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Proton beam therapy with concurrent chemotherapy is feasible in children with newly diagnosed rhabdomyosarcoma

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ABSTRACT

Background: The optimal treatment for rhabdomyosarcoma (RMS) requires multidisciplinary treatment with chemotherapy, surgery, and radiotherapy. Surgery and radiotherapy are integral to the local control (LC) of RMS. However, postsurgical and radiotherapy-related complications could develop according to the local therapy and tumor location. In this study, we conducted a single-center analysis of the outcomes and toxicity of multidisciplinary treatment using proton beam therapy (PBT) for pediatric RMS.

Materials and methods: RMS patients aged younger than 20 years whose RMS was newly diagnosed and who underwent PBT at University of Tsukuba Hospital (UTH) during the period from 2009 to 2019 were enrolled in this study. The patients' clinical information was collected by retrospective medical record review.

Results: Forty-eight patients were included. The 3-year progression-free survival (PFS) and overall survival (OS) rates of all the patients were 68.8% and 94.2%, respectively. The 3-year PFS rates achieved with radical resection, conservative resection, and biopsy only were 65.3%, 83.3%, and 67.6%, respectively ($p = 0.721$). The 3-year LC rates achieved with radical resection, conservative resection, and biopsy only were 90.9%, 83.3%, and 72.9%, respectively ($p = 0.548$). Grade 3 or higher mucositis/dermatitis occurred in 14 patients. Although the days of opioid use due to mucositis/dermatitis during the chemotherapy with PBT were longer than those during the chemotherapy without PBT [6.1 and 1.6 (mean), respectively, $p = 0.001$], the frequencies of fever and elevation of C-reactive protein were equivalent.

Conclusions: Multidisciplinary therapy containing PBT was feasible and provided a relatively fair 3-year PFS, even in children with newly diagnosed RMS without severe toxicity.

Key words: rhabdomyosarcoma; proton beam therapy; toxicity; progression-free survival; local control

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Introduction

The treatment of rhabdomyosarcoma (RMS) consists of a multidisciplinary approach including surgery, radiotherapy, and intensive neoadjuvant/adjuvant chemotherapy. Multiagent chemotherapy comprising vincristine, dactinomycin, and cyclophosphamide (VAC) is widely used for RMS. Local treatment of surgical achievement and radiotherapy are two of the main survival prognostic factors for RMS. Total tumor removal is always the goal but in some cases is not possible owing to postoperative dysfunction of the vital organs. In particular, an initial radical surgery usually could not be achieved for parameningeal tumors of the head and neck or for genitourinary tumors of the bladder/prostate [1].

The progression-free survival (PFS) rates of RMS are 90%, 60–70%, and 20–30% for low-, intermediate-, and high-risk patients, respectively, whilst acute and long-term therapeutic toxicities can be substantial [2–4]. Long-term comorbidities such as organ dysfunction, retardation of growth and development, and secondary cancer are also a serious problem for childhood cancer survivors [5]. Particle therapy, including proton beam therapy (PBT), has unique physical properties that can reduce/eliminate the unnecessary radiation doses to the surrounding normal tissues, which resulted in improvement of early and late treatment-induced toxicities [6]. Although, Mizumoto et al. [7] reported that radiation-induced toxicities occurred in 16% of pediatric patients during PBT, the evaluation of toxicity due to PBT only is very difficult. Radiotherapy was mostly conducted with chemotherapy in pediatric malignancies, and concurrent chemotherapy influences the occurrence and severity of treatment-related toxicities [8]. Sufficient data on the feasibility of multimodal therapy containing PBT for pediatric RMS are required, and to the best of our knowledge, comparison of the toxicities among multimodal treatments with/without PBT has not been previously assessed.

Since April 2016, PBT for childhood malignant solid tumors has been covered in Japan by the public health insurance system, and the number of patients who receive PBT is increasing. We conducted a retrospective cohort study to assess the feasibility of multidisciplinary therapy including PBT as well as the tumor prognosis in children with newly diagnosed RMS.

Materials and methods

Forty-eight consecutive patients aged younger than 20 years, whose RMS was newly diagnosed pathologically and who underwent PBT at UTH during the period from 2009 to 2019, were included. The patients' clinical information was collected by retrospective medical record review and included the chemotherapy regimen, surgical information, PBT plan, therapy-related toxicity, and disease status. The patients' current condition and additional clinical information were collected from the local physicians or by mailing/telephone interview with the patients/families.

Toxicities were evaluated using the Common Terminology Criteria for Adverse Events ver. 4.0 [9]. Seven patients underwent the entire course of therapy at UTH, and we investigated the number of days of fever (> 38.0°C), the highest C-reactive protein (CRP) value, and the days of opioid use for each chemotherapy cycle with/without PBT. Delay in chemotherapy or PBT was defined as 8 days or more.

The protocol for this study was in accordance with the Declaration of Helsinki and Ethical Guidelines for Medical and Health Research Involving Human Subjects of the Ministry of Education, Culture, Sports, Science and Technology, and the Ministry of Health, Labor and Welfare of Japan and was approved by the ethics committee of UTH (H27-137). Written informed consent was obtained from the patients' parents or guardians, and informed assent that was appropriately arranged according to their age and ability to understand was also obtained from the patients themselves.

PFS was defined as the time from diagnosis until the first relapse, any death, or last patient contact, at which time the patient was censored. Overall survival (OS) was defined as the time from diagnosis until any death or last patient contact, at which time the patient was censored. PFS and OS were calculated using the Kaplan-Meier method. Frequency of toxicities was evaluated using the Mann-Whitney U test. All analyses were performed with SPSS ver. 26.0 (SPSS, Chicago, IL).

Results

Patients' backgrounds

Forty-eight patients (26 boys) were included. The median age at diagnosis was 3.8 years (range, 0.2–15.1 years). The details of characteristics of the patients are shown in Table 1.

Thirteen of the 48 patients (27%) underwent radical surgical resection. Eight of these patients (61%) achieved radical resection before PBT. Eight patients (17%) underwent conservative resection to preserve organ function. Twenty-seven patients (56%) received biopsy only because severe organ damage due to surgical removal was predicted.

The irradiation doses of the PBT are shown in Table 1. The median irradiation dose was 50.4 gray equivalent (GyE) (range, 41.4–59.4). The radiation dose was significantly higher in the nonsurgical treatment group (Fig. 1, p = 0.049). Proton beam therapy can avoid irradiation of the surrounding normal tissues and maintain the targeted dose to the tumor. Figure 2 shows the distribution of radiation doses that was planned with intensity-modulated radiation therapy (IMRT) and PBT in a patient with buttock and ilium RMS. Whilst with IMRT a large area of the pelvic cavity is irradiated with 30% of the total dose to the tumor bed, PBT avoids irradiation outside the target region.

Toxicity

Acute toxicity: grade 3 mucositis, including cystitis, occurred in 12 patients in total; the irradiated tumor sites in these patients were the head and neck (6 patients), the genitourinary tract (4 patients), the perianal area (1 patient), and the retroperitoneum (1 patient) (Tab. 2). Grade 3 dermatitis occurred in 7 patients in total; the irradiated tu-

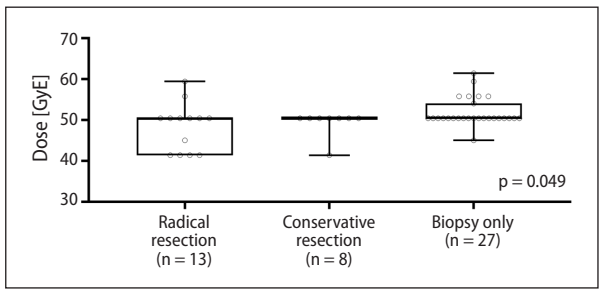

Figure 1. Radiation dose according to surgical achievement. The doses of radiation are shown by box-and-whisker plots according to the surgical achievement. The median dose [GyE (range)] of each group was as follows: radical resection [n = 13, 50.4 (41.4–59.4)]; conservative resection [n = 8, 50.4 (41.4–50.4)]; biopsy only [n = 27, 50.4 (45–61.4)]. The radiation dose was significantly higher in the biopsy only group (p = 0.049)

Table 1. Characteristics of the patients (n = 48)

	n (%)
Sex	
Male	26 (54)
Female	22 (46)
Age at diagnosis, median (range), years	3.8 (0.2–15.1)
Histology	
Embryonal	26 (52)
Alveolar	22 (48)
IRS-IV risk classification	
Low	00 (0)
Intermediate	42 (83)
High	06 (14)
Primary site	
Head and neck	24 (50)
Intracranial extension	3 (6)
Genitourinary tract	13 (27)
Trunk	3 (6)
Extremity	2 (4)
Others†	6 (13)
Transferred to UTH for PBT	
Yes	41 (85)
No	7 (15)
Follow-up period, median (range), years	3.3 (0.4–11.8)
Chemotherapy concurrent with PBT‡	
VC	40 (23)
Irinotecan-containing regimen	6 (12)
Others	1 (2)
No	2 (4)
Surgery	
Radical resection	13 (27)
Conservative resection	8 (17)
Biopsy only	27 (56)
Dose of PBT [GyE]	
41.4	5 (10)
45	2 (4)
50.4	32 (67)
54.0–59.4	9 (20)

UTH — University of Tsukuba Hospital; PBT — proton beam therapy; VC — vincristine and cyclophosphamide; GyE — gray equivalent.
†diaphragm 2 — retroperitoneum 2 — perianal area 1 — bile duct 1.
‡One patient started with platinum-containing therapy and switched to irinotecan-containing therapy during radiotherapy and was counted in both groups

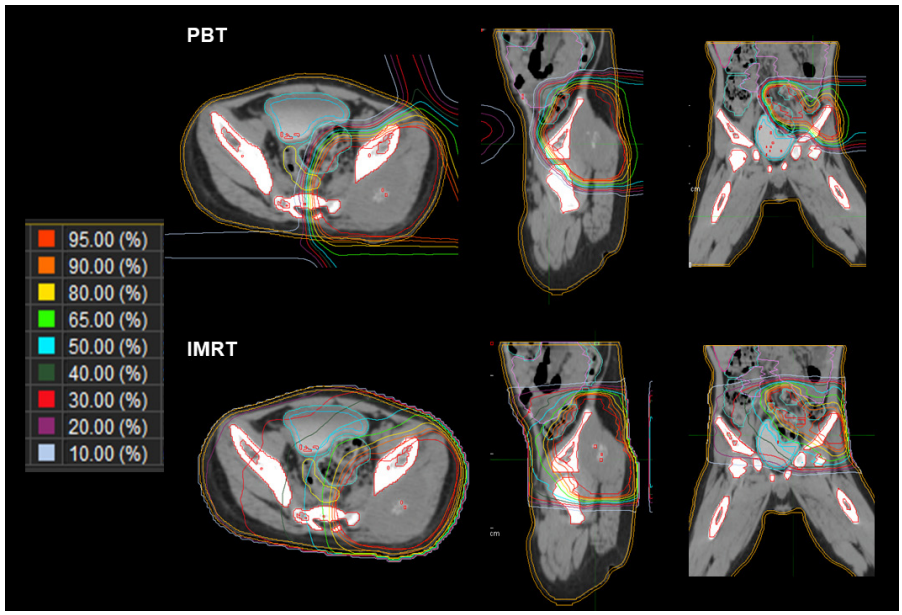

Figure 2. Dose distribution according to proton beam therapy (PBT) and intensity-modulated radiotherapy (IMRT) in a patient with buttock and ilium RMS. Representative dosimetry of normal tissue-sparing achieved PBT when compared with IMRT. PBT avoided irradiation to the right pelvic cavity bowel tract, bladder, and rectum, whereas with IMRT, a large area of the pelvic cavity was irradiated with 30% of the total dose to the tumor bed

Table 2. Nonhematological acute toxicity of grade 3 or higher

Site of irradiated primary tumor	Mucositis		Dermatitis	
	Grade 3	Grade 4	Grade 3	Grade 4
Head and neck (n = 24)	6	0	2	0
Genitourinary tract (n = 13)	4	0	4	0
Trunk (n = 3)	0	0	0	0
Extremity (n = 2)	0	0	0	0
Others (n = 6)	2†	0	1‡	0

†Perianal area and retroperitoneum, respectively. ‡perianal area

mor sites in these patients were the head and neck (2 patients), the genitourinary tract (4 patients), and the perianal area (1 patient). There were no nonhematological grade 4 toxicities. Grade 3 or 4 hematological toxicities occurred in 45 patients. Chemotherapy delay occurred in 4 patients: in all of these patients, the delay was due to delayed recovery from bone marrow suppression, and in 1 patient, it was due to concurrent grade 3 mucositis. Reduced chemotherapy dosage was selected by physicians because of severe mucositis in 4 patients, vincristine omission in 1 patient, delayed VAC with 50% reduction in cyclophosphamide in 1 patient, 75% reduction in cyclophosphamide in 1 patient, and irinotecan discontinuation in 1 patient. PBT interruption occurred in 2 of 7 patients with bladder RMS due to cystitis (interrupted for 10 and 18 days, respectively), but both resumed receiving irradiation after recovery, completed the initially planned dose, and survived without disease progression at the last censored point. No patients required dose reduction in radiotherapy. Sixteen of the 48 patients undergoing PBT with chemotherapy (35%) needed opioid use for dermatitis/mucositis (cystitis). Although 4 of the 5 bladder RMS patients treated with PBT with chemotherapy needed opioid use for cystitis, 2 patients with bladder irradiation undergoing PBT without chemotherapy did not need opioid use. Although 41 of the 48 patients (85%) were transferred to our institution to receive PBT, no chemotherapy delay due to the transfer occurred in these patients.

Table 3. Comparison of chemotherapy with and without PBT in terms of occurrence of acute toxicities

	Cx alone	Cx + PBT	p
Number of chemotherapies, cycles	75	18	
Mean duration of fever per cycle, days	1.4	2.1	0.579
Mean value of highest CRP in each cycle [mg/dL]	1.36	1.08	0.713
Mean days of opioid use per individual			
Total	120	109	
Per each chemotherapy	1.6	6.1	0.001

CRP — C-reactive protein; Cx — chemotherapy; PBT —proton beam therapy

We conducted subgroup analysis to assess the PBT toxicities in each chemotherapy course with/without PBT in the 7 patients who received multimodal therapy from the beginning at UTH. The number of days of fever (> 38.0°C), the highest CRP value, and the period of days of opioid use in all 75 courses of chemotherapy alone and in all 18 courses of concurrent chemotherapy with PBT were assessed. The mean number of days of opioid use for severe pain due to dermatitis/mucositis (cystitis) was significantly longer in the course of concurrent chemotherapy with PBT (1.6 *vs.* 6.1 days, p = 0.001). The mean duration of fever (days) and the highest CRP value did not differ significantly between the 2 groups (p = 0.579 and p = 0.713, respectively; Tab. 3). Pain due to mucositis was treated with indomethacin oral spray [10] and nonsteroidal anti-inflammatory drugs in addition to opioids according to the physicians' choice for each patient. Nasogastric tube nutrition was applied in some severe cases (data not shown). Dermatitis was treated with topical steroid ointment/petrolatum and application of appropriate skin protection materials.

Late toxicities

The number of patients and the time of late toxicities are shown in Table 4. Among the patients who received irradiation to head and neck RMS, tooth growth disorder developed in 4 patients; facial asymmetry, in 4 patients; trismus, in 2 patients; cataracts, in 5 patients; recurrent caries, in 2 patients; hypothyroidism, in 1 patient; growth hormone deficiency, in 1 patient; and recurrent otitis media, in 1 patient. Among those who received irradiation to genitourinary tract RMS, pollakiuria occurred in 2 patients, and ovarian dysfunction, in 1 patient. One patient with diaphragm RMS developed myelodysplastic syndrome (MDS), which was considered to be a chemotherapy-related toxicity.

Table 4. Late toxicities

	Number of patients	Time of occurrence after PBT [years]
Tooth growth disorder	4	2, 4, 4, 6
Facial asymmetry	4	1, 3, 7, 7
Trismus	2	0, 0
Cataracts	5	2, 2, 3, 3, 6
Recurrent caries	2	2, 2
Hypothroidism	1	2
Growth hormone deficiency	1	7
Recurrent otitis media	1	2
Pollakiuria	2	2, 6
Ovarian dysfuncrion	1	5
Myelodysplasia syndrome	1	2

Outcome

Thirty-six of the 48 patients (75%) had survived without disease progression at the time of the last follow-up. The median follow-up period was 3.3 (range, 0.4–11.8) years. The 3-year PFS and OS rates in all the patients were 68.8% [95% confidence interval (CI): 53.5–84.1%] and 94.2% (95% CI: 86.4–102%), respectively. In the intermediate- and high-risk groups, the 3-year PFS rates were 72.4 % (95% CI: 56.9–87.9%) and 50.0% (95% CI: 10.0–0.90%), respectively. In the intermediate- and high-risk groups, the 3-year OS rates were 97% (95% CI: 91.1–103%), and 83.3% (95% CI: 53.5–113.1%), respectively (Tab. 5). Twelve patients (25%) (10: alveolar type; 2: embryonal type) relapsed. Local relapse inside the irradiation field was observed in 7 of the 48 patients (15%). Local relapse outside the irradiation field, local relapse of both inside and outside the irradiation field, and intra-

Table 5. Patients' outcomes

	No.	3-year OS			3-year PFS			3-year LC		
		OS	95% CI	p	PFS	95% CI	p	LC	95% CI	p
Total	48	0.942	0.864– 1.020		0.688	0.535– 0.841		0.793	0.666–0.920	
IRS-IV risk										
Intermediate	42	0.970	0.911– 1.029	0.029	0.724	0.569– 0.879	0.239	0.793	0.656–0.930	0.961
High	6	0.833	0.535– 1.131		0.500	0.100– 0.900		0.800	0.449–1.151	
Surgical treatment										
Radical resection	13	1.000	1.000– 1.000	0.465	0.653	0.375– 0.931	0.721	0.909	0.739–1.079	0.548
Conservative resection	8	0.833	0.535– 1.131		0.833	0.535–1.131		0.833	0.537–1.129	
Biopsy only	27	0.952	0.862– 1.042		0.676	0.476–0.876		0.729	0.546–0.912	

N — number; PFS — progression-free survival; LC — local control; OS — overall survial; 95% CI — 95% confidence Interval; IRS-IV — Intergroup Rhabdomyosarcoma Study-IV

peritoneal dissemination relapse were observed in 1 patient for each. Distant metastatic relapse was observed in 2 patients. Three patients died: two from disease progression and one from complications from hematopoietic stem cell transplantation for secondary MDS.

The 3-year outcomes by surgical status were as follows: the 3-year OS rates were 100% (95% CI: 100–100%), 83.3% (95% CI: 53.5–113.1%), and 95.2% (95% CI: 86.2–104.2%) in the radical resection, conservative resection, and biopsy only groups, respectively (p = 0.47). The 3-year PFS rates were 65.3% (95% CI: 37.5–93.1%), 83.3% (95% CI: 53.5–113.1%) and 67.6% (95% CI: 47.6–87.6%) in the radical resection, conservative resection, and biopsy only groups, respectively (p = 0.72), and no significant differences were found among them (Fig. 3B). The 3-year local control (LC) rates were 90.9% (95% CI: 73.9–107.9%), 83.3% (95% CI: 53.7–112.9%), and 72.9% (95% CI: 54.6–91.2%) (p = 0.548) in the radical resection, conservative resection, and biopsy only groups, respectively, which revealed a tendency of a higher 3-year LC rate in the radical resection group (Fig. 3C).

Discussion

RMS occurs most frequently in the head and neck, in approximately one-third of all patients, followed by the genitourinary tract and the extremities [11]. In our study, the rate of head and neck RMS was 50%, which is higher than those of previous reports (Tab. 1). This higher rate may be due to the low possibility of tumor removal by surgery given that the head and neck contain many vital organs; therefore, more patients with tumors in the head and neck than patients with tumors in other sites were transferred to UTH for PBT, which reduces unnecessary radiation exposure to the surrounding tissues as compared with conventional photon beam therapy.

Nevertheless, varying degrees of PBT-related toxicity may be inevitable. Eleven percent of patients with bladder/prostate rhabdomyosarcoma were reported to have developed grade 2 proctitis after PBT [12]. Ladra et al. [13] reported grade 3 dermatitis and mucositis was observed in 9% and 2%, respectively, after PBT. In this study, grade 3 dermatitis and mucositis occurred in 15% and 25% of patients, respectively, which was more frequent than the previously reported rates. The high frequency of head and neck RMS in this study may be one of the factors for the high incidence of acute toxicity because mucositis occurs more frequently in patients with head and neck lesions and in those who received irradiation to pelvic areas (Tab. 2). Patients concurrently undergoing radiotherapy with chemotherapy developed such acute toxicity more frequently than those not undergoing concurrent chemotherapy [8]. PBT is known to cause higher amounts of skin damage due to its characteristics than does photon therapy [14]. But there are no reports about details of acute non-hematologic toxicity of photon therapy in RMS. In our study, the fact that most of the patients (46 of 48) received concurrent chemotherapy may have resulted in the high incidence of toxicities. In addition, differences in genetic background in radiation sensitivity [15, 16] and difference in the chemotherapy regimen might influence the rate of acute toxicity. However, the

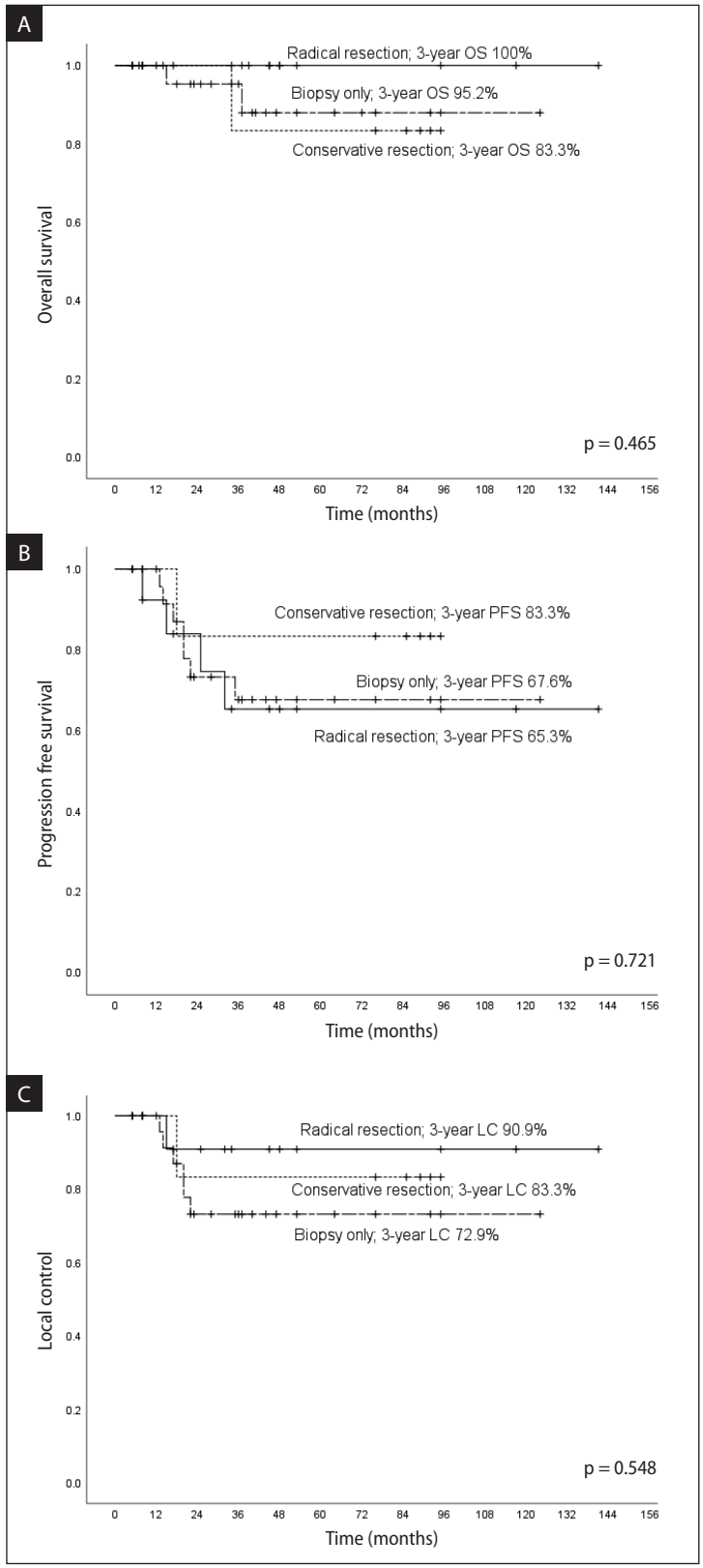

Figure 3. Overall survival, progression-free survival, and local control rate according to surgical achievement. Radical resection: n = 13; conservative resection: n = 8; biopsy only: n = 27. **A.** Overall survival calculated using the Kaplan-Meier method is shown. No significant differences were found among the 3 groups. **B.** Progression-free survival calculated using the Kaplan-Meier method. is shown. No significant differences were found among the 3 groups. **C.** Local control rate calculated using the Kaplan-Meier method. Data according to the type of surgical therapy are shown. The local control rate tends to be higher in order to the surgical achievement

planned PBT was completed without a reduction in the dose or an increase in the rate of fever/elevation of CRP in this study. Furthermore, it is notable that grade 4 nonhematological toxicities were not observed. These results indicate that PBT containing a therapeutic protocol is feasible for children with RMS under supportive care including appropriate application of opioids, granulocyte colony-stimulating factor, antibiotics, and treatment for irradiated skin according to the physician's choice.

The 3-year OS and PFS rates in this study were 94.2% and 68.8%, respectively. And the 3-year OS and PFS rates were 97.0% and 72.4% in the intermediate-risk group and 83.3% and 50.0% in the high-risk group, respectively. In Japan, in 55 children with newly diagnosed RMS who received PBT, 84.5% showed a 2-year OS [17]. In the COG trial, the 3-year PFS rates were 73% and 38% in the intermediate-risk group and the high-risk group, respectively [3, 4]. Ladra et al. [13] reported the 5-year OS and EFS were 70% and 61% for intermediate-risk patients. Compared with these reports, better outcomes in terms of the OS and PFS of the high-risk group were observed in this study. Surgical resection is one of the important factors in the survival outcome of RMS patients [18, 19]. In this study, only 13 patients achieved radical resection, 8 patients had conservative resection, and 27 had biopsy only. With this low surgical achievement, however, a fair 3-year OS rate was observed. Additionally, no significant difference was observed in the PFS and LC rates among the 3 groups (Tab. 5, Fig. 2). The relatively high radiation dose in patients who did not receive tumor resection possibly played some role in the prognosis (Fig. 1). Proton beam therapy enables sufficient irradiation to the target areas even if the tumor site is adjacent to vital organs. The treatment strategy of relatively high dosage to the unresectable tumors using PBT, which enabled markedly decreased normal tissue exposure while the high irradiation dose to the tumor bed was maintained, as shown in Figure 2 and as indicated by previous dosimetric studies, might have contributed to the improved outcome in this study [12, 20, 21].

Reduction in the irradiation dose to normal tissues in PBT may contribute to a decrease in the rate of occurrence of secondary malignancy. The cumulative incidence of subsequent malignant neoplasms (SMNs) exceeded 15–20% at 30 years after diagnosis of the primary cancer [22, 23]. Although no patient developed a solid tumor in this study, 1 patient developed secondary MDS, which was diagnosed 2 years after the RMS diagnosis. Usually, chemotherapy-related MDS and acute myeloid leukemia (t-MDS/AML) occur during a short period of latency (< 3–5 years from the primary cancer diagnosis), and the latency period for the development of radiation-related solid SMNs exceeds 10 years [24]. In addition to somatic mutations, germline mutations in cancer predisposition genes may play an important role in the development of SMNs [23, 25]. Further prospective study with a larger cohort and with a longer follow-up period would be needed to assess the efficacy and safety of PBT in more detail, which may contribute to improvement in the prognosis of pediatric RMS patients.

Although we discovered adverse events during PBT in RMS first time, our study have several limitations: the number of patients is limited compared with previous studies; the distribution of the tumor sites are slightly different from other reports [2–4]; the follow-up period is relatively short to evaluate the late toxicities, especially SMNs

Conclusion

Multidisciplinary therapy containing PBT was feasible and can provide relatively fair 3-year PFS even in patients with surgically unresectable RMS without severe toxicity.

Conflict of interest

The authors declare no conflict of interest.

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Disclosure

Informed consent from the patient's parents and approval from the institutional review board of the University of Tsukuba Hospital were obtained.

Data availability statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Author contributions

R.S., H.F., and T.F. contributed to the structure of the entire study. R.S. and H.O. prepared the manuscript. R.S. primarily analyzed the data. S.H., M.I., and Y.Y. contributed to the collection of the clinical data. K.M. contributed to the part concerning surgical treatment. H.S. and M.M. contributed to the part concerning radiotherapy. M.M. made a distribution map of the radiotherapy plan. H.T. provided critical advice on the data analysis and entire study. All authors have read and approved the final version of the manuscript for submission.

Disclosure

This paper has been previously published as a following meeting abstract: The 58[h] annual meeting of the Japanese Society of Pediatric Hematology Society December 15–17, Intensive multidisciplinary therapy with Proton Beam Therapy for rhabdomyosarcoma was conducted safely. *The Japanese Journal of Pediatric Hematology/Oncology*, volume 53, 2016.

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