The Clinical Outcomes of Stereotactic Body Radiotherapy for Liver Metastasis and Hepatocellular Carcinoma: a retrospective study

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Abstract

Purpose

This retrospective clinical study expounded the clinical application details of stereotactic radiotherapy for liver cancer established in our center.

Method

The therapeutic effect and prognosis of liver cancer patients treated with stereotactic body radiation therapy (SBRT) from 2011 to 2019 were analyzed retrospectively. The clinical and radiotherapy data were collected and analyzed. Overall survival (OS), local control (LC) rates and progression-free survival (PFS) were evaluated using Kaplan Meier analysis and log-rank test. Local progression was defined as irradiated tumor growth in dynamic computed tomography follow-up. Treatment-related toxicities were assessed according to the Common Terminology Criteria for Adverse Events version 4.3.

Results

Thirty-six patients with liver cancer were enrolled in this study. 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 1- and 2-OS rates were 59.6 and 44.2%, respectively. The median PFS time was 17.3 (95% CI:11.8–22.8) months, and the 1- and 2-year PFS rates were 65.6% and 39.1%, respectively. The 1- and 2-year local control rates were 94.2% and 83.4%, respectively. The most common grade IV toxicity was AST/ALT elevation (5.6%) followed by thrombocytopenia (2.8%). There were no cases of grade III/IV radiation pneumonia and digest discomfort.

Conclusion

The SBRT technology applied in our center for liver cancer is safe and effective. The prescribed dosage (14Gy × 3 Fractions/16Gy × 3 Fractions) we used was reliable and efficient.

Background

Liver cancer, whether primary or secondary, is one of the most common malignant tumors with a poor prognosis worldwide[1]. According to reports, Hepatocellular carcinoma (HCC), namely primary liver cancer, is the third leading cause of cancer death, and the incidence rate ranks the sixth of malignant tumors worldwide[2]. In China, HCC ranks second in the mortality of malignant tumors[3]. As for hepatic metastasis, the survival rates are also significantly decreased[4]. Surgery is the standard treatment method for HCC, including hepatic resection or liver transplantation, which results in 5-year survival rates of 30–70%[5, 6]. However, few people are suitable for surgery. Most patients have reached the middle and

advanced stages at the time of diagnosis, or the lesion is close to important blood vessels, resulting in losing the best time for surgery. Other treatments should be applied for those unresectable patients, such as transcatheter arterial chemoembolization (TACE), radiofrequency ablation (RFA) and conventional radiotherapy[7–11]. The treatment efficacy and prognosis for liver cancer patients are still not so satisfactory. As a result, SBRT has emerged as an effective, non-invasive alternative for these tumors.

The application of transcatheter arterial chemoembolization (TACE) is limited. It can be used in patients with unresectable advanced liver cancer[12, 13]. However, due to the formation of collateral circulation after embolization, the tumor grows again. The two-year survival rate of interventional therapy is 41%, and the effective rate is only 35%. Radiofrequency ablation (RFA) is only applicable to early-stage lesions with a diameter of less than 3cm[14]. There are many side effects of chemotherapy for liver tumors, while targeted therapy is a mild treatment. Recent research shows that sorafenib can improve the survival and prognosis of patients, but it should also be combined with other adjuvant therapies. Radiotherapy is a prospective and hopeful treatment for patients with liver cancer, whether primary or secondary.

At present, the radiotherapy techniques commonly used in clinical practice mainly include three-dimensional conformal radiotherapy (3DCRT), intensity-modulated radiation therapy (IMRT), stereotactic body radiation therapy (SBRT), helical tomotherapy, etc. Many studies have confirmed the significant role of radiotherapy in treating liver cancer, and radiotherapy is suitable for various stages of liver cancer. Conventional liver radiotherapy can lead to radiation hepatitis, and the tolerated dose is limited to avoid liver injury[15–17]. Therefore, technological advancements in radiation oncology have enabled 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[18, 19]. SBRT is now included in the recent version of the National Comprehensive Cancer Center Network guidelines for liver cancer under the indication for 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.

Normal liver tissue is a radiosensitive organ, which is a little lower than bone marrow, lymphatic tissue and kidney. The dose of radiotherapy for liver tumors is similar to that for poorly differentiated squamous cell carcinoma, with a lethal dose of about 60 Gy / 6 weeks[20]. However, normal liver has a strong regenerative capacity[21]. As long as enough normal liver is retained, it can compensate for partial liver function damaged by radiotherapy through hyperplasia. Therefore, based on the current limited research status, there is still a great space for exploration of radiotherapy for liver cancer in the future.

In this retrospective study, we investigated and analyzed the efficacy and feasibility of SBRT for liver cancer patients at our cancer center.

Patients And Methods

Data collection and patient characteristics

Thirty-six patients with liver cancer confirmed by pathology from July 2011 to December 2020 in Fudan University Shanghai Cancer Center (FUSCC) were enrolled in this study. Clinical records were reviewed to verify patients' treatment details, clinical outcomes and the patient characteristics. We retrospectively reviewed the medical records, RT treatment plans, and diagnostic images of patients with liver cancer who satisfied the following criteria: (1) 18–85 years of age; (2) histologically verified HCC or imaging confirmed liver metastases; (3) Child-Pugh scores: 5 or 6; (4) Eastern Cooperative Oncology Group performance status (ECOG PS) of 0–1; (5) treated with SBRT. We excluded patients with: (1) patients who underwent surgery; (2) incomplete information and follow-up failure.

The retrospective study strictly obeyed the principles of the Declaration of Helsinki. This study was approved by the Fudan University Shanghai Cancer Center Institutional Review Board and all methods were performed in accordance with the guidelines and regulations of this ethics board. Since this study is anonymous, informed consent can be exempted.

Sbrt Techniques

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

A dose of 42Gy in 3 fractions (BED: 100.8Gy) every other day was prescribed for lesions in close proximity to luminal organs at risk (OAR), such as the stomach, duodenum, and bowels. Otherwise, a dose of 48Gy in 3 fractions (BED: 124.8Gy) every other day was prescribed. Plan optimization was based on a dose–volume histogram (DVH). The prescribed isodose curve covered 95% of the PTV and the 95% isodose curve covered 99% of the PTV. The maximum dose within the PTV did not exceed 110% of the prescribed dose. OAR dose constraints followed in the treatment planning are listed in Table 1. Conformal dose distribution with rapid dose fall-off outside target volume was achieved by multiple coplanar or non-coplanar static beams or arcs of 6MV. An illustrative case is shown in Fig. 1.

Table 1
Dose Constraints Used for Liver SBRT

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

At each treatment fraction, Cone-beam CT (CBCT) imaging was performed to localized the target, and the position was corrected and approved by an attending radiation oncologist.

Table 1. *Dose Constraints Used for Liver SBRT*

Figure 1. An illustrative case for SBRT.

Statistical analysis

After the end of radiotherapy, patients are reviewed for clinical evaluation, liver function, kidney function, abdominal CT or MRI every three months. The acute adverse events within 6 months were evaluated by the National Institutes of Health-defined Common Terminology Criteria for Adverse Events (CTCAE 4.3), while the late adverse events after 6 months were evaluated according to the Toxicity Criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC) during the follow-up time[22]. Overall survival (OS) was defined as the time between the first radiotherapy session and death. Progression-free survival (PFS) 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 and local-control relapse. Distant metastasis-free survival (DMFS) was defined as the time between the first radiotherapy session and metastasis. The Response Evaluation Criteria In Solid Tumors (RESIST 1.1) were used to assess the condition after SBRT. Survival was estimated using the Kaplan-Meier method. All statistical analyses were conducted using IBM SPSS Statistics for Windows version 22.0 (IBM Corp., Armonk, N.Y., USA), and statistical significance was indicated by two-sided *p*-values with α set at 0.05.

Results

Patient characteristics

Detailed patients' characteristics and treatment details were provided in Table 2. A total of thirty-six patients were enrolled. 13 cases were Hepatocellular carcinoma. In contrast, 23 were identified as liver metastasis, including eight colorectal cancer, five pancreatic cancer, four breast cancer, two lung cancer, two gallbladder carcinoma, two esophageal cancer. The age range was between 30.6 and 82.5 years, with a total median age of 64. The follow-up time range was 4.9 to 69.1 months. Hepatitis B virus (HBV) infection was the important cause of HCC (69.2%). All patients had CP class A disease. Most patients (80.5%) had a single lesion.

Table 2
Patient characteristics and treatment data

	HCC	Liver metastasis	P value
Gender			0.452
Male	9 (69.2%)	13(56.5%)	
Female	4 (30.8%)	10(43.5%)	
Age (Year)			0.083
Median	62.6	65.9	
Average	62.4	61.8	
Range	42.8–82.5	30.6–82.5	
<=64	9 (69.2%)	9 (39.1%)	
> 64	4 (30.8%)	14 (60.9%)	
SBRT			0.050*
14Gy*3Fx	6 (46.2%)	18 (78.3%)	
16Gy*3Fx	7 (53.8%)	5 (21.7%)	
Location			0.141
Left lobe	0 (0%)	2 (8.7%)	
Right lobe	12 (92.3%)	15 (65.2%)	
Both	1 (7.7%)	6 (26.1%)	
Etiology			0.000*
Normal	4 (30.8%)	23 (100%)	
Hepatitis B virus	9 (69.2%)	0 (0%)	
Hepatic cirrhosis			0.000*
Yes	6 (46.2%)	0 (0%)	
No	7 (53.8%)	23 (100%)	
Tumor diameter, Maximum, cm			0.365

Dashes indicate not applicable.

Abbreviations: SBRT, stereotactic body radiotherapy.

	HCC	Liver metastasis	P value
< 2 cm	3(23.1%)	5(21.7%)	
≥ 2cm, < 3 cm	2(15.4%)	9(39.1%)	
≥ 3cm, <5cm	6(46.1%)	5(21.7%)	
≥ 5cm	2(15.4%)	4(17.5%)	
Child-Pugh Score			0.679
A			
5	10 (76.9%)	19 (82.6%)	
6	3 (23.1%)	4(17.4%)	
B	—	—	
C	—	—	
Follow-up time (months)			
Median	25.4	13.2	
Range	8.6–69.1	4.9–45.9	
Dashes indicate not applicable.			
Abbreviations: SBRT, stereotactic body radiotherapy.			

Table 2. *Detailed patients' characteristics and treatment data*

The feasibility of SBRT

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 1- and 2-OS rates were 59.6 and 44.2%, respectively. The median PFS time was 17.3 (95% CI:11.8–22.8) months, and the 1- and 2-year PFS rates were 65.6% and 39.1%, respectively. The 1- and 2-year LC rates were 94.2% and 83.4%, respectively.

In the follow-up process, two of the thirteen patients identified as HCC pathologically suffered from local control failure, and the 2-year LC rate reached 85.7%. Among the twenty-three patients diagnosed with secondary liver cancer, three patients failed to LC, and the two-year LC rate reached 81.6%. The survival curves for the patients were shown in Fig. 2. Although the LC rate of the patient is ideal, the OS rates of the patients were not satisfactory. We also further studied the reasons for the poor LC rate of OS and PFS. The failure pattern is mainly out-field recurrence and distant metastasis (Table 2), affecting the patients' overall prognosis.

Figure 2. The survival for all patients, HCC, liver metastasis, respectively. a, Local control rates. b, overall survival. c, progression-free survival. d, distant metastasis-free survival. Abbreviate: HCC, hepatocellular

carcinoma

Table 3. *The failure patterns in 36 patients after irradiation*

Table 3
The 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	1 (6.7%)
Distant only	0	2 (13.3%)
Locoregional and distant	2(28.6%)	7 (46.7%)

The adverse events of SBRT

The acute adverse events within six months were shown in Table 3. No deaths were seen as a consequence of SBRT. The main side effect is the adverse effect on liver function (38.9%), reflected in the elevation of aspartate transaminase (ALT) and alanine transaminase (AST) evaluation. The most common grade IV toxicity was AST/ALT elevation (5.6%), followed by thrombocytopenia (2.8%). There were no cases of grade III/IV radiation pneumonia and digest discomfort.

The late adverse events for all the patients were demonstrated in Table 4. Grade 3 and 4 liver function toxicity occurred in two (5.6%) and one (2.8%) patients, respectively.

Table 4
Acute Adverse events after stereotactic body radiation therapy within 6 months

	NCI-CTCAE Grade (%)			
Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Leukocytopenia	5(13.9)	3(8.3)	0(0.0)	0(0.0)
Neutropenia	5(13.9)	3(8.3)	0(0.0)	0(0.0)
Anemia	6(16.7)	0(0.0)	0(0.0)	0(0.0)
Thrombocytopenia	7(19.4)	1(2.8)	2(5.6)	1(2.8)
Fatigue	3 (8.3)	0 (0.0)	0 (0.0)	0 (0.0)
Nausea	9 (25.0)	2 (5.6)	0 (0.0)	0 (0.0)
Elevated AST/ALT	12 (33.3)	0 (0.0)	0 (0.0)	2 (5.6)
Elevated Bilirubin	5 (13.9)	1 (2.8)	0 (0.0)	0 (0.0)
Acute pneumonia	0(0.0)	0(0.0)	0(0.0)	0(0.0)
NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events				
version 4.3; AST, aspartate transaminase; ALT, alanine transaminase.				

Table 5
Late Adverse events after stereotactic body radiation therapy

	RTOG radiation morbidity scoring criteria (%)			
Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Liver function	12(33.3)	1 (2.8)	4 (11.1)	0 (0.0)
Radiation pneumonitis	1(2.8)	0 (0.0)	0 (0.0)	0 (0.0)
Rib fraction	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
RTOG, Radiation Therapy Oncology Group				

Table 3. *Acute Adverse events after stereotactic body radiation therapy within 6 months*

Table 4. *Late Adverse events after stereotactic body radiation therapy after 6 months*

Discussion

This retrospective study demonstrated no significant differences in treatment results between HCC and liver metastasis patients, including PFS, DMFS, LC rates. There was a difference in OS rates ($p = 0.006$), as patients diagnosed with HCC had better 2-year OS rates. The dose we used had the desired effect, with

a high LC rate but a low OS and prognosis due to out-field recurrence and distant metastases. The safety of the dosage we use is reliable, and the normal organs were well protected. SBRT for liver cancer has a clear efficacy, with a 2-year survival rate of more than 80%. Our center formulated indications for SBRT: KPS ≥ 70; Cirrhosis of the liver Child-Pugh A; less than three lesions. Respiratory control is feasible and beneficial for the movement of breath. Radiotherapy should pay attention to the protection of the normal liver.

Liver cancer was previously considered unsuitable for radiotherapy because hepatocytes are radiation-resistant. In current years, due to the development of radiotherapy technology, the design of liver irradiation field and respiratory movement have been well solved[23, 24]. It has been proved that liver is a radiosensitive organ. Kim[25] confirmed that radiotherapy plays a significant role in liver cancer, and radiotherapy combined with other treatments has also achieved a good prognosis[26]. The emergence of stereotactic radiotherapy is the result of the improvement of radiotherapy technology, which can give a large dose of radiotherapy to the tumor. At present, the devices used for stereotactic radiotherapy include cyberknife (CK), Helical Tomotherapy (HT) and linear accelerator with volume intensity modulation (VMAT). Liver cancer radiotherapy process is affected by respiratory movement, breathing exercises and breathing control should be taken. These techniques are complex, and the standard in different centers varies. Different radiotherapy technologies result in different times to complete each radiotherapy, ranging from 2 min to more than 30 min. Therefore, the biological effect of cancer cells varies with the same radiotherapy dose. At present, there is no unified quality control standard. SBRT is image-guided stereotactic radiotherapy. Its main advantage is that it can concentrate high doses in the tumor area, and the dose outside the target area drops rapidly to protect normal tissues[27]. It can effectively reduce side effects and improve patient tolerance.

At present, there are many studies on SBRT for liver cancer, but there is no unified standard for the dose of SBRT for liver cancer[28–30]. As shown in a recently published meta-analysis, The 2-year actuarial LC rates after SBRT for primary liver tumors and liver metastases were 89% and 79%, respectively [31]. The LC rates were similar to our study. The first prospective evidence for liver SBRT in 2006 demonstrated promising LC and safety in 8 patients with HCC and 34 patients with liver metastases; however, one CP-B patient experienced radiation-induced liver disease (RILD) related death[28]. In this study, no one suffered RILD. Bae SH believes that the effective rate and tumor LC rate of patients with radiation dose ≥ 48Gy / 3F are better than those with 45Gy / 3F[32]. Tomoki et al. evaluated SBRT with or without TACE in patients with HCC. The 2-year LC rates were 95.4% in SBRT group and 98.6% in SBRT with TACE group, respectively[33]. But the study demonstrated no significant differences in treatment results, including OS, PFS and LC between the groups[33]. The lower LC rates may be due to our study including more liver metastasis patients. In summary, the safety and effectiveness of SBRT in liver cancer have been confirmed in clinical practice. However, due to different treatment plans, there is still no unified standard for SBRT in liver cancer.

We discussed the feasibility of SBRT as mentioned above. Selective internal radiotherapy (SIRT) with yttrium-90 microspheres is also an effective treatment option for patients who were ineligible for

resection or ablation therapies[20]. But it has not been common in China. Considering these results, SBRT alone might be sufficient for patients with liver tumors who are ineligible for resection or ablation therapies.

This study has some shortcomings. Due to the small number of patients enrolled, the clinical data of HCC and liver metastasis was mixed for analysis. The small sample size may cause a certain bias in the results. For example, portal vein tumor thrombus is a recognized factor influencing the prognosis of HCC patients, but the results of this study are not reflected. In order to obtain high-level medical evidence, prospective randomized, controlled, multi-center large clinical studies should be actively carried out to make the conclusions more convincing and guide clinical application.

Conclusion

we have determined that SBRT with a BED of > 100Gy could be extremely effective in achieving local tumor control for patients with primary or metastatic liver tumors. Further investigation must include expanded sample size investigation and external multicenter validation.

Declarations

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Conflict of interest

All authors declare no conflicts of interest.

Ethical approval and informed consent

All procedures performed in this study involving human participants were in accordance with the ethical standards of the Fudan University Shanghai Cancer Center Ethics Committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Availability of data and materials

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

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no conflict of interest.

Author contribution

Conception and design: Rui Jiang

Provision of study materials or patients: Rui Jiang

Collection and assembly of data: Canyu Liu, Qiong Yi

Data analysis and interpretation: All authors

Manuscript writing: All authors

Final approval of manuscript: All authors

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Figures

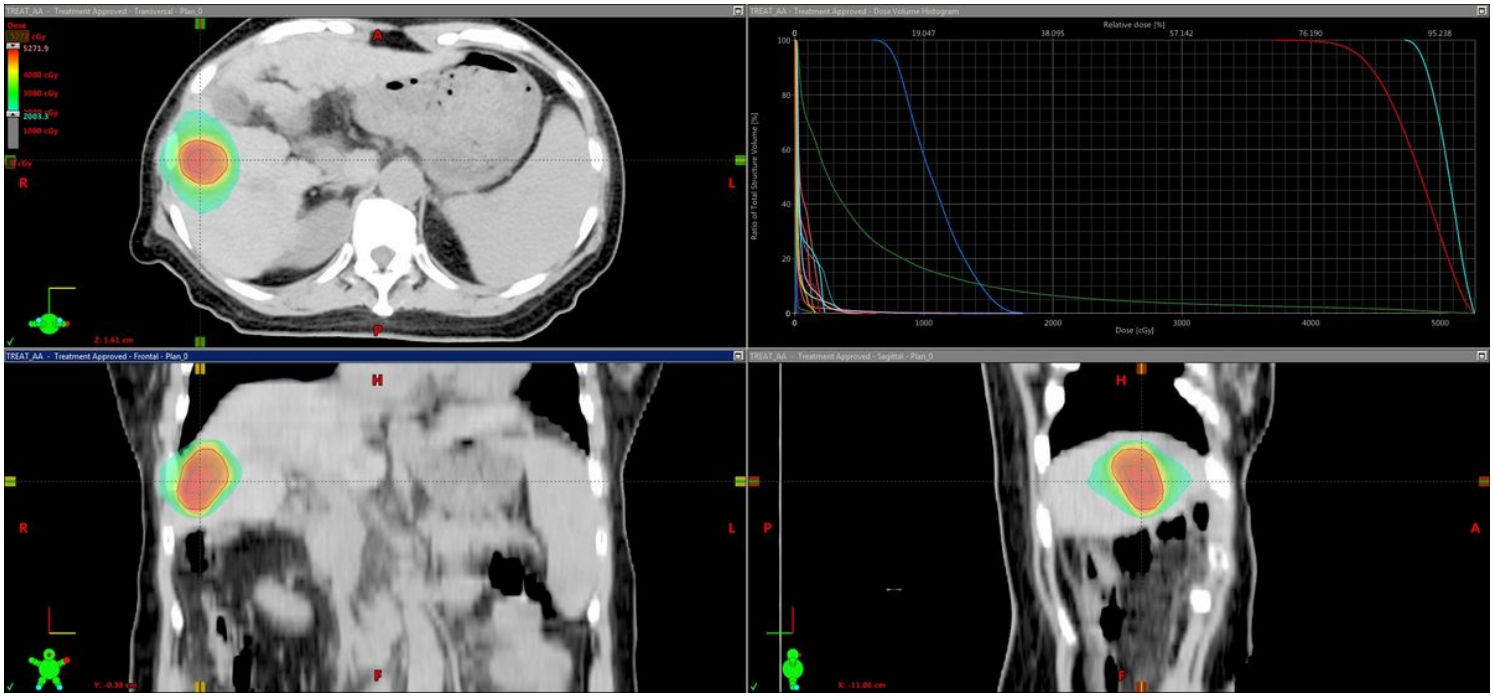

Figure 1

An illustrative case for SBRT.

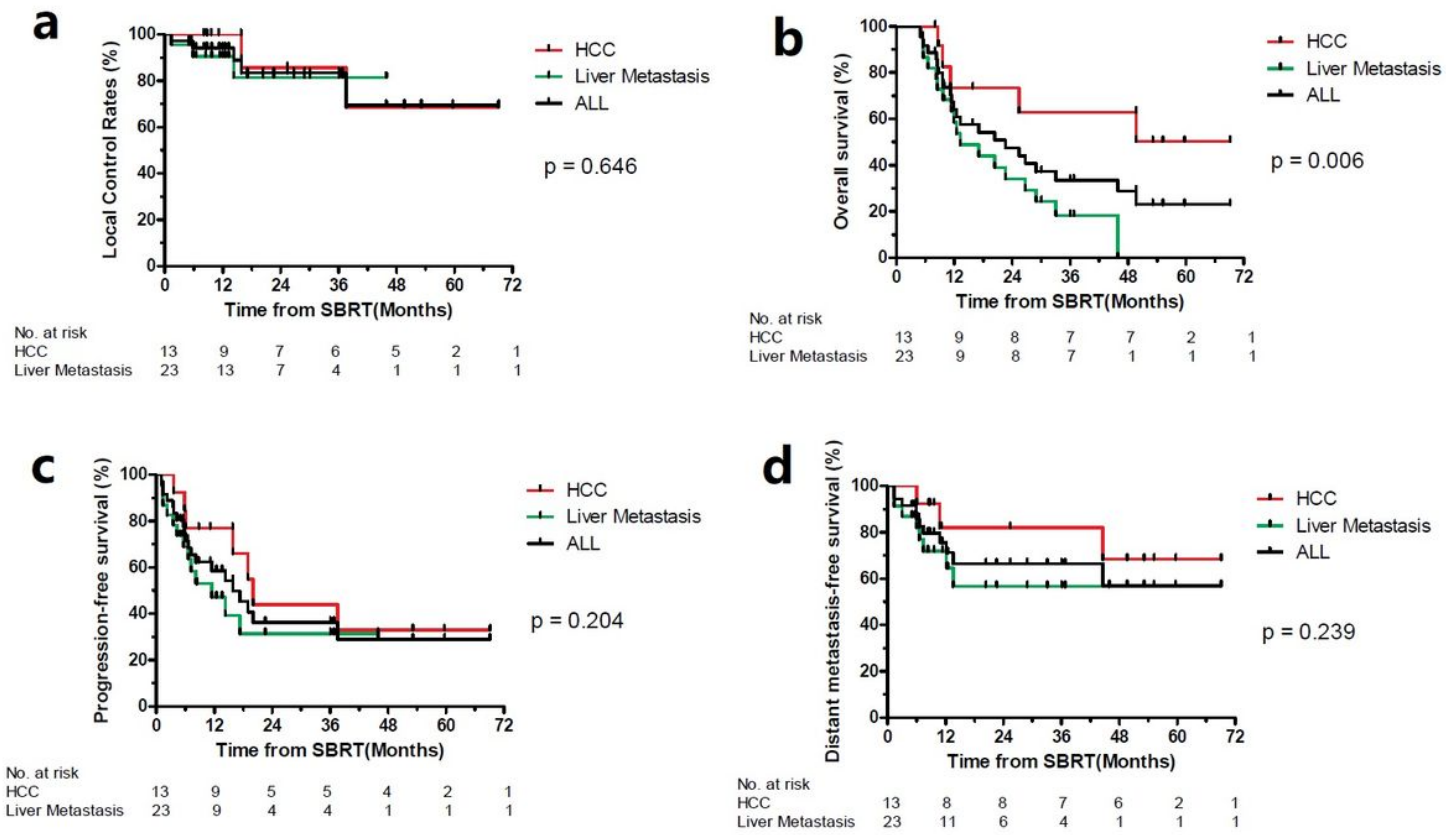

Figure 2

The survival for all patients, HCC, liver metastasis, respectively. a, Local control rates. b, overall survival. c, progression-free survival. d, distant metastasis-free survival. Abbreviate: HCC, hepatocellular carcinoma