Original Paper

Irradiation-Related Lymphopenia for Bone Metastasis from Hepatocellular Carcinoma

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Keywords

Lymphopenia · Radiotherapy · Neoplasm metastasis · Hepatocellular carcinoma · Bone marrow

Abstract

Background/Aim: In the era of immunotherapy, treatment-related lymphopenia (TRL) is gaining attention. In this study, TRL was investigated in patients with bone metastasis from hepatocellular carcinoma (HCC) treated with radiotherapy (RT). **Methods:** Clinical data of 302 patients receiving RT for 511 bone metastases from HCC between 2005 and 2018 were reviewed. Data on absolute lymphocyte count (ALC) from pre-RT to 12 months post-RT were collected. Severe TRL was defined as ALC <500 cells/mm³ and evaluated using ALC 2 months after initiating RT. Factors associated with TRL were analyzed, which include the amount of active bone marrow within the RT field. The amount of active bone marrow included in the RT field was calculated as the product of the percentage of the bone compartment included in the RT field and the active bone marrow percentage of the bone compartment. **Results:** Overall, 33.4% of patients developed TRL 2 months after initiating RT. The mean ALC decreased after initiating RT and remained persistently low during 12 months of observation. Overall survival (OS) was significantly worse in patients with TRL than in those without (median OS: 3.7 vs. 6.5 months, $p < 0.001$). In the prognostic factor analysis, TRL was an independent prognostic factor of OS ($p = 0.036$), along with known prognostic factors of HCC. The percentage of active bone marrow within the RT field was the only significant factor associated with TRL ($p < 0.001$). **Conclusion:** TRL was observed in patients receiving RT for bone metastasis from HCC, and it was associated with poor survival. The percentage of active bone marrow within the RT field significantly affected TRL development. The results suggest that a new strategy is required to prevent TRL.

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Introduction

In the era of immunotherapy, treatment-related lymphopenia (TRL) is gaining attention owing to the pivotal role of lymphocytes in antitumor immunity [1–3]. In many studies, patient survival was affected by TRL, which could ensue from cancer treatments involving radiotherapy (RT) [4–7]. Because lymphocytes are radiosensitive cell types, even small doses of radiation can significantly reduce the lymphocyte count [8]. In particular, for fractionated RT, a significant decrease in the number of circulating lymphocytes (CLs) has been reported with a small target volume, as in the mathematical model proposed by Yovino et al. [9].

RT is frequently used in patients with cancer bone metastasis; RT provides substantial improvement of not only the subjective symptoms of bone pain but also the objective risk of impending nerve compression or pathological fracture from cancer bone invasion [10]. This notion also applies to patients presenting bone metastasis from hepatocellular carcinoma (HCC) [11–13]. As patient survival has been prolonged by advancement of therapeutic modalities, bone metastases are more frequently seen in the clinic, which implicates an increasing demand for RT for those patients. However, RT for bone metastasis may cause clinically significant lymphopenia both by depleting the CLs and by damaging the proliferating bone marrow [14, 15]. Nevertheless, no study to date has reported the importance of lymphopenia in patients treated with RT for bone metastasis.

In this study, we investigated TRL after RT for bone metastasis from HCC as well as its clinical significance.

Materials and Methods

Patient Selection

Patients who received RT for bone metastases from HCC were included in the study cohort because they were less affected by systemic cytotoxic chemotherapy, which is not a standard treatment for HCC. We reviewed the medical records of 412 consecutive patients who received RT for bone metastasis from HCC between October 2005 and April 2018. The eligibility criteria for this study included the following: age >18 years, pathological or clinical diagnosis of bone metastases from HCC, detailed information about RT, and a complete blood count (CBC) panel available at a specific time point. Patients without an absolute lymphocyte count (ALC) were not considered as candidates for the study. Ten patients who underwent RT for primary or recurrent liver lesions simultaneously with bone metastasis were excluded from the study because RT to an organ containing a large amount of blood can cause lymphopenia, which may act as a confounding factor. Sixty-seven patients had severe lymphopenia (ALC <500 cells/mm³) at baseline, which might be an effect of a series of anticancer therapies (e.g., systemic chemotherapy) before RT. These populations were excluded from the analysis since the decrease in ALC caused by RT may not be accurately reflected. Thus, a total of 302 patients were included.

Data Collection

Data were collected using the ALC from the CBC panel from pre-RT up to 12 months after the initiation of RT. Typically, a CBC was performed at baseline, every 1 week during RT, and every 1 month thereafter. ALC data were categorized as baseline (most recent data within 3 months before RT) and 1, 2, 3, 6, and 12 months after the initiation of RT. TRL was evaluated based on ALC level 2 months after the initiation of RT. This time interval was based on previous studies that reported the association between the occurrence of lymphopenia 2 months after the initiation of RT and survival in patients with various solid tumors [16–18]. In patients without ALC data after 2 months, the ALC after 1 month was used. The National Cancer Institute's Common Terminology Criteria for Adverse Events (version 4.03) threshold for grade III and IV lymphopenia (ALC <500 cell/mm³) was used to define TRL since studies on TRL revealed an association between grade III and IV lymphopenia and survival in patients with various cancers [7, 17–19]. Hypersplenism, which is defined as a triad of splenomegaly, pancytopenia, and normal marrow function, may also be a cause of lymphopenia. We identified the presence of hypersplenism in all patients at the time of evaluation for TRL.

Fig. 1. Examples of the methods used in calculating the percentage of active bone marrow within the radiotherapy field and field size. **a** Thoracic and lumbar spine. **b** Humerus.

Radiation Therapy

All patients underwent external beam RT. The types and modalities of RT were chosen based on the location and size of the lesions as well as the general condition of the patients. Stereotactic body RT (SBRT) was preferred in those with good performance status and 1–3 small lesions (<5 cm), whereas the large, mass-forming metastases or the lesions close to the critical organs were preferentially treated with non-SBRT (e.g., conventionally fractionated RT). Intensity-modulated RT was considered for patients whose disease, other than bone metastasis, was well controlled, whereas those with uncontrolled, extensive disease were treated with 3-dimensional conformal RT. The gross target volume (GTV) was defined as the gross lesion determined on computed tomography, magnetic resonance imaging, or positron emission tomography. The clinical target volume (CTV) was defined as GTV plus the contiguous bone compartment with a 1- to 2-cm margin for conventionally fractionated RT, and a 0.5- to 1-cm margin for SBRT. Additional 3- to 7-mm expansions from CTV to create the planning target volume were used to account for setup errors. Based on the above-mentioned principles, the target delineation and dose prescription were determined on an individual basis.

Evaluation of the Active Bone Marrow within the RT Field and Field Size

The amount of proliferating bone marrow within the RT field may be related to the decrease in the blood cell count, including the lymphocyte count [14]. This prompted us to calculate the amount of active bone marrow within the RT field. First, we reviewed the individual RT plan of the patients and the proportion of the specific bone compartment within the RT field. To measure the amount of actively proliferating bone marrow in each bone compartment, we used the results of the study conducted by Campbell et al. [20] as reference. They analyzed the proliferating bone marrow distribution in the bones of the whole body of 51 adults using 3'-[F-18]fluoro-3'-deoxythymidine with positron emission tomography. The percentages of proliferating bone marrow cells in the skull, ribs, sternum, cervical, thoracic (T) and lumbar (L) spines, sacrum, pelvis, bilateral humerus, and femurs were 6, 16.6, 2, 3.7, 17.7, 14.8, 7.2, 22.8, 3.5, and 5.7%, respectively. Thus, the percentage of active bone marrow within the RT field was calculated as follows:

Active bone marrow within the RT field (percent) = (percentage of bone compartment included in the RT field) × (percentage of proliferating bone marrow in each bone compartment).

For example, as T12 and L1–5 vertebrae are included in field A of Figure 1, the percentage of active bone marrow within the RT field is approximately 16.275%, and this was calculated as (1/12 levels × active bone marrow percentage of T vertebra) + (5/5 levels × active bone marrow percentage of L vertebrae). If multiple sites were treated simultaneously, the active bone marrow percentages within each field were summed up. Similarly, when calculating the size of the RT field, the size of each field was calculated and then summed.

Table 1. Patient and treatment characteristics

Variable	n or median	% or range
Age, years	59	32–85
Sex		
Female	46	15.2%
Male	256	84.8%
ECOG performance status		
0	20	6.6%
1	195	64.6%
2	69	22.8%
3	17	5.6%
4	1	0.3%
Etiology		
B-viral	240	81.1%
C-viral	21	7.1%
Non-B, non-C	35	11.8%
Extrahepatic control		
Controlled	119	39.4%
Uncontrolled	183	60.6%
Intrahepatic control		
Controlled	126	41.7%
Uncontrolled	176	58.3%
Child-Pugh class		
A	238	78.8%
B	59	19.5%
C	5	1.7%
AFP	165.0	1.06–377,767.5
PIVKA-II	978.5	5.0–75,000
Baseline TLC, cells/mm ³	1,019.1	500.0–3,170
Site of metastasis		
Total	511	100%
Ribs, clavicles and scapulae	60	11.7%
Sternum	18	3.5%
Pelvis	78	15.3%
Cervical spine	30	5.9%
Thoracic spine	79	15.5%
Lumbar spine	49	9.6%
Sacrum	35	6.8%
Skull and facial bones	29	5.7%
Upper extremities	27	5.3%
Lower extremities	26	5.1%
Combined (2 sites or more)	80	15.7%
Prior anticancer therapy		
Naïve	37	12.3%
Treated	265	87.7%
Subsequent anticancer therapy		
No	104	34.4%
Yes	198	65.6%

Table 1 (continued)

Variable	n or median	% or range
Concurrent chemotherapy		
No	273	90.4%
Intra-arterial chemotherapy	4	1.3%
Systemic chemotherapy	21	6.9%
Sorafenib	4	1.3%
RT scheme		
SBRT	26	8.6%
Non-SBRT	276	91.4%
BED ₁₀ , Gy	50.7	18.8–150
Fraction number		
2–4	20	6.6%
5–20	277	91.7%
21–28	5	1.7%
Treated lesions	1	1–8
Sum of the field size, cm ²	163.7	20.4–1,987.3
Sum of the involved marrow, %	5.7	0–41.1

ECOG, Eastern Cooperative Oncology Group; AFP, α -fetoprotein; PIVKA-II, protein induced by vitamin K absence or antagonist-II; TLC, total lymphocyte count; RT, radiotherapy; SBRT, stereotactic body radiotherapy; BED₁₀, biological effective dose calculated using $\alpha/\beta = 10$.

Statistical Analysis

A box plot was used to visualize the fluctuations of ALC over time. Overall survival (OS) was measured from the initiation of RT to death or last follow-up visit. The cumulative probabilities of survivals were calculated using the Kaplan-Meier method and compared using the log-rank test. To determine the predictors of OS and TRL, Cox proportional hazards regression and logistic regression analyses were performed. All *p* values were two-sided, and *p* values <0.05 were considered statistically significant. All data were analyzed using the Statistical Package for the Social Sciences software version 23.0 (SPSS Inc., Chicago, IL, USA).

Results

Characteristics of Tumors and Patients at Baseline

The baseline characteristics of the patients are summarized in Table 1. The median age of the patients was 59 (range: 32–85) years, and 511 sites were treated. Overall, only 12.3% of the patients were treatment-naïve. After RT, 65.6% of the patients underwent subsequent anticancer therapies. The median interval from prior anticancer therapies to RT for bone metastasis was 2.1 (range: 0.2–14.3) months, and the median interval from RT for bone metastasis to subsequent anticancer therapies was 1.8 (range: 0.1–7.8) months. The systemic chemotherapy was administered concurrently with RT in 21 patients (6.9%). The median biological effective dose was 50.7 (range: 18.8–150) Gy, and the median number of treated lesions was 1 (range: 1–8). Regarding the types and the fraction numbers of RT, 26 (8.6%) and 276 patients (91.4%) received SBRT and non-SBRT, respectively, and 20 (6.6%), 277 (91.7%), and 5 patients (1.7%) received 2–4, 5–20, and 21–28 fractions, respectively.

Fig. 2. Change in total lymphocyte count after the initiation of radiotherapy.

Fig. 3. Comparison of overall survival according to the development of treatment-related lymphopenia (TRL).

Total Lymphocyte Counts over Time

Overall, 33.4% of the patients developed TRL. The change in ALC after RT is presented in Figure 2. The mean ALC at baseline was $1,117.1 \pm 500.1$ (range: 500–3,170) cells/mm³. One month after the initiation of RT, the mean ALC decreased to 630.9 ± 384.3 (range: 10–2,110) cells/mm³, and severe (grade 3 or above) lymphopenia was observed in 43.2% of the patients. The mean ALC slightly recovered to 841.1 ± 552.4 (range: 140–4,770) cells/mm³ at 2 months after the initiation of RT, and 26.6% of the patients presented with severe lymphopenia. However, during the follow-up period of 12 months, the ALC had not fully recovered compared to baseline.

Survival Outcome and Prognostic Factors for OS

At a median follow-up of 5.1 (range: 0.6–110.4) months, the median OS was 5.2 months in all patients. Patients who developed TRL after RT showed significantly worse survival than those who did not (median OS: 3.7 vs. 6.5 months, $p < 0.001$) (Fig. 3).

Table 2. Univariate and multivariate analyses of overall survival

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p value	HR (95% CI)	p value
Age	0.98 (0.97–0.99)	0.002	0.99 (0.98–1.00)	0.073
Sex	0.97 (0.69–1.35)	0.841		
ECOG performance status	1.65 (1.40–1.94)	<0.001	1.52 (1.24–1.88)	<0.001
Etiology	–	0.054		0.107
B vs. C	0.81 (0.49–1.35)	0.423	0.69 (0.38–1.23)	0.204
B vs. non-B, non-C	0.62 (0.41–0.93)	0.019	0.64 (0.41–1.02)	0.060
Intrahepatic disease				
Controlled vs. uncontrolled	3.34 (2.55–4.38)	<0.001	2.40 (1.71–3.38)	<0.001
Extrahepatic disease				
Limited vs. extensive	3.42 (2.62–4.48)	<0.001	2.76 (2.02–3.77)	<0.001
Child-Pugh class	–	<0.001		0.046
A vs. B	2.38 (1.76–3.22)	<0.001	1.54 (1.10–2.18)	0.013
A vs. C	4.31 (1.75–10.55)	0.001	1.23 (0.37–4.13)	0.738
AFP	1.00 (1.00–1.00)	0.001	1.00 (1.00–1.00)	0.183
PIVKA-II	1.00 (1.00–1.00)	<0.001	1.00 (1.00–1.00)	0.021
Baseline TLC	0.62 (0.48–0.82)	0.001	0.95 (0.69–1.30)	0.729
TRL	1.64 (1.27–2.12)	<0.001	1.38 (1.02–1.87)	0.036

HR, hazard ratio; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; AFP, α -fetoprotein; PIVKA-II, protein induced by vitamin K absence or antagonist-II; TLC, total lymphocyte count; TRL, treatment-related lymphopenia.

The univariate and multivariate OS analysis results for the prognostic factors are provided in Table 2. In the univariate analysis, age ($p = 0.002$), Eastern Cooperative Oncology Group (ECOG) performance status ($p < 0.001$), intrahepatic and extrahepatic tumor controls (defined as the absence of viable tumor in the liver and as the absence of the disease outside the liver other than treated bone metastasis, respectively) ($p < 0.001$), Child-Pugh class ($p < 0.001$), α -fetoprotein ($p = 0.001$), protein induced by vitamin K absence or antagonist-II (PIVKA-II; $p < 0.001$), baseline ALC ($p = 0.001$), and TRL ($p < 0.001$) were significantly associated with OS. In the multivariate analysis, TRL ($p = 0.036$) as well as ECOG performance status ($p < 0.001$), intrahepatic and extrahepatic tumor controls ($p < 0.001$), Child-Pugh class ($p = 0.046$), and PIVKA-II ($p = 0.021$) were significant predictors of OS.

Factors Related to the Development of Lymphopenia

We also analyzed the factors associated with TRL (Table 3). Subsequent anticancer therapy after RT ($p < 0.001$), concurrent use of chemotherapy ($p = 0.021$), presence of hypersplenism ($p = 0.019$), number of treated lesions ($p < 0.001$), critical structures (organs containing abundant blood such as great vessels and liver or lymphoid organs such as spleen and thymus) included in the RT field ($p < 0.001$), sum of field size ($p < 0.001$), and sum of the active bone marrow percentage within the RT field ($p < 0.001$) were significantly associated with TRL in the univariate analysis. However, in the multivariate analysis, only the sum of the active bone marrow percentage within the RT field was found to be an independent risk factor of TRL ($p < 0.001$).

Table 3. Univariate and multivariate analyses of treatment-related lymphopenia

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p value	HR (95% CI)	p value
Previous anticancer therapy				
Naïve vs. treated	1.35 (0.63–2.93)	0.443	1.34 (0.53–3.39)	0.532
Subsequent anticancer therapy				
No vs. yes	0.43 (0.34–0.56)	<0.001	0.98 (0.52–1.84)	0.943
Concurrent systemic chemotherapy				
No vs. yes	2.88 (1.17–7.09)	0.021	2.06 (0.66–6.47)	0.214
Hypersplenism	1.80 (1.10–2.96)	0.019	1.78 (0.96–3.29)	0.067
BED ₁₀ (Gy)	1.00 (0.98–1.01)	0.539		
Fraction number				
2–4 vs. 5–20	1.18 (0.44–3.17)	0.743		
2–4 vs. 21–28	1.56 (0.21–11.83)	0.669		
RT scheme				
SBRT vs. non-SBRT	1.14 (0.48–2.73)	0.762		
Number of treated lesions	1.92 (1.47–2.49)	<0.001	0.87 (0.58–1.30)	0.485
Critical structures included in RT field	3.08 (1.85–5.13)	<0.001	1.49 (0.79–2.82)	0.219
Sum of the field size	1.01 (1.00–1.01)	<0.001	1.00 (1.00–1.00)	0.864
Sum of the involved bone marrow (%)	1.22 (1.16–1.28)	<0.001	1.22 (1.14–1.31)	<0.001

HR, hazard ratio; CI, confidence interval; BED₁₀, biological effective dose calculated using $\alpha/\beta = 10$; RT, radiotherapy; SBRT, stereotactic body radiotherapy.

Discussion

In this study, we identified that TRL occurred in a substantial number of patients receiving RT for bone metastasis, and it was associated with survival. Second, we analyzed the factors associated with TRL to assess if the percentage of active bone marrow within the RT field significantly affected the development of TRL.

We designed the study to make the cohort as homogenous as possible and to evaluate the impact of RT on lymphopenia independent from other treatments, namely, systemic chemotherapy. The significant differences in the prognosis of various primary cancers have been a major challenge in the clinical study of bone metastasis. Thus, we confined the cohort to patients with bone metastases from primary HCC. Furthermore, the fact that systemic chemotherapy is seldom used in patients with HCC may be another strength of our study. In the current study, only a small number of patients (6.9%) received systemic cytotoxic chemotherapy. Most patients who underwent systemic therapy received targeted molecular therapy, which causes less hematological toxicity. Anticancer therapies before and after RT may act as confounding factors affecting the lymphocyte count. To exclude the effect of anticancer therapies before RT, we excluded the patients who showed severe lymphopenia (ALC <500 cells/mm³) at baseline. Regarding the subsequent anticancer therapies after RT, as the median interval between RT and subsequent anticancer therapies was 1.8 months, the impact of subsequent anticancer therapies may be minimized because TRL was evaluated 1–2 months from the initiation of RT. By these means, this

study tried to focus on the impact of RT on lymphopenia excluding the influence of other cancer treatments.

RT may act as a double-edged sword in antitumor immunity. It has an immune-stimulatory effect via activation of immunogenic cell death by expressing calreticulin, releasing high-mobility group box 1 and adenosine triphosphate, and recruiting the effector cells into the tumor microenvironment. However, it also has immune-suppressive effects by depleting the CLs and lymphoid progenitor cells, upregulating cytotoxic T lymphocyte antigen-4, and programming death domain-ligand 1 [21]. The mechanism of interplay between the immune-stimulatory and immune-suppressive effects of RT and its association with survival remains to be understood.

As the most radiosensitive cells in the hematopoietic system, the RT-induced reduction of lymphocytes occurs immediately after irradiation [22]. According to existing studies, the amount of CLs showed a nadir within 1–2 months after the initiation of RT, and it gradually recovered. Mendez et al. [23] have reported that the ALC level was lowest 2 months after the initiation of RT, and it recovered over a year; however, the value was still lower than the baseline value. In a single-institution study, Wu et al. [4] reported similar results in a study of patients with cervical cancer who received chemoradiation. In our study, the significant decrease in ALC was observed 1 month after the initiation of RT, which is consistent with previous findings, and it gradually recovered during a year of follow-up. However, a significant number of patients had persistent lymphopenia that lasted for more than a year, which is in contrast to lymphopenia caused by sepsis, chemotherapy, or other treatments [24–26]. Unlike chemotherapy, which mainly targets the proliferating cell population, irradiation to lymphoid organs such as bone marrow usually depletes the lymphoid progenitor cells, which is suspected to result in severe and persistent lymphopenia. Future studies must be conducted to clarify the mechanism.

The decrease in lymphocyte count after RT has been associated with poor survival in individuals with several solid tumors [4–7, 16–19, 23, 27, 28]. However, no report has investigated the association between lymphopenia and survival in patients who received RT for bone metastases, despite the possibility of severe and long-term lymphopenia caused by irradiation of the bone marrow, which is a central lymphoid organ. Although the prognosis itself has been known to be poor in patients treated with RT for bone metastasis, a tangible difference was observed in terms of survival between patients with and without TRL in our study. In addition, in the prognostic factor analysis, TRL was significantly associated with poor survival in addition to the known prognostic factors already reported in previous studies [13, 29]. A 38% increase in the risk of death in patients with TRL compared with those without was noted.

Although several experimental and clinical studies have shown a decrease in lymphocyte count after bone marrow irradiation [30, 31], no report has analyzed the factors associated with TRL in individuals receiving RT for bone metastases. Because the number of irradiated lymphocytes and lymphoid organs increases with larger volumes within the RT field, the field size is intuitively expected to be associated with TRL as well as the other factors such as the number of treated lesions and the use of systemic chemotherapy, which were shown to be significant factors in univariate analyses of this study. However, in multivariate analysis, the only factor significantly associated with TRL was the amount of active bone marrow within the RT field. This result implies that the actual volume of actively proliferating bone marrow within the RT field but not the field size itself is the most important predictor of TRL. In other words, as shown in Figure 1, the effects of RT on the humerus (field A) and T–L spine (field B), which are considered to have similar field sizes but contain different amounts of active bone marrow, may be considerably different in terms of TRL. It is also noteworthy that the dose-response relationship of RT was not identified. This is probably because the irradiation

volume-response relationship may be dominant for radiosensitive cells such as lymphocytes (for which the lethal dose-50% is 2 Gy) [8], assuming the dose above the significant level is achieved. Likewise, the fraction number did not appear to be a significant factor. A previous study reported a mathematical model explaining the relationship between the fraction number of RT and the decrease in lymphocyte count [9]. However, unlike the previous study, the fraction number was not a significant factor for TRL in the current study, probably because the majority of patients (91.7%) were treated with small variation of fraction numbers (5–20 fractions). Nevertheless, to the best of our knowledge, this study is the first to analyze the factors associated with TRL with the concept of active bone marrow as well as other RT parameters.

Several limitations attributed to the retrospective nature of the study should be considered. The study population is relatively heterogeneous despite our efforts to include a population that is as homogeneous as possible, and this is considered the major limitation of the study. Most patients (87.7%) received a variety of anticancer therapies before RT, and 65.6% received other anticancer therapies after RT, which might influence the lymphocyte count, even though we adopted several methods to solve the problem by excluding ineligible patients and by validating the time interval between RT and subsequent treatments. The heterogeneous RT regimen used in the current study can also be a limitation. Various forms of RT were used, including SBRT and non-SBRT such as conventionally fractionated RT, with considerably different RT schemes and doses.

Despite these limitations, our study has clinically useful findings, considering the difficulties in conducting a large, well-controlled randomized trial in a palliative setting. First, as one of the main findings of our study strongly suggests, reducing the integral dose to bone marrow may be of utmost importance. The typical field of RT for bone metastasis usually includes the upper/lower levels of the involved spine or contiguous bone compartment with sufficient margin to account for microscopic tumor spread (online suppl. Fig. 1A; for all online suppl. material, see www.karger.com/doi/10.1159/000500461). However, in patients at high risk of developing lymphopenia (e.g., patients with low baseline ALC or patients receiving systemic chemotherapy or undergoing RT for multiple lesions simultaneously), RT with a reduced field including only the involved lesions may be rather helpful to improve the survival of patients (online suppl. Fig. 1B). In addition, a clinician should monitor patients for the occurrence of TRL after RT for bone metastasis, particularly when treating a bone compartment containing an abundant active marrow. Finally, the activation of lymphogenesis can also be a solution. In this approach, although not yet used in clinical settings, the administration of exogenous IL-7 to stimulate T cell proliferation can be considered.

In conclusion, TRL was observed in patients receiving RT for bone metastasis from HCC, and it was associated with poor survival. The percentage of active bone marrow within the RT field significantly affected TRL development. The results suggest that a new strategy is required to prevent TRL.

Statement of Ethics

This study was approved by the institutional review board (2018-2104-002) of our institution. All protocols were carried out in accordance with the Helsinki Declaration of 1975 (revised in 1983).

Disclosure Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Conception and design: Jinsil Seong. Acquisition, analysis, and interpretation of data and statistical analysis: Sangjoon Park. Drafting the article: Sangjoon Park, Jinsil Seong, Hwa Kyung Byun. Critically revising the article: Jinsil Seong.

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