Effects of stereotactic body radiotherapy for clinical outcomes of patients with liver metastasis and hepatocellular carcinoma: A retrospective study

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Abstract. This retrospective clinical study described the treatment efficacy and safety of stereotactic body radiotherapy (SBRT) for patients of hepatocellular carcinoma (HCC) and liver metastasis tumors. The therapeutic effect and prognosis of patients with liver cancer treated with stereotactic body radiation therapy (SBRT) at the Fudan University Shanghai Cancer Center (Shanghai, China) between July 2011 and December 2020 were retrospectively analyzed. Overall survival (OS), local control (LC) rates and progression-free survival (PFS) were evaluated using Kaplan-Meier analysis and the log-rank test. Local progression was defined as tumor growth after SBRT on dynamic computed tomography follow-up. Treatment-related toxicities were assessed according to the Common Terminology Criteria for Adverse Events version 4. A total of 36 patients with liver cancer were enrolled in the present study. The prescribed dosages (14 Gy in 3 fractions or 16 Gy in 3 fractions) were applied for SBRT treatments. The median follow-up time was 21.4 months. The median OS time was 20.4 [95% confidence interval (CI): 6.6-34.2] months, and the 2-year OS rates for the total population, HCC group and liver metastasis group were 47.5, 73.3 and 34.2%, respectively. The median PFS time was 17.3 (95% CI: 11.8-22.8) months and the 2-year PFS rates for the total population, HCC group and liver metastasis group were 36.3, 44.0 and 31.4%, respectively. The 2-year LC rates for the total population, HCC group and liver metastasis group were 83.4, 85.7 and 81.6%, respectively. The most common grade IV toxicity for the HCC group was liver function impairment (15.4%), followed by thrombocytopenia (7.7%). There were no grade III/IV radiation pneumonia or digestive discomfort. The present study aimed to explore a safe, effective and non-invasive treatment method for liver tumors. At the same time, the innovation of the present study is to find a safe and effective prescription dose of SBRT in the absence of consensus on guidelines.

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Introduction

Whether primary or secondary, liver cancer is one of the most common malignant tumors with a poor prognosis worldwide (1). According to reports, hepatocellular carcinoma (HCC), which accounts for ~90% of primary liver cancer cases, is the third leading cause of cancer-related death (2). The incidence rate of HCC ranks sixth among malignant tumors worldwide (3). In China, HCC ranks second in terms of the mortality rate of malignant tumors (4). Surgery is the standard treatment method for HCC, including hepatic resection and liver transplantation, resulting in 5-year survival rates of 30-70% (5,6). However, only a small proportion of patients are suitable for surgery due to most patients having progressed to the intermediate and late stages of the disease when first diagnosed (2,7). In addition to surgery, multiple treatment methods, such as percutaneous transcatheter arterial chemoembolization (TACE), radiofrequency ablation (RFA), microwave ablation, absolute ethanol injection, radiotherapy and targeted therapy, may also be selected for complex HCC (8-14). While any single treatment method has certain limitations, the current comprehensive treatments may complement each other and have a synergistic therapeutic role (15). Liver transplantation may completely eliminate potentially intrahepatic micro-metastasis lesions and cirrhosis with malignant transformation potential, and

is therefore the only permanent cure for liver cancer (16). However, suitable liver source matching is currently difficult and costly. At present, the surgical resection rate for patients with liver cancer is only ~20% and a large proportion of patients need to undergo non-resection treatments (15). The 2-year survival rate of TACE interventional therapy is 41% and the effective rate is only 35% (17). RFA applies to early-stage lesions with a diameter of <3 cm and RFA treatments may have a high rate of tumor residue and recurrence for large-diameter tumors (18). Chemotherapy is toxic and is significantly so for patients with advanced HCC, particularly those with cirrhosis (19). The application of chemotherapy is limited for patients with poor liver condition and the overall response rates (ORRs) of chemotherapy reported in the literature are relatively low, ranging from 0-25% (19). By contrast, molecular targeted therapy has limited side effects, unlike traditional chemotherapy. Currently, sorafenib is the standard targeted drug for advanced HCC, but there are still significant shortcomings of this treatment method, such as a low ORR and overall survival (OS) rate of patients (15). Therefore, the treatment efficacy and prognosis for patients with HCC remain unsatisfactory. As a result, stereotactic body radiation therapy (SBRT) has emerged as an effective, non-invasive alternative for liver tumors.

Regarding hepatic metastasis, the survival rates of patients are also significantly low (20). Metastatic liver cancer is prevalent in other malignant tumors, particularly in patients with colorectal cancer. The liver is rich in sinusoids and receives blood supplies from both the hepatic artery and portal vein. Studies have indicated that 25-50% of primary tumors are able to metastasize to the liver during cancer progression (21,22). For metastatic liver cancer, chemotherapy combined with local treatment is often applied as a comprehensive treatment method (15). For patients with resectable liver metastatic lesions, adequate liver tissue should be preserved to ensure liver function. As a result, appropriate alternative therapies are sought to treat liver metastasis.

Conventional radiotherapy is a promising treatment method for patients with liver cancer that emerged many years ago (23,24). However, the limited accuracy of radiotherapy technology leads to toxicity to the surrounding normal organs, which results in high rates of radiation-induced liver disease (RILD) (23,25,26). To overcome this, technological advancements in radiation oncology have contributed to the development of SBRT, which delivers highly conformal dose distributions with a rapid dose drop-off that offers the ability to spare large portions of the liver while simultaneously allowing for dose escalation with ablative potential within the tumor (27,28). SBRT is now included in the recent version of the National Comprehensive Cancer Center Network guidelines for HCC (version 2.2021) (29), under the indication of unresectable disease or medically inoperable patients. For different studies of treatments for liver cancer, the dose of SBRT is different and there is no unified standard (30-33). SBRT is frequently administered to patients with 1-3 lesions and the dosage of SBRT is typically 30-50 Gy in 3-5 fractions, depending on liver function and normal organ constraints (34-36).

To date, various studies concerning SBRT treatment for patients with HCC have been conducted (30,33,34), but only a small number of studies have investigated SBRT treatment for patients with local metastatic liver cancer (31). Therefore, patients with metastatic liver cancer were included in the present study to examine the application value of SBRT. In the present retrospective study, the efficacy and feasibility of SBRT for patients with liver cancer at the Fudan University Shanghai Cancer Center (Shanghai, China) were investigated. The present study aimed to explore a safe, effective and non-invasive treatment method for liver tumors. In addition, the innovation of the present study was to determine a safe and effective prescription dose of SBRT in the absence of a consensus in the guidelines.

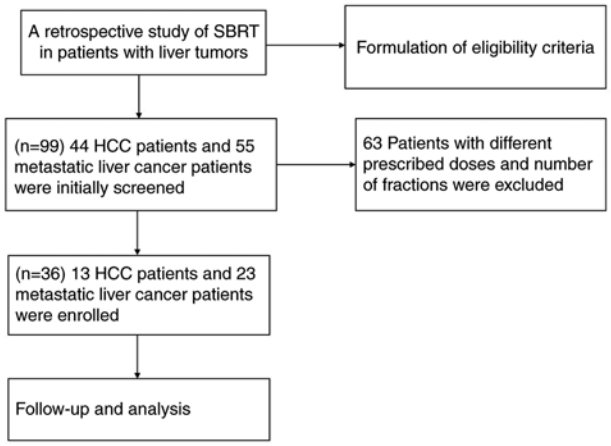

Figure 1. Study flowchart. HCC, hepatocellular carcinoma; SBRT, stereotactic body radiotherapy.

Patients and methods

Data collection and patient characteristics. The present study was conducted according to the flowchart in Fig. 1. In total, 36 patients with liver cancer confirmed by pathology at the Fudan University Shanghai Cancer Center (Shanghai, China) from July 2011 to December 2020 were enrolled in the present study. Clinical records were reviewed to retrieve patient treatment details, clinical outcomes and patient characteristics. The indication criteria for SBRT at the Fudan University Shanghai Cancer Center (Shanghai, China) are formulated based on the UK 2022 Consensus on Normal Tissue Dose-Volume Constraints SBRT guidelines (32) and a meta-analysis of 32 studies (36). The medical records, SBRT treatment plans and diagnostic images of patients with liver cancer who satisfied the following criteria were retrospectively reviewed: i) Age of 18-85 years; ii) histologically verified HCC or imaging-confirmed liver metastases; iii) Child-Pugh scores of 5 or 6 (37); iv) Eastern Cooperative Oncology Group performance status of 0-1 (38); and v) treated with SBRT in specific fractions and doses (14 Gy in 3 fractions or 16 Gy in 3 fractions). Patients with incomplete information and follow-up failure were excluded from the present study.

The present retrospective study strictly adhered to the principles of the Declaration of Helsinki and was also approved by the Fudan University Shanghai Cancer Center Institutional Review Board (Shanghai, China). All methods were performed in accordance with the guidelines and regulations of this ethics board. Written informed consent for treatment and future use

of clinical data was obtained from all participants included in the present study before their initial treatment.

SBRT techniques. Prior to SBRT treatment, a multi-disciplinary treatment discussion was held for each patient. The SRT treatment was finally formulated by multi-disciplinary senior experts (including those from the departments of radiology, pathology, surgery, medicine, oncology and radiotherapy) by means of case discussion. Certain patients with a single lesion were suitable for surgical treatment or TACE, but they refused invasive treatment due to personal preferences. However, SBRT may be a conservative treatment method for these patients (24,39).

For SBRT treatment, patients were immobilized using a customized vacuum cushion and thermoplastic mask, with arms extended over their heads. 4D computerized tomography (4DCT) was acquired during treatment to account for respiratory motion. One of the motion management methods, such as active breathing coordinator and abdominal compression, was employed based on patient characteristics. Gross tumor volume (GTV) was defined as arterial enhancing lesions with washout in the venous and/or delayed phase, including portal vein thrombosis for primary liver tumor and portal venous enhancing regions for hepatic metastases. Diagnostic MRI was also used for contouring the GTV. An ITV (internal target volume) was determined using 4DCT data and a uniform margin of 5-8 mm was added to the ITV to generate the planning target volume (PTV).

An SBRT dose of 42 Gy in 3 fractions [biological equivalent dose (BED), 100.8 Gy] every other day was prescribed for lesions close to luminal organs at risk (OAR), such as the stomach, duodenum and bowels. Otherwise, a dose of 48 Gy in 3 fractions (BED, 124.8 Gy) every other day was prescribed. Treatment plan optimization was based on a dose-volume histogram (DVH). SBRT doses were prescribed at an isodose line (80% of the maximum dose) that covered at least 97% of the PTV. OAR dose constraints followed in the treatment planning are listed in Table I. A mean dose of <15 Gy was administered to the liver, allowing for ≥700 cm^3 of the normal liver to receive <15 Gy. The dose constraints allowed a maximum dose of 18 Gy to the spinal cord and <35% of the kidney (of both sides) received 15 Gy. The maximum dose constraint for the heart did not exceed 30 Gy. Tissue inhomogeneity corrections were applied to all dose calculations. Conformal dose distribution with rapid dose fall-off outside the target volume was achieved by multiple coplanar or non-coplanar static beams or arcs of 6-MV X-ray. An illustrative case is presented in Fig. 2 and each line in the DVH graph (Fig. 2B) is described in Fig. S1.

At each treatment fraction, cone-beam CT imaging was performed to localize the target, and the position was corrected and approved by an attending radiation oncologist.

Clinical therapeutic effect evaluation. At the end of radiotherapy, patients are reviewed by clinical evaluation, assessment of liver and kidney function, as well as by abdominal CT or MRI every 3 months. The acute adverse events within 6 months were evaluated according to the National Institutes of Health-defined Common Terminology Criteria for Adverse Events (CTCAE 5.0) (40). The treatment efficacy of the total population was evaluated using the RECIST 1.1 criteria (41), which are based on MRI and CT results. The criteria for determining treatment failure by MRI and CT were as follows: i) The original lesion increased by >20%; ii) new lesions appeared; or iii) patient death.

Table I. Dose constraints used for liver stereotactic body radiotherapy.

Organ at risk	Dose constraint
Liver-GTV	Mean liver dose <15 Gy ≥700 ml of normal liver receives <15 Gy
Duodenum	V_{55Gy} <5%
Kidney	Bilateral V_{15Gy} <35%
Stomach, bowels	D_{max} <30 Gy
Spinal cord	D_{max} <18 Gy
Heart	D_{max} <30 Gy

GTV, gross tumor volume; V, volume; D_{max}, maximum dose received by the organ.

Statistical analysis. OS time was defined as the time between the first radiotherapy session and death. Progression-free survival (PFS) time was defined as the time between the first radiotherapy session and progression or death. Local control (LC) time was defined as the time between the first radiotherapy session and LC relapse. Distant metastasis-free survival (DMFS) time was defined as the time between the first radiotherapy session and metastasis. PFS, OS, DMFS and LC curves were estimated using the Kaplan-Meier method and log-rank test. The influence of various clinical factors on OS was determined in univariate and multivariate analyses using the Cox regression model. Factors with $P<0.05$ in the univariate analyses were included in the multivariate analysis. Fisher's exact test was used to evaluate differences in characteristics and the treatment toxicities between the HCC and the liver metastasis groups. All statistical analyses were performed using SPSS Statistics for Windows version 22.0 (IBM Corp.). $P<0.05$ was considered to indicate a statistically significant difference.

Results

Patient characteristics. The detailed patient characteristics and treatment details are provided in Table II. A total of 36 patients were enrolled, including 13 cases of HCC and 23 cases of liver metastasis. The number of males/females in the HCC and liver metastasis group were 9/4 and 13/10, respectively. The identified liver metastasis cases included 8 patients with colorectal cancer, 5 with pancreatic cancer, 4 with breast cancer, 2 with lung cancer, 2 with gallbladder carcinoma and 2 with esophageal cancer. The median age of the HCC and liver metastasis groups were 62.6 (range, 42.8-82.5) years and 65.9 (range, 30.6-82.5) years, respectively. The follow-up time range for the HCC and liver metastasis groups were 8.6-69.1 and 4.9-45.9 months. Hepatitis B virus (HBV) was detected in nine (69.2%) patients with HCC. All patients had a Child-Pugh score of 5 or 6. Six (46.2%) and seventeen (73.9%) patients

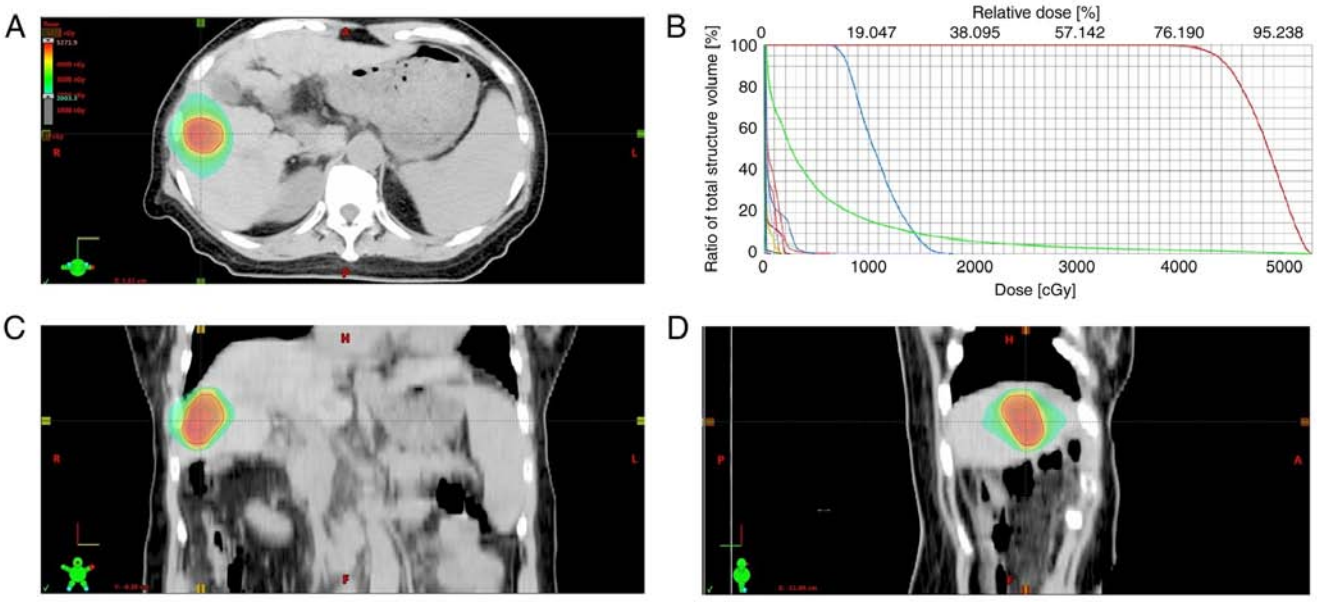

Figure 2. An illustrative case for stereotactic body radiotherapy (62 years, female). (A) Isodose curves in transverse section. (B) Dose-volume histogram curves. (C) Isodose curves in coronal section. (D) Isodose curves in median sagittal section.

in the HCC and liver metastasis groups respectively had a single lesion. There were significant differences in Hepatitis B virus infection (P<0.001), hepatic cirrhosis (P=0.001), prior treatment of chemotherapy (P<0.001) and prior treatment of TACE (P<0.001) between HCC and liver metastasis groups. There were no significant differences between the two groups in terms of gender, age, SBRT type, tumor location, tumor size, number of lesions, prior surgical and RFA treatment, and portal vein tumor thrombus.

Efficacy of SBRT. The LC, OS, PFS and DMFS curves of the total population, HCC group and liver metastasis group are presented in Fig. 3. The median follow-up time of the total population was 21.4 months, with a deadline of August 2021 for the final follow-up. The median LC and DMFS time were undefined as >50% of the subjects had not reach the target ending event by the end of follow-up period. The 2-year LC rates for the total population, HCC group and liver metastasis group were 83.4, 85.7 and 81.6%, respectively. The median OS time of the total population was 20.4 [95% confidence interval (CI), 6.6-34.2] months and the 2-year OS rates for the total population, HCC group and liver metastasis group were 47.5, 73.3 and 34.2%, respectively. The median PFS time of the total population was 17.3 (95% CI, 11.8-22.8) months and the 2-year PFS rates for the total population, HCC group and liver metastasis group were 36.3, 44.0 and 31.4%, respectively. The 2-year DMFS rates for the total population, HCC group and liver metastasis group were 66.5, 82.1 and 56.6%, respectively.

In the follow-up process, 2/13 patients pathologically diagnosed with HCC suffered from LC failure and the 2-year LC rate reached 85.7%. Among the 23 patients diagnosed with secondary liver cancer, 3 patients failed to maintain LC and the two-year LC rate reached 81.6%. The LC survival curves for these patients are presented in Fig. 3A. Although the LC rates were optimal, the OS rates of the patients were not satisfactory. The reasons for the poor rate of OS and PFS were further studied. The failure pattern was mainly due to out-field recurrence and distant metastasis (Table III), affecting the overall prognosis of the patients. In the univariate and multivariate analyses, a single lesion was a significant influencing factor of OS in patients with HCC and patients with liver metastasis (Table IV). In the univariate analysis, in patients with primary liver cancer and metastatic liver cancer, an age of >64 years, male sex, HBV infection, tumor lesions >4 cm, treatment with 14 Gy in 3 fractions and multiple lesions were associated with lower survival rates. However, there were no significant differences in age, gender, SBRT type, tumor size, SBRT type, HBV infection in univariate analysis. Of note, in the multivariate analysis, the survival rate of patients with multiple lesions was lower than that of patients with a single lesion, with a hazard ratio of 8.423 (95% CI, 0.906-78.274; P=0.069) and 3.927 (95% CI, 1.238-12.455; P=0.035) for HCC and liver metastasis, respectively. While statistical significance was not demonstrated in the HCC group (P=0.069). There was a significant difference in the liver metastasis regarding lesion numbers (P=0.035).

Adverse events of SBRT. The acute adverse events within 6 months are presented in Table V. No deaths as a consequence of SBRT were observed. There were significant differences in the adverse events of fatigue, transaminase elevation and bilirubin elevation between patients with HCC and patients with liver metastasis. The main side effect was an adverse effect on liver function in the HCC (53.8%) and liver metastasis group (21.7%), reflected in the elevation of aspartate transaminase (ALT) and alanine transaminase (AST) levels. The most common grade IV toxicity for the HCC group was liver function impairment (15.4%), followed by thrombocytopenia (7.7%). There were no cases of grade III/IV radiation pneumonia or digestive discomfort.

Table II. Patient characteristics and treatment data.

Parameter	HCC	Liver metastasis	P-value
Gender			0.501
Male	9 (69.2)	13 (56.5)	
Female	4 (30.8)	10 (43.5)	
Age, years	62.6 (42.8-82.5)	65.9 (30.6-82.5)	0.164
≤64	9 (69.2)	9 (39.1)	
>64	4 (30.8)	14 (60.9)	
SBRT			0.071
14 Gyx3 fractions	6 (46.2)	18 (78.3)	
16 Gyx3 fractions	7 (53.8)	5 (21.7)	
Location			0.241
Left lobe	0 (0)	2 (8.7)	
Right lobe	12 (92.3)	15 (65.2)	
Both lobes	1 (7.7)	6 (26.1)	
Etiology			<0.001
Normal	4 (30.8)	23 (100)	
Hepatitis B virus	9 (69.2)	0 (0)	
Hepatic cirrhosis			0.001
Yes	6 (46.2)	0 (0)	
No	7 (53.8)	23 (100)	
Tumor diameter, maximum, cm			0.347
<2	3 (23.1)	5 (21.7)	
≥2, <3	2 (15.4)	9 (39.1)	
≥3, <5	6 (46.1)	5 (21.7)	
≥5	2 (15.4)	4 (17.5)	
Number of lesions			0.281
Single	6 (46.2)	17 (73.9)	
Multiple	7 (53.8)	6 (26.1)	
Primary tumor			<0.001
Liver	13 (100)	0 (0.0)	
Colorectal	0 (0.0)	8 (34.8)	
Pancreas	0 (0.0)	5 (21.7)	
Breast	0 (0.0)	4 (17.5)	
Lung	0 (0.0)	2 (8.7)	
Esophagus	0 (0.0)	2 (8.7)	
Gallbladder	0 (0.0)	2 (8.7)	
Prior treatment			
Chemotherapy	1 (7.7)	19 (82.6)	<0.001
Surgery for primary tumor	4 (30.8)	5 (21.7)	0.693
Radiofrequency ablation	1 (7.7)	3 (13.0)	1.000
TACE	9 (69.2)	2 (8.7)	<0.001
Child-Pugh Score			0.686
A			
5	10 (76.9)	19 (82.6)	
6	3 (23.1)	4(17.4)	
B	-	-	
C	-	-	
BCLC stage			
A	4	-	
B	4		
C	5	-	

Table II. Continued.

Parameter	HCC	Liver metastasis	P-value
Portal vein tumor thrombus			0.328
Yes	3	2	
No	10	21	
Follow-up time, months	25.4 (8.6-69.1)	13.2 (4.9-45.9)	

Dashes indicate not applicable. Values are expressed as n (%) or the median (range). SBRT, stereotactic body radiotherapy; HCC, hepatocellular carcinoma; TACE, transcatheter arterial chemoembolization BCLC, Barcelona Clinic Liver Cancer.

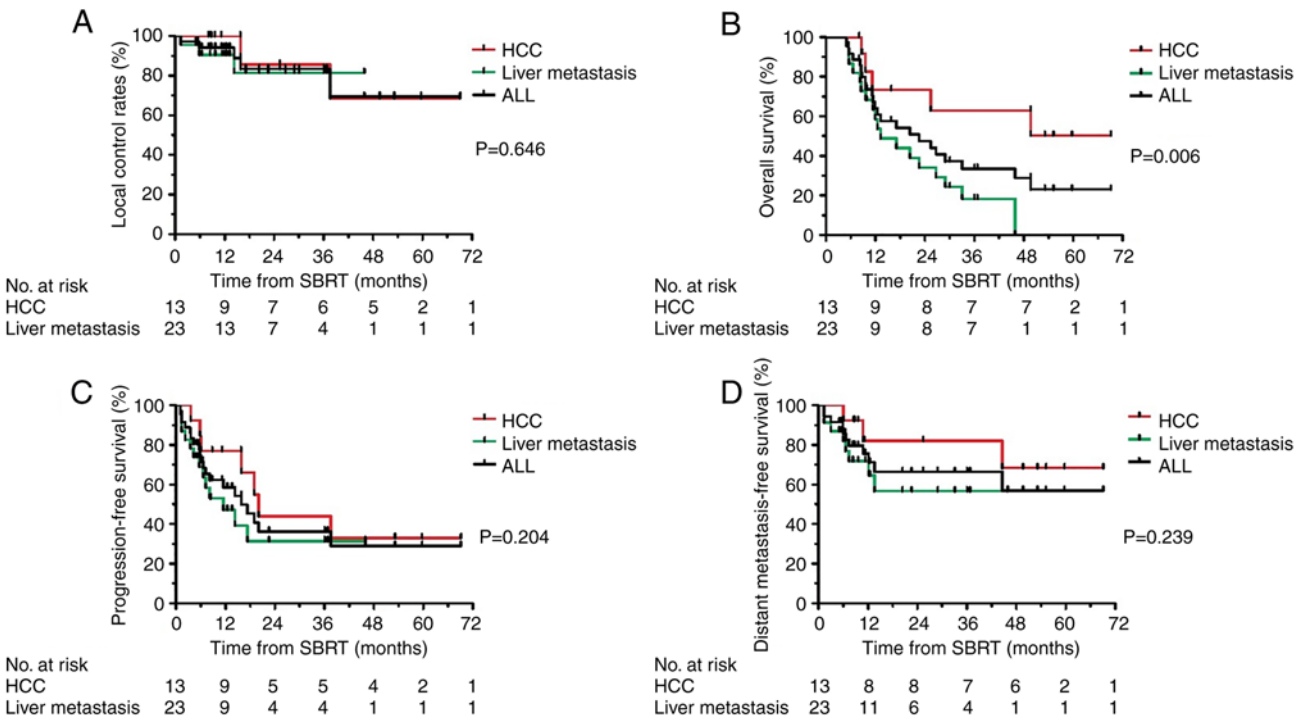

Figure 3. Survival of all patients and subgroups with HCC and liver metastasis. (A) Local control rates. (B) Overall survival. (C) Progression-free survival. (D) Distant metastasis-free survival. HCC, hepatocellular carcinoma; SBRT, stereotactic body radiotherapy.

Discussion

In the present retrospective study, using SBRT technology in 36 patients with liver tumors, the clinical LC rate was >80% and the 2-year PFS and OS rates were 36.3 and 47.5%, respectively, indicating optimal clinical outcomes. The present study demonstrated a safe and feasible local treatment method and laid a foundation for exploring a standard SBRT treatment for HCC and liver metastasis.

The present retrospective study demonstrated no significant differences in treatment results between patients with HCC and patients with liver metastasis, including in the PFS, DMFS and LC rates. However, there was a difference in OS rates (P=0.006) and patients diagnosed with HCC had higher 2-year OS rates. The dose used in the present study had the desired effect, with a high LC rate. The low OS and prognosis observed in the present study were related to out-field recurrence and distant metastasis. In the univariate and multivariate analyses, it was found that patients with a single liver lesion had a better OS than those with multiple lesions. Therefore, SBRT is a feasible local control method if RFA or surgery is unsuitable for large and single-lesion liver tumors. As the 2-year LC rate was >80%, the dosage used in the present study was reliable and the normal organs were well protected. SBRT treatment for liver cancer had an apparent efficacy, with a 2-year LC rate of >80%. The indication criteria for SBRT at the Fudan University Shanghai Cancer Center (Shanghai, China) are formulated based on the British SBRT guidelines (32) and a meta-analysis of 32 studies (36). Currently, the indications for SBRT at the Fudan University Shanghai Cancer Center (Shanghai, China) are as follows: i) Eastern Cooperative Oncology Group performance status of 0-1 (38); ii) cirrhosis of the liver Child-Pugh score of 5 or 6; iii) <3 lesions; and iv) tumor size ≤6 cm.

In the present study, the safety of the treatment was satisfactory. The most common adverse events were elevated transaminase, thrombocytopenia, leukopenia, fatigue and nausea. There were 2 patients who suffered from grade IV

Table III. Failure patterns in 36 patients after irradiation.

Failure	HCC	Liver metastasis
Total	7 (100)	15 (100)
Locoregional only		
In-field	1 (14.3)	1 (6.7)
Out-field	4 (57.1)	4 (26.6)
In-field and out-field	0 (0)	1 (6.7)
Distant only	0 (0)	2 (13.3)
Locoregional and distant	2 (28.6)	7 (46.7)

Values are expressed as n (%). HCC, hepatocellular carcinoma.

elevated transaminase and 3 cases of grade III/IV thrombocytopenia occurred. Other adverse events were grade I to II. Most of the adverse events could be relieved by symptomatic treatment.

Previously, due to the limitations of cognition and radiotherapy technology, only palliative radiotherapy was considered for primary liver cancer treatment. Modern radiobiology has demonstrated that the radiosensitivity of HCC is equivalent to that of poorly differentiated squamous cell carcinoma (42). Furthermore, with the development of radiotherapy technology, research has demonstrated that radiotherapy can achieve the goal of complete cure (43). For patients with advanced HCC, TACE combined with radiotherapy may further improve the treatment effectiveness (17). For metastatic liver cancer, systemic chemotherapy combined with local radiotherapy may also further improve treatment efficacy. SBRT is a non-invasive alternative local treatment for liver metastasis. The clinical data of secondary liver metastases were collected in the present study. In addition, the hypo-fractionated radiotherapy mode further shortens the course of treatment and improves the compliance of patients (31).

Hara *et al* (43) found that the 3-year local recurrence rate of SBRT (5.3%; 95% CI, 2.7-9.2%) was significantly lower than that of RFA (12.9%; 95% CI, 9.9-16.2%) (P<0.01). SBRT has reasonable LC rates and corresponding OS rates in patients with good liver function compensation. Thus, SBRT exhibited advantages and excelled other treatment methods. A recent meta-analysis demonstrated that ablative external beam radiotherapy was able to yield similar treatment outcomes to RFA among patients with HCC and patients with liver metastasis and suggested that it may be a more effective treatment for tumors in locations where RFA is challenging to perform (44).

Liver cancer was previously considered unsuitable for radiotherapy due to hepatocytes that are radiation-resistant. In previous years, due to the development of radiotherapy technology, the concerns of liver irradiation volume and respiratory movement have been overcome (42,45). Kim *et al* (46) confirmed that radiotherapy has a significant role in liver cancer and radiotherapy combined with other treatments has also achieved a good prognosis (17). The emergence of stereotactic radiotherapy results from the improvement of radiotherapy technology, which may administer a large dose of radiotherapy to the tumor (47). At present, the devices used for stereotactic radiotherapy include cyberknife,

Table IV. Factors of overall survival after treatments [HR (95% CI)].

	HCC				Liver metastasis			
Factor	UVA	P-value	MVA	P-value	UVA	P-value	MVA	P-value
Age (>64 years vs. ≤64 years)	2.546 (0.397-16.309)	0.324	-	-	1.632 (0.617-4.316)	0.319	-	-
Gender (male vs. female)	52.921 (0.030-93668.064)	0.298	-	-	1.147 (0.724-1.816)	0.558	-	-
HBV infection	1.192 (0.197-7.201)	0.877	-	-	-		-	-
Tumor size (>4 cm vs. ≤4 cm)	1.317 (0.217-7.995)	0.765	-	-	1.383 (0.524-3.646)	0.511	-	-
SBRT (14 Gyx3 fractions vs. 16 Gyx3 fractions)	1.940 (0.312-12.055)	0.470	1.334 (0.173-10.270)	0.782	1.349 (0.484-3.760)	0.164	1.200 (0.405-3.556)	0.553
Number of lesions (multiple vs. single)	8.423 (0.906-78.274)	0.028	9.688 (0.835-112.355)	0.069	3.927 (1.238-12.455)	0.020	3.952 (1.186-13.166)	0.035

UVA, univariate analysis; MVA, multivariate analysis; HR, hazard ratio; HBV, hepatitis B virus; SBRT, stereotactic body radiotherapy; HCC, hepatocellular carcinoma.

Table V. Acute adverse events after stereotactic body radiation therapy within 6 months (NCI-CTCAE grade).

	HCC (n=13)				Liver metastasis (n=23)				
Adverse event	Grade I	Grade II	Grade III	Grade IV	Grade I	Grade II	Grade III	Grade IV	P-value
Leukocytopenia	2 (15.4)	0 (0.0)	0 (0.0)	0 (0.0)	3 (13.0)	3 (13.0)	0 (0.0)	0 (0.0)	0.690
Neutropenia	2 (15.4)	0 (0.0)	0 (0.0)	0 (0.0)	3 (13.0)	3 (13.0)	0 (0.0)	0 (0.0)	0.690
Anemia	1 (7.7)	0 (0.0)	0 (0.0)	0 (0.0)	5 (21.7)	0 (0.0)	0 (0.0)	0 (0.0)	0.385
Thrombocytopenia	2 (15.4)	1 (7.7)	2 (15.4)	1 (7.7)	5 (21.7)	0 (0.0)	0 (0.0)	0 (0.0)	0.067
Fatigue	3 (23.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.040
Nausea	2 (15.4)	2 (15.4)	0 (0.0)	0 (0.0)	7 (30.4)	0 (0.0)	0 (0.0)	0 (0.0)	0.147
Elevated AST/ALT	7 (53.8)	0 (0.0)	0 (0.0)	2 (15.4)	5 (21.7)	0 (0.0)	0 (0.0)	0 (0.0)	0.005
Elevated bilirubin	5 (13.9)	1 (2.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.001
Acute pneumonia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	NA

NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events version 4.3; AST, aspartate transaminase; ALT, alanine transaminase; NA, not available; HCC, hepatocellular carcinoma.

helical tomotherapy and linear accelerator with volume intensity modulation (48). The liver cancer radiotherapy process is affected by respiratory movement, and therefore, breathing exercises and breathing control should be taken into consideration (49). These breathing techniques are complex and the standard in different centers varies. Different radiotherapy technologies result in different times to complete each radiotherapy session, ranging from 2 to >30 min (42). Therefore, the biological effect on cancer cells varies with the same radiotherapy dose between centers. At present, there is yet to be a unified quality control standard for SBRT treatments. SBRT is an image-guided stereotactic radiotherapy and its main advantage is that it can administer concentrated high doses to the tumor area, and the dose outside the target area drops rapidly to protect normal tissues (50). SBRT can effectively reduce side effects and improve the tolerance of patients to the treatment. The exploration of the prescribed dose is the novelty of the present study. To date, a number of studies have been published on SBRT for liver cancer, but there is no unified standard for the dose of SBTR to be used for treatment (30,33,51). Certain studies have found that BED >100 Gy is significantly associated with prognosis and that there is a dose-response relationship between local tumor progression and BED (47,52). In the present study, good prognosis results were obtained using 3-fraction SBRT technology (BED, 100.8-124.8 Gy).

As indicated in a recently published meta-analysis, the 2-year LC rates after SBRT for primary liver tumors and liver metastases were 89 and 79%, respectively (53). These 2-year LC rates are similar to those determined in the present study. The first prospective study for the use of SBRT in treating liver cancer demonstrated a promising LC rate and safety in 8 patients with HCC and 34 patients with liver metastases (51). However, one Child-Pugh B patient died in relation to RILD (51). In the present study, none of the patients suffered from RILD. Bae *et al* (54) suggested that the effective rate and tumor LC rate of patients with radiation doses ≥48 Gy in 3 fractions are higher than those with 45 Gy in 3 fractions. Kimura *et al* (55) evaluated SBRT with or without TACE in patients with HCC. The 2-year LC rates were 95.4% in the SBRT group and 98.6% in the SBRT with TACE group. However, the study demonstrated no significant differences in treatment results, including in the OS, PFS and LC among the groups (55). The lower LC rates observed in the present study may be due to the inclusion of more patients with liver metastasis. In summary, the safety and effectiveness of SBRT in the treatment of liver cancer have been confirmed in clinical practice.

Sapir *et al* (56) conducted a large single-center comparison of TACE vs. SBRT in patients with HCC, and it was found that SBRT is a safe alternative to TACE for patients with 1-2 tumors and provided an improved LC, with no observed difference in OS. Clinically, it is notable that regardless of whether HCC is in the early, intermediate or advanced stages, if liver function is normal and the normal liver volume is >700 cm^3 before radiotherapy, patients may benefit from local intervention with SBRT. Simultaneously, SBRT may also be used as a complementary treatment for patients with a poor response to drugs or TACE. However, further clinical trials are needed to confirm the treatment effect. Considering these above results, SBRT alone may be sufficient for patients with liver tumors who are ineligible for resection or ablation therapies.

The present study does however have certain shortcomings. Due to the small number of patients enrolled in the study, the clinical data of patients with HCC and liver metastasis were mixed for analysis. In addition, the small sample size may infer a particular bias in the results. For instance, portal vein tumor thrombus is a recognized factor influencing the prognosis of patients with HCC, but this is not reflected in the results of the present study. In order to obtain high-level medical evidence, prospective randomized, controlled, multicenter, extensive clinical studies should be actively conducted to add weight to conclusions and guide clinical application.

In conclusion, in the absence of guidelines and consensus, the present study preliminarily found that SBRT may be effective in achieving local tumor control for patients with primary or metastatic liver tumors. The SBRT treatment was safe, effective and feasible. The dose and fractionation modality in the present study may be a convenient and secure choice for the local treatment approach using SBRT. Further investigation

must include an expanded sample size investigation and an external multicenter randomized clinical trial validation.

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Availability of data and materials

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

Authors' contributions

Conception and design: RJ and QY. Provision of study materials or patients: RJ. Collection and assembly of data: CL, QY and XH. Data analysis and interpretation: CL, QY, and XZ. Manuscript writing: All authors. All authors have read and approved the final version of the manuscript. RJ and QY confirm the authenticity of all the raw data.

Ethics approval and consent to participate

All procedures performed in this study involving human participants were in accordance with the ethical standards of the Ethics Committee of Fudan University Shanghai Cancer Center (Shanghai, China) and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The experimental protocols were also approved by the Ethics Committee of Fudan University Shanghai Cancer Center (Shanghai, China; approval no. 1 410 140-8). Written informed consent was obtained from all individual participants included in the study.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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