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Palliative radiotherapy for multiple liver metastases: a retrospective analysis of 73 cases

Kei Ito*, Yumi Ogoshi and Takuya Shimizuguchi

Division of Radiation Oncology, Department of Radiology, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, Tokyo, Japan

*For reprints and all correspondence: Kei Ito, Division of Radiation Oncology, Department of Radiology, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, 3-18-22 Honkomagome, Bunkyo-ku, Tokyo 113-8677, Japan. E-mail: keiito@cick.jp

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Abstract

Background: Whole-liver radiotherapy for diffuse liver metastases can improve symptoms and abnormal liver-related blood data. However, whole-liver radiotherapy is uncommonly used in clinical practice in Japan. Therefore, we aimed to clarify palliative radiotherapy outcomes in Japanese patients with liver metastases.

Methods: We retrospectively reviewed databases in our institution to identify patients treated with radiotherapy (8 Gy in a single fraction) for multiple liver metastases between December 2014 and April 2021. The endpoints included pain response, liver-related blood data and adverse effects. We investigated aspartate transaminase, alanine transaminase, lactate dehydrogenase, alkaline phosphatase, γ-glutamyl transpeptidase and albumin. The mean values at whole-liver radiotherapy and after 2–4 weeks were compared using the Wilcoxon rank-sum test.

Results: A total of 73 cases in 71 patients were included. The median clinical target volume was 2118 ml (range, 133–7867 ml). Fifty-seven patients (78%) had finished aggressive treatment at the time of radiotherapy. The median follow-up period was 6 weeks. The pain response rate was 64% (18/28). The mean values of five parameters significantly improved 2–4 weeks after radiotherapy compared to those at baseline: aspartate transaminase (118 vs. 83 U/l $P < 0.01$); alanine transaminase (84 vs. 61 U/l $P < 0.01$); lactate dehydrogenase (1351 vs. 1007 U/l $P = 0.027$); alkaline phosphatase (1624 vs. 1216 U/l $P < 0.01$) and γ-glutamyl transpeptidase (663 vs. 450 U/l $P = 0.037$). No patients experienced radiation-induced liver disease.

Conclusions: Palliative radiotherapy is efficient and safe in Japanese patients with liver metastases. These findings will help encourage whole-liver radiotherapy use in Japan.

Key words: whole-liver radiotherapy, liver metastases, pain response, hepatic blood data, radiation-induced liver disease

Introduction

The liver is one of the most common sites of metastasis (1), and liver metastases (LM) often cause symptoms such as pain, discomfort and nausea (2,3). Several prospective clinical trials have demonstrated that low-dose palliative radiotherapy for LM can relieve symptoms with relatively low levels of toxicity (2,4). Accordingly, a review article has recommended low-dose whole-liver radiotherapy (WLRT) for patients with symptomatic LM refractory to standard therapies (5).

Moreover, LM can cause hepatic dysfunction (6) and result in liver failure, which is fatal (7). A few small case series suggest improvements in hepatic blood data after WLRT (7,8). Therefore, patients with diffuse LM can benefit from WLRT, which may prolong their survival. In addition, WLRT allows patients with liver dysfunction who are unsuitable for chemotherapy to resume chemotherapy.

Although WLRT for diffuse LM has several advantages, as mentioned previously, this treatment is not generally performed in Japan, and the local guidelines on radiotherapy do not include palliative

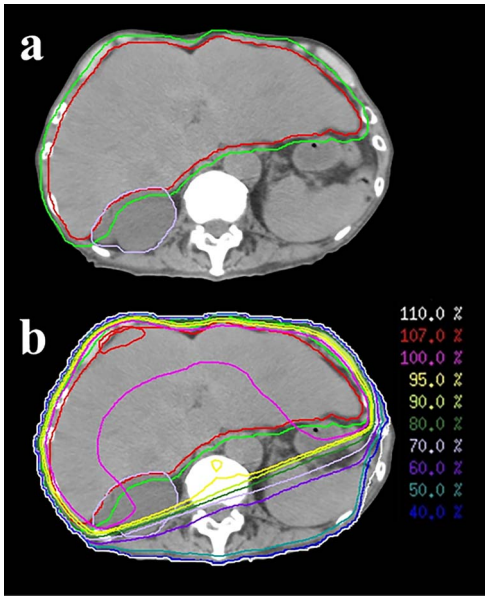

Figure 1. Representative case of a 78-year-old man with diffuse liver metastasis from prostate cancer. (a) Computed tomography (CT) images with contouring, including the clinical target volume (red, 2916 ml) and the planning target volume (green), for whole-liver radiotherapy. (b) CT images with dose distribution of whole-liver radiotherapy. The dose distribution heterogeneity was allowed.

WLRT (9). We have conducted the WLRT of 8 Gy in a single fraction based on a Phase II trial (4). Thus, this study aimed to clarify the efficacy and safety of palliative radiotherapy in Japanese patients with multiple LM.

Materials and methods

Patients and data acquisition

We retrospectively reviewed databases of Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital (Tokyo, Japan) to identify patients with LM treated with palliative radiotherapy between December 2014 and April 2021. Palliative radiotherapy was performed for patients with any symptoms of LM or abnormal values of hepatic blood test. No contraindications for WLRT based on performance status, expected survival time, hepatic function or blood tests were documented.

This study was approved by our institutional ethical review board (approval number, 2083). Written informed consent was obtained from all patients.

Whole-liver radiotherapy

Radiotherapy was planned based on free-breathing computed tomography (CT) scans. Gross tumor volume was not determined. The clinical target volume (CTV) was defined as the liver segments, including the tumor contributing to symptoms, and generally encompassed the majority or entirety of the liver. The planning target volume (PTV) margins were 5–10 mm to accommodate organ motion and setup errors (Fig. 1a). The prescribed dose was 8 Gy in a single fraction, delivered using the conventional technique of two to four ports, and the planning goal was 95% of the PTV to receive a minimum of 7 Gy (Fig. 1b).

Evaluation and statistical analyses

The study endpoints were overall survival (OS), pain response, hepatic blood data and adverse effects (AEs), including radiation-induced liver disease (RILD). OS was defined as the interval between the radiotherapy and the most recent follow-up or death from any cause. Pain status at the LM sites was self-reported by the patients and was measured using a numerical rating scale (NRS) of 0–10, where 0 represented no pain and 10 represented extreme pain. The worst score for the previous 3 days was recorded. Pain response was determined according to the International Consensus on Palliative Radiotherapy Endpoints guidelines, which evaluated pain according to the pain scale and the amount of analgesic consumption (10). Furthermore, this study investigated abnormal results from hepatic blood tests at WLRT, particularly abnormal data that were identified in >30 cases. Six parameters met this criterion: aspartate transaminase (AST), alanine transaminase (ALT), lactate dehydrogenase (LDH), alkaline phosphatase (ALP), γ-glutamyl transpeptidase (GGT) and albumin.

The primary analysis compared the mean values at the initiation of WLRT (baseline) and 2–4 weeks after WLRT to evaluate the short-term effects of WLRT. A supplementary comparison between blood tests 2–4 weeks before WLRT and baseline was conducted to evaluate disease worsening trends. RILD was defined as elevated transaminases of at least 5-fold the upper limit of normal or pre-treatment levels without any documented progressive disease (11). Other AEs were evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5 (12).

OS was estimated using the Kaplan–Meier method. The Wilcoxon rank-sum test was used to compare the mean values, and results were considered significant at P values <0.05. All statistical analyses were performed using EZR software, version 1.54 (13).

Results

Patient and tumor characteristics

A total of 73 LM cases in 71 Japanese patients were included in this study (Table 1). The median CTV was 2118 ml (range, 133–7867 ml) and 100% (range, 16.3–100%) of the total liver volume. The CTV of 44 lesions was the whole liver. The Child–Pugh classification was class A in 26 cases, B in 41 and C in 6. Index symptoms that triggered irradiation were abdominal pain in 49 (67%) cases, and other symptoms in 19 (26%) cases (the detail of other symptoms are shown in Table 2). Fifty-seven (78%) cases were not scheduled to receive any further courses of systemic therapy at the time of WLRT. The mean NRS at WLRT was 6.82 (range, 3–10), and the daily oral morphine equivalent (OME) consumption was 48.75 mg (range, 0–420 mg).

Clinical outcomes

The median follow-up after radiotherapy was 6 weeks (range, 0–39 weeks). The 1-month OS rate was 61.8%, and the median survival time was 7 weeks for the entire cohort. Among 49 cases with painful metastases at baseline, 28 cases were evaluable after 1 month (death in 12 patients, lost to follow-up in 2 cases and undocumented NRS values in 7 cases rendered those cases unevaluable). The mean change in NRS and daily OME consumption from baseline was −5 [standard deviation (SD), 2.2] and + 9.6 mg (SD, 31.78 mg), respectively. The complete response, partial response, pain progression and

Table 1. Patient and treatment characteristics

Characteristics	73 Cases in 71 patients
Sex	
Male/Female	39/32
Mean/Median age (years) (range)	62.6/63 (28–83)
ECOG PS	
0–1/2/3/4/unknown	24/17/22/9/1
Primary malignancy	
Lung	18 (25%)
Colorectal	9 (12%)
Breast	7 (10%)
Esophagus	7 (10%)
Thymus	6 (8%)
Prostate	5 (7%)
Other	21 (29%)
Clinical target volume	
Mean/Median (range)	2262 ml/2118 ml (133–7867 ml)
Child-Pugh class	
A/B/C	26 (36%)/41 (56%)/6 (8%)
Index symptom that triggered irradiation	
Pain	49
Other symptoms	19
None (abnormal blood data)	5
Systemic therapy at WLRT	
Before the start	1
Ongoing	14
After the end (supportive care)	57
Unknown	1
Abnormal value of each inspection item	
AST/ALT/LDH	57/39/68
ALP/GGT/Bilirubin	63/42/19
Albumin/PT/Cholesterol	61/11/4

Abbreviations: ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; ECOG, Eastern Cooperative Oncology Group; GGT, γ-glutamyl transpeptidase; LDH, lactate dehydrogenase; PS, performance status; PT, prothrombin time; WLRT, whole-liver radiotherapy.

Table 2. Liver metastases-related symptoms and the response to radiotherapy

Symptoms	Cases	Improved	Not improved	Unevaluable
Abdominal pain	49	18	10	21
Abdominal discomfort	17	4	3	10
Leg edema	9	6	1	2
Anorexia	6	1	1	4
Nausea	3	0	1	2
Jaundice	3	1	2	0
Dyspnea	3	1	0	2
Malaise	2	1	1	0
Ascites	1	0	0	1

indeterminate response at 4 weeks were observed in 7, 11, 0 and 10 lesions, respectively, resulting in pain response of 64%. Among 18 cases with pain response, pain re-progression was confirmed in two cases (the two cases then received a second course of WLRT). Pain response rates at 8 and 12 weeks were 90% (9 of 10 cases) and 86% (6 of 7 cases), respectively. The details of other symptoms than abdominal pain are summarized in Table 2.

The number of cases with abnormal values at the time of WLRT for AST, ALT, LDH, ALP, GGT and albumin was 57, 39, 68, 63, 42 and 61, respectively. All six parameters showed worsening trends upon comparisons of the mean values at 2–4 weeks before WLRT with the values at the baseline ($P < 0.01$ for all parameters). The mean values for all parameters except albumin showed significant improvement between baseline and 2–4 weeks after WLRT: AST (118 U/l vs. 83 U/l, $P < 0.01$); ALT (84 U/l vs. 61 U/l, $P < 0.01$); LDH (1351 U/l vs. 1007 U/l, $P = 0.027$); ALP (1624 U/l vs. 1216 U/l, $P < 0.01$) and GGT (663 vs. 450, $P < 0.01$; Fig. 2). The mean albumin concentration continued to deteriorate from 2.7 g/dl at baseline to 2.4 g/dl at 2–4 weeks after WLRT. In a comparison of values at 2–4 weeks after radiotherapy with the baseline values, there

Table 3. Adverse effects

	Grade 2	Grade 3	Grades 4–5
Nausea	4	0	0
Malaise	2	0	0
Tumor lysis syndrome	NA	3	0

Abbreviations: NA, not applicable.

Table 4. WLRT literature review

	N	Lesions	Child–Pugh classification	Prescribed dose	Symptom or pain palliation	Hepatic blood data	Severe toxicity
Bydder et al. (2)	28	LM	NA	10 Gy/2 fx	65%	NA	7%
Yeo et al. (8)	10	LM from CRC	B = 8, C = 2	21 Gy/7 fx	100%	Improvement in AST, ALP, and TB	0
Soliman et al. (4)	41	HCC and LM	A = 34, B = 7	8 Gy/1 fx	48%	NA	2%
Edyta et al. (14)	27	LM	NA	18 Gy/10 fx	100%	NA	3%
Yeung et al. (15)	52	HCC	A = 32, B = 20	8 Gy/1 fx	52%	NA	4%
Present study	73	LM	A = 26, B = 41, C = 6	8 Gy/1 fx	64%	Improvement in AST, ALT, LDH, ALP, and GGT	4%

Abbreviations: ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; CRC, colorectal cancer; GGT, γ-glutamyl transpeptidase; HCC, hepatocellular carcinoma; LDH, lactate dehydrogenase; LM, liver metastases; NA, not applicable; RILD, radiation-induced liver disease; TB, total bilirubin.

were 13, 18, 6, 12 and 8 cases that showed a major improvement ($\leq -50\%$) in AST levels, an improvement (> -50, $\leq -10\%$) in AST levels, no change ($> -10\%$, $< +10\%$) in AST levels, worsening ($\geq +10\%$) levels of AST and unevaluable levels of AST, respectively (overall improvement: 54%); 14, 10, 3, 4 and 8 cases, respectively, for ALT (overall improvement: 62%); 9, 28, 6, 15 and 10 cases, respectively, for LDH (overall improvement: 54%); 5, 30, 9, 11 and 8 cases for ALP (overall improvement: 56%) and 5, 11, 5, 5 and 16 cases, respectively, for GGT (overall improvement: 38%). In addition, 8 cases showed an improvement ($\geq +10\%$) in albumin levels, 20 cases showed no change ($< +10\%$, $> -10\%$,) in albumin levels, 22 cases showed worsening ($\leq -10\%$) albumin levels and 11 cases were unevaluable for albumin levels (overall improvement: 13%).

None of the patients experienced RILD. Pain flare was observed in five cases; however, pain flare was not included in the NCI-CTCAE. Acute Grade 2 nausea and malaise were confirmed in four and two cases, respectively (Table 3). NCI-CTCAE defined the occurrence of tumor lysis syndrome as Grade 3 or more. Although Grade 3 tumor lysis syndrome was observed in three cases, all cases improved with conservative treatment. No other Grade 2 or greater toxicity was observed. The six patients classified as Child–Pugh C did not experience severe AEs (Grade 2 nausea and tumor lysis syndrome in each patient), with a median follow-up of 3 weeks (range, 0–7 weeks). Two patients irradiated to the whole liver twice did not experience severe AEs (Grade 1 nausea in one patient).

Discussion

This retrospective case series demonstrated that palliative radiotherapy at a dose of 8 Gy could provide pain palliation with few toxicities in Japanese patients with multiple LM. In addition, liver radiotherapy achieved significant improvement in several hepatic blood tests showing exacerbation trends before radiotherapy.

The use of WLRT in the treatment of LM is not popular in Japan's clinical practice (9). In this study, we have outlined several advantages of WLRT. First, WLRT was effective and less toxic. Previous studies, including the current study, have reported reproducible results, with a pain response rate of >60% and low toxicity (Table 4). In addition, the results of this study suggest that WLRT may be effective even for end-of-life care (78% of patients in this study had completed active cancer treatment). Second, single fractionation does not significantly increase the patients' medical burden, as they only have to visit a hospital once for treatment. Third, WLRT is a versatile approach, and it can be performed using the conventional radiotherapy technique.

Various studies have reported that radiation decreases metabolic liver function (16,17); however, the results of the present study have proven otherwise. The risk of RILD is especially high in patients with low hepatic function (16). In the present study, >60% of the included patients had Child–Pugh B or C. One of the reasons for the absence of RILD and other severe AEs may be the low prescribed dose at 8 Gy. Especially for patients classified as Child–Pugh C, the number of reports on WLRT was extremely small (Table 4). In our study, WLRT of 8 Gy did not cause severe AEs in Child–Pugh C patients. Although we consider that WLRT for Child–Pugh C patients with LM is not contraindicated, the safety of this approach should be investigated in future research.

Several prospective clinical trials have demonstrated the palliative efficacy of WLRT for LM (2,4). However, whether this treatment provides any survival advantage remains unknown. Furthermore, the effects of WLRT on hepatic blood tests and liver function have not yet been identified. Our findings demonstrated a significant improvement in several liver enzymes and related factors by WLRT. Theoretically, the improvement in blood test results could have contributed to an improved liver function and subsequent prolongation of survival. Moreover, WLRT may provide additional survival benefits from resuming chemotherapy. Although the standard

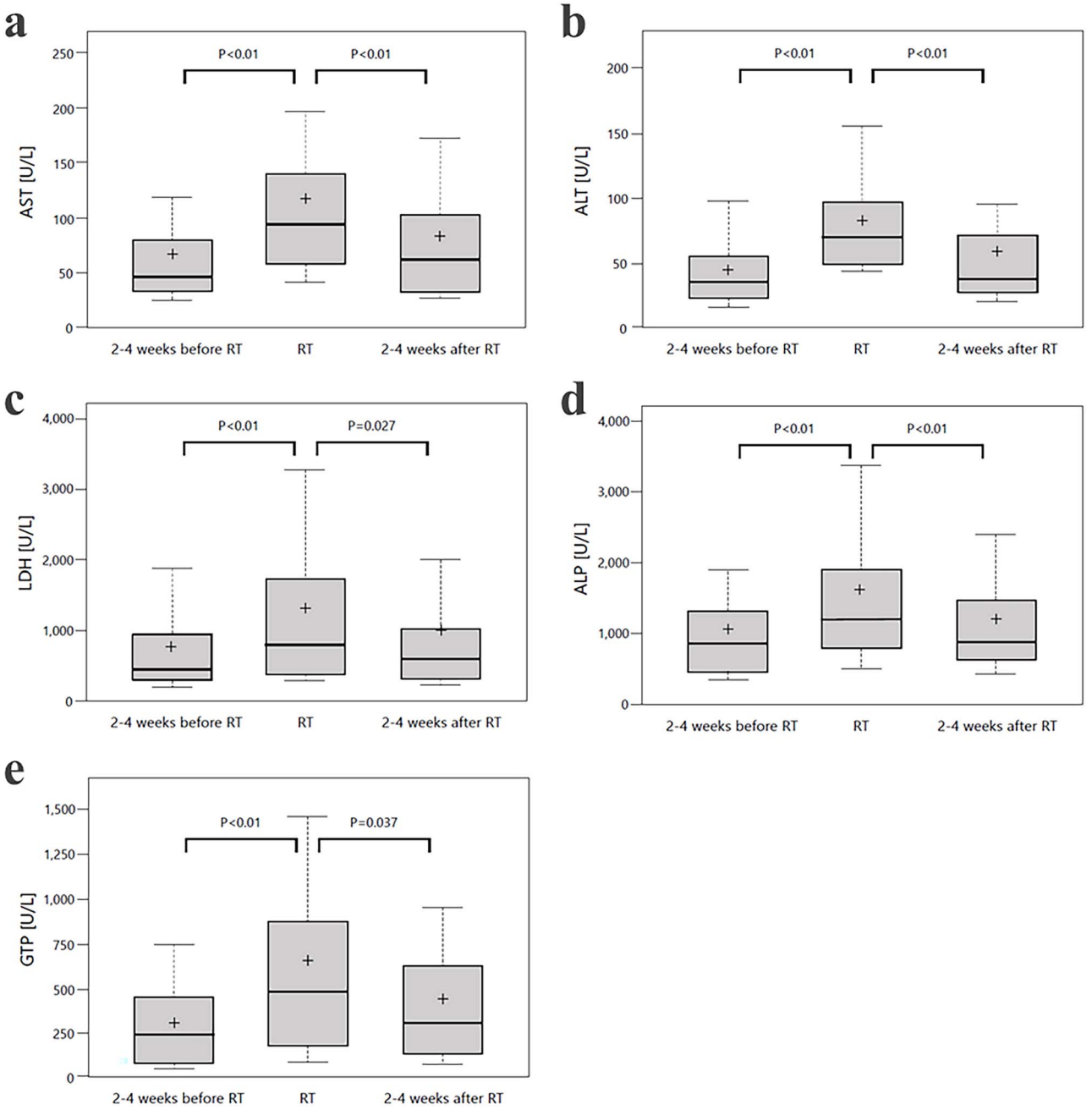

Figure 2. Box plots showing concentrations of (a) AST, (b) ALT, (c) LDH, (d) ALP and (e) GGT. The horizontal line within the box indicates the median, and '+' in the box indicates the mean. These figures show an inverted V-shaped recovery. (*Abbreviations:* AST, aspartate transaminase; ALT, alanine transaminase; LDH, lactate dehydrogenase; ALP, alkaline phosphatase; GGT, γ-glutamyl transpeptidase).

treatment for LM cases is systemic therapy, it is occasionally difficult to administer chemotherapy, such as platinum, antipyrimidine, taxanes and topoisomerase inhibitors, due to hepatic dysfunction caused by LM. A retrospective report on WLRT for diffuse LM and severe hepatic dysfunction suggested that patients who were able to resume chemotherapy after WLRT had a longer OS than those who could not (8). Thus, WLRT may be a crucial approach not only for improving symptoms but also for prolonging OS.

This study had a few limitations. First, several pain cases could not be evaluated due to death, non-compliance to follow-up, undocumented NRS values and indeterminate response because of the increase in the analgesic dose brought by other painful lesions. Second, we only showed hepatic blood tests improvements. These results alone do not confirm any positive effect of WLRT on the hepatic function or survival time. Third, the follow-up duration was short (median, 6 weeks; range, 0–39 weeks). The occurrence rate of AEs observed in our study may have been underestimated. However, in clinical practice, patients with diffuse LM have extremely short life expectancies; thus, these data would be useful in the real world. Fourth, quality of life was not measured as an endpoint because of the retrospective nature of the study. Ideally, the endpoint should be quality of life, since this treatment is classified as palliative therapy.

To clarify the impact on the quality of life, the results of a prospective randomized controlled trial conducted by the Canadian Cancer Trials Group are awaited (NCT02511522).

In conclusion, this is the first study to investigate the efficacy and safety of palliative radiotherapy in Japanese patients with multiple LM. This study demonstrated that liver radiotherapy at 8 Gy can relieve pain and improve hepatic blood data with less toxic side effects. We believe that these findings will help encourage the use of WLRT in Japan in the future.

Funding

None declared.

Conflicts of interest

The authors declare no conflict of interest.

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