Local control of bone metastasis treated with palliative radiotherapy in patients with lung cancer: An observational retrospective cohort study

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Received March 4, 2023; Accepted May 15, 2023

DOI: 10.3892/ol.2023.13889

Abstract. Bone metastasis is common in advanced lung cancer, with the incidence reported to be 30%, and radiotherapy (RT) is used for pain relief from bone metastasis. The present study aimed to identify factors affecting local control (LC) of bone metastasis from lung cancer and to assess the significance of moderate RT dose escalation. This was a retrospective cohort study, where LC of bone metastasis from lung cancer that had received palliative RT was reviewed. LC at RT sites was evaluated with follow-up computed tomography (CT). The influence of treatment-, cancer- and patient-related risk factors for LC was assessed. A total of 317 metastatic lesions in 210 patients with lung cancer were evaluated. The median RT dose (biologically effective dose calculated using an α/β of 10 Gy; BED10) was 39.0 Gy (range, 14.4-50.7 Gy). The median follow-up time for survival and median radiographic follow-up time were 8 (range, 1-127) and 4 (range, 1-124) months, respectively. The 0.5-year overall survival and LC rates were 58.9 and 87.7%, respectively. The local recurrence rate in RT sites was 11.0%, and bone metastatic progression, except in RT sites, was observed in 46.1% at the time of local recurrence or the last follow-up CT of the RT sites. According to multivariate analysis, RT sites, pre-RT neutrophil to lymphocyte ratio (NLR), post-RT non-administration of molecular-targeting agents (MTs), and non-administration of bone modifying agents (BMAs) were significant unfavorable factors for LC of bone metastasis. Moderate RT dose escalation (BED10 >39 Gy) tended to improve the LC of RT sites. In cases without MTs, moderate dose escalation of RT dose improved the LC of RT sites. In conclusion, treatment (post-RT MTs and BMAs), cancer (RT sites) and patient (pre-RT NLR)-related risk factors had a large impact on improving the LC of RT sites. Moderate RT dose escalation seemed to have a small impact on improving the LC of RT sites.

Introduction

Bone is one of the common metastatic sites, particularly in breast, prostate, lung, and kidney cancers, accounting for 75% of all patients (1). In advanced lung cancer patients, the incidence of bone metastasis was reported to be approximately 30% (2).

Radiotherapy (RT) is a well-established treatment for pain relief from bone metastasis. Many guidelines for the treatment of bone metastasis recommend 8 Gy single-fraction RT as palliative treatment (3,4). However, a previous study showed that in long-term survivors, 8 Gy single-fraction RT was associated with a higher risk of re-irradiation compared to fractionated RT (5). Moreover, some studies demonstrated that local control (LC) of bone metastatic lesions may be important (6,7). In addition, in recent years, some studies have evaluated the radiographical LC of all bone metastasis irradiated by palliative RT and suggested that RT dose contributed to LC of bone metastasis (8,9). However, these studies evaluated patients with a variety of cancers, and there was a lack of studies specific to patients with lung cancer. Because various systemic therapies are used for various cancers, the results

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Abbreviations: LC, local control; RT, radiotherapy; PS, performance status; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; BED, biologically effective dose; MT, molecular-targeting agents; TKI, tyrosine kinase inhibitor; ICI, immune-checkpoint inhibitor; BMA, bone modifying agent; NLR, neutrophil to lymphocyte ratio; ALP, alkaline phosphatase; OS, overall survival; HR, hazard ratio; CI, confidence interval; ROC, receiver operating characteristic; AT, antineoplastic agent; SBRT, stereotactic body radiotherapy

Key words: bone metastasis, lung cancer, palliative, radiotherapy, local control

of these studies may be inadequate for the selection of the optimal RT dose for bone metastasis from lung cancer.

In patients with advanced lung cancer, the 5-year survival rate was reported to be approximately 10% (10). Recently, however, the remarkable progress of new molecular-targeted therapies including immunotherapy has extended the expected life expectancy of some patients with lung cancer (11-15). Thus, advances in systemic therapy have the potential not only to improve the direct effect on bone metastasis but also to increase the demand for individualized treatment due to prolonged life expectancy. Thus, both RT dose and targeted therapy including immunotherapy appear to have an important role in LC of bone metastasis (8,9,11-15). However, to the best of our knowledge, there is no study that has comprehensively evaluated these factors specifically in bone metastasis from lung cancer. Therefore, we examined the LC of bone metastasis from lung cancer treated with palliative RT and the purpose of this study was to identify factors affecting LC and assess the significance of moderate RT dose escalation for bone metastasis in patients with lung cancer.

Patients and methods

Study protocol and lesions. Between January 2011 and December 2021, 369 lung cancer patients with 581 bone metastatic lesions received palliative RT in our institution. These bone metastatic lung cancer patients were referred from an attending physician to a radiation oncologist for palliative intent RT for the following reasons: i) Pain relief, ii) metastatic spinal cord compression (MSCC) with or without pain and/or neurological symptoms. Among these patients, i) 196 lesions in 119 patients that were not followed up by computed tomography (CT) and ii) 68 lesions in 40 patients that were not predominantly osteolytic metastatic bone lesions were excluded. Therefore, 317 lesions in 210 patients were reviewed retrospectively in this study. This observational, retrospective, cohort study design was approved by the institutional ethics review board (RIN2021-70).

Details of the lesion characteristics are shown in Table I. Thirty-nine lesions in 19 patients were small cell lung cancer (SCLC) and 278 lesions in 191 patients were non-small cell lung cancer (NSCLC). Among NSCLC lesions/patients, 213 lesions in 147 patients were adenocarcinoma, 50 lesions in 35 patients were squamous cell carcinoma, and the remaining 15 lesions in nine patients were of other histology (adenosquamous, large cell neuroendocrine, and unknown). The tyrosine kinase inhibitors (TKIs) used were gefitinib, erlotinib, afatinib, osimertinib, and crizotinib. The immune-checkpoint inhibitors (ICIs) used were nivolumab, ipilimumab, pembrolizumab, and duruvalumab. These systemic therapies were selected based on the Japanese lung cancer treatment guidelines released that year. In addition, the bone modifying agents (BMAs) used were denosumab and zoledronic acid.

The following factors were assessed: Age (<70 years vs. ≥70 years); sex (female vs. male); performance status (PS) (<3 vs. ≥3); histology (NSCLC vs. SCLC); metastasis to internal organs (excluding bone and lymph node metastasis) (yes vs. no); number of bone metastasis (single vs. multiple); bone metastatic sites (only spine vs. others); timing of RT (*de novo* vs. no); bone cortex destruction (yes vs. no); RT sites (rib vs. others);

Table I. Characteristics of lesions.

Characteristic	No. of lesions	%
Age		
<70 years	185	58.4
≥70 years	132	41.6
Sex		
Male	230	72.6
Female	87	27.4
ECOG-PS		
<2	144	45.6
2	93	29.3
>2	80	25.2
Histology		
Small cell carcinoma	39	12.3
Adenocarcinoma	213	67.2
Squamous cell carcinoma	50	15.8
Others	15	4.7
Smoking history		
Yes		
Current	89	28.1
Past	123	38.8
No	73	23.0
Unknown	32	10.1
Timing of RT		
De novo	129	40.7
Relapse or appearance	188	59.3
Bone cortex destruction		
Yes	278	87.7
No	39	12.3
Metastases on internal organs		
Yes		
Single	118	37.2
Multiple	128	40.4
No	71	22.4
Number of bone metastatic lesions		
Single	58	18.3
2-3	41	12.9
>3	218	68.8
Bone metastatic sites		
Only vertebral	55	17.4
Only non-vertebral	47	14.8
Others	215	67.8
RT sites		
Vertebral	191	60.3
Pelvis	63	19.9
Rib	13	4.1
Others	50	15.8
RT dose (BED10)		
<39.0 Gy	50	15.8
39.0 Gy	223	70.3
>39.0 Gy	44	13.9

Table I. Continued.

Characteristic	No. of lesions	%
Post-RT BMAs		
Yes	247	77.9
No	70	22.1
Pre-RT ATs		
Yes		
TKIs	41	12.9
ICIs	38	12.0
TKIs + ICIs	0	0.0
Other ATs	68	21.5
No	170	53.6
Post-RT ATs		
Yes		
TKIs	76	24.0
ICIs	37	11.7
TKIs + ICIs	17	5.4
Other ATs	98	30.9
No	89	28.1
Pre-RT laboratory data		
ALP, median [range]	304 [44.8-7,130.0]	
Ca, median [range]	9.1 [5.8-22.5]	
NLR, median [range]	4.6 [0.9-32.5]	

ECOG PS, Eastern Cooperative Oncology Group Performance Status; RT, radiotherapy; *de novo*, bone metastases eligible for palliative RT at presentation; relapse or appearance, bone metastases not eligible for palliative RT at presentation or appeared after definitive treatment; ATs, antineoplastic agents; TKIs, tyrosine kinase inhibitors; ICIs, immune checkpoint inhibitors; ALP, alkaline phosphatase; Ca, calcium; NLR, neutrophil to lymphocyte ratio.

RT dose (biologically effective dose; BED10) (≤39.0 Gy vs. >39.0 Gy); administration of molecular-targeting agents (MTs; TKIs and/or ICIs) before or after RT (yes vs. no); administration of BMAs (yes vs. no); neutrophil to lymphocyte ratio (NLR) before RT; and alkaline phosphatase (ALP) before RT.

Radiotherapy. All patients received three-dimensional conformal RT. RT was delivered using 6-10 MV photons with a linear accelerator (Varian Medical Systems, Palo Alto, California, United States). The doses of the target volumes were prescribed to be ≥90% of the RT dose, in principle. RT doses were determined at the discretion of each physician and institution and 30 Gy in 10 fractions was the most frequently used.

To compare the various fractionated schedules, BED was calculated in a linear-quadratic model (16). The BED10 (BED calculated using an α/β of 10 Gy) was calculated using the equation: n x d [1 + d/(α/β)], where d is the fraction dose, n is the number of fractions, and α/β is 10 Gy.

The median RT dose (BED10) was 39.0 Gy (=30 Gy in 10 fractions). The other fraction schedules, in sequential order, were as follows for RT of BED_{10} (=fraction schedules): 14.4 Gy (=1x8 Gy), 28.0-33.6 Gy (=5-6x4 Gy), 39.2 Gy (8x3.6 Gy), 37.9 Gy (8x3.5 Gy), 39-50.7 (10-13x3 Gy), 46.9-50.0 Gy (=15-16x2.5 Gy), and 39.7-45.6 Gy (=5x4 Gy + 3-4x3 Gy).

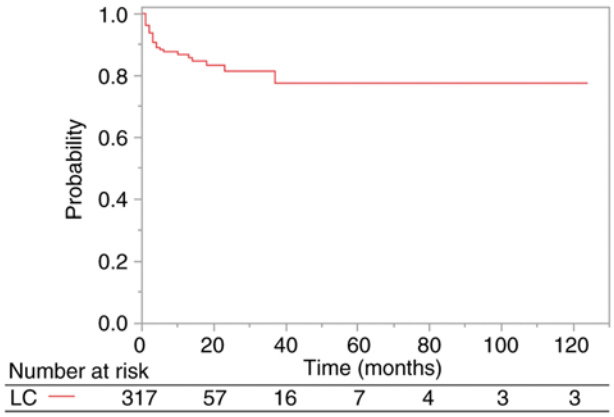

Figure 1. LC of all RT sites. The 0.5- and 1-year LC rates of all RT sites were 87.7 and 86.8%, respectively. LC, local control; RT, radiotherapy.

Effectiveness assessment. Patients were followed up by a thoracic oncologist or radiation oncologist after RT treatment. The follow-up time of physical examinations was up to the time the patient was last seen by the attending physician. The follow-up time of imaging studies was up to the last CT imaging. The follow-up timing of CT imaging was random. Local failure was defined as an enlargement of lytic change or extraosseous mass of bone metastasis at the RT sites compared with the size of osteolytic change before RT (9,17). Local control was defined as stable or shrinking the lytic change or extraosseous mass of bone metastasis at the RT sites. Two observers (a radiologist and a radiation oncologist) were blinded to the follow-up information and outcomes during the evaluation of the images.

Statistical analysis. The time of survival and the LC of RT sites were calculated from the start of palliative RT. The Kaplan-Meier method was used to generate overall survival (OS) and LC curves and P-values were calculated using the log-rank test. In the calculation of LC curves, the event was defined as the time when local failure was observed on the CT image, and censored when local failure was not observed on the final CT image. The Cox proportional hazards models to determine hazard ratios (HRs), including 95% confidence intervals (CIs) and P-value, were used for univariate and multivariate analysis to assess the predictive factors associated with LC rates of RT sites. Variables included in the multivariate models had a P-value of <0.1 in the univariate analysis. P<0.05 was considered to indicate a statistically significant difference in multivariate analysis. In addition, to determine the optimal cutoff NLR values for predicting LC in patients with lung cancer associated with bone metastasis, receiver operating characteristic (ROC) curve analysis was performed. These statistical analyses were performed using JMP software (JMP version 14.3.0; SAS Institute, Cary, NC, USA).

Results

Clinical characteristics. The median follow-up time of imaging studies and physical examinations was 4 months

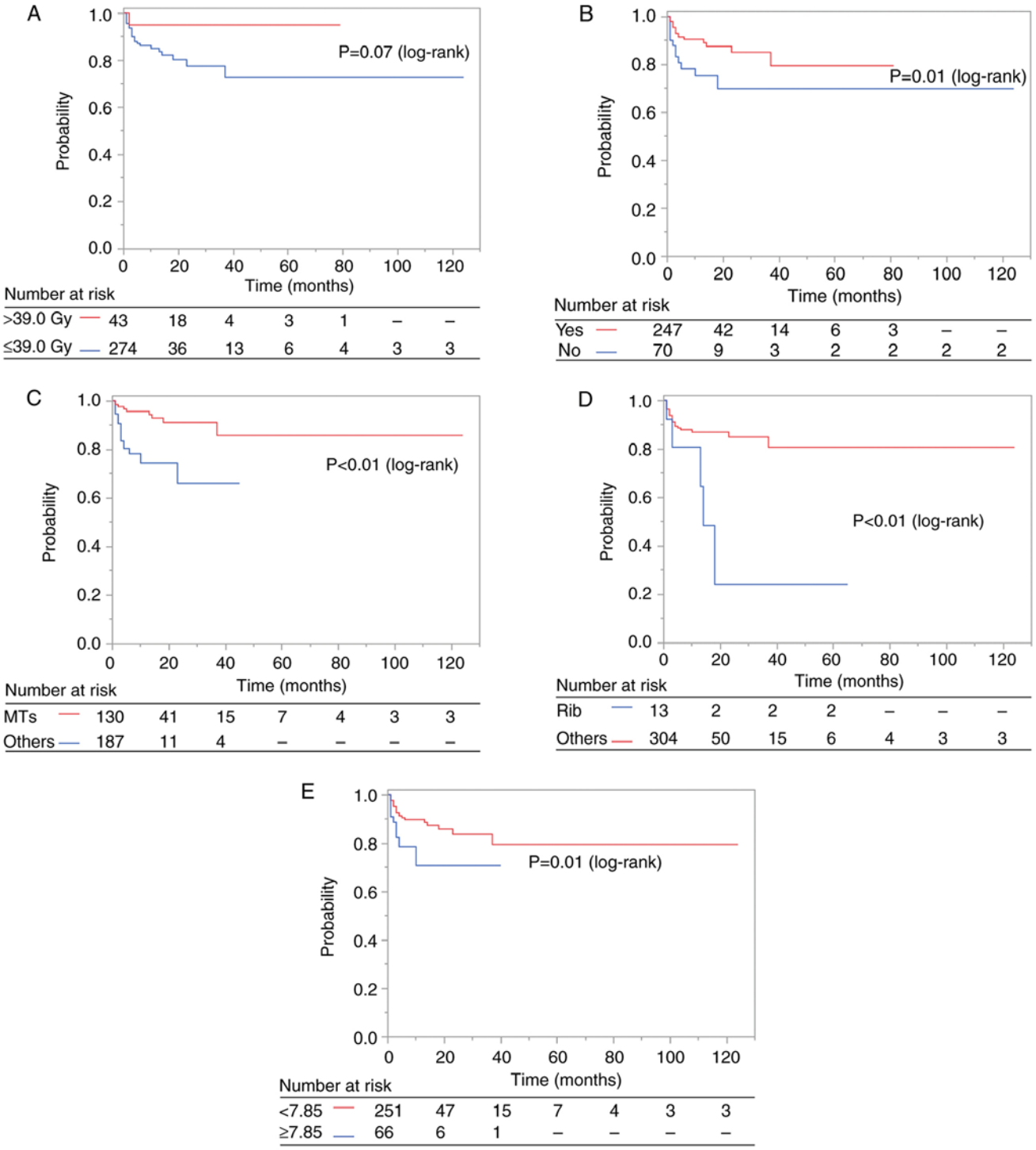

Figure 2. LC of bone metastasis from lung cancer according to each factor. (A) RT dose (BED_{10}) (≤39.0 Gy vs. >39.0 Gy); the LC rates were significantly lower in BED_{10} ≤39.0 Gy than in >39.0 Gy. (B) Post-BMAs (yes vs. no); the LC rates were significantly lower in non-post-RT BMAs than in post-RT BMAs. (C) Post-ATs (MTs vs. others); the LC rates were significantly lower in non-post MTs than in post-RT BMAs. (D) RT sites (rib vs. others); the LC rates were significantly lower in rib metastasis than in other bone metastasis. (E) NLR (<7.85 vs. ≥7.85); the LC rates were significantly lower in NLR ≥7.85 than in NLR <7.85. LC, local control; BED, biological effective dose; RT, radiotherapy; BMAs, bone modifying agents; ATs, antineoplastic agents; MTs, molecular targeting agents; NLR, neutrophil to lymphocyte ratio.

(range, 1-124 months) and 8 months (range, 1-127 months), respectively. The 0.5- and 1-year OS rates were 58.9 and 39.4%, respectively. The number of 0.5- and 1-year survival patients were 125 and 80, retrospectively. The 0.5- and 1-year LC rates of RT sites were 87.7 and 86.8%, respectively (Fig. 1). Local recurrence was observed in 11.0% (n=35) of the lesions, and the median time to recurrence was 2 months (range, 1-37 months). In addition, the 0.5- and 1-year LC rates of non-RT bone metastatic sites were 59.9 and 54.3%, respectively. Local enlargement of non-RT bone metastatic sites was observed in 46.1% (n=146) of lesions at the time of local recurrence of RT sites or the last CT evaluation of the RT sites.

Table II. Local control rates after RT and results of univariate analysis.

			Univariate analysis	
Characteristic	0.5-year, %	1-year, %	HR (95% CI)	P-value
Age				
<70 years vs. ≥70 years	90.0 vs. 84.4	90.0 vs. 82.1	1.93 (0.99-3.76)	0.06
Sex				
Female vs. male	93.3 vs. 84.6	91.0 vs. 84.8	1.23 (0.59-2.58)	0.58
ECOG-PS				
<3 vs. ≥3	86.5 vs. 93.3	85.4 vs. 93.3	0.42 0.13-1.39)	0.16
Histology				
NSCLC vs. SCLC	87.3 vs. 89.8	86.3 vs. 89.8	0.43 (0.10-1.78)	0.24
Metastases on internal organs				
Yes vs. no	86.8 vs. 90.1	86.8 vs. 87.5	0.57 (0.25-1.33)	0.19
Number of bone metastatic lesions				
Single vs. multiple	87.6 vs. 88.0	84.3 vs. 88.0	0.73 (0.35-1.52)	0.39
Bone metastatic sites				
Only spine vs. others	86.4 vs. 88.1	86.4 vs. 86.9	0.97 (0.42-2.22)	0.94
Timing of RT				
De novo vs. relapse or appearance	88.2 vs. 87.2	88.2 vs. 85.6	1.57 (0.77-3.20)	0.22
Bone cortex destruction				
Yes vs. no	88.1 vs. 84.9	87.1 vs. 84.9	0.57 (0.25-1.32)	0.19
RT sites				
Rib vs. others	80.8 vs. 88.0	80.8 vs 87.0	0.27 (0.10-0.69)	<0.01
RT dose (BED10)				
≤39.0 Gy vs. >39.0 Gy	86.2 vs. 95.0	85.0 vs. 95.0	0.27 (0.06-1.13)	0.07
Post-RT BMAs				
Yes vs. no	90.5 vs. 78.2	90.5 vs. 75.3	2.45 (1.25-4.83)	0.01
Pre-RT MTs				
Yes vs. no	93.1 vs. 86.0	93.1 vs. 84.8	1.03 (0.47-2.28)	0.93
Post-RT MTs				
Yes vs. no	95.7 vs. 78.3	95.7 vs. 74.3	4.30 (1.94-9.54)	<0.01
Pre-RT NLR				
<7.85 vs. ≥7.85	89.8 vs. 78.6	89.8 vs. 70.8	2.44 (1.18-5.02)	0.02
Pre-RT ALP				
Normal vs. abnormal	87.4 vs. 88.6	85.8 vs. 88.6	1.01 (0.52-1.98)	0.97

ECOG PS, Eastern Cooperative Oncology Group Performance Status; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; RT, radiotherapy; *de novo*, bone metastases eligible for palliative RT at presentation; relapse or appearance, bone metastases not eligible for palliative RT at presentation or appeared after definitive treatment; BED, biologically effective dose; BMAs, bone modified agents; MTs, molecular-targeting agents; NLR, neutrophil to lymphocyte ratio; ALP, alkaline phosphatase.

Influence of treatment-related risk factors. BED10, administration of BMAs, administration of antineoplastic agents (ATs) before RT (pre-RT ATs), and administration of ATs after RT (post-RT ATs) were treatment-related risk factors. ATs included MTs and other cytotoxic agents.

Radiotherapy. The 0.5-year LC rates were lower in BED10 ≤39.0 Gy than in >39.0 Gy (86.2% vs. 95.0%; HR, 0.27; 95% CI 0.06-1.13; P=0.07; Fig. 2A; Table II). In detail, the 0.5-year LC rates were lower in BED10=39.0 Gy than in >39.0 Gy (85.6% vs. 95.0%; HR, 0.25; 95% CI 0.06-1.06; P=0.06; Table SI). There was no significant difference between BED10=39.0 Gy and <39.0 Gy (85.6% vs. 85.3%; HR 1.73; 95% CI 0.53-5.69; P=0.37; Table SI).

Systemic therapy. The 0.5-year LC rates of post-RT BMAs were significantly different between patients who did and did not receive post-RT BMAs (90.5% vs. 78.2%; HR, 2.45; 95%

Table III. Local control rates after RT and results of multivariate analysis.

			Multivariate analysis	
Characteristic	0.5-year (%)	1-year (%)	HR (95% CI)	P-value
Age				
<70 years vs. ≥70 years	90.0 vs. 84.4	90.0 vs. 82.1	1.78 (0.89-3.55)	0.10
Sex				
Female vs. male	93.3 vs. 84.6	91.0 vs. 84.8	-	-
ECOG-PS				
<3 vs. ≥3	86.5 vs. 93.3	85.4 vs. 93.3	-	-
Histology				
NSCLC vs. SCLC	87.3 vs. 89.8	86.3 vs. 89.8	-	-
Metastases on internal organs				
Yes vs. no	86.8 vs. 90.1	86.8 vs. 87.5	-	-
Number of bone metastatic lesions				
Single vs. multiple	87.6 vs. 88.0	84.3 vs. 88.0	-	-
Bone metastatic sites				
Only spine vs. others	86.4 vs. 88.1	86.4 vs. 86.9	-	-
Timing of RT				
De novo vs. relapse or appearance	88.2 vs. 87.2	88.2 vs. 85.6	-	-
Bone cortex destruction				
Yes vs. no	88.1 vs. 84.9	87.1 vs. 84.9	-	-
RT sites				
Rib vs. others	80.8 vs. 88.0	80.8 vs 87.0	0.33 (0.12-0.93)	0.04
RT dose (BED10)				
≤39.0 Gy vs. >39.0 Gy	86.2 vs. 95.0	85.0 vs. 95.0	0.26 (0.06-1.13)	0.07
Post-RT BMAs				
Yes vs. no	90.5 vs. 78.2	90.5 vs. 75.3	2.11 (1.02-4.38)	0.04
Pre-RT MTs				
Yes vs. no	93.1 vs. 86.0	93.1 vs. 84.8	-	-
Post-RT MTs				
Yes vs. no	95.7 vs. 78.3	95.7 vs. 74.3	3.80 (1.65-8.73)	<0.01
Pre-RT NLR				
<7.85 vs. ≥7.85	89.8 vs. 78.6	89.8 vs. 70.8	2.80 (1.32-5.97)	0.01
Pre-RT ALP				
Normal vs. abnormal	87.4 vs. 88.6	85.8 vs. 88.6	-	-

ECOG PS, Eastern Cooperative Oncology Group Performance Status; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; RT, radiotherapy; *de novo*, bone metastases eligible for palliative RT at presentation; relapse or appearance, bone metastases not eligible for palliative RT at presentation or appeared after definitive treatment; BED, biologically effective dose; BMAs, bone modified agents; MTs, molecular-targeting agents; NLR, neutrophil to lymphocyte ratio; ALP, alkaline phosphatase.

CI, 1.25-4.83; P=0.01; Fig. 2B; Table II). Eighty-nine patients with 121 bone metastases with BMAs and 29 patients with 36 bone metastases without BMAs survived at 0.5-year after RT.

The 0.5-year LC rates of post-RT ATs were significantly different between patients who did and did not receive post-RT ATs (91.2% vs. 71.1%; HR, 3.23; 95% CI 1.60-6.54; P<0.01; Table SI). At the time of local recurrence or the last CT evaluation of the RT sites, 159 lesions (local recurrence, 18; local control, 141) did not have any ATs and the other 158 lesions (local recurrence, 17; local control, 141) did. On the other hand, the 0.5-year LC rates of pre-RT ATs were not significantly different between patients who did and did not receive pre-RT ATs (90.2% vs. 85.2%; HR, 1.08; 95% CI 0.56-2.11; P=0.82).

Post-RT ATs were i) TKIs (n=76), ii) ICIs (n=37), iii) TKIs+ICIs (n=17), and iv) other ATs (n=98). Post-RT ATs were divided into two groups MTs (TKIs and/or ICIs) (n=130) vs. others (n=98) according to the 0.5-year LC rates (TKIs, 98.7%; ICIs, 93.8%; TKIs+ICIs, 88.3%; and others, 78.3%,

Fig. S1A). There were statistically significant differences between post-RT MTs and others (0.5-year LC rates, 95.7% vs. 78.3%; HR, 4.30; 95% CI, 1.94-9.54; P<0.01; Fig. 2C; Table II). Meanwhile, there were no statistically significant differences between pre-RT MTs and others (0.5-year LC rates, 93.1% vs. 86.0%; HR, 1.03; 95% CI, 0.47-2.28; P=0.93, Fig. S1B). Sixty patients with 79 bone metastases with pre-MTs and 58 patients with 78 bone metastases without pre-MTs survived at 0.5-year after RT.

In the cases without post-RT MTs, the 0.5-year LC rates were lower in BED10 ≤39.0 Gy than in >39.0 Gy (75.6% vs. 94.1%; HR, 0.23; 95%CI 0.02-1.18; P=0.08). In cases with post-RT MTs, there was no significant difference between BED10 ≤39.0 Gy and <39.0 Gy (95.7% vs. 95.7%; HR 0.47; 95%CI 0.06-3.81; P=0.48).

Influence of cancer-related risk factors. Cancer-related risk factors included histology, bone cortex destruction, metastasis to internal organs, number of bone metastatic lesions, bone metastatic sites, and RT sites.

The 0.5-year LC rate according to RT sites was significantly different between rib and other sites (80.8% vs. 88.0%; HR, 0.27; 95% CI, 0.10-0.69; P<0.01; Fig. 2D; Table II). In addition, the 0.5-year LC rates were not significantly different between vertebral and pelvic bone metastasis (88.6% vs. 83.7%; HR, 1.06; 95% CI, 0.78-1.44; P=0.69). Any other cancer-related risk factors were not significantly different in the LC of RT sites (Table II).

Influence of patient-related risk factors. Age, sex, the timing of RT, ALP, and NLR, were analyzed as patient-related risk factors. The area under the ROC curves for LC was 0.50 (sensitivity, 31.4%; specificity, 80.0%) for NLR. For LC, an NLR of 7.85 corresponded to the maximum sum of sensitivity and specificity (data not shown).

The 0.5-year LC rate according to NLR was significantly different between <7.85 and ≥7.85 (89.8% vs. 78.6%; HR, 2.44; 95% CI, 1.18-5.02; P=0.02; Fig. 2E; Table II). A total of 101 patients with 135 bone metastases of NLR <7.85 and 17 patients with 22 bone metastases of NLR ≥7.85 survived at 0.5-year after RT. The 0.5-year LC rate according to age was higher in those <70 years than in those ≥70 years (90.0% vs. 84.4%; HR, 1.93; 95% CI, 0.99-3.76; P=0.06; Fig. S1C; Table II). Any other patient-related risk factors were not significantly different in terms of LC of RT sites (Table II).

Multivariate Cox regression analysis. On multivariate analysis, RT sites (rib), post-RT BMAs (no), post-RT MTs (no), and pre-RT NLR (≥7.85) were found to be significant unfavorable factors for LC of bone metastasis (Table III). In addition, there was a difference between BED10 ≤39.0 Gy and >39.0 Gy (HR, 0.26; 95% CI, 0.06-1.13; P=0.07; Table III).

Discussion

This study showed that the 0.5-year OS rate was approximately 50% in patients who received palliative RT for bone metastasis from lung cancer. RT sites, post-RT BMAs, post-RT MTs, and pre-RT NLR were important factors associated with LC of RT sites in patients with lung cancer treated with palliative RT. In addition, although RT dose was not significantly associated with LC, moderate dose escalation tended to improve the LC of RT sites (especially in the cases without post-RT MTs).

Previous studies have demonstrated that bone metastatic sites were an important factor for LC of RT sites (9,17). In our study, only rib metastasis had unfavorable LC compared with other bone metastatic sites. Zeng *et al* suggested that the presence of extraosseous mass, as identified by tumors with epidural and/or paraspinal extension via magnetic resonance image, was a significantly unfavorable factor for LC of RT sites (18). In our study, we could not evaluate the presence of extraosseous mass formation because CT image alone could not clearly define the difference between bone cortex destruction and extraosseous mass formation. However, many rib metastases with bone cortex destruction formed large masses. In our study, although bone cortex destruction including extraosseous mass formation did not correlate with the LC of RT sites, extraosseous mass may influence the worsening of LC of rib metastasis.

Post-RT systemic therapy was important for LC of bone metastatic sites. Administration of BMAs is a well-established method for the treatment of bone metastasis (19-21). In our study, post-RT BMAs had a large impact on the LC of bone metastasis. Some studies suggested that a combination of RT and BMAs, such as denosumab, zoledronic acid, or ibandronate, may be more effective than either RT or BMAs alone (22-24). In this study, these BMAs were administered for bone metastasis. The combination of RT and BMAs is important for LC of bone metastasis.

In addition, some studies reported the influence of ATs on bone metastasis (25,26). Furthermore, a previous study showed that post-RT ATs were important for better LC of bone metastasis (9). However, the type of ATs (TKIs, ICIs, or other cytotoxic chemotherapies) that was most effective for bone metastasis of RT sites was unclear because various primary tumors were included in this previous study. In our study, post-RT ATs for lung cancer were divided into two groups [MTs (TKIs and/or ICIs) vs. others] according to the 0.5-year LC rates. The impact of each group on LC was assessed. As a result, post-RT MTs had a larger impact on LC of bone metastasis compared with post-RT with other ATs (cytotoxic chemotherapy agents and/or antibody agents) or no ATs. Therefore, a combination of RT and MTs seems to be important for the LC of bone metastasis.

Palliative intent RT [most frequent RT dose: 10x3 Gy (BED10=39.0 Gy)] reduced the local failure of bone metastatic sites. Previous studies showed that moderate dose escalation from RT (BED10) of 39.0 Gy had a small impact on improving the LC of RT sites (9). In our study, although dose escalation in RT for bone metastasis from lung cancer tended to improve LC of RT sites (especially in the cases without post-RT MTs), the influence of moderate RT dose escalation seemed to be comparatively small. However, LC of bone metastasis irradiated at >39.0 Gy was adequately favorable (1-year LC, 95.0%). Recently, some studies suggested that stereotactic body radiotherapy (SBRT) improved the LC of bone metastasis compared with conventional RT (18,27). Therefore, in terms of LC of RT sites, although SBRT was a useful option for the treatment of bone metastatic lung cancer and predicted favorable prognosis, moderate dose escalation of RT seemed to be

an acceptable irradiation method especially when MTs were not combined with RT.

Inflammation plays a major role in tumor progression through the tumor microenvironment (28-30). Inflammation potentially has a large impact on tumor progression and treatment outcomes. It often leads to an increased neutrophil and decreased lymphocyte count and reduces survival in patients with various solid tumors (31,32). Therefore, many studies suggested that NLR, which is one of the inflammation markers, was an important factor for OS (33,34). Meanwhile, few studies suggested that inflammation markers were important for LC of treatment sites (35). Therefore, we used ROC analysis to determine the optimal NLR cut-off value for the LC of RT sites. Tumor aggressiveness may increase due to inflammation and lead to the activation of tumor cells in the sites where many tumor cells remained (28-30). In contrast to definitive local treatments, many tumor cells may remain in the local treatment site after palliative local treatments. Therefore, the high potential for residual tumor cells in the palliative RT sites might be one of the possible explanations why NLR correlated with LC of RT sites.

There were some limitations in our study owing to its retrospective nature. First, there may be a selection bias in the determination of RT doses because many radiation oncologists were involved in the management of patients due to the long-term study design. Second, evaluation of an antitumor effect on bone metastasis is generally difficult. Response Evaluation Criteria in Solid Tumor classifies bone metastasis as nontarget lesions (36). Furthermore, local failure of osteoblastic bone metastasis was difficult to evaluate because local failure as the RT-induced recalcification and/or the BMAs induced osteoblastic changes. Therefore, in our study, LC was evaluated as only osteolytic bone metastasis and the definition of local failure was enlargement of lytic changes of the RT sites. Third, the impact on LC of bone metastatic sites may be difficult to assess in detail because of the small number of cases with rib metastasis. Although further investigation is required, as rib metastasis showed a significant unfavorable factor for LC in the multivariate analysis in our study, it may be one of the unfavorable factors for LC of bone metastasis. Finally, this study failed to assess pain relief and skeletal-related events which were important factors for palliative RT. However, with the progress of systemic therapy, precision medicine is gaining importance in palliative RT. For the patients with a favorable prognosis, LC of bone metastasis, even when palliative RT was performed, may be important. This study provided one perspective on precision medicine. In the future, following significant progress in systemic therapy, the LC rates of bone metastasis should be updated regularly with the improvement of treatment methods as we have seen that ATs improved the LC of bone metastasis.

In conclusion, treatment-related risk factors (post-RT MTs and BMAs), cancer-related risk factors (bone metastasis other than rib), and a patient-related risk factor (lower pre-RT NLR) had a large impact on favorable LC of bone metastasis in patients with lung cancer. Moderate dose escalation of BED10 of 39.0 Gy (10x3 Gy) seemed to have a small impact on improving the LC of RT sites in these patients. These results should be considered for the individualization of RT for bone metastasis from lung cancer.

Acknowledgements

The authors would like to thank Ms. Natsumi Yamashita MD (Department of Clinical Research, National Hospital Organization Shikoku Cancer Center), for her statistical support.

Funding

No funding was received.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

All authors had full access to the data in the study, and take responsibility for the integrity of the data and the accuracy of the data analysis. KM and YH confirm the authenticity of all the raw data. KM designed the study concepts. KM, YH, HK, KN and TK collected and analyzed patient data, and drafted the article. KM, YH, HK, KN and TK collaborated in the discussion. KM and YH prepared the manuscript, and HK edited the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This study design was approved by the Ethics Committee of Shikoku Cancer Center (Matsuyama, Ehime, Japan; approval reference no. RIN2021-70) and informed consent was waived due to the retrospective nature of the study. The study followed international and national regulations and is in agreement with The Declaration of Helsinki.

Patient consent for publication

Not applicable.

Competing interests

Toshiyuki Kozuki received an honorarium from MSD, Ono, Kyowa Hakko Kirin, AstraZeneca, Boehringer Ingelheim, Chugai, TAIHO, Eli Lilly, Bristol Myers Squibb, Pfizer, Merck Biopharma, Nippon Kayaku, Novartis, Bayer, Sawai and AMGEN, received consulting fees from Chugai, AstraZeneca, Ono, Pfizer, Daiichi-Sankyo, Bayer, and Abbvie, and received research funding from MSD, Kyowa Hakko Kirin, AstraZeneca, Eli Lilly, Pfizer, Chugai, TAIHO, Ono, Bristol-Myers, Merck Biopharma, Daiichi-Sankyo, AbbVie, AMGEN, Sanofi, Eisai and Labcorp Development. All other authors declare that they have no conflict of interest.

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