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Original research article

Interinstitutional patient transfers between rapid chemotherapy cycles were feasible to utilize proton beam therapy for pediatric Ewing sarcoma family of tumors

Tomohei Nakao[a,b], *Hiroko Fukushima*[c], *Takashi Fukushima*[c,*], *Ryoko Suzuki*[c], *Sho Hosaka*[b], *Yuni Yamaki*[b], *Chie Kobayashi*[c], *Atsushi Iwabuchi*[c], *Kazuo Imagawa*[b], *Aiko Sakai*[b], *Toko Shinkai*[d], *Kouji Masumoto*[d], *Shingo Sakashita*[e], *Tomohiko Masumoto*[f], *Masashi Mizumoto*[g], *Ryo Sumazaki*[c], *Hideyuki Sakurai*[g]

[a] *Department of Radiation Oncology, University of Tsukuba Hospital, 2-1-1, Amakubo, Tsukuba, Ibaraki 305-8576, Japan*

[b] *Department of Pediatrics, University of Tsukuba Hospital, 2-1-1, Amakubo, Tsukuba, Ibaraki 305-8576, Japan*

[c] *Department of Child Health, Faculty of Medicine, University of Tsukuba, 1-1-1, Tennodai, Tsukuba, Ibaraki 305-8575, Japan*

[d] *Department of Pediatric Surgery, Faculty of Medicine, University of Tsukuba, 1-1-1, Tennodai, Tsukuba, Ibaraki 305-8575, Japan*

[e] *Department of Diagnostic Pathology, Faculty of Medicine, University of Tsukuba, 1-1-1, Tennodai, Tsukuba, Ibaraki 305-8575, Japan*

[f] *Department of Radiology, Faculty of Medicine, University of Tsukuba, 1-1-1, Tennodai, Tsukuba, Ibaraki 305-8575, Japan*

[g] *Department of Radiation Oncology, Faculty of Medicine, University of Tsukuba, 1-1-1, Tennodai, Tsukuba, Ibaraki 305-8575, Japan*

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ABSTRACT

Aim: To assess the feasibility of transferring to the University of Tsukuba Hospital for proton beam therapy (PBT) during intensive chemotherapy in children with Ewing sarcoma family of tumors (ESFT) who had been diagnosed and started their first-line treatment at prefectural or regional centers for pediatric oncology.

Abbreviations: PBT, proton beam therapy; ESFT, Ewing sarcoma family of tumors; VDC-IE, vincristine, doxorubicin, cyclophosphamide, ifosfamide and etoposide; UTH, University of Tsukuba Hospital; EFS, event-free survival; OS, overall survival; DFS, disease-free survival.

* *Corresponding author.*
E-mail addresses: tnakao-tuk@umin.ac.jp (T. Nakao), fkhiroko@md.tsukuba.ac.jp (H. Fukushima), tksfksm@md.tsukuba.ac.jp (T. Fukushima), rsuzuki-tuk@umin.ac.jp (R. Suzuki), hosaka-tuk@umin.ac.jp (S. Hosaka), yamaki-kgs@umin.ac.jp (Y. Yamaki), ckobayashi@md.tsukuba.ac.jp (C. Kobayashi), a.iwabuchi@md.tsukuba.ac.jp (A. Iwabuchi), imagawa-tuk@umin.ac.jp (K. Imagawa), sakai-ygt@umin.ac.jp (A. Sakai), tshinkai@md.tsukuba.ac.jp (T. Shinkai), kmasu@md.tsukuba.ac.jp (K. Masumoto), s_sakashita@md.tsukuba.ac.jp (S. Sakashita), masumoto-tky@umin.ac.jp (T. Masumoto), mizumoto@pmrc.tsukuba.ac.jp (M. Mizumoto), rsuma@md.tsukuba.ac.jp (R. Sumazaki), hsakurai@pmrc.tsukuba.ac.jp (H. Sakurai).

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Background: The treatment of ESFT relies on a multidisciplinary approach using intensive neoadjuvant and adjuvant chemotherapies with surgery and radiotherapy. Multi-agent chemotherapy comprising vincristine, doxorubicin, cyclophosphamide, ifosfamide, and etoposide (VDC-IE) is widely used for ESFT, and the interval between each course is very important for maintaining the intensity and effect of chemotherapy.
Materials and methods: Clinical information of patients who received PBT and VDC-IE between April 2009 and May 2016 was collected retrospectively. The intervals between each course of VDC-IE and adverse events were assessed.
Results: Fifteen patients were evaluated. No delays in the intervals of chemotherapy due to transfer were observed. There were no adverse events caused during/just after transfer and no increases in adverse events. The estimated 4-year overall and event-free survival rates were 94.6% and 84.8%, respectively.
Discussion: Although the results of efficacy are preliminary, survival rates were comparable with past studies. More experience and follow-up are required to further assess the efficacy of PBT for patients with ESFT.
Conclusion: Multidisciplinary therapy for children with ESFT involving transfer to our hospital for PBT during VDC-IE was feasible without treatment delay or an increase in adverse events.

1. Introduction

Ewing sarcoma family of tumors (ESFT) is an aggressive sarcoma of bone or soft tissue with a peak incidence during adolescence and young adulthood. The treatment of ESFT relies on a multidisciplinary approach using intensive neoadjuvant and adjuvant chemotherapies together with surgery and radiotherapy. Multi-agent chemotherapy comprising vincristine, doxorubicin, cyclophosphamide, ifosfamide, and etoposide (VDC-IE) is widely used for ESFT, and the interval between each course is very important to maintain the intensity of chemotherapy. Womer et al. showed that VDC-IE administered every 2 weeks was more effective than that administered every 3 weeks, improving the 5-year event-free survival rate from 65% to 73% without increasing toxicities.[1] Although overall survival in patients with localized disease now approaches 65–75%, the acute and long-term toxicities of therapy are substantial. Reduction in quality of life due to retardation of growth and development and secondary cancer are also significant problems in pediatric patients.[2,3]

Particle therapy, including proton beam therapy (PBT), has unique physical properties that allow for the reduction or elimination of unnecessary radiation doses to normal tissues.[4] It is believed that reduced normal tissue exposure will translate into decreased rates of both early and late treatment-induced toxicities. Fukushima et al. reported that the quality of life of childhood brain/head and neck tumor survivors treated with PBT was similar to that of healthy controls and favorable compared to patients treated with photon beam therapy.[5]

In Japan, PBT for childhood malignant solid tumors has been approved by the public health insurance system since April 2016. Although 13 institutions can provide PBT in Japan, only four institutions have treated children. Most pediatric patients with malignant solid tumors, including ESFT, need to continue concurrent chemotherapy during radiotherapy. Since PBT facilities that treat pediatric cases are limited, most children with malignant tumors have to be transferred for PBT during intensive multimodal treatment without incurring any delays in chemotherapy or surgery. Rombi et al.[6] has reported 30 cases with ESFT receiving multidisciplinary treatment, including chemotherapy and PBT, at a single institution, although pediatric patients with ESFT receiving multimodal treatment involving interinstitutional transfer have not been reported. From 1984 to 2015, more than 200 pediatric patients with tumors were referred to the University of Tsukuba Hospital (UTH) for PBT, accounting for approximately 60% of all cases in Japan, which is the largest cohort; UTH is one of the most experienced PBT facilities in the world.[7–12]

Since the feasibility of PBT concurrent with multimodal treatment involving interinstitutional patient transfer has not been explored, we retrospectively analyzed the feasibility and early outcomes of the approach in the subset of children with ESFT who had undergone PBT, surgery and VDC-IE chemotherapy.

2. Materials and methods

Patients who were newly diagnosed with ESFT at age <20 years who had started their first-line treatment with VDC-IE at prefectural or regional institutions and who were referred to UTH for PBT with chemotherapy from April 2009 to May 2016 were included.

At UTH, patients are followed-up at least once a year after PBT.

Chemotherapy was performed according to the following protocol[13]: for VDC, patients received 1.5 mg of vincristine per square meter of body-surface area (maximal dose, 2 mg) and 1200 mg of cyclophosphamide per square meter, followed by mesna, given to prevent hemorrhagic cystitis caused by cyclophosphamide. At UTH, doxorubicin, normally given at 75 mg per square meter was omitted to prevent toxicity during irradiation (VC-IE). For the IE component, 1800 mg of ifosfamide per square meter per day was given for five days,

together with mesna, and 100 mg of etoposide per square meter per day were administered on the same days. Filgrastim was used prophylactically at the discretion of the treating physicians at UTH in cases with previous neutropenia (<500/uL), to maintain the interval between each chemotherapy course or in cases with infectious events during neutropenia.

Local tumor control was attempted with surgical resection and/or PBT. The time schedule of local control was individualized for each case based on past reports and guidelines.[1,13–17]

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. PBT was administered according to the following protocol[16–17]: 45.0–50.4 GyE for microscopic residual tumor and 54.0–55.8 GyE for gross residual tumor given in 1.8 GyE daily fractions. The photon equivalent dose (GyE) was defined as the physical dose (Gy) × relative biological effectiveness of the proton beam, which was assigned the value of 1.1. PBT was first delivered to an initial clinical target volume defined as any visible bony or soft tissue tumor seen on preoperative and prechemotherapy MRI/CT/PET scans plus a 10–15 mm anatomical margin. After 41.4–45 GyE had been administered, the clinical target volume was reduced to the area of macroscopically residual tumor. The margin for the clinical target volume was then reduced to 5–10 mm.

All patient transfers to UTH were designed to occur just after recovery from neutropenia, so that the next course of chemotherapy could be started without any delay.

The patients' clinical information was collected by retrospective medical record review. Clinical data, including chemotherapy regimens, surgery, dose of PBT, adverse events, and disease status, were collected from the time of diagnosis until the last contact at the outpatient clinic or by telephone interview. Adverse events were evaluated using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) ver4.0.[18] Acute adverse events were defined as complications that occurred during PBT and chemotherapy at UTH. Latent adverse events were defined as complications that occurred after recovery from the final dose of chemotherapy.

The interval between each chemotherapy course was defined as being delayed when it took more than 22 days, according to what has been previously reported.[1]

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, and it was approved by the Ethics Committee of the University of Tsukuba Hospital. Written informed consent for study inclusion was obtained from the patients' parents or guardians, and informed assent, appropriate to their age and ability to understand, was also obtained from the patients themselves.

All patients who experienced disease progression, developed a second malignant neoplasm, or died of any cause were classified as having experienced an event. Event-free survival (EFS) was defined as the time from initiation of chemotherapy at the home institution until the first occurrence of an event or last patient contact, at which time the patient was censored. Each event was further classified as local and/or systemic recurrence, death from any cause, or second malignant neoplasm. The outcome measures were overall survival (OS) and EFS defined from initiation of chemotherapy at the home institution. OS and EFS were calculated by the Kaplan-Meier method using IBM SPSS statistics 24 (International Business Machines Inc., Armonk, NY, USA).

3. Results

The characteristics of the patients are shown in Table 1. Fifteen patients (3 boys and 12 girls) were included in the study. The median age at diagnosis was 4 years (range, 1–14 years). Fusion genes were analyzed and positive at diagnosis in 13 patients (*EWS/FLI1* and *EWS/ERG* fusion genes in 10 and 3 patients, respectively). Disease status in each case at the time of starting PBT was complete response in two cases (cases 3 and 10), and partial response in 13 cases. None of the patients, except case 15, experienced grade 3–4 nonhematological acute adverse events before receiving PBT at UTH (Table 1). All the patients were initially diagnosed and had started induction chemotherapy at their home institutions nationwide, and were subsequently transferred to UTH (Fig. 1).

The initial chemotherapy at prefectural or regional institutions was as follows: four patients (cases 5, 8, 11, and 14) were given VAC (vincristine, actinomycin D, and cyclophosphamide); one patient (case 4) was given an induction course (1200 mg/m^2 cyclophosphamide, 1.5 mg/m^2 vincristine, 40 mg/m^2 pirarubicin, and 100 mg/m^2 cisplatin); one patient (case 2) was given prednisolone, vincristine, and cyclophosphamide; and one patient (case 14) was given an induction course for non-Hodgkin lymphoma before being diagnosed as having ESFT. After being diagnosed with ESFT, all 15 patients were administered VDC-IE (Table 1).

At UTH, VDC-IE was performed as chemotherapy in all 15 patients (Table 2). The courses of chemotherapy were administered every 2 weeks.

Irradiation doses given as PBT to each case are shown in Table 2; they were 45.0 GyE for one patient (case 10), 50.4 GyE for one patient (case 3), and 55.8 GyE for 13 patients (cases 1,2, 4–9, 11–15). The median irradiation dose was 55.8 GyE. The median planning target volume (PTV) was 136.7 cc (range, 26.9–466.9 cc) (Table 3).

The intervals between courses of chemotherapy at the home institute before the patients were transferred to UTH are shown in Table 4.

The interval between the last course at the home institute and the first course at UTH was within 21 days in 10 patients. All patients experienced transient grade 4 hematological adverse events after each course of chemotherapy which subsided before the next chemotherapy course and did not cause any delays in successive chemotherapy courses. In cases 1, 4, 5, 12, and 15, the interval was longer than 22 days because all of them had surgery or procedures other than chemotherapy just before or after their transfer. There were

Table 1 – Characteristics of the patients included in this study.

Case No.	Sex	Age at diagnosis (years)	Primary site	Fusion gene	Metastasis	Chemotherapy	Status at transfer	NHAEs before PBT
1	M	1	nasal cavity	EWS/FLI1	–	VDC-IE	PR	none
2	F	1	nasal cavity	EWS/ERG	–	PSL/VCR/CPA VDC-IE	PR	none
3	F	2	orbit	EWS/FLI1	–	VDC-IE	CR	none
4	F	3	adrenal gland	EWS/FLI1	Lung	VCR/CPA/THP/CDDP VDC-IE	PR	none
5	F	4	maxillary sinus	EWS/FLI1	–	VAC VDC-IE	PR	none
6	F	4	cervical spine (C1-2)	ND	Neck node (A/S)	VDC-IE	PR	none
7	F	4	skull base	EWS/FLI1	–	VDC-IE	PR	none
8	F	4	maxillary sinus	EWS/FLI1	–	VAC VDC-IE	PR	none
9	F	4	abdomen	EWS/ERG	–	VDC-IE	PR	none
10	F	5	maxillary sinus	EWS/ERG	–	VDC-IE	CR	none
11	M	8	maxillary sinus	EWS/FLI1	–	VAC VDC-IE	PR	none
12	F	9	sacral bone	EWS/FLI1	–	VDC-IE	PR	none
13	F	12	iliac bone	EWS/FLI1	–	VDC-IE	PR	none
14	F	12	spine (Th5)	EWS/FLI1	–	NHL induction VAC VDC-IE	PR	none
15	M	14	kidney	ND	Lung	VDC-IE	PR	Acute appendicitis

NHAEs, non-hematological adverse events, VDC-IE, vincristine, doxorubicin, cyclophosphamide, ifosfamide, and etoposide; PR, partial response; PSL, prednisolone; VCR, vincristine; CPA, cyclophosphamide; THP, pirarubicin; CDDP, cisplatin; CR, complete response; VCR/CPA/THP/CDDP, 1.5 mg/m^2 VCR, 1200 mg/m^2 CPA, 40 mg/m^2 THP, and 100 mg/m^2 CDDP; VAC, vincristine, actinomycin-D, cyclophosphamide; ND, no data; A/S, affected side; SD, stable disease; NHL, non-Hodgkin lymphoma.

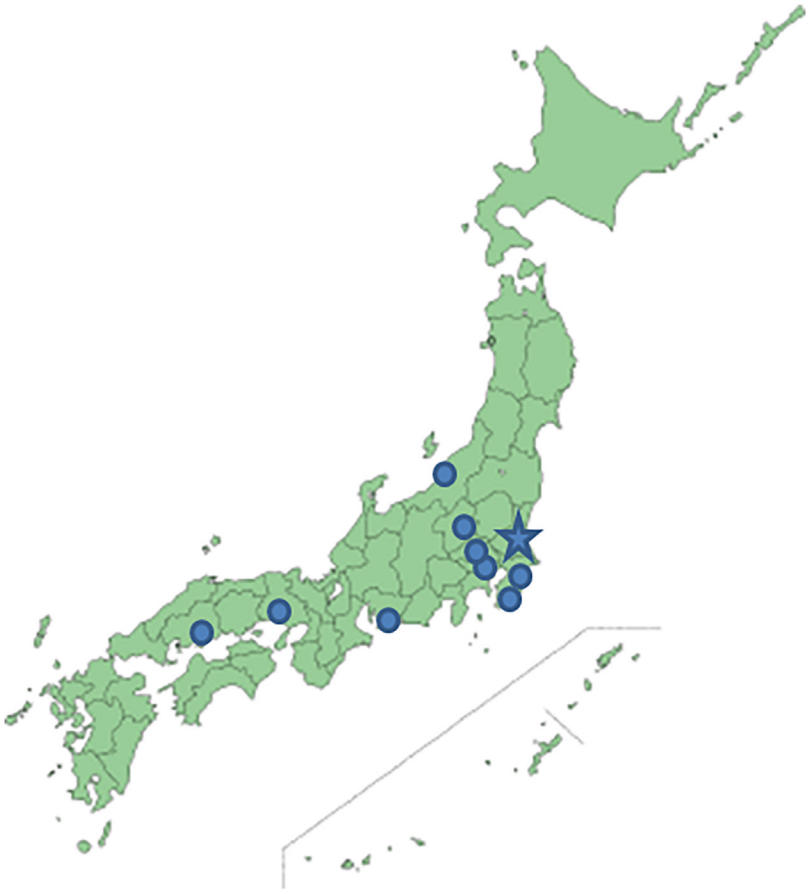

Fig. 1 – The locations of University of Tsukuba Hospital (UTH) and the patients' home institutions. ⋆, UTH; ●, home institutions.

Table 2 – Treatments given to the patients.

CT with PBT	VDC-IE regimen (doxorubicin omitted)[a]		15
CT as initial treatment before starting VDC-IE	VAC regimen		4
	1200 mg/m^2 CPA, 1.5 mg/m^2 VCR, 40 mg/m^2 THP, and 100 mg/m^2 CDDP		1
	PSL, VCR, CPA		1
	NHL induction regimen		1
Surgery[b]	Biopsy only		11
	Tumor resection before PBT		3
	Appendectomy before PBT		1
PBT	Dose (GyE)	45	1
		50.4	1
		55.8	13

CT, chemotherapy; PBT, proton beam therapy; VDC-IE, vincristine, doxorubicin, cyclophosphamide, ifosfamide, and etoposide; VAC, vincristine, actinomycin-D, cyclophosphamide; CPA, cyclophosphamide; VCR, vincristine; THP, pirarubicin; CDDP, cisplatin; PSL, prednisolone; NHL, non-Hodgkin lymphoma.

[a] All 15 cases were treated with VDC-IE once they were transferred.

[b] three cases had surgery just before being transferred to University of Tsukuba Hospital.

no cases in which the administration of VDC-IE was delayed due to the transfer (Table 4).

The non-hematological acute adverse events during PBT and chemotherapy at UTH are shown in Table 5. A total of 59 courses of chemotherapy were given to 15 patients, while there were 18 non-hematological acute adverse events of > grade 2 severity. Grade 3 bacteremia (2 cases), grade 3 cellulitis (1 case), grade 3 in-field pharyngeal abscess (1 case), grade 3 febrile neutropenia (6 cases), grade 3 dermatitis (3 cases), grade 3 mucositis (4 cases), and grade 3 AST and ALT elevations (1 case) occurred. There were no non-hematological grade 4 adverse events or adverse events that occurred during or just after the transfer. Latent non-hematological adverse events are shown in Table 5. Eight of 15 cases (53.3%) suf-

Table 3 – Doses of proton beam therapy at University of Tsukuba Hospital.

Case No.	PTV (cc)	Irradiation dose (GyE)
1	26.9	55.8
2	88.8	55.8
3	151.9	50.4
4	327.8	55.8
5	166.7	55.8
6	171.6	55.8
7	62.2	55.8
8	153.5	55.8
9	466.9	55.8
10	25.6	45.0
11	96.8	55.8
12	76.7	55.8
13	426.9	55.8
14	136.7	55.8
15	120.5	55.8
Median	136.7	55.8

PTV, planned target volume.

fered from latent adverse events: two had growth hormone (GH) deficiency (cases 1, 7); two had alopecia (cases 3, 8); one had spinal atrophy (case 6); one had an eyelid function disorder (case 10); one had corneal opacity (case 11); and one patient had adhesive ileus (case 15) (Table 6).

All patients successfully completed their first-line treatment schedule. The outcomes of the patients are shown in Table 6. Ten of 15 patients (66.7%) achieved complete response and remained free of disease. Only three patients (cases 1, 4, and 10) underwent total tumor resection. Four patients (cases 2, 3, 5, and 9) were alive with disease at the last analysis: one patient with osteosarcoma as a secondary neoplasm (in-field) and three with residual tumor without progression. One patient (case 14) died of combined local and distant recurrences of the disease (6.7%). The median follow-up period was 52 months (range, 12–90 months). Four-year EFS and OS were 84.8% and 94.6%, respectively.

4. Discussion

In the present study, an attempt was made to quantify the feasibility of referring patients for PBT during administration of intensive chemotherapy. Transferring patients during chemotherapy courses increases their risk of contracting infectious diseases due to bone marrow suppression. At our center, all transfers were designed to occur just after recovery from neutropenia, so that the next course of chemotherapy could be started without any delay. All patients received the full course of planned PBT and chemotherapy without

Table 4 – Intervals between courses of chemotherapy.

Case No.	Intervals at home institute (days) [median (range)]	Surgery or procedures just before or after transfer to UTH	Interval between therapy at home institute and UTH (days)
1	21.5 (20–25)	Yes (tumor resection)	41 (POD12)
2	17 (17–21)	None	19
3	21 (19–23)	None	21
4	22 (18–22)	Tumor resection	35 (POD13)
5	20 (19–21)	PBSC harvesting	36 (5 days after harvesting)
6	14 (14)	None	14
7	15 (15)	None	20
8	16 (16)	None	17
9	15 (14–16)	None	14
10	21 (21–31)	None	18
11	18 (16–19)	None	15
12	19 (16–21)	Spacer insertion	30 (POD2)
13	14 (14)	None	14
14	14.5 (14–15)	None	20
15	22.5 (21–25)	Appendectomy	29 (POD11)

VDC-IE, vincristine, doxorubicin, cyclophosphamide, ifosfamide and etoposide; UTH, University of Tsukuba Hospital; POD, postoperative day; PBSC, peripheral blood stem cell.

Table 5 – Non-hematological grade 3 or 4 acute adverse events observed during proton beam therapy (PBT) with chemotherapy at University of Tsukuba Hospital (UTH) (total of 59 courses).

CTCAE grade	Grade 3	Grade 4	AEs per course (%)
Bacteremia	2	0	3.4
Cellulitis	1	0	1.7
Pharyngeal abscess (in-field)	1	0	1.7
FN	6	0	10.1
Dermatitis	3	0	5.1
Mucositis	4	0	6.8
AST, ALT elevation	1	0	1.7

CTCAE, Common Terminology Criteria for Adverse Events, version 4.0; AEs, adverse events; FN, febrile neutropenia; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

Table 6 – Latent non-hematological adverse events observed during proton beam therapy with chemotherapy at University of Tsukuba Hospital and the outcomes of the cases.

Case No.	Latent adverse events (CTCAE grade)	Outcome	Follow-up period (months)
1	GH deficiency (2)	CR	87
2	None	PR (no progression)	16
3	Alopecia (1)	PR (no progression)	61
4	None	CR	46
5	–	Secondary malignancy (osteosarcoma, in-field)	54
6	Spinal atrophy (2)	CR	80
7	GH deficiency (2)	CR	50
8	Alopecia, short stature (1)	CR	34
9	None	PR (no progression)	17
10	Eyelid function disorder (2)	CR	82
11	Corneal opacity (1)	CR	39
12	None	CR	68
13	None	CR	52
14	–	DOD	12
15	Adhesive ileus (3)	CR	

GH, growth hormone; CR, complete response; PR, partial response; DOD, died of disease.

any delay between the treatment courses and no increase in adverse events during or after the transfer. No grade 4 adverse events other than hematological adverse events were observed during PBT and chemotherapy at UTH. All patients experienced transient grade 4 hematological adverse events after each course of chemotherapy, although without any delays in successive chemotherapy courses. Hence, we believe that the hematological adverse events were due to chemotherapy rather than PBT. Further, since transfer of all the cases was scheduled considering bone marrow suppression and neutropenia due to chemotherapy, all the transfers were feasible without delays or an increase in adverse events. Womer et al. reported that in 284 patients with ESFT receiving a bi-weekly VDC-IE regimen, grade 3 and 4 adverse events associated with infection occurred in 16.4% of cases in 604 cycles of chemotherapy.[1] Although grade 3 non-hematological adverse events were observed in 16.9% of cases, no grade 4 non-hematological adverse events were seen in our cohort. Since there was no increase in adverse events during or just after the transfer, it suggests that it is feasible to transfer patients and continue chemotherapy from the home institution without prolonging the interval between successive chemotherapy courses.

Reduced toxicity is expected in children receiving PBT because of the favorable dose distribution compared with photon beam therapy. Some reports have shown reduced risks of secondary cancer and organ irradiation.[19–23] Thus, we believe that it is useful for children to be referred to PBT centers, even if it involves a transfer to an external institution.

Four-year OS and EFS in the present cohort were 94.6% and 84.8%, respectively. Mizumoto et al. reported 30 pediatric cases with ESFT receiving PBT in Japan, in whom the estimated 1-, 3-, and 5-year OS were 88.6%, 73.1%, and 56.8%, respectively.[7] Rombi et al. reported a retrospective study of 30 pediatric patients with ESFT receiving multidisciplinary treatment including chemotherapy, surgery and PBT; the 3-year OS, EFS, and disease-free survival (DFS) were 89%, 60%, and 70%, respectively.[6] The estimated survival rates in the present cohort were comparable to those in previous reports. The median follow-up periods were 22.6 months (range, 0.4–374.3 months) in Mizumoto's report and 38.4 months (range, 17.4 months to 7.4 years) in Rombi's report, while the median follow-up period was 52 months (range, 12–90 months) in the present cohort. A relatively better outcome in the present cohort may be due to the fact that recurrent or refractory cases were included in Mizumoto's cohort, while the present cohort only included patients receiving treatment for their primary disease. The present results may suggest that better outcomes may be achieved with multidisciplinary treatment for pediatric patients with ESFT when PBT is included in first-line treatment.

Our study has several limitations and interpretation of its results must be considered in light of these limitations.

The first limitation is the small number of patients included due to the rarity of this disease in Asian populations. However, to our knowledge, the largest cohort describing exploration of PBT for children with ESFT was reported by Rombi et al.,[6] where the cohort consisted of 30 cases. The present study is the first to report the early clinical outcomes in children receiving PBT, chemotherapy and surgery as multidisciplinary treatment for ESFT, focusing on patients who were transferred during intensive multimodal treatment.

Second, as the study was conducted retrospectively, the indications and timing of surgical interventions were up to each home institution's decision instead of according to uniform criteria. In the present cohort, only three patients (1, 4, and 10) underwent total tumor resection. Two patients (cases 2 and 3) did not undergo total tumor resection; all of them were alive with residual disease without progression. Eight patients (cases 6–9, 11–13, and 15) achieved CR without total tumor resection after the completion of chemotherapy and PBT. Of the 13 cases that were in PR at the time of referral to UTH, nine finally achieved CR, while one patient died of disease (case 14), one patient experienced secondary neoplasm (case 5), and one patient (case 2) remained in PR without tumor progression. From these data, it appears that total tumor resection may not always be necessary to achieve progression-free survival in the treatment of ESFT.

Third, the observation period was relatively short to evaluate late adverse effects and the risk of secondary malignancies, given that secondary malignancies were seen from 2 years to more than 10 years after treatment in previous studies.[23–28] Four (13%) of the cases in Rombi's report died, three of disease progression and one of acute myeloid leukemia (AML). Four patients developed secondary malignancies, three patients developed AML, and one patient, myelodysplastic syndrome (MDS).[6] In Mizumoto's report, one of 30 cases had MDS as a secondary malignancy 3.1 years after PBT.[7] Fukushima et al. reported two patients with secondary neoplasms (one with breast cancer 10 years after initial therapy and one with meningioma within the radiation field 12 years after PBT).[5] In the present cohort, one patient developed osteosarcoma in the radiation field as a secondary malignancy (case 5) 38 months after diagnosis (32 months after PBT). The median observation period in Rombi's study (38.4 months (range, 17.4 months to 7.4 years)) was similar to that in the present study, in which the median observation period was 52 months (range, 12 to 90 months). Hematological malignancies are known risks of cyclophosphamide, etoposide, and doxorubicin exposure. The risk of secondary malignancy after standard treatments for ESFT has been reported; the incidence ranges from 1% to 15%, including both solid and hematological malignancies, depending on the type and cumulative dose of chemotherapy, as well as the type and dose of radiation therapy and the duration of follow-up.[23–28] In these reports, hematological malignancies tended to occur more often than solid tumors as secondary malignancies. Rombi et al. reported 2-year and 3-year incidences of secondary malignancies of 7% and 15%, respectively, where all the 4 cases with secondary malignancies were hematological malignancies (3 with AML, one with MDS), and none were solid tumors.[6] Bhatia et al. reported a cumulative incidence of MDS/AML of 11% at 5 years in patients with metastatic disease treated with INT-0091, which included VDC-IE.[26] In the present cohort, there were no patients with secondary AML/MDS. A further investigation with a larger cohort and longer follow up period is now on-going at UTH to evaluate the long-term efficacy, safety and risk of secondary malignancies compared to photon treatment.

5. Conclusion

Multidisciplinary therapy was feasible for children with ESFT transferred to UTH for PBT and VDC-IE. Transfer during intensive chemotherapy did not increase adverse events. PBT for ESFT was well tolerated, with few acute adverse effects. Although the results of efficacy are preliminary, the survival rates were comparable with those previously reported. Further establishment of the efficacy and safety of PBT in pediatric patients with ESFT will require accumulation of more cases and longer follow-up in a prospective study.

Conflicts of interest

The authors report no conflicts of interest.

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