Cancer Center Hospital, Nagaizumi, Shizuoka; [3]Division of Radiation Oncology and Particle Therapy, National Cancer Center Hospital East, Kashiwa, Chiba; [4]Department of Radiology, Hyogo Ion Beam Medical Center, Tatsuno, Hyogo; [5]Department of Child Health, University of Tsukuba, Tsukuba; [6]Division of Pediatrics, Shizuoka Cancer Center Hospital, Nagaizumi, Shizuoka; [7]National Center for Child Health and Development, Tokyo; [8]Department of Radiation Oncology, Hokkaido University Hospital, Sapporo, Japan

Key words

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Correspondence

Hideyuki Sakurai, M.D., Ph.D., Proton Medical Research Center, University of Tsukuba, 1-1-1 Tennoudai, Tsukuba, Ibaraki, 305-8575 Japan.
Tel: +81-29-853-7100; Fax: +81-29-853-7102;
E-mail: hsakurai@pmrc.tsukuba.ac.jp

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Proton beam therapy (PBT) is a potential new alternative to treatment with photon radiotherapy that may reduce the risk of late toxicity and secondary cancer, especially for pediatric tumors. The goal of this study was to evaluate the long-term benefits of PBT in cancer survivors. A retrospective observational study of pediatric patients who received PBT was performed at four institutions in Japan. Of 343 patients, 62 were followed up for 5 or more years. These patients included 40 males and 22 females, and had a median age of 10 years (range: 0–19 years) at the time of treatment. The irradiation dose ranged from 10.8 to 81.2 GyE (median: 50.4 GyE). The median follow-up period was 8.1 years (5.0–31.2 years). The 5-, 10- and 20-year rates for grade 2 or higher late toxicities were 18%, 35% and 45%, respectively, and those for grade 3 or higher late toxicities were 6%, 17% and 17% respectively. Univariate analysis showed that the irradiated site (head and neck, brain) was significantly associated with late toxicities. No malignant secondary tumors occurred within the irradiated field. The 10- and 20-year cumulative rates for all secondary tumors, malignant secondary tumors, and malignant nonhematologic secondary tumors were 8% and 16%, 5% and 13%, and 3% and 11%, respectively. Our data indicate that PBT has the potential to reduce the risk of late mortality and secondary malignancy. Longer follow-up is needed to confirm the benefits of PBT for pediatric tumors.

Recent progress in treatment of pediatric tumors has improved survival and almost 70% of patients can now be cured.[1] However, late toxicities of radiotherapy may occur in long-term survivors, and reduction of quality of life due to growth and development retardation and secondary cancer is a significant problem for pediatric patients.[2,3] Armstrong *et al.*[4] showed that mortality due to the original malignancy begins to plateau beyond 20 years, while death from non-recurrence causes increases. Between 15 and 30 years, the cumulative mortality attributable to the primary disease only increases from 6.3% to 7.8%, while that due to non-recurrence causes increases from 2.0% to 7.0%. Schoot *et al.*[5] found that 77% of long term survivors (median follow-up 10.5 years, $n = 31$) after radiotherapy for pediatric head and neck tumor experience late toxicities of grade 3 or 4; Ducassou *et al.*[6] showed that 23% of survivors for 5 or more years ($n = 22$) after radiotherapy for neuroblastoma experienced late toxicities of grade 3 or more; and Perwein *et al.*[7] found that 50% of long-term survivors (median follow-up 7.4 years, $n = 16$) after radiotherapy for neuroblastoma experienced late toxicity of grade 3 or more.

Proton beam therapy (PBT) is likely to have reduced risks of late toxicity and secondary cancer, and Sethi *et al.*[8] found a 10-year cumulative incidence of 0% for all in-field secondary malignancies after PBT. However, long-term follow-up is difficult because of tumor recurrence or cases lost in follow-up, and this results in limited information on late toxicity after radiotherapy. This is particularly true for PBT because of the relatively short history of the technique. Here, we evaluated late toxicity in long-term follow-up after PBT in a multicenter study in Japan.

All data were published in a previous report.[9] The current manuscript examines late toxicity in long-term survivors.

Materials and Methods

A retrospective observational study in pediatric patients who received PBT was performed at four institutions in Japan. Institutional Review Boards approved the study at all institutes. All 343 patients aged <20 years old at the time of receiving PBT at these sites from January 1983 to August 2014 were initially enrolled. Previously, we report the overview of this retrospective observational study.[9] In the report we mainly analyzed overall survival and late toxicities of all patients. The study showed that main purpose of PBT was to

reduce the risk of late toxicity and secondary cancer. We consider that long-term follow-up is an essential condition to evaluate the risk of late toxicity and secondary cancer. However, the study included a number of short follow-up patients. So here we perform the secondary analysis focused on long-term survivors.

Of these patients, 62 were followed-up for 5 or more years. There were 40 males and 22 females, and the median age at treatment was 10 years old (range: 0–19). The irradiated site were head and neck (n = 24), brain (n = 22), body trunk (n = 9) and others (n = 7). The irradiation dose ranged from 10.8 to 81.2 GyE (median: 50.4 GyE). The median follow-up period in the 62 patients was 8.1 years (range: 5.0–31.2 years).

Statistical analysis. Rates for late toxicities and secondary tumors were calculated using the Kaplan–Meier method. A log-rank test was used to examine differences for age, gender, irradiated site, irradiation dose, and irradiation volume. All analyses were performed with SPSS v. 11.0 (SPSS Inc., Chicago, IL, USA). Toxicities were graded using the Common Terminology Criteria for Adverse Events ver. 3.0.

Results

At the final follow-up, 22 of 62 patients had late toxicities of grade 2 or more, with a median time from the first day of PBT to the day of diagnosis of the late toxicity of 4.5 years (range: 0.8–28.2 years). Four of the 22 patients had multiple late toxicities of grade 2 or more, and 6 had deformities of grade 2 or more, with all deformities occurring in patients irradiated in the head and neck or brain. The 5-, 10- and 20-year rates of late toxicities of grade 2 or more were 18% (95% CI 8–27%), 35% (95% CI 22–49%) and 45% (95% CI 24–65%) respectively, and those for late toxicities of grade 3 or more were 6% (95% CI 0–13%), 17% (95% CI 5–28%) and 17% (95% CI 5–28%), respectively (Fig. 1).

Univariate analysis showed that the irradiated site (head and neck, brain) was significantly associated with late toxicity (Fig. 2). The 5- and 10-year late toxicity rates after head and neck or brain irradiation were 22% (95% CI 11–33%) and 42% (95% CI 27–57%) at grade 2 or more and 8% (95% CI 0–16%) and 20% (95% CI 7–32%) at grade 3 or more. For patients who did not have a head and neck or brain tumor, no late toxicity of grade 2 or more occurred within 20 years. Age (>10 or ≤10 years old), gender, irradiation dose (>40 or ≤40 GyE) and irradiation volumes (<100 or ≤100 mL) were not significantly associated with late toxicity. Multivariate analysis showed no significant difference in late toxicities for any factors. Six patients had late toxicity after the age of 20. And 11 of 30 late toxicities occurred after the age of 20. Figure 3 presents the relationship between onset age and Grade of late toxicity.

As previously reported several patients had a secondary tumor.[9] In this report, four of 62 patients had a secondary tumor after PBT, including three malignant tumors (osteosarcoma, thyroid cancer and acute myelocytic leukemia (AML)) and one case of pituitary adenoma. All malignant secondary tumors occurred outside the irradiated field, with only pituitary adenoma occurring within the irradiated field. The 10- and 20-year cumulative incidences for all secondary tumors (osteosarcoma, thyroid cancer, AML and pituitary adenoma), malignant secondary tumors (osteosarcoma, thyroid cancer and AML) and malignant solid secondary tumors (osteosarcoma and thyroid cancer) were 8% (95% CI 0–18%) and 16% (95% CI 0–33%), 5% (95% CI 0–11%) and 13% (95% CI 0–29%), and 3% (95% CI 0–9%) and 11%(95% CI 0–27%), respectively. The incidences of all malignant secondary cancers and in-field malignant secondary cancers are shown in Figure 4.

Discussion

Comprehensive data from this study have been reported elsewhere, but this previous analysis included cases with a variety of tumors and a short follow-up time.[9] The advantages of PBT for pediatric patients are likely to be fewer late adverse events and a reduced risk secondary malignancy, since comparisons of dose distribution between PBT and photon radiotherapy indicate a decreased dose to normal tissue in PBT.[10,11] Late toxicity has been found in long-term follow-up of pediatric patients after photon radiotherapy. In an analysis of 17 patients who survived for at least 5 years (median 20 years) after radiotherapy for head and neck pediatric rhabdomyosarcoma, Paulino *et al.* found late effects of treatment in 11 cases with facial growth retardation, nine with neuroendocrine dysfunction, nine with visual/orbital problems, seven

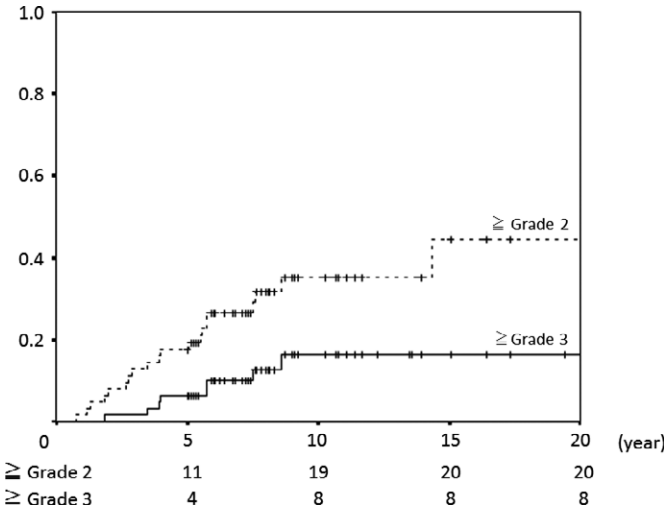

Fig. 1. Incidence of late adverse events in all patients.

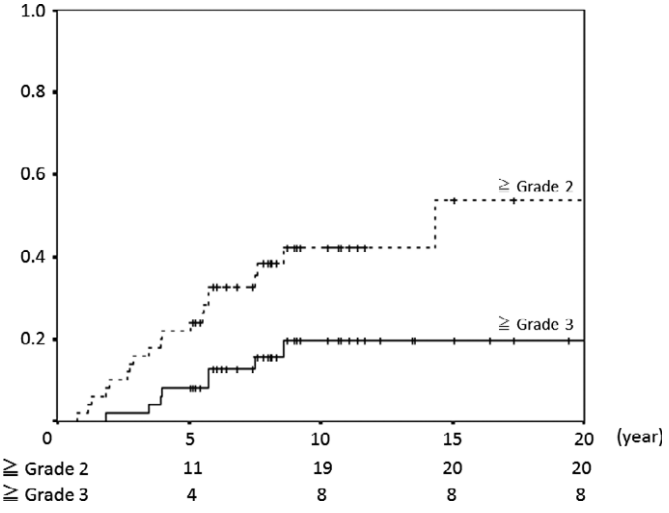

Fig. 2. Incidence of late adverse events in cases of head and neck or brain tumor.

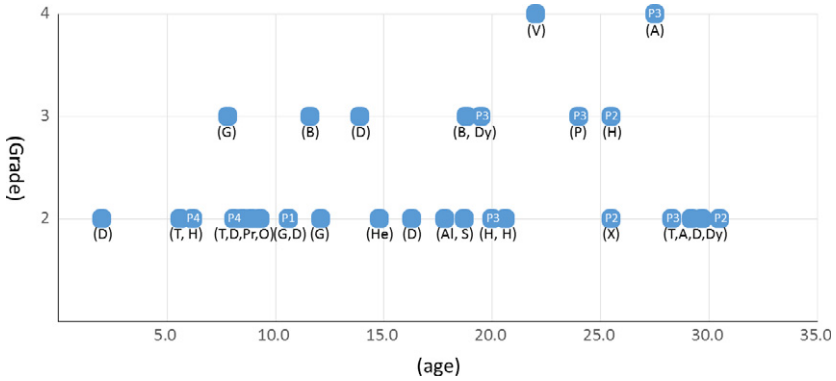

Fig. 3. Figure between brackets indicates kind of late toxicity. A, Angiostenosis; Al, Alopecia; B, Brain injury; D, Deformity; Dy, Dysphagia; G, Growth hormone deficiency; H, Hearing impairment; He, Headache; O, Otitis media; P, Pneumonitis; Pr, Precocious puberty; S, Seizure; T, Thyroid dysfunction; V, Visual impairment; X, Xerostomia. Four patients (P1, P2, P3, P4) had multiple late toxicities.

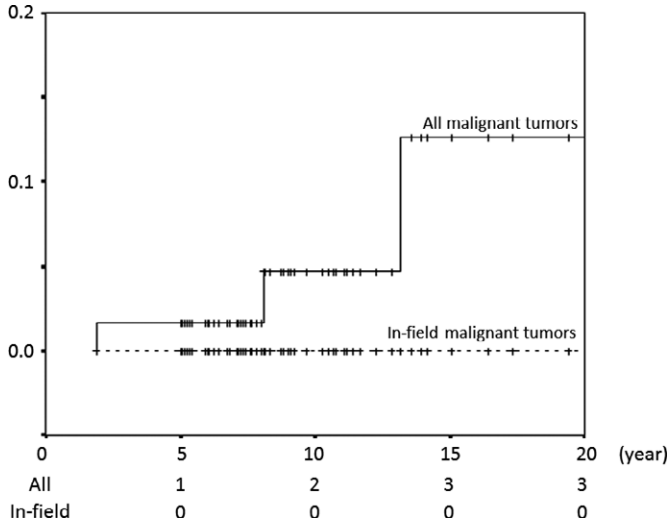

Fig. 4. Incidences of all malignant secondary cancers and in-field malignant secondary cancers.

with dental abnormalities, and six with hearing loss.[12] The severity was unclear, but these data show a high rate of late toxicity and similar late toxicities to those found in our patients (deformation, neuroendocrine dysfunction, and hearing impairment).

Our data showed 10-year late toxicity rates after PBT for head and neck cancer of 42% at grade 2 or more and 20% at grade 3 or more, respectively. Based on a simple comparison with the above rates for photon radiotherapy, PBT appears to reduce the risk of late toxicity. In a preliminary study of PBT for pediatric rhabdomyosarcoma, Ladra *et al.* found rates of late toxicity of 28% for grade 2 and 7% for grade 3, but it should be noted that the cases included truncal site tumors and the follow-up period was relatively short.[13] In patients with parameningeal rhabdomyosarcoma, Childs *et al.*[14] found that PBT in a relatively small group of 10 patients reduced long-term toxicities compared with a historical control group treated with photon radiotherapy. At this time, more than a third of late toxicities occurred age 20 or older. This result indicates that a routine follow-up is needed in adult life to evaluate the precise late effect of PBT.

There is also limited information on secondary malignancy after PBT.[8] Some reports have shown that PBT can reduce the risk of secondary malignancy,[15,16] and recently Sethi *et al.* showed that the 10-year cumulative incidences of secondary tumors in survivors of retinoblastoma were significantly lower in those treated with PBT compared to photon therapy for both in-field (0% *vs* 14%) and all (5% *vs* 14%) secondary malignancies. In our analysis, the 10-year cumulative rates of in-field and all secondary malignancies were 0% and 5%, respectively, which are exactly the same as those in Sethi *et al.* Stringent comparison with photon radiotherapy is difficult because of variation in patient backgrounds, but these data suggest that PBT has a lower risk of radiotherapy-induced malignancy.

The risk of subsequent malignancy continues to increase after 40 years old,[17] and at age 55 the cumulative incidence of new malignancy reaches 16.3%. This shows that radiotherapy is a risk factor for late mortality and subsequent malignancy. Improved outcomes of pediatric tumors requires increased long-term survival after radiotherapy, and our data indicate that PBT has the potential to reduce the risk of late mortality and subsequent malignancy. However, the follow-up period was still short and the number of patients was insufficient for comparison with photon historical data, in particular. Longer follow-up is needed to confirm these advantages of PBT for pediatric tumors.

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