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ORIGINAL ARTICLE

Significance of liver metastasis volume in breast cancer patients treated with stereotactic body radiotherapy

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Abstract

Purpose This study analyzed the impact of liver metastasis (LM) volume on treatment outcomes in breast cancer (BC) patients treated with stereotactic body radiotherapy (SBRT).

Methods This single-institution retrospective analysis included 40 oligometastatic (≤5 metastases) BC patients with 58 liver metastases treated with SBRT between April 2013 and March 2021. The prognostic factors for local control (LC), overall survival (OS), and progression-free survival (PFS) rates were assessed.

Results Median follow-up time was 28.1 months. Isolated and solitary LM were seen in 26 (65%) and 24 (60%) patients, respectively. Median time to disease recurrence was 10.7 months post liver SBRT. The 2-year OS, PFS, and LC rates were 71.4%, 27.5%, and 86.8%, respectively. In univariate analysis, patients with a gross tumor volume (GTV) of ≤6 cc and a planning target volume (PTV) of ≤38 cc demonstrated a significantly better median OS than those with GTV >6 cc and PTV >38 cc. In multivariate analysis, the predictive factors for worse OS were GTV >6 cc (HR = 3.07 [95% CI, 1.14–8.22; $p = 0.03$]) and PTV >38 cc (HR = 5.91 [95% CI, 1.92–18.21; $p = 0.002$]). No significant factor for PFS was found. Only 2 patients experienced rib fracture at 4 and 6 months post treatment, and 1 patient had a grade II duodenal ulcer.

Conclusion Liver SBRT is an effective and safe treatment option for oligometastatic BC patients with excellent LC, promising survival, and limited toxicity. Patients with smaller tumors displayed better OS than their counterparts, validating the effectiveness of a local treatment for this group.

Keywords Breast cancer · Liver metastasis · Radiotherapy · Stereotactic radiotherapy · Stereotactic ablative body radiotherapy · Tumor volume

Introduction

Breast cancer (BC) is the most common malignancy and the leading cause of cancer-related death in women [1]. In BC patients, metastatic disease remains a big challenge, with a 5-year survival rate of approximately 25% [2]. The most common sites of distant metastases in BC patients are the bones, lungs, liver, and brain. Patients with liver or brain metastases show dismal survival, with a survival time of 4–8 months if left untreated, compared with patients with bone or lung metastasis [2]. However, oligometastatic patients display different characteristics and better outcomes relative to diffuse metastatic patients. The term oligometastases was coined by Hellman and Weichselbaum [3] to describe the intermediate state of limited metastatic disease, where curative strategies may be effective.

Although most cases of breast cancer liver metastasis (BCLM) are treated with systemic treatment with palliative intent, local treatment options may be considered in selected patients with the aim of a possible cure [4]. Current data show excellent local control (LC) and longer survival outcomes after local aggressive treatments, such as surgical resection or ablative options, in selected BCLM patients [5–7]. Intensive local treatment modalities, including surgery, trans-arterial chemoembolization [8], radiofrequency ablation (RFA) [5, 7], and radiotherapy (RT) [9, 10], have been employed alone or in combination with systemic chemotherapy to improve outcomes in BCLM patients.

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Despite the lower radiation tolerance of liver parenchyma, high radiation doses can be safely applied to small volumes of liver by using high-technology radiation delivery systems [9]. Stereotactic body radiotherapy (SBRT) is a highly conformal RT technique that allows delivery of high radiation doses to a tumor with a steep dose gradient, while simultaneously better sparing normal tissues. The feasibility of SBRT in liver metastasis (LM) has been demonstrated in numerous prospective and retrospective studies, with LC rates of 80–90% [10–12]. Recently, we demonstrated that SBRT is a safe and effective treatment option in BCLM patients; however, we were unable to find any significant prognostic factors affecting survival and LC in 22 patients with 29 liver metastatic lesions [13].

Although tumor size in primary hepatocellular carcinoma has been widely investigated and has been proven to be a significant predictor for survival in SBRT-treated patients [14–16], data on the significance of LM size on treatment outcomes in BC patients treated with ablative techniques is limited, and a few studies have focused on the impact of tumor volume in SBRT-treated BCLM patients [7, 8]. Thus, this study aimed to analyze the impact of LM volume and other prognostic factors on clinical outcomes in BC patients who received SBRT and systemic treatment.

Materials and methods

Patients and data collection

The clinical parameters of 40 BCLM patients treated with SBRT between April 2013 and March 2021 were retrospectively analyzed. The inclusion criteria were as follows: Karnofsky performance status of ≥ 70, Child–Pugh status A–B, maximum LM diameter of ≤ 6 cm, absence of coagulation abnormalities, and life expectancy of > 3 months. Patients who had metastatic foci other than the liver and whose metastasis is under control with systemic chemotherapy and/or RT were included. Patients with uncontrolled disseminated metastases or those unsuitable for SBRT were excluded. LM was detected with 18-fluorodeoxyglucose positron-emission computed tomography (FDG-PET/CT) either at diagnosis or during distant progression. Some patients in this study were included in our previous study, demonstrating the feasibility of SBRT in patients with BCLM [13].

Treatment planning

The SBRT technique has been described previously [13]. The patients were positioned supine with arms above the head and immobilized using a BodyFIX® bluebag with a vacuum wrap (Elekta, Stockholm, Sweden); an abdominal compress was used to minimize target volume motion. No fiducial markers were implanted during planning and SBRT delivery. In order to measure organ movement, CT images were taken during deep inspiration and deep expiration periods. During treatment, 4D-CBCT acquisitions were carried out in an Elekta X-ray volume imaging (XVI) Symmetry™ 4DCBCT system (v. 4.5; Elekta AB, Stockholm, Sweden).

The gross tumor volume (GTV) included the visible gross tumor mass in the contrast-enhanced planning CT; FDG-PET/CT and/or MRI images were fused with the planning CT for better delineation of the GTV. The planning target volume (PTV) was generated by 7-mm expansion in all directions, except for the craniocaudal axis, where 12 mm was used. Healthy liver (liver volume subtracted by GTV), kidneys, stomach, duodenum, heart, spinal cord, small intestine, esophagus, and ribs were the organs at risk (OARs) according to the localization of the GTV.

All patients were treated according to our institutional SBRT protocol. The prescribed dose was 54 Gy divided into three fractions and delivered every other day. The planning goal for the PTV was to deliver at least 95% of the prescribed dose, and the dose was prescribed to the 90% isodose line. No specific constraint for maximum dose at PTV was considered. Previously published OAR dose constraints during liver SBRT were used [17, 18]. The dose constraints are summarized in Table 1.

The plans were calculated with the Monaco Treatment Planning System (Elekta Ltd, Crawly, UK) using the Monte Carlo algorithm as previously described. All treatment plans were delivered with an Axesse Linear Accelerator (Elekta AB, Stockholm, Sweden). Volumetric modulated arc therapy plans consisting of double or triple arcs depending on the target volume and OAR dose constraints were used. All patients were treated with image-guided RT using daily cone-beam CT to overcome setup inaccuracies. The three-dimensional positions of the entire liver, bones, main blood vessels, and diaphragm were used as surrogates for tu-

Table 1 Dose constraints for organs at risk

Critical organs	Constraints
Liver	V15 < 700 cc
Kidneys	V15 < 35%
Spinal cord	D1cc < 18 Gy
Stomach/duodenum	D1cc < 21 Gy
Small intestine	D1cc < 21 Gy
Esophagus	D1cc < 21 Gy
Heart	D1cc < 30 Gy
Ribs	D30cc < 30 Gy

V15 Volume receiving 15 Gy dose, *D1cc* dose receiving 1 cc of organ, *D30cc* dose receiving 30 cc of organ

mor position. Couch repositioning was performed after automatic matching of cone-beam CT images to reference CT images; manual refining was performed by the treating physician.

Follow-up

Patients were followed up every 3 months, except for the first visit, which was scheduled 45 days after SBRT for toxicity assessment. Physical examination, liver function tests, and abdominal ultrasonography were performed at all visits. The initial imaging modality was repeated in patients for treatment response assessment 3 months post liver SBRT. Toxicity was evaluated and scored according to the Common Toxicity Criteria for Adverse Events version 4.

Statistical analysis

Statistical analyses were performed using SPSS 22.0 software (SPSS for Windows, IBM Corp., Armonk, NY, USA). The OS was calculated as the period from LM diagnosis to the date of death or last visit; progression-free survival (PFS) was defined as the time between LM and the date of death or when the first clinical or imaging evidence of disease recurrence was obtained. The OS, PFS, and LC rates were estimated by the Kaplan–Meier method. Multivariate analysis was performed using a Cox proportional hazards model; hazard ratios (HRs) and 95% confidence intervals (95% CIs) were estimated using all the significant factors identified in the univariate analysis. A p-value of <0.05 was considered statistically significant.

Results

Patient characteristics

Patient characteristics are summarized in Table 2. A total of 40 BCLM patients with 58 lesions were treated with SBRT between April 2013 and March 2021. The median patient age was 47 (range: 24–78) years. Twenty-six patients (65%) had isolated LM, and 24 (60%) had solitary LM. Thirty-two patients (80%) had LM at a median disease progression time of 35.4 (8.7–105.0) months after initial diagnosis. The median GTV and PTV were 6 cc (range: 0.7–55.3 cc) and 38 cc (range: 9.3–165.3 cc), respectively.

Twenty-two patients (55%) received chemotherapy and 14 patients (35%) received hormonotherapy and/or trastuzumab following liver SBRT. Four patients (10%) did not receive any additional treatment after liver SBRT. These four patients had single LM showing complete response after SBRT at the first visit, and they refused additional treatment.

Table 2 Patient and tumor characteristics

Variables	*n*	%
Median age (range), years	47 (24–78)	
Histology		
Invasive ductal carcinoma	26	65
Invasive lobular carcinoma	2	5
Invasive carcinoma (not otherwise specified)	12	30
Metastasis time		
Synchronous	8	20
Metachronous	32	80
Hormone status		
Estrogen positive	36	90
Progesterone positive	26	65
Her2/neu rich	29	72.5
Triple negative	2	5
Metastasis site		
Liver only	26	65
Liver + bone	13	32.5
Liver + bone + lung	1	2.5
Number of liver metastasis		
1	24	60
2	14	35
3	2	5
Systemic treatment before SBRT		
Chemotherapy	30	75
Hormonotherapy/trastuzumab	2	5
None	8	20
Systemic treatment after SBRT		
Chemotherapy	22	55
Hormonotherapy/trastuzumab	14	35
None	4	10

SBRT stereotactic body radiation therapy

Treatment outcomes

The median follow-up time was 28.1 (range: 4.4–59.4) months. All patients had disease recurrence at a median time of 10.7 months (95% CI: 2.5–33.6 months) post liver SBRT. Among the patients, 1 (2.5%) had isolated local recurrence at the SBRT site, 3 (7.5%) had both locoregional and distant recurrence, and 36 (90%) had distant metastasis. At the last follow-up, 24 patients (60%) had died because of disease progression, and 16 (40%) were alive with the disease.

The 2-year OS and PFS rates were 71.4% and 27.5%, respectively (Fig. 1a,b). The 1- and 2-year LC rates per lesion were 97.2% and 86.8%, respectively (Fig. 1c). Four patients (10%) with five lesions had local recurrence at the SBRT site. One patient with isolated local recurrence was treated with RFA, and the three other patients with local

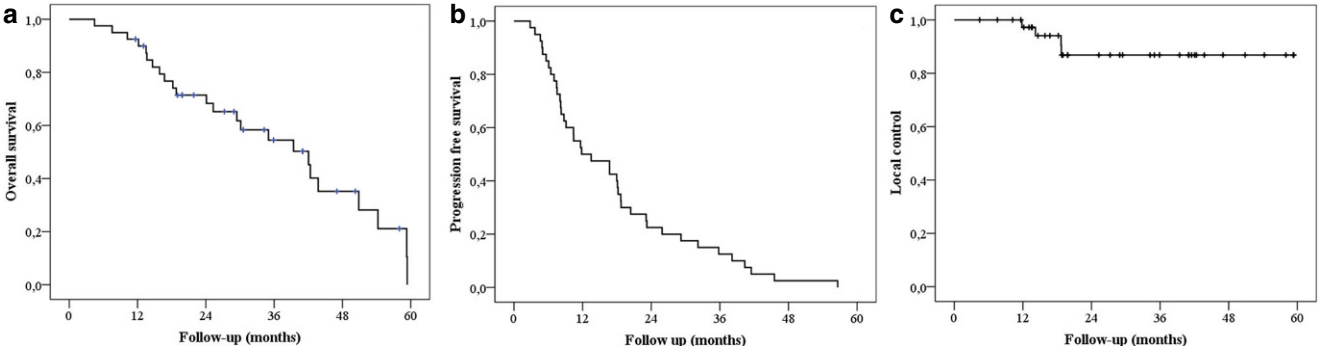

Fig. 1 **a** Kaplan–Meier curve demonstrating overall survival, **b** progression-free survival, and **c** local control starting from the date of liver metastasis diagnosis

recurrence received systemic chemotherapy because of additional distant disease recurrence.

Prognostic factors

In the univariate analysis, the GTV and PTV were the significant prognostic factors for OS (Table 3). Median values of GTV and PTV were used for stratification. Median OS was significantly higher in patients with GTV ≤6 cc than in patients with GTV >6 cc (50.9 months [95% CI, 39.1–62.6 months] vs. 18.8 months [95% CI, 7.3–30.3 months]; $p=0.01$; Fig. 2a). The median OS time was 59.3 months (95% CI, 39.8–64.3 months) in patients with PTV ≤38 cc and 18.8 months (95% CI,

Table 3 Univariate analysis for overall survival and progression-free survival

Characteristic	*n*	2-year OS (%)	*p*-value	2-year PFS (%)	*p*-value
Age					
<45 years	17	81.3	0.31	47.1	0.22
≥45 years	23	59.7	–	13	
Metastasis time					
Synchronous	8	100	0.43	50	0.19
Metachronous	32	63.9		15.6	
Metastasis site					
Liver only	26	91.7	0.43	28.6	0.75
Multiple organs	14	61.5		19.2	
Number of liver metastases					
1	24	69.8	0.48	37.5	0.19
2–3	16	74		6.3	
ER status					
–/+	14	70.1	0.29	21.4	0.88
++/+++	26	71.1		24.0	
PR status					
–/+	26	68.2	0.75	23.1	0.98
++/+++	14	76.2		23.4	
Her2/neu status					
–/+	17	70.6	0.88	17.6	0.93
++/+++	23	70.9		27.3	
GTV					
≤6 cc	20	94.4	0.01	25	0.84
>6 cc	20	50		20	
PTV					
≤38 cc	19	100	0.001	26.5	0.64
>38 cc	21	47.6		19	

ER Estrogen receptor, *PR* progesterone receptor, *GTV* gross tumor volume, *PTV* planning target volume

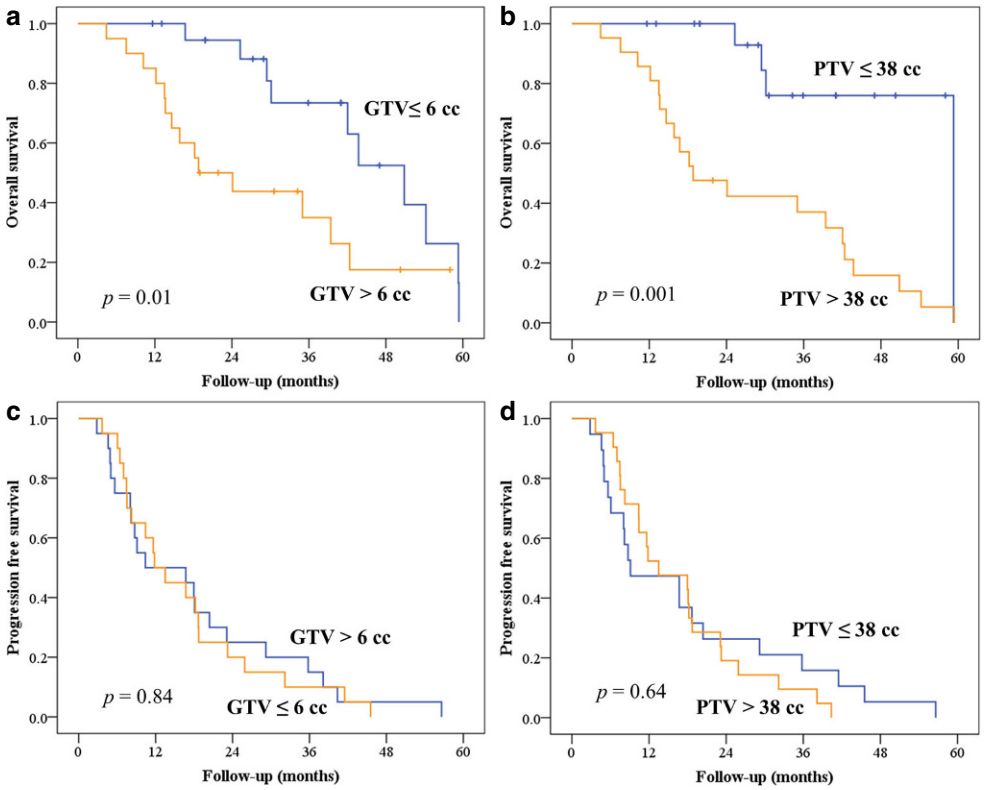

Fig. 2 Overall survival rates of patients with **a** gross tumor volume (*GTV*) greater than 6 cc (*yellow line*) and lower than or equal to 6 cc (*blue line*) and with **b** planning target volume (*PTV*) greater than 38 cc (*yellow line*) and lower than or equal to 38 cc (*blue line*). Progression-free survival rates of patients with **c** GTV greater than 6 cc (*blue line*) and lower than or equal to 6 cc (*yellow line*) and with **d** PTV greater than 38 cc (*blue line*) and lower than or equal to 38 cc (*yellow line*)

8.2–54.6 months; $p=0.001$) in patients with PTV >38 cc (Fig. 2b). In the univariate analysis, no additional significant prognostic factor including age, LM status, other organ metastasis, and number of liver metastases for OS was identified (Table 3). No difference in PFS in relation to GTV and PTV was seen (Fig. 2c,d), and no significant prognostic factor for PFS was observed in the univariate analysis. The LC rates for patients with GTV ≤6 cc and GTV >6 cc were 94.1% vs. 75.3% ($p=0.19$), and it were 87.5% for patients with PTV ≤38 cc and 85.0% for patients with PTV >38 cc ($p=0.84$).

The predictive factors for worse OS in multivariate analysis were GTV >6 cc (HR = 3.07 [95% CI, 1.14–8.22; $p=0.03$]) and PTV >38 cc (HR = 5.91 [95% CI, 1.92–18.21; $p=0.002$]).

Toxicity

No patients experienced grade 4 or 5 toxicity. Only 2 patients (5%) experienced rib fracture at 4 and 6 months post treatment, and 1 patient had a grade II duodenal ulcer that resolved after proper medication. No radiation-induced liver disease was observed.

Discussion

This study demonstrated that SBRT is an effective and safe treatment option for patients with BCLM either diagnosed upon BC diagnosis or during progression. Patients with a small LM volume had significantly better OS than those with a larger LM volume. However, no prognostic factors were significant for PFS. Although excellent LC rates were achieved through SBRT in the BCLM patients, the majority of patients had distant disease recurrence at a median time of 10.7 months after liver SBRT. The liver SBRT was well tolerated, with only 2 patients (5%) having grade 3 late toxicity.

The benefit of SBRT in an oligometastatic case has been increasingly evaluated. In a randomized phase II study, the SABR-COMET trial, oligometastatic patients were assigned to palliative conventional treatment or to standard of care plus SBRT for all metastatic lesions [7]. Although median OS was better in the SBRT arm than in the conventional treatment, adverse events were higher in the SBRT arm (29 vs. 9%, $p=0.026$). The results of this study should be evaluated with caution because 13% of the SBRT arm had LM and only 13% of the patients had BC histology. Although patients with metastatic BC are unlikely to be cured of their disease by any means, the potential of prolonging their survival should be considered. In another study on heterogeneous primary cancers, Milano et al. [6] reported

Table 4 Summary of studies reporting the significance of LM size in BC patients

Study	Primary	No. of BC patients	LM cut-off value	Technique	Follow up (months)	LC (in %)	OS (in %)
Barral et al. [8]	Breast	79	≤ 2, 2–4, > 4 cm	RFA	18.4	2-year 76.1	2-year 95.5
Meloni et al. [7]	Breast	52	2.5 cm	RFA	37.2	5-year 75	5-year 27
Weykamp et al. [20]	Breast	58	NR	SBRT	21	2-year 89	2-year 62
Rusthoven et al. [12]	Various	4/47	3 cm	SBRT	16	2-year 92	2-year 30
Mahadevan et al. [19]	Various	42/427	40 cc	SBRT	14	2-year 72	2-year 49
Present study	Breast	37	6 cc GTV 38 cc PTV	SBRT	28.1	2-year 86.8	2-year 71.4

BC breast cancer, *LM* liver metastasis, *LC* local control, *OS* overall survival, *RFA* radiofrequency ablation, *SBRT* stereotactic body radiotherapy, *GTV* gross tumor volume, *PTV* planning target volume

noteworthy improvements in long-term LC, OS, and freedom from distant metastasis, which reached over 6 years with SBRT. The existing data highlight a great variety of primary tumors with varying metastatic status as well as treatment options.

Limited data demonstrate the efficacy of local ablative treatment options in BCLM patients (Table 4). In a series of 79 BC patients, Barral et al. [8] investigated the results of percutaneous thermal ablation on 114 metastases, of which 50 were located in the liver. The authors reported the 2-year OS and LC rates to be 95.5 and 76.1%, respectively, and they emphasized that LC and disease-free survival decreased with increased tumor size. Meloni et al. [7] presented the results of 52 RFA-treated BCLM patients (25 of whom had liver metastases only and 27 of whom had liver and other organ metastases) [12]. Local progression was observed in 25% of the patients, and the only factor that was predictive for survival was tumor size, with a cut-off value of 2.5 cm. In a multi-institutional phase I/II trial, Rusthoven et al. [12] investigated the results of SBRT for LM in different metastatic primary cancers; only 4 of the 47 patients had BC. The 2-year LC and OS rates were 92 and 30%, respectively. In a subset analysis that further divided the patients into two groups according to size (≤ 3 and > 3 cm), the 2-year LC was significantly decreased in the group with larger LM. Mahadevan et al. [19] conducted a multi-institutional study involving 427 patients, of whom 42 (9.8%) had primary BC. The authors grouped the LM volumes as $< 40\,cm^3$ or $\geq 40\,cm^3$, and they found a significantly better median survival for the group with smaller LM. Weykamp et al. [20] found that solitary metastasis was an independent prognostic factor for better distant control and PFS, and OS was independently inferior for patients treated at a higher age.

Despite the robust evidence supporting the prognostic power of tumor size in many primary cancers treated with SBRT, there are limited clinical data specifically addressing the tumor volume of LM treated with SBRT in the BC population. The available reports included diverse patient groups with different tumor characteristics. On top of that, BC itself entails a variety of subgroups. The current data should be interpreted carefully. In concordance with the available literature detailed here, we found an LC rate of 86.8% at 2 years with considerably high OS and PFS rates. Of note, all three local recurrences had GTV ≥ 6 cc and PTV ≥ 38 cc, suggesting that increased LM size is associated with worse LC. Lack of association with PFS can be surmised to be due to distant disease recurrence. Since PFS is affected by other metastases as well as by LM, a lack of significant improvement on that front is expected.

This single-institution retrospective analysis has several limitations, including the limited patient number. Its primary inherent limitations are its retrospective nature and the associated selection biases. Moreover, the LM detected with FDG-PET/CT could not be confirmed histopathologically; thus, we could not exclude the FDG-PET/CT false-positive areas, and we might have underestimated the false-negative results. Moreover, the systemic treatments varied depending on the physicians' preferences before and after liver SBRT, which potentially influenced the treatment outcomes. Despite these limitations, this study is noteworthy because it involved a homogenous patient population consisting of patients with BC treated with the same SBRT protocol in terms of dose and fractionation. In our previous report with 22 patients, which had a median follow-up of 16 months, we demonstrated the feasibility of SBRT in patients with BCLM; however, we could not find any prognostic factor for predicting survival and local control [13]. However, in the current study with the larger patient population and a longer follow-up, we found that GTV and PTV were independent prognosticators for OS. Additionally, we could ascertain a threshold metastasis volume prognostic for treatment outcomes in oligometastatic BCLM patients treated with liver SBRT.

Conclusion

To our best knowledge, this study is the first to evaluate the impact of LM volume on outcomes in SBRT-treated BC patients. Patients with larger LM with GTV >6 cc and PTV >38 cc during SBRT had worse OS compared with their counterparts, indicating that patients with smaller LM benefitted from the curative treatment approach. It is possible that with a larger number of patients and longer follow-up, the survival benefit may become apparent. Liver SBRT is a feasible, effective, and safe approach in the treatment of oligometastatic BC patients with excellent LC, promising survival, and minimal toxicity. While LM volume could be used as a surrogate for selecting appropriate candidates for liver SBRT in BC patients, prospective trials and further research involving a large patient population are warranted to support our findings.

Conflict of interest E. Oymak, O.C. Guler, and C. Onal declare that they have no competing interests.

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