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Original Research Article

Definitive particle therapy using protons or carbon ions for dedifferentiated liposarcoma

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ABSTRACT

Background: Particle therapy is effective for the treatment of soft tissue sarcomas. However, the clinical outcomes of definitive particle therapy, particularly for dedifferentiated liposarcoma (DDLS), remain unknown.
Purpose: To analyze the treatment outcomes of proton and carbon ion particle therapies for DDLS.
Methods: We retrospectively included patients with DDLS who were treated with particle therapy between 2008 and 2022. The local control (LC), progression-free survival (PFS), and overall survival (OS) rates were evaluated.
Results: Fifty-seven patients were included in this analysis. The median patient age was 68 years (range, 36–91 years). The most common tumor site was the retroperitoneum (n = 37), with a median gross tumor volume (GTV) of 181 cm^3. Twenty-nine patients received proton therapy, and 28 patients received carbon ion therapy. The most common fractionation dose was 70.4 Gy (relative biological effectiveness) in 32 fractions (72.7 Gy equivalent dose in 2 Gy fractions [EQD2]). The median follow-up time was 33 months (range, 1–128 months). The 3-year LC, PFS, and OS rates were 73.1 %, 44.6 %, and 70.6 %, respectively. Patients who received a higher prescribed dose (≥72.7 Gy EQD2) showed significantly better LC ($p = 0.04$) than did those who received a lower prescribed dose. Moreover, those with a larger GTV (≥181 cm^3) had significantly worse OS ($p = 0.04$) than did those with a smaller GTV. Late adverse events occurred in five (9 %) patients.
Conclusions: Particle therapy using protons or carbon ions for the treatment of DDLS is safe and provides good OS and LC. However, further studies with longer follow-up periods and larger cohorts are warranted.

1. Introduction

Dedifferentiated liposarcoma (DDLS) is a type of soft tissue sarcoma (STS). Liposarcomas include a wide spectrum of pathological variations, including well-differentiated liposarcoma/atypical lipomatous tumor, myxoid liposarcoma, pleomorphic liposarcoma, and myxoid pleomorphic liposarcoma [1]. DDLS is believed to originate from an atypical lipomatous tumor or well-differentiated liposarcoma with high-grade and aggressive features. Dedifferentiation occurs in up to 10 % of well-differentiated liposarcomas [1,2]. The incidence of DDLS is reported to be < 0.1 per 1,000,000 annually [3]. DDLS can occur in the mediastinum, inguinal regions, extremities, trunk, and head and neck; however, the retroperitoneum is the most common site [1,3].

Surgical resection is the standard of care for most localized high-grade STSs, including DDLS [4]. The addition of preoperative or postoperative radiation therapy (RT) to surgery for STS achieves excellent local control (LC) [5]. Definitive RT or systemic chemotherapy can be indicated for STS that is unresectable or unfit for surgery [4]. Although definitive RT is one of the options for curative treatment of patients with unresectable STS or those who are unfit for surgery, high-dose irradiation is needed to control STS because of its radioresistant nature, especially for non-myxoid liposarcoma [6]. However, high-dose irradiation without an increase in the incidence of adverse events is challenging. STS treatment outcome with conventional photon therapy has been reported to result in a 5-year LC of 29–45 % and a 5-year overall survival (OS) of 25–35 % [7–10]. In contrast, particle therapy has a dose concentration superior to that of photon therapy owing to the Bragg peak effect. Carbon ion therapy (CIT) offers the potential for improved

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biological effects that result in a 5-year LC of 65–69 % and a 5-year OS of 46–50 % for STS [11,12].

The clinical outcomes of definitive particle therapy, particularly for DDLS, remain unknown. Previous studies have analyzed the clinical outcomes of definitive photon or particle therapy for STS, including heterogeneous histological types [11,12]. STS is a heterogeneous group of tumors arising from various mesenchymal cells; therefore, the radiosensitivity of STS can differ between histologies [6]. In particular, in liposarcoma, radiosensitivity differs between the myxoid and non-myxoid types. Non-myxoid liposarcomas are more radioresistant than myxoid liposarcomas [6,13,14]. We hypothesized that the clinical outcome focusing on DDLS alone may not be consistent with the outcomes reported in previous studies on heterogeneous histological types of sarcomas.

Data on the clinical outcomes of particle therapy limited to DDLS are scarce; thus, the beneficial effects of these therapies, particularly for DDLS, remain controversial. This study aimed to evaluate the efficacy and safety of particle therapy in patients with DDLS.

2. Materials and methods

2.1. Study population

A retrospective chart review was performed for patients with DDLS who underwent particle therapy between January 2008 and March 2022 at our institution. Patients diagnosed with DDLS who declined or were unamenable to surgery were included in this study. The indication for surgery was discussed at the multi-disciplinary tumor board. Unresectability was determined by multiple factors, mainly difficulty of complete resection with adequate margin (especially retroperitoneum and mediastinum), expected unacceptable severe functional impairment, poor surgical candidate, and advanced age. A central pathological review was not performed, and MDM2 gene amplification and/or staining were evaluated in recent cases but not in previous ones. Patients were excluded if they had received particle therapy with palliative intent, were administered postoperative particle therapy without gross targets, had a history of prior RT for the target lesion, or had not completed the planned particle therapy. Data were obtained from patients' medical records. This study was approved by the Human Research Ethics Committee of our institute (No.05–04).

2.2. Particle therapy for DDLS

To immobilize the patients, a custom-made thermoplastic cast was placed in the supine or prone position, depending on the tumor location. Computed tomography images were acquired for treatment planning. Magnetic resonance imaging was performed to evaluate tumor invasion. The clinical target volume was defined as the gross tumor volume (GTV) plus a 5.0-mm margin, with appropriate modification according to the anatomic boundaries and physician preference. The planning target volume added an additional 5.0-mm setup margin to the clinical target volume, with an appropriate internal margin under the respiratory gating system, as necessary. The policy for selecting proton therapy (PT) or CIT was based on the dose distribution. Although both PT and CIT are charged particle therapies, slight differences exist in their physical characteristics. With respect to monoenergetic beams, CIT shows a superior penumbra but a shorter range compared with PT. The greatest difference in the mechanical aspects of these approaches is that a rotating gantry is available only for PT. We used the same dose constraints for organs at risk in both PT and CIT; therefore, the beam type that achieved better target coverage was selected for each patient after a discussion among several radiation oncologists. Passive scattering techniques have been used for the PT and CIT, whereas active scanning techniques have only been available for the PT since 2020. Dose fractionation was determined based on the distance from the target volume to the organs at risk. Because various dose fractionations were used, the biologic effects were compared using an equivalent dose in 2 Gy fractions (EQD2). A value of 4 Gy for the α/β ratio was used for STS in a linear-quadratic model [15]. The EQD2 was calculated using the following formula: total dose (dose per fraction + 4)/6. When the target volume was located near the digestive tract organs and safe delivery of a radical dose was difficult, surgical spacer placement was performed before particle therapy to separate tumors from the adjacent organs at risk, according to the physician's decision and with the patient's consent. Although the placement of expanded polytetrafluoroethylene (ePTFE) sheets, artificial blood vessels, or autologous grafts of the greater omentum had been performed for the spacer, Neskeep® (Alfresa Pharma Corporation, Osaka, Japan), which is a nonwoven fabric bioabsorbable spacer [16–18], has been available for spacer since April 2020 (Fig. 1).

2.3. Patients follow-up

After treatment, patients were followed up at 3-month intervals for 3 years and 6-month intervals thereafter. The follow-up evaluation records included physical examination reports, diagnostic images (computed tomography and/or magnetic resonance imaging), and laboratory examinations. Fluorodeoxyglucose positron emission tomography or biopsy of the primary lesion was performed whenever necessary. Objective response was evaluated according to Response Evaluation Criteria in Solid Tumours ver. 1.1. Toxicities were evaluated according to the National Cancer Institute Common Toxicity Criteria, version 4.0. Late toxicities were defined as adverse events that occurred 90 days after treatment completion. Toxicities of grade 3 or higher were recorded.

2.4. Statistical analysis

LC was calculated from the date of irradiation initiation to the date of local relapse and was defined as the regrowth of the irradiated lesion on the last follow-up imaging. Progression-free survival (PFS) was defined as the period between the date of irradiation initiation and the date of disease progression or the last follow-up imaging. OS was defined as the period between the date of irradiation initiation and the last follow-up or death due to any cause. LC, PFS, and OS were calculated using the Kaplan–Meier method. The log-rank test for univariate analysis and Cox proportional hazard models for multivariate analysis were used to assess potential factors associated with LC, PFS, and OS. Statistical significance was set at two-sided $p < 0.05$. Continuous variables of potential factors were categorized into two groups based on the median values. Variables with a $p < 0.05$ in univariate analysis or two variables with the smallest p-value in univariate analysis were entered into the multivariate model. All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R (R Foundation for Statistical Computing, Vienna, Austria) [19].

3. Results

A total of 69 patients received particle therapy during the study period. Twelve patients were excluded from analysis (Fig. 2). Therefore, 57 patients were included. The patient-, tumor-, and treatment-related characteristics are shown in Table 1. Thirty-four patients had undergone prior surgery, and the median number of prior surgeries was 2 (range, 1–5). The most common tumor site was the retroperitoneum, including the kidney in one case. The median GTV was 181 cm^3 (range, 1–1972 cm^3). Regarding the type of particle therapy, 29 (51 %) patients were treated with PT, and 28 (49 %) patients were treated with CIT. The median prescribed dose was 72.7 Gy EQD2 (70.4 Gy [RBE] in 32 fractions). No patients received concurrent chemotherapy. The median follow-up durations for the entire cohort and living patients were 33 months (range, 1–128 months) and 37 months (range, 9–128 months), respectively. At treatment completion, out of 57 patients, two (4 %) had

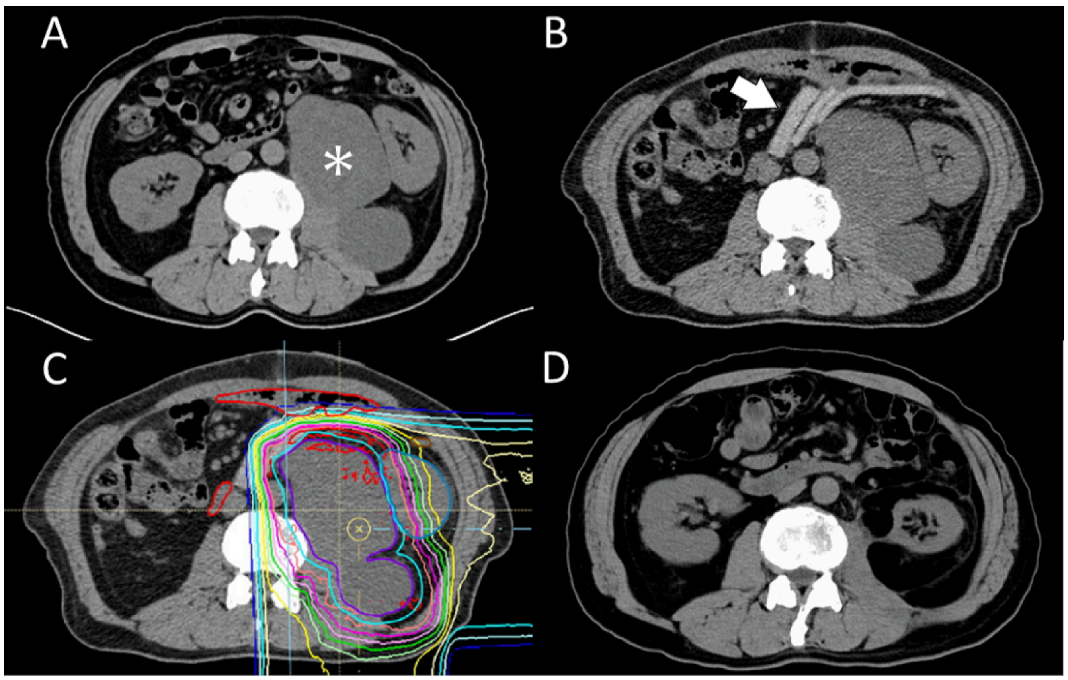

Fig. 1. Representative case of dedifferentiated liposarcoma in a 70-year-old man. (A) Asterisk indicates the dedifferentiated liposarcoma. (B) Before proton therapy, a spacer placement (arrow) generated a sufficient distance between the tumor and the intestines. (C) Dose distribution of proton therapy using 70.4 Gy (RBE) in 32 fractions. (D) No recurrence after 32 months of the therapy.

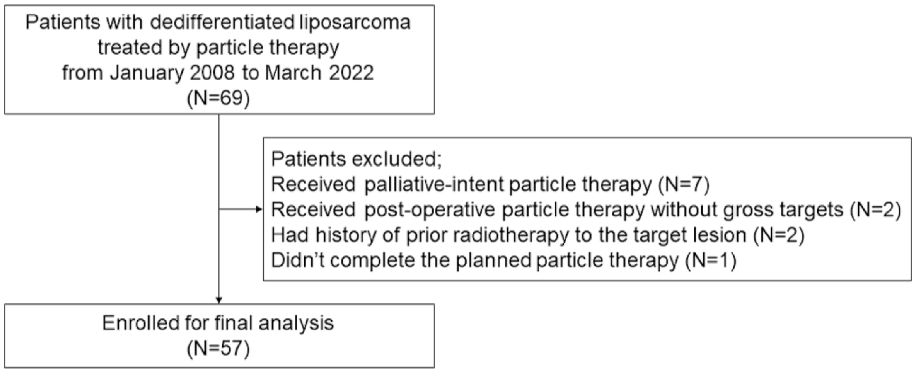

Fig. 2. Flowchart of patient selection.

a partial response (PR), 53 (93 %) maintained stable disease (SD), and two (4 %) developed progressive disease (PD). Fifty-three patients (93 %) could be evaluated for objective response approximately 3–6 months after irradiation initiation, and we found seven PRs (12 %), 44 SDs (77 %), and two PDs (4 %). During the follow-up, 32 (56 %) patients experienced disease progression. Regarding initial progression, eight patients experienced local progression, including two patients with concurrent out-of-field recurrence, while 24 patients experienced only out-of-field recurrence. The details of the patterns of initial treatment failure and salvage treatment after particle therapy are presented in Appendix Table A1.

The 3-year and 5-year LC rates were 73.1 % and 67.8 %, respectively. The LC curves are shown in Fig. 3A. The univariate analysis demonstrated that male sex, tumor location in the mediastinum, and a lower prescribed dose of < 72.7 Gy EQD2 were factors associated with the worst LC (Table 2). With respect to the 3-year LC according to the type of beam, no significant correlation was observed between the type of particle therapy and LC (PT vs. CIT=70.3 % vs. 76 %; $p = 0.83$). The multivariate analysis demonstrated that patients who received a higher prescribed dose ($\geq$72.7 Gy EQD2) had better LC than did those who received a lower dose (hazard ratio = 0.21; 95 % confidence interval = 0.05–0.94; $p = 0.04$) (Table 3).

The 3-year and 5-year PFS rates were 44.6 % and 36.3 %, respectively (Fig. 3B). The univariate analysis showed that a higher prescribed dose was significantly associated with good PFS (Table 2). The multivariate analysis showed that none of the factors were correlated with PFS (Table 3).

The 3-year and 5-year OS rates were 70.6 % and 62.7 %, respectively (Fig. 3C). The univariate analysis identified no significant factors that correlated with OS, whereas a higher GTV tended to be a factor for poor OS (Table 2). In the multivariate analysis, lower GTV was the only factor associated with good OS (hazard ratio = 2.73; 95 % confidence interval = 1.03–7.21; $p = 0.04$) (Table 3).

Grade 3 and higher acute adverse events were observed in five patients (9 %). Grade 3 dermatitis was observed in three patients (5 %), and grade 3 esophageal and tracheal stenosis in one patient (2 %). One patient (2 %) died of an infection after spacer placement. Because this episode occurred in the early days of spacer placement, the placement technique was still being explored, and artificial blood vessels, not bioabsorbable spacers, were used as spacers.

Table 1
Patient, tumor, and treatment characteristics (N = 57).

Characteristics		N (%) or median (range)
Age (years)		68 (36–91)
Sex		
	Male	40 (70)
	Female	17 (30)
ECOG PS		
	0	25 (44)
	1	30 (53)
	2	1 (2)
	3	1 (2)
Tumor status		
	Primary	26 (46)
	Recurrence	31 (54)
Prior treatment		
	None	19 (33)
	Surgery	34 (60)
	Chemotherapy	8 (14)
Tumor location		
	Retroperitoneum	37 (65)
	Mediastinum	8 (14)
	Inguinal region	4 (7)
	Extremity	3 (5)
	Others	5 (9)
Resectability		
	Unresectable	46 (81)
	Incompletely resected	4 (7)
	Resectable	7 (12)
GTV (cc)		181 (1–1972)
Particle therapy		
	Proton	29 (51)
	Carbon ion	28 (49)
Dose (Gy [RBE])/fraction (Gy EQD2 [$\alpha/\beta = 4$])		
	70.4/16 (98.6)	11 (19)
	74/37 (74)	1 (2)
	70.4/32 (72.7)	40 (70)
	70/35 (70)	2 (4)
	66/33 (66)	1 (2)
	60/30 (60)	2 (4)
Spacer		
	Yes	11 (19)
	No	46 (81)

ECOG PS – Eastern Cooperative Oncology Group Performance Status.
GTV – Gross Tumor Volume.
Gy – Gray (unit of ionizing radiation dose).
Gy (RBE) – Gray Relative Biological Effectiveness.
Gy EQD2 – Gray Equivalent Dose in 2 Gray fractions.

Grade 3 and higher late adverse events were observed in five patients (9 %). Grade 3 peripheral nerve injury was observed in two patients (4 %), grade 4 dermatitis in one patient (2 %), and grade 3 pneumonitis in one patient (2 %). One patient (2 %) died of gastric perforation due to chronic pressure on the spacer for which ePTFE sheets were used.

4. Discussion

To the best of our knowledge, this is the first study to report the outcomes of particle therapy using PT or CIT for DDLS. In this retrospective study, our data showed excellent results for 3-year LC (73.1 %) and 3-year OS (70.6 %) after particle therapy. Our findings are promising given that the majority of cases in this study were unresectable, for which the effect of systemic therapy or photon therapy was limited. Therefore, particle therapy may be an important therapeutic strategy.

In the current study, the outcomes of particle therapy for DDLS were similar to those of previous studies on particle therapy for STS, including heterogeneous histological types [11,12]. STS has traditionally been considered radioresistant; however, it has been suggested that radiosensitivity varies depending on the histological type [6]. In particular, Yang et al. reported that their genomics-based analysis of a prospective sarcoma tissue collection identified non-myxoid liposarcoma, including DDLS, as the least radiosensitive histology [6]. Therefore, we

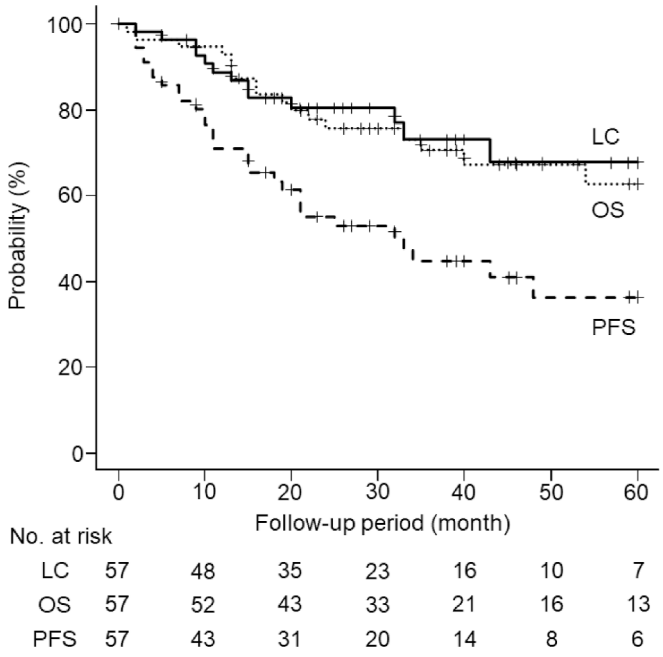

Fig. 3. Kaplan–Meier curves showing outcomes for patients with dedifferentiated liposarcoma treated using particle therapy: local control (LC), overall survival (OS), and progression-free survival (PFS).

hypothesized that a study that included only DDLS would have a poorer outcome compared to previous reports that consisted of heterogeneous histological types of STS treated with particle therapy. In previous reports on particle therapy for STS, Serizawa et al. reported that the OS rates at 2 and 5 years were 75 % and 50 %, respectively, and the LC rates at 2 and 5 years were 77 % and 69 %, respectively, after CIT for unresectable retroperitoneal sarcomas, including three cases (13 %) of liposarcoma [11]. Imai et al. reported that the 5-year LC and OS were 65 % and 46 %, respectively, after CIT for unresectable localized axial STS, including 12 cases (9 %) of liposarcoma (well-differentiated in three patients, others in nine patients) [12]. The current study, which specializes in DDLS, suggests that particle therapy enables good LC and OS, which is in line with the results of previous studies. However, our results are superior to those of previous studies on photon therapy for STS (including heterogeneous histological types), even when recent techniques were used. The outcome of photon therapy has been considered to be a 5-year LC of 29–45 % and 5-year OS of 25–35 % [7–10], whereas Allignet et al. reported that the outcome of photon therapy using recent techniques was a 5-year local failure of 46.5 % [20]. Stereotactic body radio therapy (SBRT) or brachytherapy may also provide effective local control; SBRT has been reported to have an excellent local recurrence rate of 1.7 % at 2 years for metastatic sarcoma (median sizes of metastases treated with SBRT were 3.4 cm,) [21]. Moreover, SBRT may be useful for the management of metastatic sarcomatous tumors, particularly relatively small lesions. A retrospective study (n = 23) reported that CT-guided ^{125}I seed implantation resulted in good local control (87.0 %) for inoperable retroperitoneal sarcoma [22]. It may be worthwhile to consider the use of this technique in patients in whom it is safe. In the current study, the 3-year PFS was 44.6 % owing to out-of-field recurrence, mostly due to peritoneal dissemination recurrence. Re-local treatment, such as particle therapy or surgical therapy to out-of-field recurrence sites, may have resulted in excellent OS (Appendix Table A1).

In our study, a higher prescribed dose (≥72.7 Gy EQD2) was a significant factor for good LC. Particle therapy enabled the achievement of a median dose of 72.7 Gy (RBE) EQD2 owing to the Bragg peak effect. In a previous photon therapy study on heterogeneous histological types of STS, a dose of > 63 Gy was reported to be significantly associated with a

Table 2
Univariate analysis.

Variable		N	3y-LC	P value	3y-PFS	P value	3y-OS	P value
Sex	Male	40	60.7		41.7		65.1	
	Female	17	100	0.01	50.5	0.84	81.9	0.28
Age	<68	27	76.3		45		72.3	
	≥68	30	69.9	0.45	47.2	0.52	67.8	0.61
Tumor status	Primary	26	79.7		58.4		72.7	
	Recurrence	31	68	0.32	33.9	0.07	69.6	0.76
Prior chemotherapy	Yes	8	57.1		42.9		56.2	
	No	49	76	0.21	45.5	0.71	72.9	0.65
Prior surgery	Yes	34	71.2		35.3		72.8	
	No	23	76.3	0.63	61.3	0.15	69.1	0.47
Tumor location	Mediastinum	8	46.9		37.5		72.9	
	Others	49	76.9	<0.01	45	0.16	70.4	0.85
GTV (cc)	<181	29	78.7		43.3		79.6	
	≥181	28	66.1	0.33	48.8	0.81	63.4	0.08
Particle therapy	Proton	29	70.3		44.9		78.7	
	Carbon ion	28	76	0.83	44.5	0.97	64.7	0.14
Prescribed dose	<72.7 Gy*	5	20		20		100	
	≥72.7 Gy*	52	79.1	0.00	46.8	0.05	68.6	0.24
Spacer	Yes	11	70		19.3		58.4	
	No	46	73.6	0.96	48.6	0.65	73.8	0.44

*72.7 Gy EQD2 (α/β = 4) = 70.4 Gy (RBE)/ 32 fr.
3y-LC – 3-Year Local Control.
3y-PFS – 3-Year Progression-Free Survival.
3y-OS – 3-Year Overall Survival.
Gy – Gray (unit of ionizing radiation dose).
GTV – Gross Tumor Volume.

Table 3
Multivariate analysis.

	LC			PFS			OS		
Variable	HR	95 % CI	P value	HR	95 % CI	P value	HR	95 % CI	P value
Sex (male/female)	7.37E+08	0 – Inf	1.00						
Tumor status (recurrence/primary)				1.79	0.82 – 3.91	0.15			
Tumor location (mediastinum/others)	1.93	0.51 – 7.31	0.33						
GTV (cc) (≥181/〈181)							2.73	1.03 – 7.21	0.04
Particle therapy (proton/carbon ion)							2.42	0.91 – 6.48	0.08
Prescribed dose* (≥72.7/<72.7)	0.21	0.05 – 0.94	0.04	0.46	0.15 – 1.40	0.17			

LC – Local Control.
PFS – Progression-Free Survival.
OS – Overall Survival.
HR – Hazard Ratio (used in survival analysis to describe the relative risk of an event occurring at any given point in time).
95 % CI – 95 % Confidence Interval (statistical range with a 95 % probability that the true value of a parameter lies within it).
Gy – Gray (unit of ionizing radiation dose).
GTV – Gross Tumor Volume.
* 72.7 Gy EQD2 (α/β = 4) = 70.4 Gy (RBE)/ 32 fr

good prognosis in patients with unresectable STS [7]. However, Imai et al. showed that escalating the dose above 70.4 Gy (RBE) in 16 fractions with CIT did not improve LC. Thus, 72.7 Gy (RBE) EQD2 was a reasonable cutoff for LC for DDLS. Spacers are another option to deliver a higher prescribed dose to the target volume, although spacer replacement was not a significant factor in LC in this study. There are some technical problems related to the application of high doses to retroperitoneal lesions, which are common sites of DDLS, owing to their proximity to critical organs such as the intestine. The space between the tumor and critical organs ensures the tumor dose without increasing gastrointestinal toxicity. The greater omentum, artificial blood vessels, and ePTFE sheets have been used as spacers, although adverse events, such as intestinal perforation, are problematic when foreign objects are present in the abdominal cavity for a long period. Recently, bioabsorbable spacers have been developed that are expected to reduce adverse events [16–18]. Shiba et al. demonstrated that dose improvements in the target tumor and rectum were observed with spacer placement in a patient with sacral chordoma adjacent to the rectum treated with CIT [23].

Patients who had lower GTV (<181 cm^3) tended to be associated with better OS of 79.6 % at 3 years compared to those who had higher GTV (≥181 cm^3), experiencing a 63.4 % 3-year OS in the univariate analysis in this study; GTV was a significant prognostic factor in multivariate analysis. Although previous studies included heterogeneous histological types of bone and STSs, tumor volume has been reported to be a significant prognostic factor [12,24].

There were no differences in clinical outcomes, including LC, PFS, or OS, according to the type of particle therapy in the current study.

Compared with photon therapy, both CIT and PT enable the delivery of high-dose radiation to a target because of the Bragg peak effect. In contrast, CIT is classified as high linear energy transfer radiation and has a strong biological effect; therefore, it is expected to have better clinical outcomes compared to photons or PT. As expected, previous reports, including heterohistological types of STS, have shown favorable clinical outcomes for CIT [11,12]. In contrast, Demizu et al. reported no apparent differences between PT and CIT in the treatment outcomes of particle therapy using PT or CIT for unresectable or incompletely resected bone sarcoma and STS of the pelvis [24]. Although a randomized controlled study of CIT or PT is currently being conducted for radioresistant tumors [25] or chordomas [26], and it is necessary to validate our results, both PT and CIT can be selected for the treatment of DDLS based on the results of the current study.

The present study had several limitations. This was a retrospective study, which is a design that has an inherent selection bias. Another limitation of this study was the heterogeneity of the sample. Other limitations were a limited follow-up period (median 33 months) and a small sample size (n = 57), due to DDLS's rarity. Nonetheless, this first study revealed encouraging outcomes for DDLS using particle therapy. Despite approximately 81 % of the cohort having unresectable disease and a median GTV of 181 cm3, disease control was favorable with minimal late toxicity. These results establish a benchmark for clinical practice and future DDLS trials.

In conclusion, our study demonstrated that particle therapy, whether through PT or CIT, effectively treats DDLS, offering sustained LC and superior OS with minimal toxicity. These outcomes align with earlier research on STS particle therapy across various histological types. Further research with extended follow-ups and larger cohorts is needed to validate these results.

Author contributions

HK and YD designed the study, the main conceptual ideas, and the proof outline. HK, YD, and ST collected the data. KI, NF, DT, SCP, YM, KT, and ST aided in interpreting the results and worked on the manuscript. TO and TS supervised the project. HK wrote the manuscript with support from YD. All authors have read and agreed to the published version of the manuscript.

Data statement

The data that support the findings of this study are available from the corresponding author, YD, upon reasonable request.

Funding statement

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix

Table A1
Patterns of initial treatment failure and the salvage treatment after particle therapy.

		Salvage treatment for initial failure (N)				
Failure pattern	N	Particle therapy	Surgery	Systemic therapy	BSC	Unknown
Local progression (+)						
Local alone	6	–	–	3	3	–
Local/peritoneum	1	–	–	–	–	1
Local/soft tissue	1	–	–	–	1	–
Local progression (−)						
Peritoneum	14	2	6	4	1	1
Mediastinum	2	1	–	1	–	–
Lymph node	2	1	1	–	–	–
Lung	2	–	1	1	–	–
Retroperitoneum	1	1	–	–	–	–
Pleura	1	1	–	–	–	–
Bone	1	1	–	–	–	–
Bone/liver	1	–	–	1	–	–

*BSC; best supportive care.

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