Clinical Study of 2 Radiotherapy Techniques for Semi-Hepatic Alternating Radiotherapy on Diffuse Liver Metastasis in Patients with Breast Cancer

Jiangzhou Zhang, MD¹, Shuheng Bai, MD¹, Xingzhou Zhang, MS², Yanli Yan, MD¹, Haojing Kang, MD¹,³, Guangzu Li, MD¹, Zhaode Feng, MD¹, Wen Ma, MD¹, and Juan Ren, MD, PhD¹

Abstract

Objective: To compare the effects of 2 techniques of semi-hepatic alternating radiotherapy on diffuse hepatic metastasis in patients with breast cancer. Methodology: A total of 68 breast cancer patients with diffuse liver metastasis were randomly divided into Group A (semi-hepatic alternating radiotherapy) and Group B (semi-hepatic sequential radiotherapy). In Group A (semi-hepatic sequential radiotherapy), the liver was divided into the first semi-liver and second semi-liver and alternatively treated with semi-hepatic intensity-modulated radiation therapy (IMRT). The interval between the 2 instances of semi-hepatic radiotherapy was 6 h. The average radiotherapy dose to the semi-livers was both 2 Gy/fraction, once a day, 5 times per week, with a total dose of 30 Gy for 15 days. The total radiation therapy time in Group A was 15 days in Group B (semi-hepatic sequential radiotherapy), the livers were divided into the first semi-liver and second semi-liver and treated with semi-hepatic sequential IMRT. The first semi-liver was first treated in the initial stage of radiation therapy, the average radiotherapy dose to the semi-liver was 2 Gy/fraction, once a day, 5 times per week, with a total dose of 30 Gy for 15 days. The second semi-liver was treated next in the second stage of radiation therapy, the average radiotherapy dose to the semi-liver was 2 Gy/fraction, once a day, 5 times per week, with a total dose of 30 Gy for 15 days. The total radiation therapy time in group B was 30 days.

Results: The objective response rate (complete response + partial response) of Group A and Group B were 50.0% and 48.5%, respectively (p = .903). The median survival time after metastasis (median survival of recurrence) of Group A and Group B was 16.7 months and 16.2 months, respectively (p = .411). The cumulative survival rates of 6 months, 1 year, 2 years, and 3 years of Group A and Group B were 90.6% (29 of 32) and 84.8% (28 of 33) (p = .478), 65.6% (21 of 32) and 60.6% (20 of 33) (p = .675), 31.2% (10 of 32) and 27.3% (9 of 33) (p = .725), and 15.6% (5 of 32) and 0 (0 of 33) (p = .018), respectively. The differences between the 2 groups showed no statistical significance in terms of cumulative survival rates in 1 year, 2 years, however, the 3-year survival rate was significantly different. The main toxic reactions were digestive tract reactions, abnormal liver functions, and myelosuppression. The incidence of I to II degree gastrointestinal reactions was 78.13% (25 of 32) in Group A and 72.73% (24 of 33) in Group B (p = .614). The incidence of I to II abnormal liver function was 53.13% (17 of 32) in Group A and 48.48% (16 of 33) in Group B (p = .708). The differences between the 2 groups showed no statistical significance.

¹ Department of Radiotherapy, Oncology Department, First Affiliated Hospital of Xi’an Jiaotong University, Xi’an, Shaanxi Province, China
² Oncology Department, Wuhan Chinese Medicine Hospital, Wuhan, Hubei Province, China
³ Department of Chemotherapy, Oncology Department, First Affiliated Hospital of Xi’an Jiaotong University, Xi’an, Shaanxi Province, China

Hong Sun and Juan Ren contributed equally.

Corresponding Authors:
Juan Ren, PhD, Department of Radiotherapy, Oncology Department, First Affiliated Hospital of Xi’an Jiaotong University, Xi’an, Shaanxi 710061, P.R. China. Email: 869491533@qq.com
Hong Sun, MD, Department of Chemotherapy, Oncology Department, First Affiliated Hospital of Xi’an Jiaotong University, Xi’an, Shaanxi 710061, P.R. China. Email: 2900532897@qq.com

Creative Commons Non Commercial CC BY-NC: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 License (https://creativecommons.org/licenses/by-nc/4.0/) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access page (https://us.sagepub.com/en-us/nam/open-access-at-sage).
Approximately 25% to 30% of breast cancer patients will progress to distant metastasis, and the 5-year survival rate decreases to 25% in metastatic patients. The most common metastatic sites of breast cancer are bones, lungs, liver, and brain. Patients with bone or lung metastasis have better survival rates when compared to patients with liver or brain metastasis. Although systemic therapies have advanced, the prognosis for patients with breast cancer liver metastasis (BCLM) remains poor. Moreover, some research suggests that the median survival for untreated BCLM was no more than 6 months, while the median survival rates for patients after treatment did not exceed 15 months. Untreated patients with BCLM have reported median survival of ~3 to 6 months from diagnosis. Although systemic treatment can prolong survival, the peak median survival reported for patients who responded to systemic therapy is only 15 months, and surviving longer than 5 years is exceptional with medical therapy alone. Furthermore, patients with diffuse metastases have different characteristics and prognoses compared to patients with oligometastases, by an unlikely slow progression. Systemic therapy is not frequently the appropriate treatment for patients with liver metastases, because the diffuse metastatic liver disease may cause severe impairments to liver function and endanger the patient. As a result, it is especially crucial for us to choose the appropriate treatment protocols early on.

Due to the extent and locations of diseases and physical conditions, surgical excision or tumor ablation strategies are often considered for patients with limited disease and favorable histology. Moreover, breast cancer diffuse liver metastases are almost not eligible for surgery. Many types of breast cancer were sensitive to radiotherapy, which led to radiotherapy on breast cancer patients with diffuse liver metastasis. Low-dose radiation therapy administered to the whole-liver radiation therapy (WLRT) is not regularly used for patient palliation with massive liver metastases. Despite the treatment opinion for BCLM being palliative, different local treatment modalities have been applied together with systemic treatment to improve the outcomes.

Because of the extensive liver involvement with cancer, borderline liver functions, and/or the presence of extra-hepatic metastases, many patients are not applicable for high-dose radiotherapy. Furthermore, the risk of classic radiation-induced liver disease (RILD) was estimated to be 5% when the whole liver was treated with 30 Gy in 2 Gy per fraction. Although WLRT was possibly effective in palliating symptoms related to liver metastases, it was only occasionally used because of dose tolerance limits of the liver with liver diffuse metastatic lesions. According to the relationship between the dose tolerance and the volume of irradiation for liver cancer, a larger volume of irradiation meant a lower dose tolerance. Compared with the WLRT, the volume of fractionated irradiation was reduced by semi-liver radiotherapy, the radiation response from normal liver cells could be further reduced, and protecting liver functionality was effective. Compared with stereotactic body radiation therapy (SBRT), the average dose of radiotherapy for semi-liver radiotherapy was relatively lower, late tissue damage was reduced. However, until now, there have been no reports on radiotherapy for diffuse liver metastasis of breast cancer. Therefore, semi-liver radiotherapy has been creatively applied in our research. The preliminary results are summarized as follows.

Materials and Methods

Patient Characteristics (Table 1)
The present study of semi-hepatic alternate radiotherapy for breast cancer patients with diffuse liver metastasis was approved by the ethics committee of the Fifth Hospital of Wuhan (Wuhan, Hubei, China) (November 11, 2014) and
Table 1. General Data and Clinical Characteristics of the Cases in the 2 Groups (n).

| Clinical features                        | Group A (n = 34) | Group B (n = 34) | p     |
|------------------------------------------|-----------------|-----------------|-------|
| Age                                      |                 |                 |       |
| 32-49 years                              | 15              | 17              | .627  |
| 50-65 years                              | 19              | 17              |       |
| Child-Pugh grade                         |                 |                 |       |
| A grade                                  | 26              | 28              | .549  |
| B grade                                  | 8               | 6               |       |
| Pathological type                        |                 |                 |       |
| Invasive ductal carcinoma                | 24              | 25              | .787  |
| Invasive lobular carcinoma               | 10              | 9               |       |
| Transaminase                             |                 |                 |       |
| ALT < 40 units/L                         | 7               | 6               | .912  |
| ALT ≥ 40-100 units/L                    | 10              | 12              |       |
| AST < 40 units/L                        | 5               | 6               |       |
| AST ≥ 40-100 units/L                   | 12              | 10              |       |
| Volume of metastases (cm³)              | 18.28 ± 3.27    | 17.95 ± 4.36    | >.05  |
| Number of countable liver metastases    | 123 ± 19        | 129 ± 17        | >.05  |
| Supportive treatment                     | Yes             | Yes             | –     |
| Simultaneous metastasis of all liver lobes | Yes           | Yes             | –     |

Table 2. Targeted and Organ-threatenng Doses of Radiotherapy in the 2 Groups.

| Clinical features                | Group A          | Group B          | P     |
|----------------------------------|-----------------|-----------------|-------|
| PTV1 (Gy)                        | 30.12 ± 1.61    | 30.13 ± 1.14    | >.05  |
| PTV2 (Gy)                        | 30.14 ± 0.73    | 30.12 ± 0.97    | >.05  |
| Stomach max (Gy)                 | 33.93 ± 0.99    | 34.15 ± 0.87    | >.05  |
| Stomach (V45, %)                 | 0               | 0               |       |
| Spinal cord max (Gy)             | 26.14 ± 0.12    | 26.15 ± 0.09    | >.05  |
| Bilateral lungs (V20, %)         | 7.13 ± 0.02     | 7.14 ± 0.05     | >.05  |
| Small Intestine (V50, %)         | 0               | 0               |       |
| Bilateral kidneys (V20, %)       | 2 ± 3.1         | 21 ± 2.7        | >.05  |
| Liver (V30, %)                   | 29.5 ± 1.9      | 29.7 ± 1.6      | >.05  |

Abbreviations: PTV1, planning target volume 1; PTV2, planning target volume 2.

was initiated after compliance with procedures in December 2015. Written informed consent was obtained from the patients for participating in the study.

From December 2015 to January 2018, 68 cases of diffuse liver metastasis from breast cancer were treated by semi-liver alternating intensity-modulated radiotherapy (IMRT) in our department (all confirmed by percutaneous liver biopsy, pathology, or cytology). Liver function was compensatory in all cases. Sixty-eight patients recruited were first-line radiotherapy instead of standard chemotherapy, targeted therapy or hormonal treatment Eastern Cooperative Oncology Group performance status of the patients was 2 to 3 scores. The median age was 48 years (32-65 years). All of them had simultaneous metastases of the left and right lobes of the liver with more than 4 lesions in each lobe. The Child-Pugh grade of liver function was A or B, and transaminase was normal or slightly elevated (transaminase < 100 units/L). The patients were divided into Group A (34 cases) and Group B (34 cases) by a random number table.

**Semi-Hepatic Alternate Radiotherapy on Diffuse Liver Metastasis in Patients with Breast Cancer**

**Radiotherapy Equipment.** An Elekta electron linear precise accelerator (configuration iView-GT portal imaging verification system, 40 pairs of electric MLC; Elekta AB [Publ], 2008, Stockholm, Sweden), Xinhua SL-11 simulator (Shandong Xinhua Medical Instrument Co., Ltd), Philips 64-slice spiral computed tomography scanner (Brilliance 64, Philips Medical Systems), Elekta Precise 3-dimensional (3D) treatment planning system (Elekta AB [Publ]), immobilization vacuum pad (Shanghai Gerui Co., Ltd) and an abdominal bandage (Hengshui Runde Medical Instrument Co., Ltd) were used in the present study.

**Radiotherapy Treatment Protocol.** The patients were randomly divided into 2 groups (n = 34): Group A and Group B. For the alternating semi-hepatic radiotherapy group (Group A). The livers from Group A were divided into first and second semi-livers based on the anatomical features of the liver, planning target volume 1 (PTV1), and PTV2, and treated with semi-hepatic alternate IMRT. The interval between the radiotherapy treatments for PTV1 and PTV2 semi-livers was 6 h to avoid radiation hot spots. The average radiotherapy dose to the first and second semi-livers were both 2 Gy/fraction, once a day, 5 times per week, treating the clinical tumor volume with a total dose of 30 Gy for 15 days. The total radiation therapy duration was 15 days.

For the semi-hepatic sequential radiotherapy group (Group B), The livers from Group B were divided into the first and second semi-livers and treated with semi-hepatic sequential radiotherapy. The first semi-liver was treated in the first stage of radiation therapy, and the average radiotherapy dose to the semi-liver was 2 Gy/fraction, once a day, 5 times per week, treating the PTV1 with a total dose of 30 Gy for 15 days. The second semi-liver was treated in the second stage of radiation therapy, and the average radiotherapy dose to the semi-liver was 2 Gy/fraction, once a day, 5 times per week, treating the PTV2 with a total dose of 30 Gy for 15 days. The total radiation therapy duration was 30 days.

Radiotherapy was performed with the Elekta electron linear accelerator and precise treatment planning system. The abdominal bandage was used to control breathing during radiotherapy to reduce tumor motion. Target volume delineation was performed by the same doctor and medical physicist for all patients. To perform palliative radiotherapy, an electronic image treatment verification system (Elekta AB [Publ]) was used to improve the precision. Based on the clinical target volume (CTV), the crown sagittal axis of the PTV was extended outwards by 3 mm and was extended outwards by 5 mm along
Figure 1. Dose distribution of a patient.

Figure 2. (A, B, C) Dose–volume histogram of a patient given. (continued)
the axis of the body. In total, 7 to 9 irradiation fields were designed, and 85% to 90% of the isodose curve covered the PTV. Protection was provided for the normal liver and adjacent organs (maximum dose of stomach ≤40 Gy, stomach V45 ≤ 15%, maximum dose of spinal cord ≤40 Gy, small intestine V50 ≤15%, bilateral kidneys V20 ≤30%, normal liver V30 < 50%) as much as possible, using the Elekta Precise 3D treatment planning system. During radiotherapy, the patients were treated with liver protection drugs reductive glutathione (1.2-2.4 g/day, intravenous drip, Shanghai Fudan Fuhua Pharmaceutical Co. Ltd) and magnesium isoglycyrrhizinate (0.1-0.3 g/day, intravenous drip, Chia Tai Tianqing Pharmaceutical Group Co. Ltd). Regular inspections of peripheral blood and liver function were conducted during the course of treatment.13–15

Follow up. Patients were monitored over the 2 to 3 months following treatment, and trimonthly thereafter. Regular blood tests, liver function tests, measurements of magnetic resonance imaging (MRI; Achieva 1.5T, Philips Medical Systems) of the liver were performed at every follow-up appointment. Treatment responses were evaluated by MRI every 3 months with the modified response evaluation criteria in solid tumors. The treatment responses were defined as complete response (CR) was defined as the disappearance of the target lesion; partial response (PR) was defined as at least 30% decrease in size of the target lesion; progression of disease (PD) was defined as at least a 20% increase

| Key | Structure | Plan | Min Dose (Gy) | Max Dose (Gy) | Mean Dose (Gy) | Total Vol (cc) |
|-----|-----------|------|---------------|---------------|---------------|---------------|
| Spinal cord | Current | 11 | 71 | 31 | 43.6 |
| B. kidney | Current | 55 | 222 | 45 | 131.4 |
| L. kidney | Current | 4 | 75 | 8 | 186.2 |
| Heart | Current | 0 | 103 | 13 | 582.0 |
| Spleen | Current | 4 | 13 | 3 | 361.9 |
| Stomach | Current | 21 | 149 | 8 | 410.4 |
| Duodenum | Current | 148 | 336 | 289 | 1190.2 |

Figure 2. Continued.
in the size of the target lesion; and stable disease was defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.\textsuperscript{16,17} Adverse reactions to radiotherapy were evaluated according to the standard criteria of the American Radiation Therapy Oncology Group (RTOG). Survival was evaluated from the date treatment commenced. The follow-ups were completed in April 2019.

### Statistical Analysis

SPSS 22.0 statistical software (SPSS, Inc.) was used for statistical analysis. Effective rates, survival rates, and the incidence of adverse reactions were analyzed using the chi-square test. The Kaplan–Meier method was used to estimate survival rates, and the log-rank test was used to compare differences in survival. A 2-sided $P<.05$ was considered to indicate a statistically significant difference.

### Results

Dose comparisons of PTV and peripheral organs at risk between Group A and Group B are given in Table 2. Figures of dose distribution and dose–volume histogram of a patient were given (Figures 1 and 2). A figure of CTV and PTV

![Table 2: Dose Comparisons](image1)

![Figure 1: Dose Distribution](image2)

![Figure 2: Continued.](image3)
delineation was given (Figure 3). There were no significant differences in average PTV1 and PTV2 doses between Group A and Group B. There were no significant differences in the maximum doses of gastric and cord and bilateral lung V20.

Short-Term Efficacy
In Group A, 2 patients failed to complete radiotherapy due to severe intolerable radiotherapy reactions, such as abdominal pain, nausea, and vomiting. In Group B, 1 patient failed to complete radiotherapy due to a fear of the side effects of radiotherapy. Treatment responses were evaluated by MRI every 3 months, using the modified response evaluation criteria in solid tumors. The overall response rates of the 2 groups were equivalent \((p = .903)\), but the total effective rate of Group A exhibited a tendency to improve when compared with Group B (see Table 3). One of the patients in Group A was found to have significantly reduced lesions after radiotherapy (see Figure 4A and B). One of the patients in Group B was found to have smaller lesions after radiotherapy (see Figure 4C and D).

Follow-up Survival Rates
The follow-ups ended in January 2021. The median survival time for Group A was 16.7 months, compared with 16.2 months for those in Group B (see Figure 5). The median survival time for Group A was slightly longer than that of Group B, with no significant difference \((p = .411)\). The 6-month, 1-year, 2-year, and 3-year overall survival rates of the 2 groups were similar (see Table 4). The differences in survival rates of the 2 groups at 6 months, 1 year, and 2 years were not statistically significant, however, 3 years were statistically significant. It could be related to the inadequate number of cases.

Treatment Associated Toxicity
The criterion for evaluating toxicities was RTOG. The main toxic reactions during treatment were gastrointestinal reactions, abnormal liver functions, and myelosuppression. RILD usually occurs within 3 months after radiotherapy. The I to II degree gastrointestinal reactions, I to II degree abnormal liver functions, I to II degree myelosuppression, and radiation-induced liver diseases of the 2 groups were similar (see Table 5). RILD was diagnosed by an elevation of alkaline phosphatase level of \(\geq 2\)-fold and/or elevated transaminases of \(\geq 4\)-fold of the upper limit of normal levels.

Discussion
Current treatments for BCLM include systematic therapy, such as endocrine therapy, targeted therapy, chemotherapy, and local
therapy, such as radioembolization, chemoembolization, microwave ablation, and stereotactic body radiotherapy.\textsuperscript{20,21} Despite comparing patients with primary versus metastatic liver cancers, the risk of developing nonclassic RILD differs considerably, as patients with primary liver cancers have a higher chance of having this toxicity after external beam radiation.\textsuperscript{19}

For patients with diffuse liver metastasis of advanced breast cancer with compensatory or decompensatory liver function, there was still more to explore for the therapeutic effects and toxicity of the radiotherapy. Diffuse BCLM was difficult to implement because of its scattered focus and no specific target area. The sublethal injuries were repaired during alternating irradiation intervals by dividing the liver into the first and second semi-livers for irradiation, so that the cells could proliferate again, thus increasing the tolerance of normal tissues to radiation. Alternate irradiation could also redistribute cancer cells in the alternating irradiation interval, which increased the sensitivity to subsequent radiation and increased the fatality rate of cancer cells. With better oxidation of the tumor margin, the death of radiation-sensitive cells, and the retraction of lesion masses, the blood supply to deep hypoxic cells was increased, and the hypoxic cells in the center of the lesion with an interval of alternate irradiation were reoxidized to increase radiosensitivity.\textsuperscript{22}

For patients with diffuse liver metastasis of advanced breast cancer with compensatory or decompensatory liver function, there was still more to explore for the therapeutic effects and toxicity of the radiotherapy. Diffuse BCLM was difficult to implement because of its scattered focus and no specific target area. The sublethal injuries were repaired during alternating irradiation intervals by dividing the liver into the first and second semi-livers for irradiation, so that the cells could proliferate again, thus increasing the tolerance of normal tissues to radiation. Alternate irradiation could also redistribute cancer cells in the alternating irradiation interval, which increased the sensitivity to subsequent radiation and increased the fatality rate of cancer cells. With better oxidation of the tumor margin, the death of radiation-sensitive cells, and the retraction of lesion masses, the blood supply to deep hypoxic cells was increased, and the hypoxic cells in the center of the lesion with an interval of alternate irradiation were reoxidized to increase radiosensitivity.\textsuperscript{22}

Until now, diffuse hepatic metastasis of breast cancer has been rarely reported by radiotherapy around the world. Although for diffuse metastatic hepatocellular carcinoma, both mobile strip radiotherapy and whole-liver field radiotherapy have been used all over the world, mobile strip technology was gradually abandoned because the equipment of radiotherapy had been greatly developed, the repeatability of daily irradiation was very poor, the dose distribution was very uneven.\textsuperscript{23}
A. Despite there being no significant difference between Group A and Group B, the median survival time of Group A was slightly longer than that of Group B, and there was a trend of prolongation. Although the equivalent biological effect doses of Group A and Group B were different, the differences between curative effects were not significant. The reason could be related to the advanced stages of the 2 groups, insensitivity to treatment, and small sample size. Despite no significant differences in adverse reactions between Group A and Group B, the adverse reactions in Group B had a declining trend when compared with Group A.

To summarize, semi-liver IMRT was an effective palliative treatment for diffuse liver metastasis of breast cancer. Semi-liver alternating IMRT could prolong the survival time of diffuse liver cancer of breast cancer. Semi-liver alternating IMRT showed a prolonged trend in survival when compared with half-liver sequential IMRT. Compared with the former, the latter tended to see a decrease in side effects, and the therapy could be well tolerated. However, due to the small number of cases, it is necessary to expand the sample sizes in further studies. The emergence of modern radiotherapy techniques has helped to minimize the toxic side effects from radiation to the liver, and ongoing studies will help refine the clinical indications for radiation treatment for patients with liver tumors. However, given the limited sample size and retrospective nature of this study, further studies are needed to elucidate the optimal dose-fractionation schemes for treating such patients.

### Table 4. Comparison of the 6-Month, 1-Year, 2-Year, and 3-Year Overall Survival Rates of the 2 Groups.

| Time    | Group A (n = 32) | Group B (n = 33) | p   |
|---------|------------------|------------------|-----|
| 6-month | 90.6% (29)       | 84.8% (28)       | .478|
| 1-year  | 65.6% (21)       | 60.6% (20)       | .675|
| 2-year  | 31.2% (10)       | 27.3% (9)        | .725|
| 3-year  | 15.6% (5)        | 0 (0)            | .018|

| Table 5. Toxic and Side Effects of the 2 Patient Groups (% [case]).

| Side effects                      | Group A (n = 32) | Group B (n = 33) | p   |
|-----------------------------------|------------------|------------------|-----|
| I to II degree digestive tract reaction | 78.13% (25)     | 72.73% (24)     | .614|
| I to II degree abnormal liver function | 53.13% (17)     | 48.48% (16)     | .708|
| I to II degree myelosuppression | 59.38% (19)      | 51.52% (17)     | .524|
| Radiation-induced liver disease | 6.2% (2)         | 3.0% (1)        | .536|

The criterion for evaluating toxicities was radiation therapy oncology group (RTOG).

Semi-liver intensity-modulated radiation therapy (IMRT) was creatively used to treat diffuse BCLM, expecting to prolong the survival time with few radiation responses. Group A and Group B were both administered with semi-liver radiotherapy. In this study, the radiotherapy targets were divided into 2 areas: the first and second semi-livers. When one-half of the liver was irradiated, the other half of the liver was not, so that normal liver metabolism could be maintained. Most of the sublethal injuries were repaired within 6 h after a radiotherapy session concluded, and the dose intensity in the radiation field could be adjusted by intensity-modulated radiotherapy technology according to needs, which could maximize high-dose irradiation of targets, reducing the doses to at-risk organs around the radiation field, and the occurrences of radiation-induced liver injuries. Shortening the total treatment time will increase tumor death, and generally aggravate the injuries of early response tissues. So, early response tissue damage in Group A was greater than in Group B. Compared with SBRT, the average dose of radiotherapy of semi-liver alternating IMRT was relatively lower, and late-reaction tissue damage was reduced. Compared with Group B, the biologically effective dose of tumors in Group A was higher, the tumors were more difficult to repair, and they were more prone to apoptosis.

The total irradiation time was 15 days in Group A and 30 days in Group B. The total irradiation time in Group A was half of that in Group B. Because of the different total irradiation times, the biological effect doses of the 2 groups were different, and the equivalent biological effect doses in Group A were larger than that in Group B. For RILD, there was no significant difference between Group A and Group B, but there seemed to be a decreasing trend in Group B when compared with Group A. Despite there being no significant differences in short-term efficacies between Group A and Group B, the total effective rate of Group A presented an upward trend, when compared with Group B. Despite these being no significant differences between Group A and Group B, the median survival time of Group A was slightly longer than that of Group B, and there was a trend of prolongation. Although the equivalent biological effect doses of Group A and Group B were different, the differences between curative effects were not significant. The reason could be related to the advanced stages of the 2 groups, insensitivity to treatment, and small sample size. Despite no significant differences in adverse reactions between Group A and Group B, the adverse reactions in Group B had a declining trend when compared with Group A.

To summarize, semi-liver IMRT was an effective palliative treatment for diffuse liver metastasis of breast cancer. Semi-liver alternating IMRT could prolong the survival time of diffuse liver cancer of breast cancer. Semi-liver alternating IMRT showed a prolonged trend in survival when compared with half-liver sequential IMRT. Compared with the former, the latter tended to see a decrease in side effects, and the therapy could be well tolerated. However, due to the small number of cases, it is necessary to expand the sample sizes in further studies. The emergence of modern radiotherapy techniques has helped to minimize the toxic side effects from radiation to the liver, and ongoing studies will help refine the clinical indications for radiation treatment for patients with liver tumors. However, given the limited sample size and retrospective nature of this study, further studies are needed to elucidate the optimal dose-fractionation schemes for treating such patients.

### Declaration of Conflicting Interests
The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

### Funding
The authors received no financial support for the research, authorship, and/or publication of this article.

### ORCID iDs
Wen Ma https://orcid.org/0000-0001-6873-5984
Juan Ren https://orcid.org/0000-0002-8360-8286

### Supplemental material
Supplementary material for this article is available online.

### References
1. He ZY, Wu SG, Peng F, et al. Up-regulation of RFC3 promotes triple negative breast cancer metastasis and is associated with poor prognosis via EMT. *Transl Oncol*. 2017;10(1):1-9.
2. Onal C, Guler OC, Yildirim BA. Treatment outcomes of breast cancer liver metastasis treated with stereotactic body radiotherapy. *Breast*. 2018;42:150-156.
3. Bai G, Wang Y, Zhu Y, et al. Prediction of early response to chemo-therapy in breast cancer liver metastases by diffusion-weighted MR imaging. *Technol Cancer Res Treat*. 2019;18:1533033819842944.
4. Goldhirsch A, Gelber RD, Castiglione M. Relapse of breast cancer after adjuvant treatment in premenopausal and perimenopausal women: patterns and prognoses. *J Clin Oncol.* 1988;6:89-97.

5. Wyld L, Gutteridge E, Pinder SE, et al. Prognostic factors for patients with hepatic metastases from breast cancer. *Br J Cancer.* 2003;89(2):284-290.

6. O’Reilly SM, Richards MA, Rubens RD. Liver metastases from breast cancer: the relationship between clinical, biochemical and pathological features and survival. *Eur J Cancer.* 1990;26(5):574-577.

7. Goodman BD, Mannina EM, Althouse SK, et al. Long-term safety and efficacy of stereotactic body radiation therapy for hepatic oligometastases. *Pract Radiat Oncol.* 2016;6(2):86-95.

8. Bale R, Putzer D, Schullian P. Local treatment of breast cancer liver metastasis. *Cancers.* 2019;11(9):1341.

9. Mendez Romero A, Hoyer M. Radiation therapy for liver metastases. *Curr Opin Support Palliat Care.* 2012;6(1):97-102.

10. Yeung CSY, Chiang CL, Wong NSM, et al. Palliative liver radiotherapy (RT) for symptomatic hepatocellular carcinoma (HCC). *Sci Rep.* 2020;10(1):1254.

11. Dawson LA, Ten Haken RK. Partial volume tolerance of the liver to radiation. *Semin Radiat Oncol.* 2005;15(4):279-283.

12. Mazzola R, Ferrino S, Alongi P, et al. Stereotactic body radiation therapy for liver oligometastases: predictive factors of local response by (18)F-FDG-PET/CT. *Br J Radiol.* 2018;91(1088):20180058.

13. Ji Y, Si W, Zeng J, et al. Niujiaodihuang detoxify decoction inhibits ferroptosis by enhancing glutathione synthesis in acute liver failure models. *J Ethnopharmacol.* 2021;279:114305.

14. Liu M, Zheng B, Liu P, et al. Exploration of the hepatoprotective effect and mechanism of magnesium isoglycyrrhizinate in mice with arsenic trioxide-induced acute liver injury. *Mol Med Rep.* 2021;23(6):438.

15. Gao Y, Tian Y, Zhang X, et al. Magnesium isoglycyrrhizinate ameliorates concanavalin A-induced liver injury via the p38 and JNK MAPK pathway. *Immunopharmacol Immunotoxicol.* 2020;42(5):445-455.

16. Lee DD, Samoylova M, Mehta N, et al. The mRECIST classification provides insight into tumor biology for patients with hepatocellular carcinoma awaiting liver transplantation. *Liver Transpl.* 2019;25(2):228-241.

17. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer.* 2009;45(2):228-247.

18. Kim J, Jung Y. Radiation-induced liver disease: current understanding and future perspectives. *Exp Mol Med.* 2017;49(7):e359.

19. Koay EJ, Owen D, Das P. Radiation-induced liver disease and modern radiotherapy. *Semin Radiat Oncol.* 2018;28:321-331.

20. Yao B, Kavishwar A, Wang P, et al. Therapy targeted to the metastatic niche is effective in a model of stage IV breast cancer. *Sci Rep.* 2017;7:45060.

21. Franzese C, Comito T, Vigano L, et al. Liver metastases-directed therapy in the management of oligometastatic breast cancer. *Clin Breast Cancer.* 2020;20(6):480-486.

22. Anne P, Cosset JM, Van Limbergen E, et al. Radiobiology: Foundation and new insights in modeling brachytherapy effects. *Semin Radiat Oncol.* 2020;30:4-15.

23. Yan F. Why should no longer use bar field irradiation technology. *Chin J Radiat Oncol.* 1996;12(1):72.