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Appropriate radiation dose for symptomatic relief and local control in patients with adult T cell leukemia/lymphoma

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ABSTRACT

Adult T-cell leukemia/lymphoma (ATL) is an aggressive peripheral T-cell neoplasm that occurs only in patients with human T-cell leukemia virus type 1. No large study or randomized trial investigating radiotherapy (RT) for ATL has been performed. We retrospectively reviewed 55 courses of RT for 41 consecutive patients with ATL who underwent RT between 2000 and 2016 at our institutions. The results showed that RT for local ATL lesions can achieve symptomatic improvement in 92% of cases. Local remission, either complete remission (CR) or partial response (PR), was achieved in 100% of the patients (CR: 89%, PR: 11%) with ≥ 40 Gy irradiation. CR or PR was achieved in 71% (CR: 29%, PR: 43%) with 30–39 Gy and in 73% (CR: 6.7%, PR: 67%) with ≤ 29 Gy irradiation. The mean total radiation dose in the CR and PR groups differed significantly (38 vs 25 Gy, $P = 0.0002$). The maximum acute toxicity was Grade 0–2 in all patients, except for one patient experienced Grade 3 radiation dermatitis. In-field relapses occurred in 36% of patients, and the frequency of in-field relapses was 11%, 30% and 71% among those who achieved CR, PR and SD, respectively. All 9 patients who received total skin irradiation experienced cutaneous relapses, with a median of 63 days (range, 7–210 days). Almost all (39 of 41) patients with ATL experienced out-of-field progression after RT. In conclusion, RT was confirmed to be effective and safe for palliative treatment of local ATL lesions.

Keywords: radiotherapy; adult T-cell leukemia/lymphoma; human T-cell leukemia virus type 1; palliative radiotherapy

INTRODUCTION

Adult T-cell leukemia/lymphoma (ATL) is an aggressive type of peripheral T-cell neoplasm that occurs only in patients with human T-cell leukemia virus type 1 (HTLV-1) [1]. The clinical manifestation

of ATL is highly heterogeneous among patients [2]. It can present as leukemia or as lymphoma and cause multiple lymphadenopathy and extranodal lesions such as cutaneous lesions. Patients with ATL also often develop hypercalcemia and opportunistic infections [3]. HTLV-

1 is prevalent in Southwestern Japan, Caribbean islands, sub-Saharan Africa, South America, parts of the Middle East, and Australo-Melanesia [4]. Currently, at least ~5–10 million individuals are infected with HTLV-1 worldwide [5], and ATL develops in ~3–5% of the patients infected with HTLV-1 several decades after primary infection [6].

ATL is classified into four clinical types: acute, lymphoma, chronic and smoldering [3]. The chronic type is further divided into favorable and unfavorable subtypes according to several prognostic factors. The acute and lymphoma types and the chronic unfavorable subtype are considered to be aggressive ATL, with short median survivals of 8.3, 10.6 and 27 months, respectively. Meanwhile, the chronic favorable subtype and the smoldering type have a relatively high 4-year survival rate of 60% and 52%, respectively; therefore, they are considered to be indolent ATL [7, 8].

The standard treatment for aggressive ATL is multidrug chemotherapy and/or hematopoietic stem cell transplantation (HSCT) [9]. RT may be the best treatment option for a patient with aggressive ATL when chemotherapy is not tolerable for the patient with a few detectable lesions, or when the patient needs symptomatic improvement [10, 11]. Regarding treatment of indolent ATL, RT may be used as a part of skin-directed treatment for patients with mainly cutaneous lesions [8, 12].

No large study or randomized trial has investigated the role of RT in the treatment of ATL. To the best of our knowledge, only two prior case series of patients with ATL treated with RT have been published. One of the studies included 30 patients treated more than 25 years ago using an older radiation technique [13], and the other reported the effectiveness of RT for local control of ATL with a modern radiation technique in 2012. However, the number of patients in the latter study was only 10 [11]. Therefore, the role of RT in ATL treatment, and the appropriate radiation dose for ATL remain unclear.

Herein, we review our experience with RT for ATL. This study aimed to evaluate the role of RT in symptomatic relief and local control of ATL lesions and to determine the appropriate radiation dose for ATL.

MATERIALS AND METHODS

Patients

This study reviewed 41 consecutive patients with ATL treated with RT at the University of the Ryukyus Hospital between 2000 and 2016. Patients who received only total body irradiation with or without central nervous irradiation as a preparative regimen for HSCT were excluded from this study. ATL was diagnosed based on clinical conditions consistent with ATL, evidence of HTLV-1 antibody in sera, and pathologic confirmation of T-cell leukemia/lymphoma. The patients were classified as having acute, lymphoma, chronic or smoldering types in accordance with the Shimoyama Classification [3].

RT for the patients was divided into three types: RT for patients with no disease outside of the radiation field at the time of RT (Group 1), RT for patients with known disease outside of the field at the time of RT (Group 2), and total skin irradiation (TSI) for patients with multiple cutaneous lesions (Group 3). This categorization was performed to investigate and compare patient outcomes

for either patients with only localized ATL lesions at the time of RT or those with multiple lesions who underwent TSI.

Patients who had multiple cutaneous lesions and who were treated with TSI were classified into the RT treatment Group 3, not RT treatment Group 1, because the fractionated dose used in TSI was different that used for the other groups. When a patient had multiple lesions and all lesions were treated concurrently with multiple radiation fields, the patient was classified into Group 1. When multiple lesions were all treated concurrently with multiple radiation fields using the same radiation source and radiation dose, the courses were defined as one RT course.

Additionally, RT for patients was classified according to the RT policy as follows: curative, adjuvant or palliative.

Other than in TSI, the clinical target volume was delineated with an appropriate margin for the gross tumor volume. Regional lymph nodes or prophylactic areas were not included in the clinical target volume.

The institutional review board at our hospital approved this retrospective study (No. 1143), and the need for informed consent was waived. This study was conducted in accordance with the Declaration of Helsinki and Japanese ethical guidelines for epidemiologic research.

Evaluation

Patients were mainly assessed and treated by hematological oncologists or dermatologists. In addition, they were evaluated weekly by radiation oncologists during RT. Due to the long period covered by this retrospective study, surveillance after RT was non-uniform. Patient assessment included physical examination, blood examination, computerized tomography, magnetic resonance imaging, and fluorodeoxyglucose positron emission tomography (FDG-PET). The timing and the method of assessment were at the discretion of the treating hematological oncologist or dermatologist.

Treatment response to RT was assessed using the Japan Clinical Oncology Group criteria for ATL, modified according to the International Consensus Meeting recommendations [14]. Unconfirmed complete remission (uCR) was also defined as partial remission (PR) in this study because precisely distinguishing between uCR and PR was difficult. Bone marrow and hematological status, such as absolute lymphocytic count or percentage of circulating abnormal lymphocytes, were not used to evaluate treatment response to RT. Acute and late non-hematological toxicities were scored according to the Common Terminology Criteria for Adverse Events Version 4.0 and the Radiation Therapy Oncology Group and the European Organization for Research and Treatment of Cancer, respectively [15]. Hematological toxicities were not evaluated in this study because they were strongly influenced by the state of ATL and chemotherapy.

Follow-up was terminated when the patient died or during the last visit to the hospital. In-field and out-of-field progression after RT were defined as (i) both regrowth and new detectable lesions within the treatment field and (ii) development of new lesions or systemic disease and enlargement of known lesions outside the treatment field, respectively. The time of re-exacerbation of symptoms and in-field relapses after RT were determined based on medical records. When no data on in-field relapses were available or

when in-field relapses apparently occurred but the timing was unknown, censored data were used for calculating local progression-free survival (LPFS) at the most recent time point when it could be confirmed that no in-field relapses occurred.

When in-field or out-of-field progression was not indicated in the clinical record at the last follow-up, the patient status during the last evaluation was determined according to the most recently recorded status of in-field or out-of-field disease.

Statistical analysis

The Student's *t*-test and one-way analysis of variance with the *post hoc* Tukey test were used for analysis of continuous variables. Meanwhile, the Chi-squared test and Fisher's exact test for discrete variables were used to compare proportions. The Kaplan–Meier method was used to estimate overall survival (OS) and LPFS. The log-rank test was used for comparison of OS and LPFS between groups. *P* values of <0.05 were considered significant. All statistical analyses were performed using the JMP version 12.0.1 software (SAS Institute).

RESULTS

Patients

Within the study period, 41 consecutive patients with ATL received a total of 55 courses of RT. The median patient age was 66 years (range, 33–85 years). The cohort comprised 24 male patients (59%) and 17 female patients (41%). A total of 16 (39%), 14 (34%), 2 (5%) and 9 (22%) patients had acute, chronic, and smoldering ATL, respectively. All patients with chronic ATL were diagnosed with favorable subtype. In total, 4 (9.8%) and 30 (73%) patients received HSCT and chemotherapy (curative intent, *n* = 20; palliative intent, *n* = 10), respectively, before RT.

Cutaneous lesions and the lesions close to the body surface (*n* = 22) were treated with electron beams (3–12 MeV). Otherwise (*n* = 33), lesions were treated with photon beams (4–15 MV).

After RT, 3 (7.3%) patients received HSCT, while 24 (59%) received chemotherapy (curative, *n* = 12; palliative, *n* = 12). During the observation period, 10 of the 11 patients (91%) with indolent ATL progressed to aggressive ATL. The median follow-up for the entire cohort was 209 days (range, 8–5240 days). At the last evaluation, 8 of the 41 patients were alive, while the other 33 were dead. The median survival time (MST) after initial RT was 245 days (aggressive ATL, 189 days; indolent ATL, 294 days). The 1-, 2- and 5-year OS rates after initial RT were 37% (aggressive ATL, 32%; indolent ATL, 50%), 25% (aggressive ATL, 19%; indolent ATL, 40%) and 15% (aggressive ATL, 15%; indolent ATL, 20%), respectively.

Patients with no disease outside of the radiation field at the time of RT

Eleven courses of RT were performed for 10 patients with in-field-only disease (Table 1). In this cohort, the RT policy comprised curative (*n* = 3), adjuvant (*n* = 5) and palliative RT (*n* = 3). The median age of the patients in this group was 63 years (range, 33–84 years). The Eastern Cooperative Oncology Group performance status (ECOG PS) was 0–1 in all 10 patients. The median

maximum diameter of the evaluable five lesions was 70 mm (range, 20–100 mm).

In this group, a median dose of 40 Gy (range, 22–50 Gy) in 1.5–3 Gy per fraction was used. In-field relapses were observed in four lesions of 3 patients. After RT, 9 of the 10 patients (90%) experienced out-of-field progression. The median follow-up for this group was 294 days (range, 74–5240 days).

Patients with known disease outside of the field at the time of RT

In this group, 25 patients received a total of 35 courses of RT (Tables 2 and 3). Of the 35 courses of RT, 32 courses for 24 patients were aimed at symptomatic relief. The remaining 3 courses of RT for 1 patient with smoldering-type ATL were performed with curative intent. Of the 35 courses of RT performed, 26 courses had preceded systemic chemotherapy (curative, *n* = 17; palliative, *n* = 9). Most of the patients (21 of 25) had aggressive ATL, while the rest had indolent ATL. The median maximum diameter of the evaluable 10 lesions was 50 mm (range, 20–100 mm). In this group, target lesions mainly consisted of nodal (*n* = 12), cutaneous (*n* = 11) or bone (*n* = 7) lesions.

The patients were treated with various dose-fractionation regimens because patient characteristics such as age, ECOG PS [16], and expected prognosis varied significantly. RT was discontinued in 5 of the 35 courses due to deteriorating general condition.

All 25 patients experienced out-of-field progression after RT, and 24 patients were dead at the last evaluation. The median follow-up of the patients of this group was 158 days (range, 8–5086 days).

Total skin irradiation

Nine patients with multiple cutaneous lesions underwent TSI (acute, *n* = 3; lymphoma, *n* = 1; chronic, *n* = 2; smoldering, *n* = 3). The median age was 75 years (range, 52–85 years) and the ECOG PS was 0–1 in all 9 patients. Before TSI, 4 patients were administered chemotherapy (curative, *n* = 2; palliative, *n* = 2), but the remaining 5 patients did not receive any prior systemic therapy. All 4 patients with aggressive ATL had lesions in areas other than the skin and underwent TSI for palliative intent. All 5 patients with indolent ATL had only cutaneous lesions and underwent TSI for curative (*n* = 4) or palliative (*n* = 1) intent. The patients were treated with 15–30 Gy in 1 Gy per fraction with 3–4 MeV electron beams.

CR, PR and SD were achieved in 3, 5 and 1 patient(s), respectively. After TSI, 8 of the 9 patients were administered chemotherapy (curative, *n* = 4; palliative, *n* = 4). In-field relapses occurred in all 9 patients (regrowth only, *n* = 1; new detectable lesions only, *n* = 4; both regrowth and new detectable lesions, *n* = 4), and the median time to in-field relapses was 63 days (range, 7–210 days) (Fig. 1). LPFS tended to be longer in patients with indolent ATL than in those with aggressive ATL, but the difference was not significant (see Supplementary Figure 1). No considerable difference was observed in the Kaplan–Meier curve of LPFS when patients were categorized according to the RT policy (curative or palliative) and treatment response to RT (CR or non-CR). Out-of-field

Table 1. Patients with no out-of-field disease at the time of RT

Patient	ATL type	Prior systemic therapy	RT site	Lesion type	RT policy	RT energy	Total dose, Gy	Fractionated dose, Gy	In-field treatment response	In-field relapses	Out-of-field progression	Additional systemic therapy after RT	Time from RT to last evaluation (days)	Status at last evaluation (disease/metastatic status)
16	Lymphoma	HSCT	Axilla	Nodal	Curative	6 MV	50	2	CR	No	Yes	Natural killer cell infusion	897	Alive
20-1	Lymphoma	CHOP/CEP	Inguinal region	Nodal	Adjuvant	9 MeV	40	2	CR	Yes (N)	Yes	ETP, CPA	154	Dead (local, distant)
20-2	Lymphoma	CHOP/CEP	Chest	Cutaneous	Adjuvant	9 MeV	40	2	CR	Yes (Re)	Yes	ETP, CPA	151	Dead (local, distant)
23	Lymphoma	CHOP	Abdomen	Nodal	Adjuvant	18 MV	30	1.5	SD	Yes (Re)	Yes	CHOP	204	Dead (local, distant)
26	Smoldering	CHOP ^a	Paranasal sinus	Extra-nodal	Curative	6 MV	50	2	CR	No	Yes	CHOP/ESHAP/ETP, CPA	961	Dead (distant)
27	Acute	CHOP	Neck	Nodal	Adjuvant	6 MV	45	1.8	CR	No	No	No	5240	Alive
36	Smoldering	No	Elbow	Cutaneous	Palliative	9 MeV	22 ^b	2	PR	No	Yes	No	74	Alive (distant)
37	Smoldering	No	Multiple cutaneous	Cutaneous	Curative	9-12 MeV	40	2	PR	No	Yes	CHOP/DHAP	294	Dead (distant)
39	Acute	C-MOP(P)/THP-CO(P)/ETP	Inguinal region	Nodal	Palliative	10 MV	30	3	SD	Yes (Re)	Yes	THP-CO(P)	184	Dead (local, distant)
41	Acute	HSCT	Shoulder	Muscle	Palliative	4 MV	40	2	CR	No	Yes	No	331	Dead (distant)
43	Lymphoma	CHO/CHOP/DHAP	Abdomen	Nodal	Adjuvant	N/A	40	2	CR	No	Yes	ETP	525	Alive (distant)

RT = radiotherapy, HSCT = hematopoietic stem cell transplantation, CR = complete remission, CHOP = cyclophosphamide + doxorubicin + vincristine + prednisolone, CEP = cyclophosphamide + etoposide + prednisolone, N = new detectable lesions, ETP = etoposide, CPA = cyclophosphamide, Re = regrowth, SD = stable disease, ESHAP = etoposide + methylprednisolone + high-dose cytarabine + cisplatin, PR = partial remission, DHAP = dexamethasone + high-dose cytarabine + cisplatin, C-MOP(P) = cyclophosphamide + vincristine + procarbazine, THP-CO(P) = pirarubicin + cyclophosphamide + vincristine, CHO = cyclophosphamide + doxorubicin + vincristine, N/A = not available. MV indicates photons were used; MeV indicates electrons were used as the radiation source. In the column 'Disease at last evaluation', 'local' indicates that the patient had in-field disease including relapses and residual disease, and 'distant' indicates that the patient had out-of-field disease.

^aThis patient was treated sequentially with CHOP, 20 Gy radiation, CHOP, 20 Gy radiation, CHOP, and 10 Gy radiation. In the week CHOP was given, RT was stopped for a week.

^bInitially, 30 Gy was planned, but this patient did not complete RT.

Table 2. Patients with known out-of-field disease at the time of RT

Patient characteristics	Number	%
Age, years		
≥80	3	12
70–79	6	24
60–69	5	20
50–59	9	36
≤49	2	8
Sex		
Male	15	60
Female	10	40
ECOG PS ^a		
0–1	12	48
2	5	20
3	4	16
4	3	12
ATL type		
Acute	11	44
Lymphoma	10	40
Chronic	1	4
Smoldering	3	12

ECOG = Eastern Cooperative Oncology Group, PS = performance status, ATL = adult T-cell leukemia/lymphoma.

^aThe ECOG-PS of one patient was unknown.

progression occurred in 8 of the 9 patients. The median follow-up of this group was 372 days (range, 84–2413 days). At the last evaluation, 3 patients (acute, $n = 1$; smoldering, $n = 2$) were alive, and the other 6 were dead. MST after TSI of all the 9 patients in the group was 443 days (aggressive ATL, 168 days; indolent ATL, 443 days). The 1-year OS rate after TSI was 56% (aggressive ATL, 50%; indolent ATL, 60%), while the 2- and 5-year OS rates were similar at 28% (aggressive ATL, 0%; indolent ATL, 40%).

Curative RT

In total, 10 courses of RT with curative intent were performed for 8 patients (lymphoma, $n = 1$; chronic, $n = 1$; smoldering, $n = 6$). In this group, four TSI courses were performed for the 4 patients with indolent ATL (chronic, $n = 1$; smoldering, $n = 3$). One patient with lymphoma-type ATL underwent RT for a relapsed lesion after intensive systemic therapy including HSCT, another patient with smoldering-type ATL underwent sequential chemoradiotherapy

Table 3. Radiotherapy for the patients with known out-of-field disease at the time of RT

	Number	%
RT policy		
Palliative	32	91
Curative	3	9
Dose-fractionation regimens		
50 Gy/25 Fr	3	9
30 Gy/10 Fr	8	23
30 Gy/15 Fr	3	9
25 Gy/10 Fr	7	20
20 Gy/10 Fr	4	11
Others ^a	10	29
In-field treatment response to RT		
CR	7	26
PR	13	48
SD	7	26
In-field relapses ^b		
Yes (regrowth)	7	29
(New detectable lesions)	1	4
No	16	67

Fr = fraction, RT = radiotherapy, CR = complete remission, PR = partial remission, SD = stable disease.

Percentages in this column may not add up to exactly 100% because of rounding off. Cases that could not be assessed were excluded from analysis of symptomatic improvement, in-field treatment response, and in-field relapses.

^aOthers includes five cases that did not complete RT.

^bNo patient in this group experienced both regrowth and new detectable lesions within the treatment field.

with cyclophosphamide, doxorubicin, vincristine and prednisolone, and the other 6 patients did not receive chemotherapy or HSCT before RT.

The patients who underwent TSI were treated with 20 or 30 Gy in 1-Gy per fraction, and the other patients were treated with 40 or 50 Gy in 2-Gy per fraction. CR ($n = 5$) or PR ($n = 5$) was achieved for all lesions. After curative RT, 6 of the 8 patients were administered chemotherapy for curative ($n = 4$) or palliative ($n = 2$) intent.

In addition to the 4 patients who underwent TSI, only 1 patient with smoldering-type ATL experienced in-field relapses 317 days after RT. The other 3 patients did not have in-field relapses. Out-of-field progression occurred in 7 of the 8 patients. At the last evaluation, 3 patients (lymphoma, $n = 1$; smoldering, $n = 2$) were alive, and the other 5 were dead. MST after curative RT was 754 days, and the 1- and 2-year OS rates after curative RT were similar at

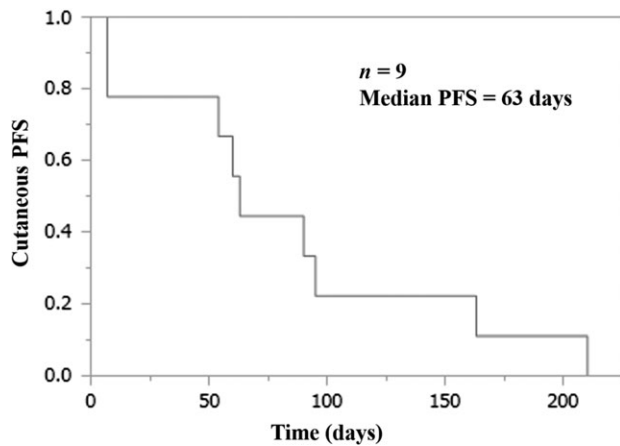


Fig. 1. Cutaneous progression-free survival (PFS) after total skin irradiation (TSI). Cutaneous relapses with a median time of 63 days (range, 7–210 days) were observed in all nine patients who received TSI.

63%. Meanwhile, the 5-year OS rate was 33%. The number of days from first course of RT to death was used to calculate OS in the 1 patient who received 3 courses of RT.

Adjuvant RT for residual lesions after intensive chemotherapy

Five RT courses with adjuvant intent were performed for 4 patients (acute, $n = 1$; lymphoma, $n = 3$) for residual lesions immediately after intensive chemotherapy (Patients 20, 23, 27 and 43 in Table 1).

The patients were treated with regimens of 30 Gy in 20 fractions ($n = 1$), 40 Gy in 20 fractions ($n = 3$) or 45 Gy in 25 fractions ($n = 1$). CR was achieved in four lesions of 3 patients, and SD was observed in one lesion. After RT, 3 of the 4 patients were adminis-

tered chemotherapy.

In-field relapses occurred in three lesions of 2 patients, and the median time to in-field relapses was 37 days (range, 11–50 days). All patients experienced out-of-field progression. At the last evaluation, 2 patients were alive, and the other 2 were dead. In this group, MST from RT was 204 days, and the 1, 2 and 5-year OS rates were similar at 50%. The number of days from first course of RT to death was used to calculate OS in the 1 patient who received two courses of RT.

Palliative RT

In total, 40 RT courses with palliative intent were performed for 31 patients (acute, $n = 15$; lymphoma, $n = 11$; chronic, $n = 2$, smoldering, $n = 3$). Two patients in this group had previously received RT with curative intent. Five TSI courses were performed in this group.

The median age was 66 years (range, 34–84 years). The ECOG PS was 0–1 in 19 patients, 2–3 in 9 patients, and 4 in 2 patients. The PS of 1 patient was unknown. Prior to palliative RT, four patients received HSCT, 19 patients received chemotherapy (curative, $n = 10$; palliative, $n = 9$) and 8 patients did not receive any prior systemic therapy. The major symptoms were pain ($n = 16$), cosmetic distress ($n = 10$), discomfort due to mass ($n = 7$), neuropathy ($n = 6$) and airway obstruction ($n = 5$) (Table 4).

Various dose-fractionated regimens were used in palliative RT, and the frequently used regimens were 20–30 Gy in 10 fractions ($n = 20$) or 30 Gy in 15 fractions ($n = 3$). Two lesions were irradiated with a dose of >30 Gy for symptom palliation, and the regimen of these two courses was both 40 Gy in 20 fractions. Nine courses of RT used regimens of <20 Gy in total dose.

After palliative RT, 3 patients received HSCT, and 18 patients were administered chemotherapy (curative, $n = 6$; palliative, $n = 12$). Ten patients did not receive systemic therapy after palliative RT.

Symptomatic improvement after palliative RT was assessable in 36 of the 40 cases; it was achieved in 92% (33/36) of the cases. Re-exacerbation of symptoms after palliative RT was observed in 10 of

Table 4. Symptomatic improvement and time to re-exacerbation

Symptom ^a	Number	Symptom improvement			Duration of symptomatic improvement ^b (days) Median (range)	Re-exacerbation			Time to re-exacerbation ^c (days) Median (range)
		Yes	No	N/A		Yes	No	N/A	
Pain	16	14	0	2	74 (7–430)	7	6	1	63 (7–120)
Cosmetic distress	10	9	0	1	95 (7–393)	5	4		10 (7–262)
Discomfort due to mass	7	5	1	1	260 (51–5086)	0	4	1	
Neuropathy	6	4	2		326 (100–431)	0	4		
Airway obstruction	5	5	0		49 (19–66)	0	4	1	
Itchiness	2	2	0		161 (60–262)	2	0		161 (60–262)
Effusion/bleeding	2	2	0		98 (60–137)	1	1		60

^aSymptoms included are overlapping.

^bDuration of symptomatic improvement was calculated from the data for all patients who had symptomatic improvement; the number of days to the last evaluation, including death, was used for the calculation for patients who had no re-exacerbation.

^cTime to re-exacerbation was calculated only from the data for patients who had re-exacerbation of symptoms.

the 33 cases. The presence or absence of symptom recurrence was not assessable in 3 patients because they transferred to another hospital after palliative RT. The median duration of symptom improvement was 95 days (range, 7–5086 days).

At the last evaluation, 4 patients were alive and 27 were dead in this group. MST after palliative RT was 167 days (aggressive ATL, 126 days; indolent ATL, 167 days). The 1-year OS rate after palliative RT was 26% (aggressive ATL, 26%; indolent ATL, 25%), while the 2- and 5-year OS rates were similar at 4.4% (aggressive ATL, 5.2%; indolent ATL, 0%). The patients who underwent curative RT before palliative RT were excluded from the calculation of OS. The number of days from first course of palliative RT to death or last visit to the hospital was used to calculate OS in the patients who received two or more courses of palliative RT.

Treatment response to radiotherapy

In this study, treatment response to RT was examined in 41 courses of RT for 41 patients. The treatment response to the first course of RT was examined in those patients who received 2 or more courses of RT to reduce the influence of bias. Treatment response to RT could not be evaluated in 3 of the 41 patients because their general condition rapidly worsened during RT, and local lesions were not assessed sufficiently.

Among the 38 evaluable cases, CR was achieved in 13 (34%), PR was achieved in 17 (45%) and SD was achieved in 8 (21%) of the cases. Progressive disease was not observed.

The differences in patient characteristics and methods of treatment between the groups that achieved CR, PR and SD were investigated. The mean total radiation dose of the CR group was 38 Gy (range, 20–50 Gy), and it was significantly higher than that of the PR group at 25 Gy (range, 10–40 Gy; $P = 0.0002$) and the SD group at 23 Gy (range, 9–30 Gy; $P = 0.0005$) (Fig. 2). However, the mean total radiation dose did not differ significantly between the PR and SD groups.

Because various dose-fractionation regimens were used, the relationship between equivalent dose in 2 Gy fractions (EQD2) (assumed $\alpha/\beta = 10$) and treatment response to RT was examined. The mean EQD2 of the CR group (46 Gy) was significantly higher than that of the PR (30 Gy; $P = 0.0002$) and SD groups (28 Gy; $P = 0.0008$).

The relationship between total radiation dose and local response is shown in Table 5. In 9 lesions irradiated with ≥ 40 Gy, CR (89%, $n = 8$) or PR (11%, $n = 1$) was achieved at a rate of 100%. In 14 lesions irradiated with 30–39 Gy, CR (29%, $n = 4$) or PR (43%, $n = 6$) was obtained at a rate of 71%. In 15 lesions irradiated with ≤ 29 Gy, CR (7%, $n = 1$) or PR (67%, $n = 10$) was obtained at a rate of 73%.

ATL types, lesion types (e.g. cutaneous versus non-cutaneous) and lesion size showed no significant differences in terms of treatment response to RT.

The OS curve differed significantly between patients who achieved CR and SD ($P < 0.0001$), and between those who achieved PR and SD ($P = 0.001$) (Fig. 3). MST after the first RT course was 686, 294 and 33 days; the 1-year OS rates were 62%, 38% and 0%; the 2-year OS rates were 45%, 23% and 0%; and the 5-year OS rates were 24%, 15% and 0% in the patients who achieved CR, PR and SD, respectively.

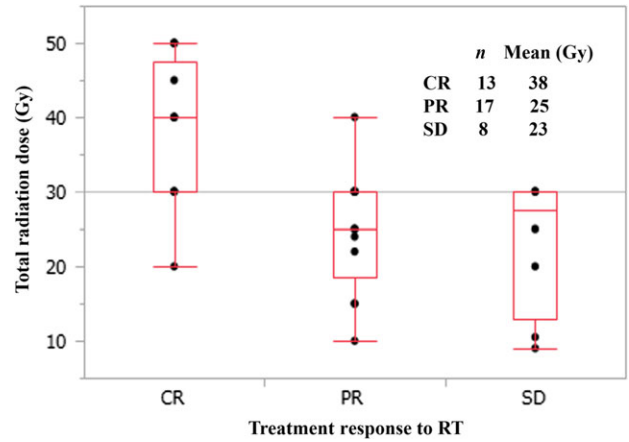


Fig. 2. Total radiation dose and treatment response to RT. The mean total radiation dose differed significantly between the complete remission (CR) and partial remission (PR) groups (38 vs 25 Gy, respectively; $P = 0.0002$) and between the CR and stable disease (SD) groups (38 vs 23 Gy, respectively; $P = 0.0005$). However, the mean total radiation dose did not differ significantly between the PR and SD groups. The *post hoc* Tukey test was used for the analysis.

Table 5. Relationship between total radiation dose and local response

	CR	PR	SD
≥ 40 Gy	8	1	0
30–39 Gy	4	6	4
≤ 29 Gy ^a	1	10	4

^aTreatment response to RT could not be evaluated in 3 of 41 patients because their general condition rapidly worsened during RT, and assessment of local lesions was insufficient. All of those 3 patients received ≤ 29 Gy irradiation.

In-field relapses

In-field relapses after the first course of RT were investigated in patients who underwent 2 or more courses of RT to reduce the influence of bias. Moreover, the nine patients who received TSI were excluded from the calculation of in-field relapses because they all had in-field relapses; they have been described in the section ‘Total skin irradiation’. The presence or absence of in-field relapses during follow-up was assessable in 28 of the 32 patients; 36% ($n = 10$) of the patients with lesions treated with their first course of RT experienced in-field relapses.

The frequency of in-field relapses was 11% (1/9), 30% (3/10) and 71% (5/7) among the patients who achieved CR, PR and SD, respectively, and the difference between the three groups was significant ($P = 0.04$). In-field relapse also occurred in 1 of 2 lesions in which treatment response to RT was not evaluable.

ATL types, lesion types (e.g. cutaneous versus non-cutaneous), lesion size, the presence or absence of out-of-field disease, and the

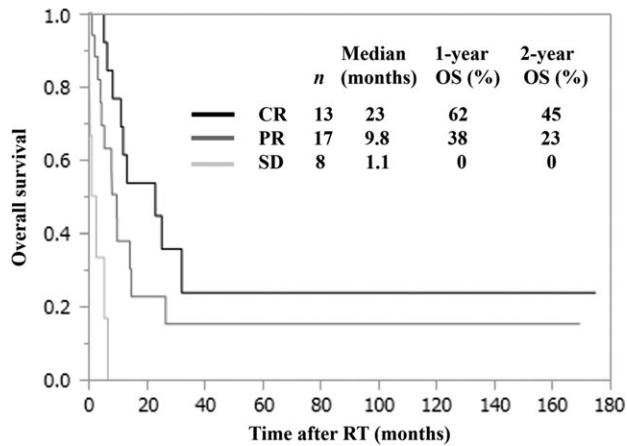


Fig. 3. Overall survival (OS) after radiotherapy (RT). OS after RT differed significantly between patients who had achieved complete remission (CR) and those who had achieved stable disease (SD) ($P < 0.0001$), and between the partial remission (PR) and SD groups ($P = 0.001$). Median survival times (MSTs) after the first RT course were 23, 9.8 and 1.1 months in the CR, PR and SD groups, respectively. The 1-, 2- and 5-year OS rates were 62%, 45% and 24%, respectively, in the CR group and 38%, 23% and 15%, respectively, in the PR group. No patient who achieved SD in the first course of RT survived for 1 year after RT.

presence or absence of additional chemotherapy showed no significant differences between patients with respect to in-field relapse.

The LPFS rate of the target lesions was 8–5240 days. The median time of LPFS was 76 days (CR, 355; PR, 74; SD, 19 days). The 1- and 2-year LPFS rates were 50% and 40%, 18% and 9%, and both 0% in those who achieved CR, PR and SD, respectively.

The Kaplan–Meier curve of LPFS differed significantly between the lesions that achieved CR and SD ($P < 0.0001$), and between those that achieved PR and SD ($P = 0.0022$) (Fig. 4). The Kaplan–Meier curve of LPFS was also significantly different when the patients were classified according to total radiation dose (≥ 40 , 30–39, ≤ 29 Gy, $P = 0.04$). By contrast, no significant difference was observed when patients were categorized according to ATL type (aggressive vs indolent, $P = 0.93$) and RT policy ($P = 0.10$).

Out-of-field progression

After RT, 39 of the 41 patients (95.1%) experienced out-of-field progression. One patient who did not experience out-of-field progression only had in-field nodal lesions and was treated with adjuvant RT of 45 Gy after receiving chemotherapy for acute ATL (Table 1). Another patient did not experience out-of-field progression, but experienced in-field relapse after TSI of 30 Gy for smoldering ATL. Neither of the patients received any additional chemotherapy after RT.

Toxicity

Acute radiation-related toxicities consisted mainly of mild dermatitis, mucositis, and fatigability. The maximum acute toxicity was Grade 2

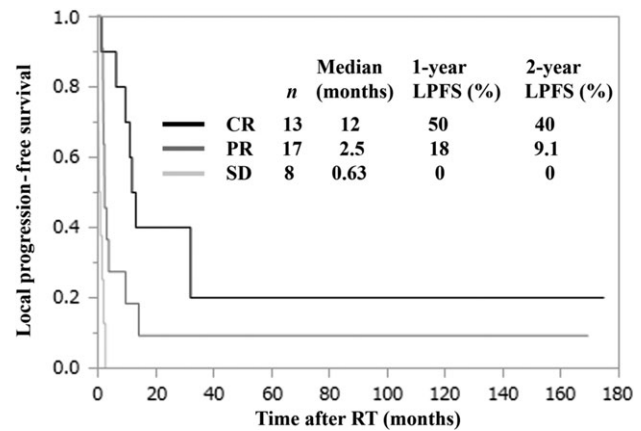


Fig. 4. Local progression-free survival (LPFS) and treatment response to radiotherapy (RT). The Kaplan–Meier curve of LPFS differed significantly between patients who achieved complete response (CR) and those who achieved stable disease (SD) ($P < 0.0001$) and between those who achieved partial remission (PR) and those who achieved SD ($P = 0.0022$). The median time of LPFS was 2.5 months (CR, 12; PR, 2.5; SD, 0.63 months). The 1- and 2-year LPFS rates were 50% and 40% in the CR group, 18% and 9.1% in the PR group, and both 0% in the SD group, respectively. The nine patients who received total skin irradiation were excluded from this calculation.

in all patients, except for only one patient who was treated with electrons of 50 Gy and experienced Grade 3 radiation-induced dermatitis. No patient had Grade 4–5 acute toxicities, and no late radiation-related toxicities were observed.

DISCUSSION

This study confirmed the effectiveness of palliative RT for patients with ATL. Symptomatic improvement was achieved in 92% of the cases, and the rate was similar to that found in another study [11].

Re-exacerbation of symptoms after palliative RT was observed in approximately one-third of the lesions. The frequency of re-exacerbation differed depending on the type of symptoms. Pain, cosmetic distress, itchiness, and effusion/bleeding were re-exacerbated in $>50\%$ of patients. Furthermore, the time to re-exacerbation of these symptoms was relatively short. In particular, the time to re-exacerbation was short in the lesions with a symptom of cosmetic distress, and the median time was only 10 days. This result was probably due to the inclusion of patients in whom palliative TSI was performed to improve cosmetic distress, but they had new cutaneous lesions within a short time after TSI. The result might have been better if the evaluation included a comparison of the degree of cosmetic distress before and after palliative RT.

Nevertheless, the symptoms of airway obstruction, discomfort due to mass, and neuropathy did not re-exacerbate. Although airway obstruction did not re-exacerbate, the median duration of airway obstruction improvement was relatively short at 49 days, indicating that the patients with airway obstruction died shortly after palliative RT. By contrast, the symptoms of neuropathy and discomfort due to mass had relatively long duration of symptomatic improvement.

It seemed reasonable that these two symptoms showed a similar trend because both are caused by compression or tumor invasion. The lowest rate of symptomatic improvement was in neuropathy at 67%. This might be due to the adverse effect of chemotherapy.

Regarding total radiation dose, >30 Gy was rarely employed for palliative RT in this study, and the radiation dose might be insufficient for long-term control of pain, cosmetic distress, itchiness, or effusion/bleeding. Considering the maximum time to re-exacerbation, a higher radiation dose may be appropriate for these symptoms if the prognosis of the patients appears to be longer than 4 months for symptoms of pain and 8 months for cosmetic distress and itchiness.

One study reported the efficacy of low-dose palliative radiotherapy for other cutaneous T-cell lymphomas (mycosis fungoides) [17]. CR was achieved in 92% using the regimen of 8 Gy in 2 fractions in that study. ATL and mycosis fungoides are both peripheral T-cell lymphoma; however, it was difficult to obtain CR in ATL with such a low radiation dose. Therefore, the regimen of 8 Gy in 2 fractions might not be suitable for the palliation of cutaneous symptoms of ATL.

By contrast, short courses of RT would be appropriate for the palliation of the patients with airway obstruction because the prognosis of these patients was extremely poor.

As for treatment response to RT, CR or PR was achieved in 30 of the 38 cases (79%) [CR: 13/38 (34%); PR: 17/38 (45%)] in the present study. Simone *et al.* investigated 20 ATL lesions treated with RT, and they reported that CR or PR was achieved in 100% of the 20 lesions (CR, 40%; PR, 60%) [11]. No remarkable difference in treatment was noted between our study and that by Simone *et al.*, but the subjects' ethnicity was different. All the patients in the present study were Japanese, while they were all Caribbean in the study by Simone *et al.* In addition, the present study included more patients. Thus, the difference in the rate might be due to differences in the patient characteristics or the number of patients included in the two studies. In the current study, the mean total radiation dose of the CR group was 38 Gy, but the total radiation dose for each patient varied significantly, ranging from 20 to 50 Gy. This result would be affected by the differences in combined chemotherapy or in clinical forms of ATL.

The patients who achieved local CR or PR via RT had a better OS rate than those who achieved SD; however, this result was considerably affected by a selection bias. For example, the patients who achieved CR were treated with a higher radiation dose than the patients who obtained SD because they were considered to have a better prognosis at the time of RT. In addition, almost all patients with ATL experienced out-of-field progression after RT, even if local CR was achieved. Therefore, the contribution of local CR via RT to survival remains unclear.

It may be meaningful to receive RT with a relatively high dose to achieve local CR in patients who have a possibility of long-term survival, because in-field relapses were as low as 11% in the lesions that achieved CR. Excessive radiation doses should not be used because the frequency and severity of radiation-related adverse events depend on the radiation dose [18]. To achieve a good treatment response to RT, we consider that a radiation dose of 40–50 Gy is feasible. This is

because CR was achieved at 89% of lesions, CR plus PR was obtained at 100% of lesions treated with ≥ 40 Gy irradiation, and no patient treated with ≤ 50 Gy radiation dose developed any severe adverse event in the current study. Despite no clear evidence on efficacy, a dose of 40–60 Gy empirically has often been used to treat aggressive T-cell lymphoma, including ATL in reference to the 30–50 Gy radiation dose frequently used for aggressive B-cell lymphoma [19, 20]. The optimal dose determined in the present study was consistent with the empirical therapeutic dose for the treatment of aggressive T-cell lymphoma, including ATL.

The patients who obtained SD via RT had short OS, indicating that low-dose RT was performed in the patients who were expected to have a poor prognosis then obtained SD, not in the patients who died within a short time after RT because of local treatment failure. In-field relapses were common for the lesions of patients who achieved SD, although the survival period was short in these patients. This result may indicate that in patients with extremely poor prognosis due to ATL progression, in-field relapses often occurred even shortly after RT. Symptomatic improvement was achieved at a high rate with regimens of <30 Gy of total radiation dose. Therefore, it would be reasonable to treat patients with such regimens of palliative RT when the patient prognosis seems to be poor.

Because the clinical course of the patients varied considerably, various dose-fractionation regimens were included in this retrospective study. The concept of EQD2 and biological equivalent dose (BED) is useful for quantifying the different dose-fractionation regimens in many cases [21]. In the current study, the mean EQD2 (assumed $\alpha/\beta = 10$) of the CR group was significantly higher than that of the PR and SD groups, but this was almost consistent with the findings on the relationship between total radiation dose and treatment response to RT. In addition, the true α/β of ATL was unknown. Therefore, the usefulness of EQD2 or BED was considered to be limited in the current study.

Treatment response to RT with respect to ATL types, lesion types (e.g. cutaneous vs non-cutaneous) and lesion size did not differ significantly in this study. Simone *et al.* also reported that RT can achieve excellent local control and symptomatic improvement in several lesion types and ATL types [11]. The results of our study are consistent with theirs. However, the result regarding the relationship between treatment response to RT and lesion size should be interpreted with caution, because large lesions might have been treated with high doses, and only 15 lesions were assessable for size in this study.

Regarding in-field relapses after RT, subsequent in-field relapses were not seen for 70% of the lesions, even with PR. This result might have been affected by chemotherapy. However, it may indicate the limitation of evaluating treatment response only in terms of morphology. The previous study reported the clinical usefulness of FDG-PET for evaluating ATL; as such, FDG-PET may be able to predict whether ATL lesions will have tumor regrowth after RT [22].

All 9 patients who received TSI experienced in-field relapses within 7 months. The total radiation dose for these patients was relatively small. In addition, uniformly irradiating all cutaneous lesions was difficult, and some parts of a cutaneous lesion would be irradiated with a small dose. We initially thought that the small

treatment dose might cause treatment failure and lead to a very high rate of recurrence after TSI. However, the development of in-field relapses was also observed in all the patients who achieved CR with TSI, although the rate of in-field relapses after achieving CR was low in the patients who received RT other than TSI. Thus, cutaneous relapses were considered to be likely caused by the characteristics of ATL manifesting mainly as multiple cutaneous lesions. From this result, we strongly believe that TSI is not suitable for the treatment of ATL with curative intent, at least in a conventional method. In contrast, TSI may be useful for symptomatic relief for a short period, because CR or PR was achieved at the high rate of 89% (8/9 of the patients). A study reported the effectiveness of palliative TSI for 18 patients with other cutaneous T-cell lymphomas [23]. In that study, the frequently used regimen was 25 Gy in 1 Gy per fraction, which is similar to that of the present study. The rate of symptom improvement reported in that study was 89%, which is also similar to that in the present study. The 1-year RFS rate was 24% in that study, and the rate was better than that in the current study. This difference might be due to difference in the disease included, that is, most patients in that study had mycosis fungoides.

This study has several limitations. The number of included patients was small, and they were limited to patients who received RT in only one institution. There might be a selection bias of pre-RT status of the patients, for example, progressive disease status or refractory status, or having large lesions, because patients with ATL are typically treated with chemotherapy as initial treatment. The medical records were sometimes insufficient because this study was conducted retrospectively. There was no photograph of the skin lesions in many cases, and we had to rely on the medical record for the evaluation. Thus, the evaluation might have included errors in some cases, for example, uCR might have been described as CR in the medical record at that time. We could not evaluate the degree of symptomatic improvement, because no unified measurement tool was employed for assessment. There was often no data on chemotherapy response for local lesions in the medical record, and the influence of chemotherapy on patient outcomes could not be analyzed. The timing of patient assessment was heterogeneous. The clinical courses of the patients and dose-fractionation regimens varied. Because OS and PFS of the patients with or without RT were not compared in this study, the impact of RT on the prognosis of patients with ATL remains unclear.

The institution where this study was conducted is located in an area where HTLV-1 is prevalent, and many patients with ATL are treated there. We plan to perform further analysis with more cases in the future.

In conclusion, RT was confirmed to be effective and safe for the palliative treatment of local ATL lesions.

SUPPLEMENTARY DATA

Supplementary data are available at *Journal of Radiation Research* online.

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CONFLICT OF INTEREST

The authors have no competing financial interests.

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