Optimal Application of Stereotactic Body Radiotherapy and Radiofrequency Ablation Treatment for Different Multifocal Hepatocellular Carcinoma Lesions in Patients With Barcelona Clinic Liver Cancer Stage A4–B1: A Pilot Study

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Research

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Abstract

Backgrounds

In clinical practice, many hepatocellular carcinoma (HCC) patients in Barcelona Clinical Liver Cancer (BCLC) stage A4–B1 can not receive curative treatment of liver transplantation, resection and RFA which were recommended options by liver cancer guidelines. Our aim is to study the feasibility of radiofrequency ablation (RFA) and stereotactic body radiotherapy (SBRT) as curative treatment for different multifocal HCCs in BLCL stage A4–B1 patients.

Methods

From September 2014 to August 2019, 39 multifocal HCC lesions (median diameter, 16.6 mm) from 15 patients (median age, 73.2 years) were retrospectively enrolled. Among them, 23 were treated by RFA and the other 16 by SBRT because of predictable insufficiency and/or risk for RFA performance. The indicators for evaluating this novel therapy were tumor response, prognosis (recurrence and survivals), and adverse effect (deteriorated laboratory test values and severe complications).

Results

Median follow-up duration was 31.3 months (range: 15.1–71.9 months). The numbers of one-year complete response, stable disease, and disease progression were 11, 1, and 3, respectively. In total, eight and two patients had confronted intrahepatic and local recurrence, respectively. The one-year progression-free survival rate and local control rate were 80% (12/15 patients) and 97.4% (38/39 lesions), respectively. Median time to progression was 20.1 (2.8–45.1) months. The one- and two-year survival rates were 100%, and 88.9%, respectively. During one week to 3–5 months' observation, no patient showed severe complications. Seven, four, and two patients had slight changes in white blood cells, platelet count, and albumin–bilirubin grade, respectively.

Conclusions

For patients with BCLC stage A4–B1, RFA and SBRT treatment for different multifocal HCCs may be a potential option because of their favorable prognosis and safety. However, before setting assured application in clinical practice, prospective, controlled, large-scale studies are needed to further confirm our conclusions.

Introduction

Hepatocellular carcinoma (HCC) is a very heterogeneous disease. The management of the therapeutic approach may vary and is strongly related to the states of patients, characteristics of lesions, as well as tumor stage. According to the most commonly used staging system, Barcelona Clinical Liver Cancer (BCLC) [1], and the recently developed Kinki Criteria [2], HCC patients in high-level early stage (stage A4) and low-level intermediate stage (stage B1), which are characterized as small, multiple lesions and relatively good liver function, have the opportunity to receive potentially curative treatment [3] rather than palliative treatment. As patients in BCLC stage B1 have comparable prognosis (overall survival and disease-free survival) as those in BCLC stage A, a recent study suggested that BCLC stage B1 patients be re-classified into early stage [4]. Percutaneous image-guided radiofrequency ablation (RFA) is a recommended therapy as given its advantages of minimal invasion, promising long-term survival, and up to 90% tumor local control for small-sized HCCs [5, 6]. However, in daily clinical practice, RFA performance is sometimes dangerous, insufficient, or even unfeasible due to anatomical factors (e.g., diameter > 3 cm, adjacent to the liver capsule or main vessels, deep-located near dome or subphrenic area) and technical ultrasound (US) factors involving poor conspicuity [7, 8]. In particular, perivascular lesions (though maybe small in size) inevitably produce the heat-sink effect, which possibly results in residue.

Stereotactic body radiotherapy (SBRT) is an emerging non-surgical locoregional treatment modality that involves the delivery of very high individual doses of radiation with high geometric precision and accuracy to the targeted lesion [9]. Though not recommended in the latest international guideline to treat early-stage HCC [10, 11], SBRT is a promising treatment option for early-stage and small HCCs, with many reports of favorable local control rates, prolonged progression-free survival (PFS), and improved overall survival (OS), with minimal blood vessel, bile duct, and hepatocyte toxicities [6, 12–14]. Specifically, for patients population with a mean Child–Pugh score of 6.4 (A5–C11) and HCC lesions with mean size of 2.7 cm (1.1–5.6 cm), the reported local control rate, PFS, and OS in one year using SBRT treatment were 95%, 66%, and 87%, respectively [15]. When compared to RFA treatment in patients with similar basic characteristics, SBRT treatment exhibited excellent local control (2-year local control rate was 32.1% after SBRT and 18.7% after RFA) and comparable OS (1- and 2-year OS rates were 70% and 53% after RFA, and 74% and 46% after SBRT, respectively) [16, 17]. By comparative analysis of a Markov model, Seo et al. [6] proposed SBRT as the preferred treatment option over RFA for 2–3 cm HCC lesions. Recently, to overcome the limitations of insufficient ablation in certain locations, an SBRT method to treat post-ablative local progression has been developed. Good results of 1-year local control rate (81.8–86.6%), PFS (63.3–69.9%), and OS (85.4–85.6%) were reported [18]. To treat local recurrence of initial RFA, SBRT was considered to be comparable and more cost-effective than repeated RFA [19], especially for patients with larger tumors or tumors abutting major vessels [20].

Inspired by the previously successful combined application of RFA and SBRT in HCC patients in a relative early stage [18, 19], and the requirement for an effective treatment strategy for early multifocal HCCs, especially those ineligible or unavailable for RFA performance, we propose a novel treatment strategy combining SBRT and RFA for different HCC lesions coexisting in the same patient. We performed a retrospective single-arm study by applying RFA and SBRT treatment in 39 multifocal HCC lesions from 15 patients in BCLC stage A4–B1, evaluating the benefit to prognosis and possible adverse effect during follow-up, then determining their comprehensive therapeutic consequences. We expect this novel strategy to be feasible and effective, thus can be an alternative curative strategy for multiple small lesions in patients with good liver function.

Methods

Patient Enrollment

From September 2014 to February 2019, 294 consecutive patients with a total of 480 HCC lesions, which were treated by RFA or SBRT, were initially enrolled. HCC was diagnosed according to the Japan Society of Hepatology Guideline [21]; these lesions all had a typical imaging appearance of HCC and/ or HCC was histologically proven by biopsy. All RFA was performed at Yokohama City University Medical Center; SBRT treatment was provided at Ofuna Chuo Hospital. Data collection and analysis received institutional review board approval, and the requirement for informed consent was waived.

The exclusion criteria were as follows: (1) patients in BCLC stage 0–A3 (170 patients with 170 lesions); (2) patients in BCLC stage greater than B1 (9 patients with 30 lesions); (3) patients who lost contact prior to one year's follow-up (13 patients with 30 lesions); (4) unable to meet the modified Response Evaluation Criteria in Solid Tumors (mRECIST) [22] for the selection of target lesions (less than two lesions ≥ 1 cm and failed to show pre-treatment enhancement on arterial phase (AP) of CT or MRI examination; 37 patients with 79 lesions); (5) the initial treatment for multifocal lesions in one patient were the same (all by RFA or all by SBRT; 46 patients with 123 lesions); (6) treatment intervals between RFA and SBRT of more than three months (4 patients with 9 lesions).

Treatment Strategy

RFA Procedure

As described by Wang et al. [22] and Hao et al. [24], RFA was performed with the guidance of real-time CT/MRI and US fusion imaging by one of the three senior hepatologists (K.N., K.O., and H.F.), each having more than 20 years of experience in interventional techniques. One to three insertions were performed according to the tumor size and shape, requiring an ablative safety margin of no less than 5 mm around the treated lesions. Post-operative contrast-enhanced ultrasonography was performed to determine the adequacy of ablation. If residual tumor was detected, additional RFA was performed.

SBRT Procedure

We previously described our SBRT methods in detail [25]. When the tumors were not near the gastrointestinal tract, SBRT with total doses of 35–40 Gy were delivered in 5 fractions over 5–7 days. The total dose of 35 Gy was administered to patients with Child–Pugh class A or B disease, with > 20% of the normal liver receiving > 20 Gy, and a total dose of 40 Gy in the other patients. For the tumors near the gastrointestinal tract, a total dose of 36–45 Gy was delivered in 12–15 fractions over 16–21 days. The treatment was planned to enclose the planning target volume with a 60–80% isodose line of the maximal dose.

Interpretation and Assessment of Outcome Data

Adverse Effects

The first targets of observation in this study were treatment-related adverse effects, which were evaluated by both laboratory testing (objective findings) and clinically-visible complications (constitutional symptoms) [26]. The laboratory parameters, including serum alanine transaminase (ALT), aspartate transaminase (AST), leukocytes counts, platelets counts, total bilirubin (T-BIL), albumin (ALB), were recorded. Hematologic toxicity by radiation, a principal cause of acute myelosuppression, was evaluated by the decline in leukocytes and platelets. albumin–bilirubin (ALBI) score was calculated according to the value of T-BIL and Alb. ALBI grade, ALT, and AST were used to assess treatment-related side effects on liver function. The time points for laboratory evaluations were one or three days before treatment, one week after completion of later therapy (either RFA or SBRT), and three to five months thereafter. In addition, clinically-visible complications were recorded and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03. The adverse events grade ≥ 3 were recorded for later analysis.

Tumor Response and Prognosis

The secondary targets for observation were tumor response and local control. Tumor response was evaluated one year after treatment completion of both RFA and SBRT. According to mRECIST for patients with multifocal HCC lesions, the longest viable tumor diameter of the two selected target lesions was measured [27]. Local control was assessed by follow-up radiologic imaging and defined as no tumor recurrence/progression in the primary site.

The tertiary observation target was prognosis, including time to progression, 1- and 2-year PFS, and OS. They were calculated from the date of the earlier therapy (either RFA or SBRT). Local control was evaluated on lesion basis; tumor response, PFS, and OS were evaluated on a patient rather than lesion basis. Cumulative rates of PFS and OS were estimated using the Kaplan–Meier method.

Attention Points for Imaging Evaluation

Contrast-enhanced CT and MRI were used as first-line imaging modalities for evaluating tumor response and recurrence. Contrast-enhanced ultrasound examination was used for patients with renal dysfunction or contrast allergy. Radiological images were all independently evaluated by two hepatologists (enhanced CT and MRI: M.C. and K.H.; contrast-enhanced ultrasound: H.N. and K.O.) who were unaware of any laboratory test information, clinical history, or our therapy strategy. Any interpretation discrepancies were resolved by consensus with the participation of a third expert hepatologist (K.N.) with 20 years of experience in HCC diagnosis and treatment.

Results

Enrolled Patients

Fifteen patients were eligible for this study. The study population selection is presented in Fig. 1. Twelve of them initially received RFA therapy and subsequently SBRT, whereas the other three patients first received SBRT treatment and then RFA. There was no strict guideline followed for the order of these two therapeutic approaches. The treatment order depended on the available schedules of patients and doctors with a consensus. The median treatment interval of SBRT and RFA treatment was 26 (4–60) days. The baseline characteristics of the enrolled patients and lesions are summarized in Tables 1 and 2, respectively.

Table 1

Baseline characteristics of enrolled patients /lesions[1].

Patient No.	No. lesions	Sex (M/F)	Age (years)	Etiology	Child–Pugh grade	ALBI grade	BCLC stage	AFP (ng/ml)	ALB (g/dL)
1	2	M	63	HCV	A6	2	B1	153	3.3
2	2	F	81	HCV	A6	2	A4	56	3.2
3	2	M	66	HCV	A5	1	B1	581	4.6
4	5	M	65	HCV	A5	1	B1	2	4.1
5	2	M	66	HCV	A5	2	A4	9	4.0
6	3	M	80	Alc	A5	1	B1	62	4.6
7	2	F	60	HCV	A6	2	A4	144	3.4
8	4	F	70	HCV	A5	2	B1	11	3.5
9	4	M	74	NBNC	A5	1	B1	4	4.3
10	2	M	80	HCV	A5	2	A4	9	3.9
11	2	F	72	HCV	A5	1	A4	7	4.7
12	2	M	82	HCV	A6	1	B1	66	4.4
13	2	F	80	HCV	B7	1	A4	12	4.7
14	3	M	86	NBNC	A5	2	A4	4	4.0
15	2	M	67	HCV	A5	1	A4	2	4.9
Total[2]	2.7 (2–5)	10/5	73.2 (63–86)	12/2/1	9/4/1	8/7	8/7	73.2 (2-581)	4.1 (3.2–4.7)

[1] HCC: Hepatocellular carcinoma; HCV: hepatitis C virus; HBV: hepatitis B virus; NBNC: non-HBV non-HCV; Alc: Alcohol abuse; BCLC: Barcelona Clinic Liver Cancer; ALBI:albumin–bilirubin; AFP: alpha-fetoprotein; ALB: Albumin; M:male; F:female.

[2] In this line, the order for etiology is HCV, NBNC, and Alc; for Child–Pugh grade, the order is A5, A6, and B8; while for BCLC stage, it is A4 and B1.

Table 2

Baseline characteristics of RFA and SBRT treatment on different multifocal lesions[1].

Patient No.	Lesion No.	Size (mm)	Segmental location	Treatment modalities	Reason for choosing SBRT
1	1	11	5	RFA	Close to diaphragm and hepatic vein
	2	40	7	SBRT	
2	3	22	2	RFA	Close to dome of diaphragm
	4	25	8	SBRT	
3	5	18	7	RFA	Adjacent to portal vein
	6	33	8	SBRT	
4	7	13	8	RFA	Unavoidable hepatic vein (> 3 mm in diameter) in puncture path
	8	11	8	RFA	
	9	7	8	RFA	
	10	14	1	SBRT	
	11	11	1	SBRT	
5	12	10	5	RFA	Adjacent to portal vein
	13	14	2	SBRT	
6	14	12	8	RFA	Large size and close to dome
	15	12	8	RFA	
	16	40	8	SBRT	
7	17	18	6	RFA	Close to dome of diaphragm
	18	20	4	SBRT	
8	19	18	3	RFA	5 mm distance from heart
	20	9	8	RFA	
	21	10	8	RFA	
	22	17	4	SBRT	
9	23	20	8	RFA	Close to dome of diaphragm
	24	10	4	RFA	
	25	8	8	RFA	
	26	11	8	SBRT	
10	27	21	3	RFA	Close to dome of diaphragm
	28	17	7	SBRT	
11	29	16	8	RFA	Undetectable in US and unclear in CEUS
	30	22	7	SBRT	
12	31	11	6	RFA	Close to dome of diaphragm
	32	32	8	SBRT	
13	33	10	7	RFA	Close to dome of diaphragm
	34	17	7	SBRT	

[1] HCC: Hepatocellular carcinoma; RFA: radiofrequency ablation; SBRT: stereotactic body radiotherapy; US: ultrasound; CEUS: contrast-enhanced US.

[2] In this line, the order of segmental location is 1 to 8. The order of treatment modalities was RFA and SBRT. The value of size is displayed as mean and range.

Patient No.	Lesion No.	Size (mm)	Segmental location	Treatment modalities	Reason for choosing SBRT
14	35	17	8	RFA	Close to dome of diaphragm
	36	17	8	RFA	
	37	8	4	SBRT	
15	38	15	6	RFA	Close to heart
	39	10	3	SBRT	
Total [2]	/	16.6 (7–40)	2/2/3/4/2/3/6/17	23/16	/

[1] HCC: Hepatocellular carcinoma; RFA: radiofrequency ablation; SBRT: stereotactic body radiotherapy; US: ultrasound; CEUS: contrast-enhanced US.

[2] In this line, the order of segmental location is 1 to 8. The order of treatment modalities was RFA and SBRT. The value of size is displayed as mean and range.

Tumor Response and Prognosis

Table 3 shows that according to mRECIST, at the end of one-year's follow-up, the numbers (rate) of one-year complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) were 11 (73.3%), 0 (0%), 1 (6.7%), and 3 (20%), respectively (Fig. 2). Three PD came from one local tumor progression (No. 12 patient in Table 3, developed from incompletely-treated RFA, shown in Fig. 3), and two intrahepatic distance recurrences occurred at 12 and 2.8 months (No. 3 and 14 patients in Table 3, respectively). According to mRECIST, as the local recurrence satisfied the criteria of a more than 20% increase in size, it was counted as PD. Because of this local recurrence at 4.2 months, the 1-year local control was 97.4% (38 of 39 lesions). During the follow-up one year later, six additional intrahepatic distance recurrences (after achieving CR) and one local tumor response (developed from incomplete treated SBRT after a SD) were detected. The cumulative numbers of local tumor progression and intrahepatic distance recurrence in the whole follow-up were 2 and 8 out of 15 patients, respectively. The 1- and 2-year PFS rates were 80% and 52.5%, respectively (Fig. 4). The median time to progression was 20.1 (2.8–45.1) months. One female patient (No. 2) suffered from multiple intrahepatic distance recurrences and eventually died from the rapid progress of HCC due to portal vein tumor thrombus in 30 months. With a median follow-up period of 31.3 (15.1–71.9) months, the other 14 patients were still alive at the endpoint of follow-up (26 August 2020). The 1- and 2-year OS rates were 100% (15/15) and 89.9% (8/9), respectively.

Table 3

Positive and adverse effects of RFA and SBRT treatment on different multifocal lesions[1].

No.	Treatment intervals	Possible adverse reaction						Possible patient benefit			
	(days)[2]	leukocytes	platelets	AST	ALT	T-BIL	ALBI stage	Tumor response[3]	Recurrence type	PFS (months)	OS (months)
1	−12	↓	N	↑	N	↑	N	CR	IDR	44.8	71.9
2	20	↓	N	N	N	N	N	CR	IDR	15.6	30.0
3	26	↓	N	N	N	N	N	PD	IDR	12.0	60.9
4	34	N	N	N	N	N	N	CR	IDR	28.7	61.2
5	20	↓	N	N	N	↑	N	CR	No	58.8	58.8
6	−4	N	N	N	N	N	N	CR	IDR	24.7	46.2
7	−11	↓	↓	N	N	N	N	CR	IDR	20.1	31.3
8	19	N	↓	N	N	N	First↓then↑	CR	No	34.1	34.3
9	45	N	N	N	N	↑	N	CR	IDR	17.1	34.3
10	48	↓	N	N	N	N	↓	SD	LTP	13.0	23.9
11	48	↓	N	N	N	N	N	CR	No	23.3	23.3
12	60	N	N	N	N	N	First↓then↑	PD	LTP	4.2	15.1
13	13	N	↓	N	N	N	N	CR	No	16.9	16.9
14	41	N	↓	↑	↑	N	First↓then↑	PD	IDR	2.8	18.5
15	55	N	N	N	N	↑	N	CR	No	22.5	22.5
Total[4]	26 (4–60)	/	/	/	/	/	4/11	11/0/1/3	2/8/5	20.1 (2.8–45.1)	31.3 (15.1–71.9)

[1] AST: glutamic oxaloacetic transaminase; ALT: glutamic pyruvic transaminase; T-BIL: total bilirubin; AFP: alpha-fetoprotein; PFS: progression-free survival; OS: overall survival; ALBI: albumin–bilirubin; CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; LTP: local tumor progression; IDR: intrahepatic distant recurrence.

[2] Here, a positive value indicates RFA was performed before SBRT, while negative values indicate that SBRT was performed before RFA.

[3] The tumor response was evaluated one year after the latter treatment (either RFA or SBRT).

[4] In this line, the order of ALBL is abnormal and normal. The order of tumor response is CR, PR, SD, and PD. The order of recurrence type is LTP, IDR, and no recurrence. The value of treatment intervals, PFS, and OS are displayed as median and range.

Adverse Effects

As shown in Table 3, in terms of the hematologic toxicity, slight (unmultiplied) reductions in leukocytes and platelets counts were found in 46.7% (7/15) and 26.7% (4/15) patients, respectively. In terms of hepatotoxicity, the elevation rates of ALBI grade from one week to 3–5 months post-treatment was 28.5% (4/15). Among them, three patients first demonstrated an increase and then a decline in ALBI grade, whereas the grade deteriorated in the remaining patient in measurements at two different time point. For the other 11 patients, the ALBI grade showed no change after treatment. After 5 months, the abnormal values of laboratory parameters, which suggested the hematologic and hepatocyte toxicity, were reversed by conservative and supportive treatment in follow-up (data not shown).

Discussion

HCC cannot be controlled completely by single treatment even using transplantation. Multi-modality treatment strategies are thus recommended [5]. So far, this study is the first to report the application of RFA and SBRT treatment for different HCC lesions coexisting in the same patients, typically as a curative strategy for patients with relatively good liver reservation (BCLC stage A4–B1). Most of the lesions treated by SBRT in our study were located in segment seven and eight, which are blind areas hidden by the lung gas during the patient's deep breathing (nine cases). Other conditions included lesions adjacent to main portal or hepatic vein (three cases), located close to the heart (two cases), and had poor conspicuity in US and contrast-enhanced ultrasound images (one case). As the risk for insufficient ablation and difficult operation are predictable, we directly planned SBRT as the foremost treatment for these lesions, other than previously using SBRT as a salvage therapy after incomplete RFA

performance [18, 20], which yielded a 1–3 years' local control rate of 81.8–86.6% and OS rate of 85.4–85.6%. Comparatively, our therapy achieved a much better treatment effect with a high 1-year local control rate (97.4%), a promising prognosis with an acceptable 1-year PFS (80%), and a higher OS rate (100% and 89.9% for 1 and 2 years, respectively). Given the feasibility and effectiveness of our RFA and SBRT treatment on different multifocal HCCs, this novel treatment strategy might be indicated for cases for which RFA is contraindicated.

Regarding HCCs primarily with sufficient hepatic reserve (Child–Pugh A), the reported adverse events with grade ≥ 3 for RFA treatment are mainly related to mechanical or thermal damage, which include pneumothorax, pleural hemorrhage, sepsis, duodenal and colonic perforation, hepatic hemorrhage, biliary fistula, and skin burn [16, 28]. For SBRT treatment, the reported adverse events (grade ≥ 3) mainly include radiation-induced liver disease of hepatomegaly and anicteric ascites, gastrointestinal bleeding, and duodenal ulcer [16]. Before this study was conducted, we speculated that our SBRT and RFA treatment strategy may cause cumulative adverse effects because of the short treatment intervals between RFA and SBRT (4–60 days). Abdominal compression, radiation at SBRT treatment, and ablation at RFA treatment might result in anatomical deformation in both the treated zone and surrounding liver tissues [26, 29]. From this perspective, if the two lesions close to each other, the first treatment operation (especially if the SBRT is carried out first) may change the location, shape, and texture of the lesions, thus increasing the difficulty of the later treatment. High doses of radiation stimulation from SBRT treatment cause some degree of reactive hyperemia, hepatic cell loss, hyperplasia, or parenchymal fibrosis [26, 29]. However, unexpectedly, our novel RFA and SBRT treatment exhibited no adverse grade 3 + events. The hematologic and hepatocyte toxicities were mild and could be well controlled (reversed by conservative and supportive treatment). In this context, we think that this novel treatment strategy is safe. The adverse effects were comparable with or even lower than those of using RFA and SBRT alone (reported adverse events of grade 3 + for RFA and SBRT treatment alone are 2.6–11% and 1.6–5%, respectively [11, 16, 31]).

Radiological examinations were performed every three months in the first year of follow-up, every 3–6 months in the second year, and every 6–12 months in the subsequent years depending on the clinical needs [30]. Notably, because of reactive hyperemia by high-dose radiation stimulation, AP hyperenhancement can occur after SBRT in successfully treated HCCs and may not represent residual viable tumor. The irradiated zone after SBRT treatment usually shows as AP hyperenhancement that could be easily mistaken as a recurrence or mask a PR/CR [32]. Mendiratta-Lala et al. [33] found that 78% (39/50) of SBRT-treated lesions that had shown persistent AP hyperenhancement in MR images at 3–6 months gradually disappeared in the first 12 months of follow-up. Considering the possible interference of radiation-induced inflammation in the accurate judgement of recurrence, in our study, the tumor response was evaluated at the end of one-year's follow-up.

For HCCs less than 2 cm, the initial CR rates of RFA treatment were reported to be as high as 96% [18]. Unfortunately, in the case of multinodular or large HCC lesions, the initial CR sharply drops to almost 50% [18]. Insufficient RFA would possibly promote the proliferation of residual HCCs [34], accelerate metastasis in a variety of ways [35], and further contribute to a lower OS rate in patients with HCCs treated by RFA [36]. Because RFA does not remove the corresponding hepatic segment fed by the tumor-bearing portal tributaries [37], arterioportal fistula and intratumoral shunt develop, intratumoral pressure suddenly increases during RFA treatment, resulting in the intravascular spread of tumor cells [36]. In this setting, the satellite foci around the target lesions possibly progress after the RFA operation. Reportedly, histopathological examinations identified satellite foci in 44% of RFA-treated HCC lesions during follow-up [38]. Our novel treatment strategy had a favorable therapeutic effect on many aspects such as CR rate, PFS rate, local control rate, and OS rate. We speculate that as the lesions treated by SBRT and by RFA were located close to one another (60% lesions were in the same or adjacent segments), SBRT after RFA may inhibit the progression of satellite foci around the RFA-treated lesions, as SBRT provides 60–80% of the radiation dose to the surrounding area of the target lesions (Fig. 2). This explanation needs to be verified through in-depth research and reliable data.

The first limitation of our study is the small number of patients and its retrospective nature. If a prospective study is planned with large sample size, the results regarding adverse effects and prognosis might be different. Secondly, as a preliminary attempt with a novel therapy, this study was not elaborately organized with a control group and statistical analysis. The comparison of effectiveness with previously published articles may have an underlying problem of heterogeneity between different studies. Lastly, we excluded the lesions with a non-hyperenhanced appearance in the AP of radiological examination. Most HCC-related guidelines do not allow a definitive diagnosis of HCC without AP hypervascularity (even though high-risk patients with liver cirrhosis or chronic B/C hepatitis show hypointense appearance in hepatobiliary phase) [39]. According to the mRECIST, evaluating viable target lesions for tumor response after locoregional treatment is only applicable to AP hypervascular/ hyperenhanced lesions [27]. Therefore, unfortunately, the feasibility and its effectiveness of our novel treatment strategy may not apply to non-hypervascular HCC lesions.

Conclusions

This study is unique as we are the first to describe a feasibility of applying RFA and SBRT treatment in different multifocal lesions in one patient. The good tumor response and survival, low recurrence, and acceptable tolerance of adverse effects suggest the efficacy and feasibility of this novel treatment strategy. Nonetheless, to confirmed application with confidence in clinical practice, a well-designed study with a large sample size and strictly selected control group must be conducted.

Abbreviations

HCC: Hepatocellular carcinoma; SBRT:stereotactic body radiotherapy; RFA:radiofrequency ablation; BCLC:Barcelona Clinical Liver Cancer; PFS: progression-free survival; OS: overall survival; ALBI: albumin–bilirubin; CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; mRECIST: modified Response Evaluation Criteria in Solid Tumors; AP: arterial phase; ALT: serum alanine transaminase, AST: aspartate transaminase; T-BIL: total bilirubin; ALB: albumin; ALBI: albumin–bilirubin.

Declarations

Ethics approval and consent to participate

This study was conducted with the approval of institutional review board of Medical Center of Yokohama City University (approval number: B170200026) and Ofuna Chuo Hospital (approval number: 2016-016).

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available

from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Not applicable.

Authors' Contributions

Conceptualization, K.N.; methodology, W.F.; validation, A.T.; formal analysis, Y.T.; investigation, H.N. and K.O.; data curation, M.C. and H.F.; writing—original draft preparation, K.O. and W.F.; writing—review and editing, K.H. and K.N.; visualization, A.T.; supervision, S.M. All authors critically reviewed the manuscript, and all approved the final version submitted for publication.

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Figures

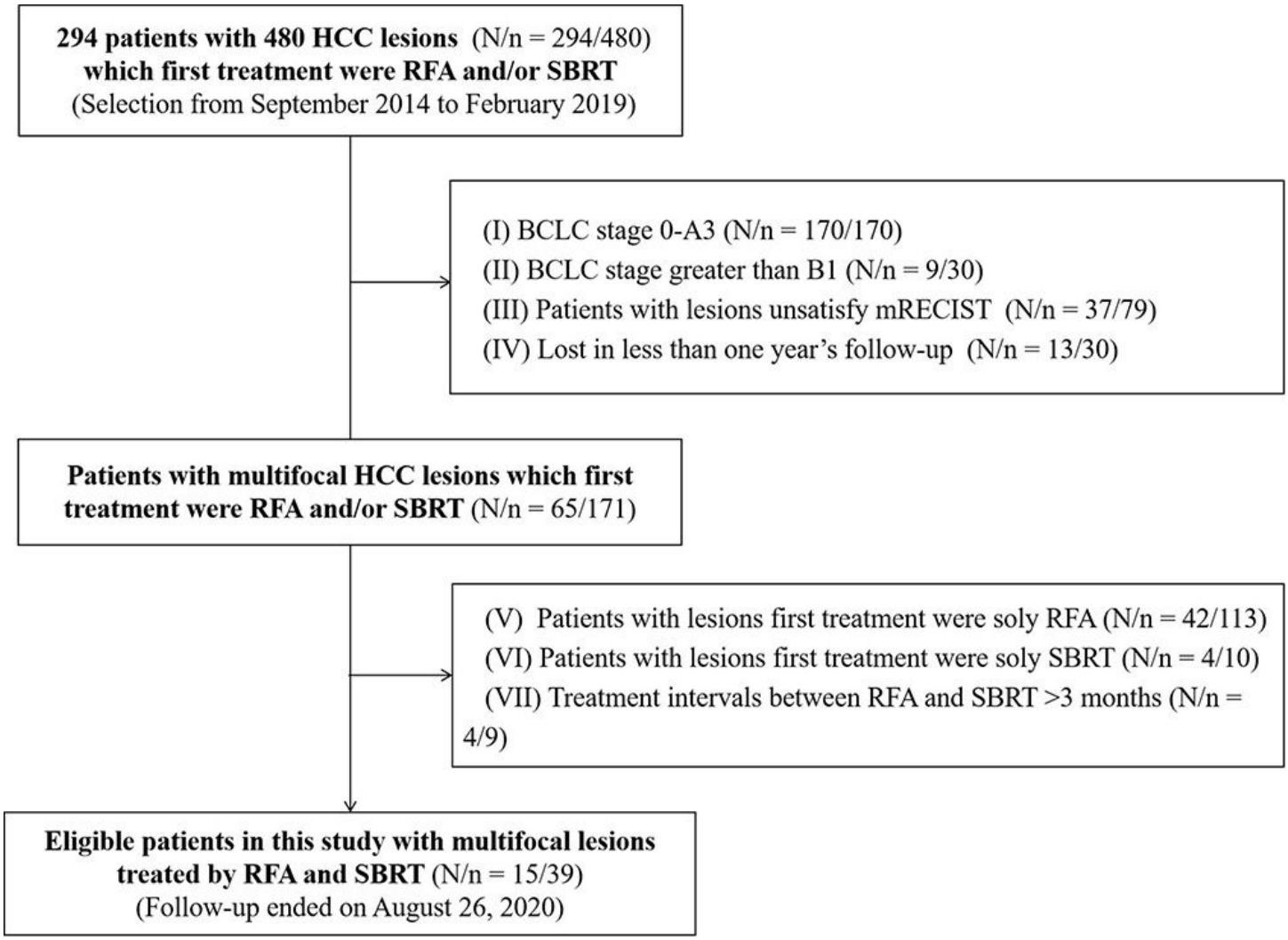

Figure 1

Flowchart of the study population. In total, 39 and 16 lesions and patients were finally used for data analysis, respectively. One exclusion criteria (III) indicates that the patient had all small lesions (less than two lesions ≥1 cm) and failed to show pre-treatment enhancement on the arterial phase of CT or MRI examination. Abbreviations: HCC: hepatocellular carcinoma; RFA: radiofrequency ablation; SBRT: stereotactic body radiotherapy; BLCL:Barcelona Clinical Liver Cancer; mRECIST: modified Response Evaluation Criteria in Solid Tumors.

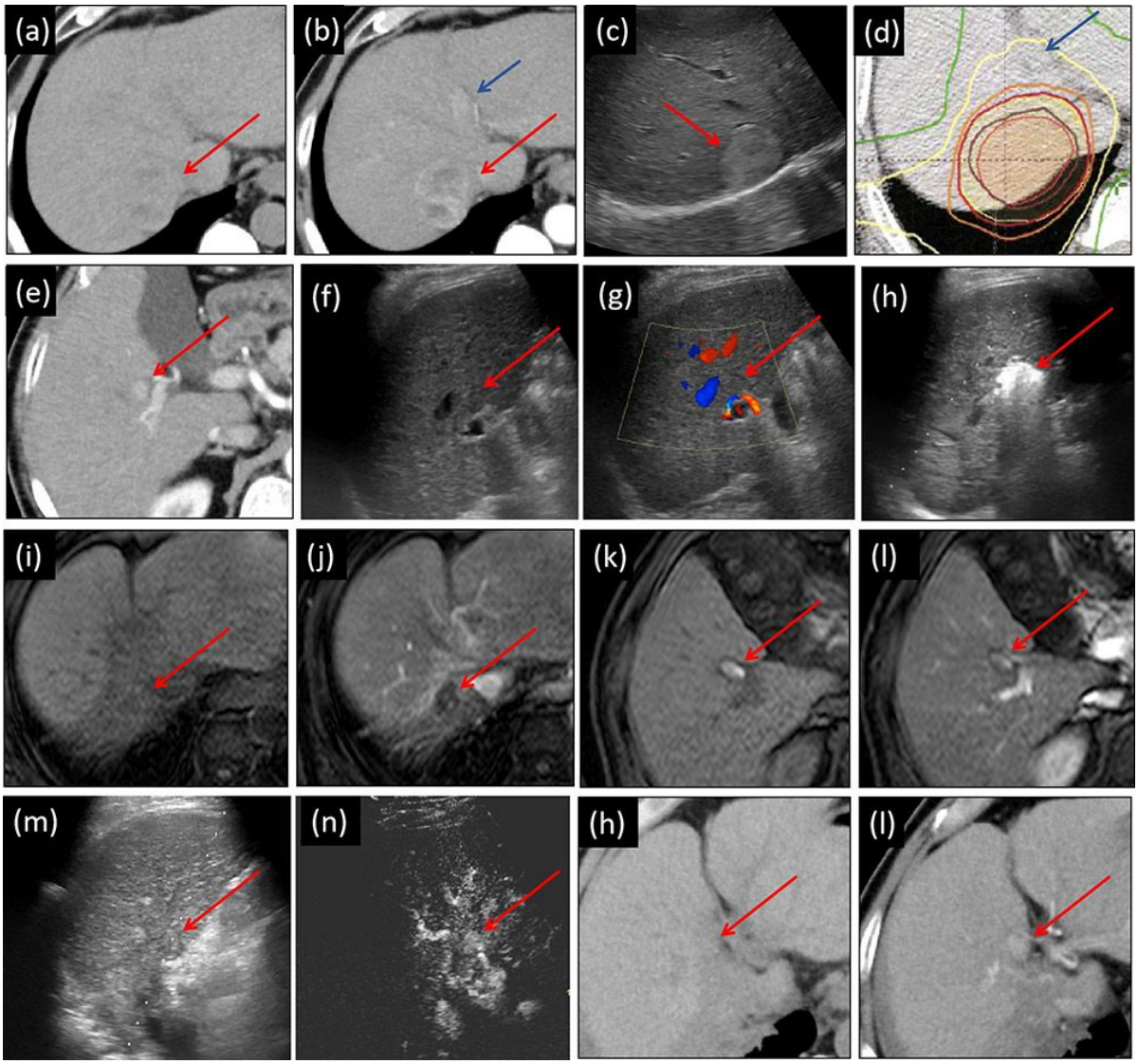

Figure 2

A case of complete tumor response and intrahepatic distal recurrence. (a,b) A 40 mm lesion in segment (S)7 was planned for SBRT, showing unenhanced CT and arterial phase (AP) of contrast-enhanced CT images, respectively. The lesion was partial hyperenhanced. (c) Grayscale ultrasound (US) image shows the lesion in S7 located adjacent to the diaphragm and hepatic vein. It was estimated that ablation would be risky because of its location. The lesion was well-defined and with a nodule-in-nodule appearance. (d) A dose distribution picture of SBRT treatment plan was generated. A total dose of 40 Gy (red isodose line) was delivered in 5 fractions. The central part received 55 Gy radiation. (e) An 11 mm lesion located in S5 was detected in the AP of the contrast-enhanced CT image. (f,g) Grayscale US and color Doppler flow image of the lesion. (h) Grayscale US image in the process of RFA. (i,j) Compared with unenhanced T1-weighted MR image (i), at the one-year follow-up, the SBRT-treated area considerably decreased and changed into totally hypoenhancement (j). (k,l) At the one-year follow-up, the RFA-treated area changed into hyperenhanced scars in both the unenhanced T1-weighted image (k) and the AP of Gadolinium-Ethoxybenzyl-Diethylenetriamine Pentaacetic Acid MRI (EOB-MRI) (l). (m,n) After 44.8 months' follow-up, a new 10 mm lesion was detected in S4. In grayscale US (m), it appeared as slightly hyperechoic and poorly defined. In the AP of contrast-enhanced US (n), the lesion displayed hypervascularity. In the unenhanced CT(h) taken as a reference, the AP of the contrast-enhanced CT image (l) showed hyperenhancement. Red arrows in (a–c) and (e–l) indicate the location of the target lesion or post-treated area. Dark blue arrows in (b) and (d) show the approximate position of the S7 lesion. This case corresponds to the No. 1 patient shown in the tables.

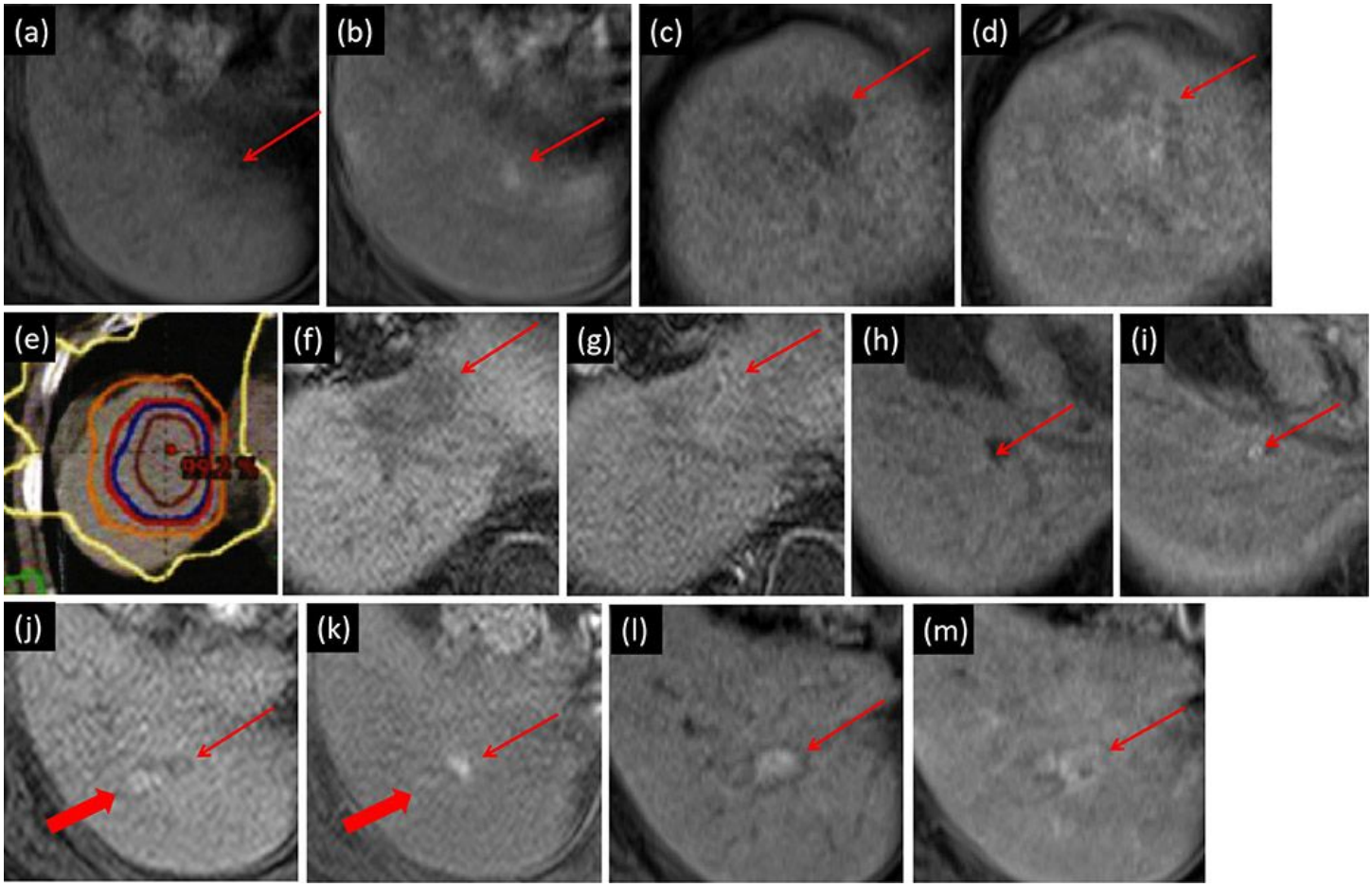

Figure 3

A case of progressive tumor disease and local tumor progression. (a,b) RFA was planned for an 11 mm lesion in segment (S)6, showing unenhanced T1-weighted image and AP of EOB-MRI, respectively. The lesion was hyperenhanced. (c,d) A 32 mm lesion located in S8 was visible in both the T1-weighted image (c) and the AP of the EOB-MR image (d). Because of blind areas hidden in the lung gas, RFA treatment was impossible. (e) A dose distribution picture of SBRT treatment plan was generated. As this lesion was located adjacent to the gastrointestinal tract, radiotherapy with mild hypofractionation was performed. The total dose of 42Gy (red isodose line) was delivered in 14 fractions. The central part received 60 Gy radiation. (f,g) Compared with the unenhanced T1-weighted MR image (f), at the one-year follow-up, the SBRT-treated area changed to isoenhancement (g). There was a slight liver deformation caused by radiation irritation due to SBRT treatment. (h,i) About one month after RFA treatment, in the unenhanced T1-weighted image (h) and the AP of the EOB-MR image (i), the ablation area showed scars from treatment but no appearance of recurrence. (h–k) However, a T1-weighted image was taken (h) as a reference at the 4 months' follow-up. A hyperenhanced area, just adjacent to the initial ablated area (thick arrow, hyperenhanced scars of ablated trace), was found in the AP of the EOB-MRI (k). The local recurrence was repeatably treated by RFA. (l,m) Two months after the second RFA treatment, the ablated area appeared as hyperenhanced scars in both the unenhanced T1-weighted image (l) and the AP of the EOB-MRI (m). Thin arrows in (a–d) and (f–m) indicate the location of the target lesion or post-treated area. This case corresponds to the No. 12 patient shown in the three tables.

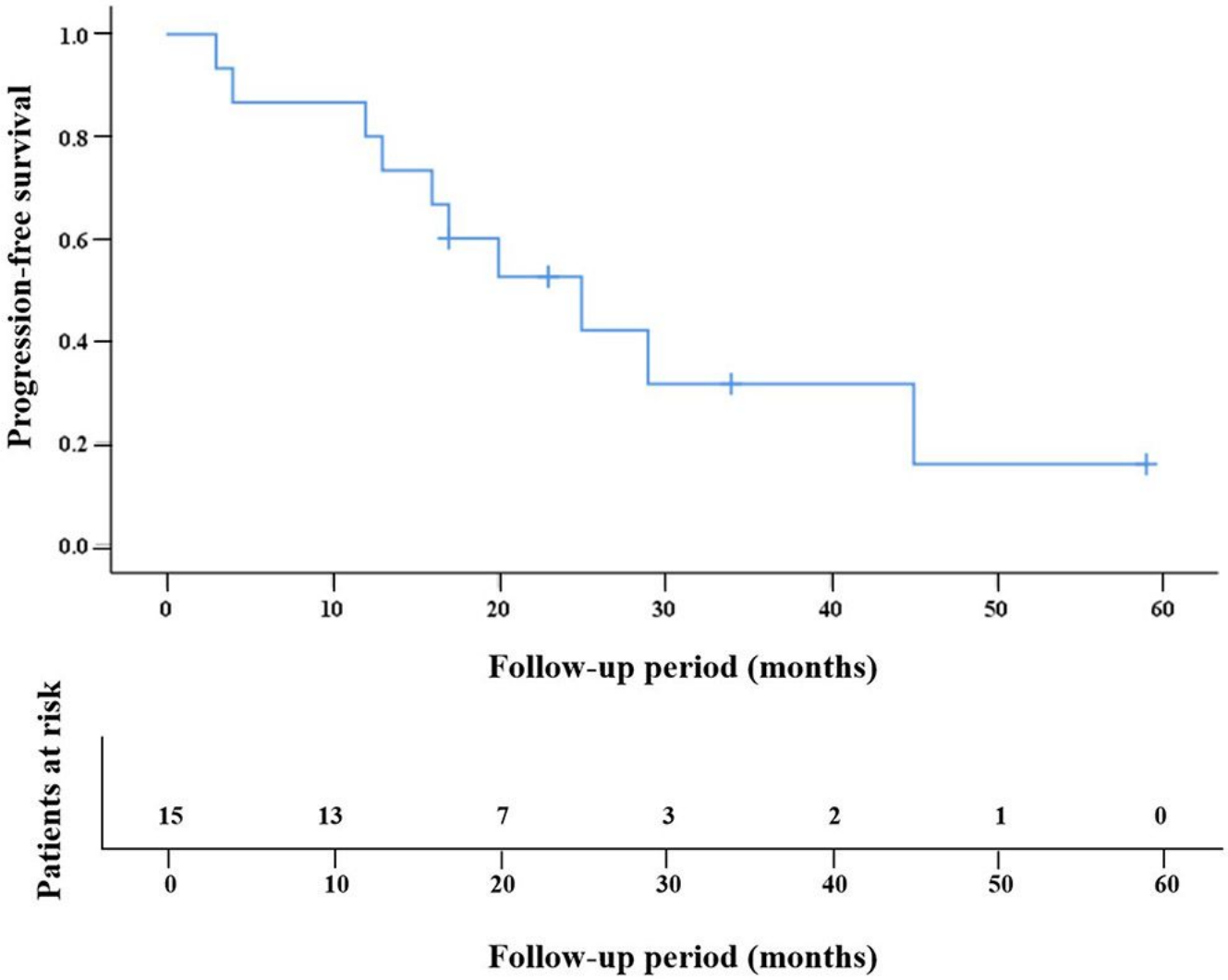

Figure 4

Progression-free survival (PFS) of our novel RFA and SBRT treatment strategy for 15 patients.

Supplementary Files

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