




# Stereotactic body radiotherapy in patients with hepatocellular carcinoma in a multimodal treatment setting

Sabine Gerum<sup>1,5</sup> · Christian Heinz<sup>1</sup> · Claus Belka<sup>1</sup> · Franziska Walter<sup>1</sup> · Philipp Marius Paprottka<sup>2</sup> · Enrico N De Toni<sup>3</sup> · Falk Roeder<sup>1,4,5</sup> 

Received: 17 April 2019 / Accepted: 23 October 2019 / Published online: 15 November 2019  
© Springer-Verlag GmbH Germany, part of Springer Nature 2019

## Abstract

**Purpose** Retrospective evaluation of stereotactic body radiation therapy (SBRT) in patients with hepatocellular carcinoma (HCC).

**Methods** We retrospectively analyzed 36 patients (45 lesions) treated between 2011 and 2017. Twenty-seven had previous treatments. Current treatment consisted of SBRT alone ( $n=15$ ) or selective transarterial chemoembolization (TACE) followed by SBRT to the same lesions ( $n=21$ ). Eight patients received additional local treatments to different lesions. Liver function was predominantly moderately restricted (Child A: 29, Child B: 6, Child C: 1). Treatment planning was based on 4D-computed tomography, dose/fractionation varied depending on location and size, most commonly 3 fractions of 12.5 Gy (65% isodose) and 5 fractions of 8 Gy (80% isodose).

**Results** Median follow-up was 15 months. Local recurrence was observed in 3 lesions (7%), resulting in 1- and 2-year local control rates of 93%. The only significantly predicting factor was the use of abdominal compression. New hepatic lesions occurred in 19 patients (52%), 1- and 2-year freedom-from-hepatic-failure (FFHF) was 39% and 32%, respectively. Only the number of treated lesions was predictive for FFHF. Sixteen patients have died, resulting in 1- and 2-year overall survival (OS) of 64% and 41%, respectively, significantly impacted by the number of treated lesions and Child–Pugh class. Severe acute and late toxicity ( $\geq$ grade 3) was observed in 3% and 8%, respectively. 6 patients (17%) received liver transplantation (OLT) after SBRT, of whom 5 showed pathological complete remission.

**Conclusion** SBRT ( $\pm$ TACE) in highly pretreated HCC is effective and associated with excellent LC and low toxicity. SBRT may be used as definitive or bridging treatment prior to OLT. Patients with multifocal lesions have significantly decreased 1- and 2-year FFHF and OS.

**Keywords** Liver · Hepatocellular carcinoma · Stereotactic body radiation therapy · Orthotopic liver transplantation · Multimodal treatment

**Availability of data and materials** The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Sabine Gerum  
s.gerum@salk.at

Christian Heinz  
christian.heinz@med.uni-muenchen.de

Claus Belka  
claus.belka@med.uni-muenchen.de

Franziska Walter  
franziska.walter@med.uni-muenchen.de

Philipp Marius Paprottka  
philipp.paprottka@tum.de

Enrico N De Toni  
Enrico.deToni@med.uni-muenchen.de

✉ Falk Roeder  
f.roeder@salk.at

<sup>1</sup> Department of Radiation Oncology, University Hospital LMU Munich, Marchioninstr. 15, 81377 Munich, Germany

<sup>2</sup> Department of Interventional Radiology, University Hospital TU Munich, Ismaninger Str. 22, 81675 Munich, Germany

<sup>3</sup> Department of Internal Medicine, University Hospital LMU Munich, Marchioninstr. 15, 81377 Munich, Germany

<sup>4</sup> CCU Molecular Radiation Oncology, German Cancer Research Center, Heidelberg, Germany

<sup>5</sup> Department of Radiotherapy and Radiation Oncology, Paracelsus Medical University Salzburg, Landeskrankenhaus, Müllner Hauptstraße 48, 5022 Salzburg, Austria

## Stereotaktische Bestrahlungstherapie bei Patienten mit hepatozellulärem Karzinom im Rahmen multimodaler Behandlung

### Zusammenfassung

**Ziel** Ziel war die retrospektive Evaluation der Bestrahlungstherapie mittels Körperstereotaxie (SBRT) beim hepatozellulären Karzinom (HCC).

**Methoden** Die retrospektive Analyse umfasst 36 Patienten (45 Läsionen), welche zwischen 2011 und 2017 behandelt wurden. Lokale Vorbehandlungen erhielten 27 Patienten. Aktuell wurden 15 Patienten mittels alleiniger SBRT und 21 mittels SBRT nach selektiver transarterieller Chemoembolisation (TACE) der gleichen Läsion behandelt. Bei 8 Patienten erfolgten zusätzlich lokale Behandlungen anderer Läsionen. Die Leberfunktion war überwiegend gering eingeschränkt (Child A: 29, Child B: 6, Child C: 1). Die Therapieplanung erfolgte mittels 4-D-Computertomographie, die Dosis/Fraktionierung war abhängig von Lokalisation und Größe, üblicherweise  $3 \times 12,5$  Gy (65%-Isodose) oder  $5 \times 8$  Gy (80%-Isodose).

**Ergebnisse** Die mediane Nachbeobachtungszeit betrug 15 Monate. Es traten 3 Lokalrezidive auf (7%) auf, die Ein- und 2-Jahres-Lokalkontrollrate betrug 93%. Der einzige signifikante prädiktive Faktor war die Verwendung einer Bauchpresse. Bei insgesamt 19 Patienten (52%) traten neue hepatische Läsionen auf, das leberspezifische krankheitsfreie Ein- und 2-Jahres-Intervall (FFHF) betrug 39% bzw. 32%. Lediglich die Zahl der behandelten Läsionen zeigte sich als prädiktiv für das FFHF. Es starben 16 Patienten, das Ein- und 2-Jahres-Gesamtüberleben (OS) betrug 64% bzw. 41%. Die Anzahl der behandelten Läsionen und die Child-Pugh-Klasse waren signifikant mit dem OS assoziiert. Schwere akute oder späte Nebenwirkungen ( $\geq$ Grad 3) traten bei 3% bzw. 8% der Patienten auf. Bei 6 Patienten (17%) wurde eine Lebertransplantation nach SBRT durchgeführt, hiervon zeigten 5 eine komplette pathologische Remission.

**Schlussfolgerung** Die SBRT ( $\pm$ TACE) bei multipel vorbehandeltem HCC ist effektiv, toxisitätsarm und erzielt eine exzellente Lokalkontrolle. Sie eignet sich als definitive Therapiealternative oder als Überbrückung vor Lebertransplantation. Patienten mit multifokalen Herden zeigten ein signifikant reduziertes Ein- und 2-Jahres-FFHF und -OS.

**Schlüsselwörter** Leber · Hepatozelluläres Karzinom · Körperstereotaktische Bestrahlungstherapie · Orthotope Lebertransplantation · Multimodale Therapie

### Abbreviations

4D-CT	four-dimensional computed tomography
AFP	alpha-fetoprotein
BCLC	Barcelona Clinical Liver Cancer
BED	biologically effective dose
CBCT	cone beam computed tomography
ccm	cubic centimeters
CP class	Child–Pugh class
CT	computed tomography
CTCAE	Common Toxicity Criteria for Adverse Events
FFHF	freedom from hepatic failure
GTV	gross tumor volume
HCC	hepatocellular carcinoma
IF	in-field
IMRT	intensity-modulated radiation therapy
ITV	internal target volume
KPS	Karnofsky performance score
LC	local control
LR	local recurrence
MRI	magnetic resonance imaging
OLT	orthotopic liver transplantation
OS	overall survival
pCR	pathologic complete response
PFS	progression-free survival
pPR	pathologic partial response

PTV	planning target volume
RFA	radiofrequency ablation
RILD	radiation-induced liver disease
SBRT	stereotactic body radiation therapy
SIRT	selective internal radiotherapy
TACE	transarterial chemoembolization

### Background

Primary liver tumors are among the most common malignancies and tumor-related causes of death worldwide [1]. Resection or orthotopic liver transplantation (OLT) are the main curative treatment options, with 5-year survival rates of up to 60% after resection and 50–70% after transplantation [2]. Unfortunately, many patients are not suitable for resection due to comorbidities, poor liver function, major vascular involvement or multifocal spread of disease [1, 3]. According to common guidelines, locoregional therapies should be considered in these patients as definitive treatment or as bridging in patients awaiting liver transplantation [4]. Locoregional treatments are broadly categorized into arterially directed therapies (transarterial chemoembolization [TACE], transarterial chemoembolization with drug-eluting beads [DEB-TACE], or selective internal radiother-

apy [SIRT]) and into local ablative techniques like radiofrequency ablation (RFA), percutaneous alcohol injection, microwave ablation, or minimally invasive stereotactic body radiotherapy (SBRT). Each of these treatments has its limitations and must be weighed in particular against the anticipated remaining liver function, the extent and location of the disease, and the existing co-morbidities. For example, lesions directly adjacent to major vessels or bile ducts are not well suited for RFA [5, 6] and patients with portal vein thrombosis are not eligible for TACE [2, 6]. Radiotherapeutic treatment paradigms have changed in the last decades in favor of highly conformal and precise treatment techniques such as intensity-modulated radiotherapy (IMRT) and stereotactic body radiation therapy (SBRT). The latter is a highly conformal technique delivering large doses in a small number of fractions [5]. It sufficiently spares dose to adjacent organs at risk due to its sharp dose fall-off outside the target, resulting in low toxicity rates, especially regarding radiation-induced liver disease (RILD), compared to the historical reports using conventional radiation therapy techniques [7–10]. Due to the enhanced biological effectivity of large single doses, adequate tumor control is maintained, as shown by the experience from other body sites [11–13]. For example, in stage I lung cancer, SBRT has shown to result in at least equal local control and overall survival rates compared to surgery [14]. After its first description in HCC patients by Bloomgren et al. in 1995 [15], liver SBRT has gained increasing attraction in the last decade mainly due to its low toxicity profile. Several retrospective studies have shown encouraging outcomes, with low to moderate toxicity and high local control rates (1 year LC: 90–100%) [1], but no randomized trials comparing SBRT to other local treatment options have been conducted so far and only scarce prospective data on the employment of SBRT in the treatment of HCC are available. Moreover, no generally accepted criteria for patient selection or a generally accepted dose and fractionation concept exists. We therefore report our experience with SBRT with or without prior selective TACE to the same lesion in patients with HCC.

## Methods

SBRT has been implemented for HCC treatment at our center in 2011. Patient numbers steadily increased in the following years, with most of the included patients treated since 2015. For the current analysis, we retrospectively analyzed all HCC patients who underwent SBRT to 1–2 liver lesions.

## Patient evaluation

Pretreatment investigations included at least MRI and/or contrast-enhanced multiphasic liver CT, CT staging to exclude distant metastases, and liver function tests. The indication for SBRT was seen in patients ineligible for other local treatment options (except TACE) or in case of multifocal HCC in combination with other local treatments. SBRT was scheduled based on multidisciplinary evaluation as a definitive treatment or bridging prior to planned orthotopic liver transplantation (OLT). The decision for listing was made by an interdisciplinary transplant board (without the presence of a radiation oncologist) based on internationally accepted criteria (Milan criteria, Model for End-Stage Liver Disease = MELD score) and legal considerations regarding transplant surgery. Patients suitable for OLT according to the transplant board decision and able to tolerate major surgery were scheduled for OLT. Afterwards, the decision about the adequate bridging strategy was made by another interdisciplinary board including surgeons, gastroenterologists, medical oncologists, interventional radiologists, and radiation oncologists. The strategy for bridging was chosen based on the size, localization, and number of lesions as well as on patient-related factors such as tolerability of surgery, comorbidities, and performance status, taking into account all possible advantages and disadvantages of the available techniques on an individual basis.

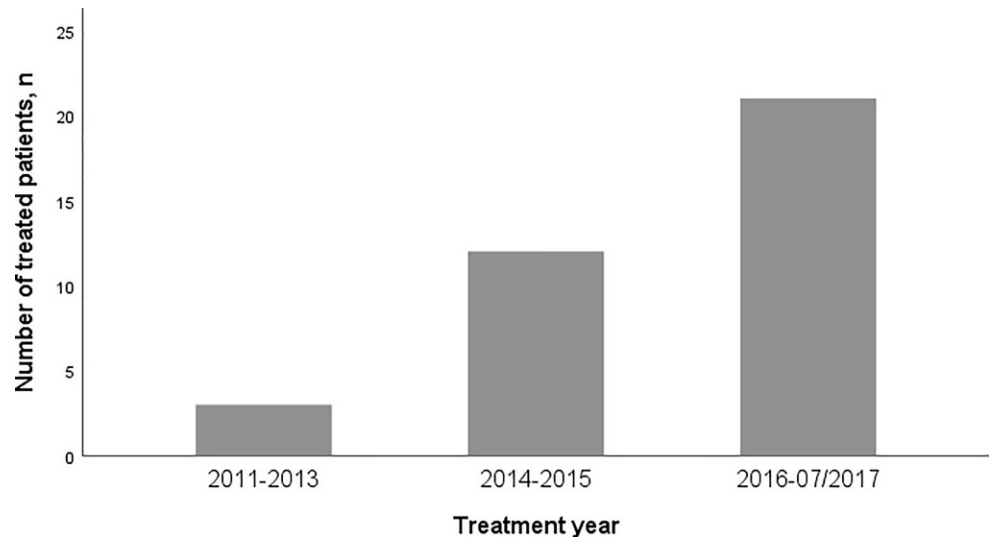
## Treatment

Treatment of the irradiated lesions consisted of SBRT alone in 15 patients, while 21 patients received selective TACE to the same lesions upfront of SBRT (within 6 weeks). Additional local treatments to different lesions within 6 weeks of SBRT were performed in 8 patients. Of these patients, 6 received RFA, one received selective TACE, and one a combination of RFA and TACE. 27/36 patients had a median of 2 (range 1–8) previous local treatments (surgery, RFA, TACE, or SIRT), only 9 patients were treatment naïve. In 9 patients (25%), two lesions were treated at the same time, while 27 patients (75%) received SBRT to one lesion. OLT was performed in 6 patients after SBRT with a median interval of 6 months (range 1–8), including the only patient with Child-Pugh class C (CP C) cirrhosis.

Prior to SBRT, patients usually received CT-guided implantation of 1–3 fiducials (Visicoil™, IBA dosimetry GmbH, Schwarzenbruck, Germany or Gold-Anchor™, MBP Scherer Medizinprodukte, Krustetten, Austria) per lesion ( $n=25$ ), unless enhancement of lipiodol in patients with prior TACE ( $n=11$ ) was deemed sufficient to guide the procedure.

Patients were immobilized using a vacuum pillow in combination with an alpha-cradle. Abdominal compression

**Fig. 1** Number of treated patients per year from 2011 to 2017



was implemented in 2014, and since then, only discarded in patients not able to tolerate compression (for example, patients with large herniations after previous surgery). Patients treated prior to 2014 received SBRT using an ITV concept without abdominal compression. In total, 22 patients (66%) were treated with abdominal compression.

Treatment planning was based on contrast-enhanced 4D-CT. Gross tumor volume (GTV) was contoured as the visible tumor on the free-breathing CT and on all respiratory phases of the 4D-CT supplemented by information from MRI, if available. An internal target volume (ITV) was constructed and enlarged by an isotropic margin of 6 mm to obtain the planning target volume (PTV). Dose was generally prescribed to the PTV-surrounding isodose. Dose and fractionation varied dependent on localization, size, motion, and liver function. The most common schemes were 3 fractions of 12.5 Gy prescribed to the 65% isodose (64%) and 5 fractions of 8 Gy to the 80% isodose (22%) delivered every other day. No general difference in dose prescription was made between definitive and bridging treatments. Implanted fiducials or lipiodol enhancement were contoured to receive a fiducial or lipiodol ITV, which was used for daily patient set-up. Treatment was performed using daily CBCT image guidance.

Follow-up examinations (including physical examination, laboratory tests and MRI/CT of the liver) regularly took place at our department or the departments of gastroenterology/oncology every 3 months for the first year, every 6 months for the second year, and annually thereafter.

### Statistical and legal considerations

Acute and late toxicity was scored according to CTCAE v4.03. Acute toxicity included events from the time of

SBRT until 90 days after; late toxicity was defined as events occurring after more than 90 days from SBRT until disease progression. Severe toxicity was defined as  $\geq$  grade 3. Marked deterioration of liver function was defined as an increase in CP class or in case of CP C, as acute liver failure from SBRT until disease progression. Biologically effective dose (BED) at isocenter (maximum dose) was calculated according to the formula  $BED = nd[1 + d/\alpha]$  with  $n$  being the number of fractions,  $d$  the single dose, and  $\alpha = 10$  for tumor control. Local control (LC) was defined as absence of tumor progression in the region of the treated lesion. Freedom-from-hepatic-failure (FFHF) was defined as absence of tumor progression in the liver. All time-to-event data were calculated from the first day of SBRT using the Kaplan–Meier method. All endpoints and subgroup analyses are reported referring to patients (not lesions) unless otherwise specified. Differences in subgroups were assessed by the log-rank test for univariate analysis. Due to the low number of events, multivariate analysis was not performed.  $P$ -values  $< 0.05$  were considered significant. Patients who received OLT after SBRT were censored at the time of transplantation, except for in the comparison of OLT and non-OLT patients. The analysis was in accordance with the declaration of Helsinki in its latest version and was approved by our independent Ethics Committee.

### Results

The majority of included patients had been treated since 2015 (Fig. 1), resulting in a median follow-up of 15 months for the entire cohort (3–73 months).

**Table 1** Patients characteristics

Patients and treatment characteristics	n (%)	
	All patients	OLT patients
Number of patients	36	6
Number of lesions	45	7
Single/multiple lesions	27 (75)/9 (25)	5 (83)/1 (17)
Gender (male/female)	26 (72)/10 (28)	2 (33)/4 (67)
Age (median/range in years)	63/31–83	56/31–63
KPS (median/range in %)	90/60–100	90/70–100
Follow up (median/range in months)	15/3–73	18/7–73
Child–Pugh stage <i>n</i> (A/B/C)	29 (81)/6 (17)/1 (3)	3 (50)/2 (33)/1 (17)
BCLC score (A/B/C/D)	9(25)/12(33)/14(39)/1(3)	3(50)/1(17)/1(17)/1(17)
Fiducials	25 (70)	4 (69)
Sufficient lipiodol enhancement after TACE	11 (30)	2 (33)
Abdominal compression	22 (61)	2(33)
Lesion diameter (median/range in cm)	2.45/1–6	2.8/1–5
GTV per lesion (median/range in ccm)	6.7/0.8–249	6.7/0.8–98.1
PTV per lesion (median/range in ccm)	60.3/14.9–512	67.5/43.2–220.4
Dose concept (3 × 12.5/5 × 8/other in Gy)	23 (64)/8 (22)/5 (14)	5 (83)/0/1 (17)
BED (median/range in Gy)	168/50–168	168/86–168
Current treatment		
SBRT alone	15 (42)	2 (33)
TACE + SBRT (same lesion)	21 (58)	4 (67)
Additional treatments (different lesions)	8 (22)	0 (0)
OLT	6 (17)	6 (100)

*n* number, % percentage, *OLT* orthotopic liver transplantation, *KPS* Karnofsky performance score, *BCLC* Barcelona Clinic Liver Staging System, *TACE* Transarterial chemoembolization, *cm* centimeter, *GTV* gross tumor volume, *PTV* planning target volume, *Gy* Gray, *BED* biologically effective dose, *SBRT* stereotactic body radiation therapy

## Patient characteristics

We analyzed 36 patients with 45 treated lesions. Median age was 63 years (31–83), 72% were male and the median Karnofsky performance score (KPS) was 90% (60–100%). HCC was based on liver cirrhosis in all patients, with a moderately restricted liver function in the majority (Child A: 29 [81%], Child B: 6 [17%], Child C: 1 [3%]). BCLC score was often advanced (BCLC A: 9 [25%], BCLC B: 12 [33%], BCLC C: 14 [39%], BCLC D: 1 [3%]). The main causes of the underlying liver cirrhosis were toxic (28%) and infectious (hepatitis B/C) liver damage (31%), 2 patients had autoimmune hepatitis (6%) and the remaining 13 (36%) had cryptogenic liver cirrhosis. Median GTV volume on free-breathing CT was 6.7 ccm (0.8–249) per lesion and median PTV volume per lesion was 60.3 ccm (14.9–512). For detailed patient characteristics see Table 1.

## Local control

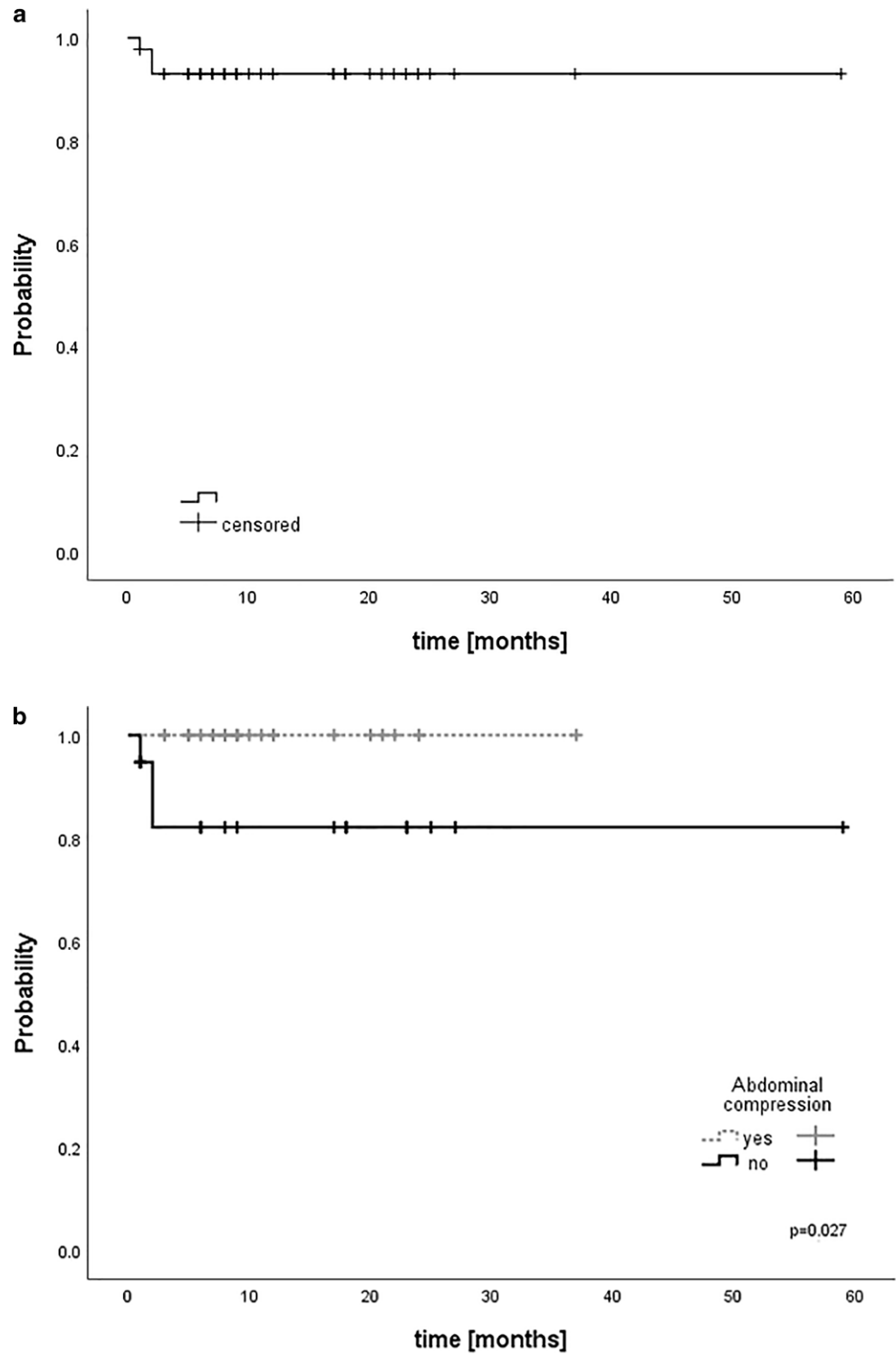
Local recurrence (LR) was observed in 2/36 patients (6%) and in 3/45 lesions (7%), translating into estimated 1- and 2-year LC rates of 93% (per lesion, Fig. 2). Both patients with local recurrences also showed hepatic progression out-

side the irradiated region at the same time and died shortly afterwards of progressive liver disease. The use of abdominal compression was the only factor with a significant impact on LC (100% vs. 82% with vs. without abdominal compression,  $p=0.027$ ; Fig. 2). Pretreatment alpha-fetoprotein values (AFP)  $\geq 10$  showed a trend for poorer 1- and 2-year local control ( $p=0.067$ ; 100% vs. 83% after 1 and 2 years) and larger GTV volumes tended to have worse LC (100 vs. 86% after 1 and 2 years;  $p=0.088$ ). No significant association between BED and local control was observed (Table 2).

## Freedom-from-hepatic-failure

A total of 19 patients (52%) showed hepatic failure, resulting in estimated 1- and 2-year FFHF rates of 39% and 32%, respectively (Fig. 3a). Median time to hepatic progression in those patients was 5.5 months (range 1–37). Only the number of lesions treated with SBRT (1-year FFHF single 46% vs. 0% multiple,  $p=0.006$ ) was significantly predictive for FFHF (Fig. 3b). The same result was seen in patients treated with any local ablative therapy in multiple lesions (two lesions with SBRT ± TACE or one with SBRT ± TACE and one with RFA/TACE) compared to those treated with

**Fig. 2** Local control (**a** entire cohort, **b** according to the use of abdominal compression)

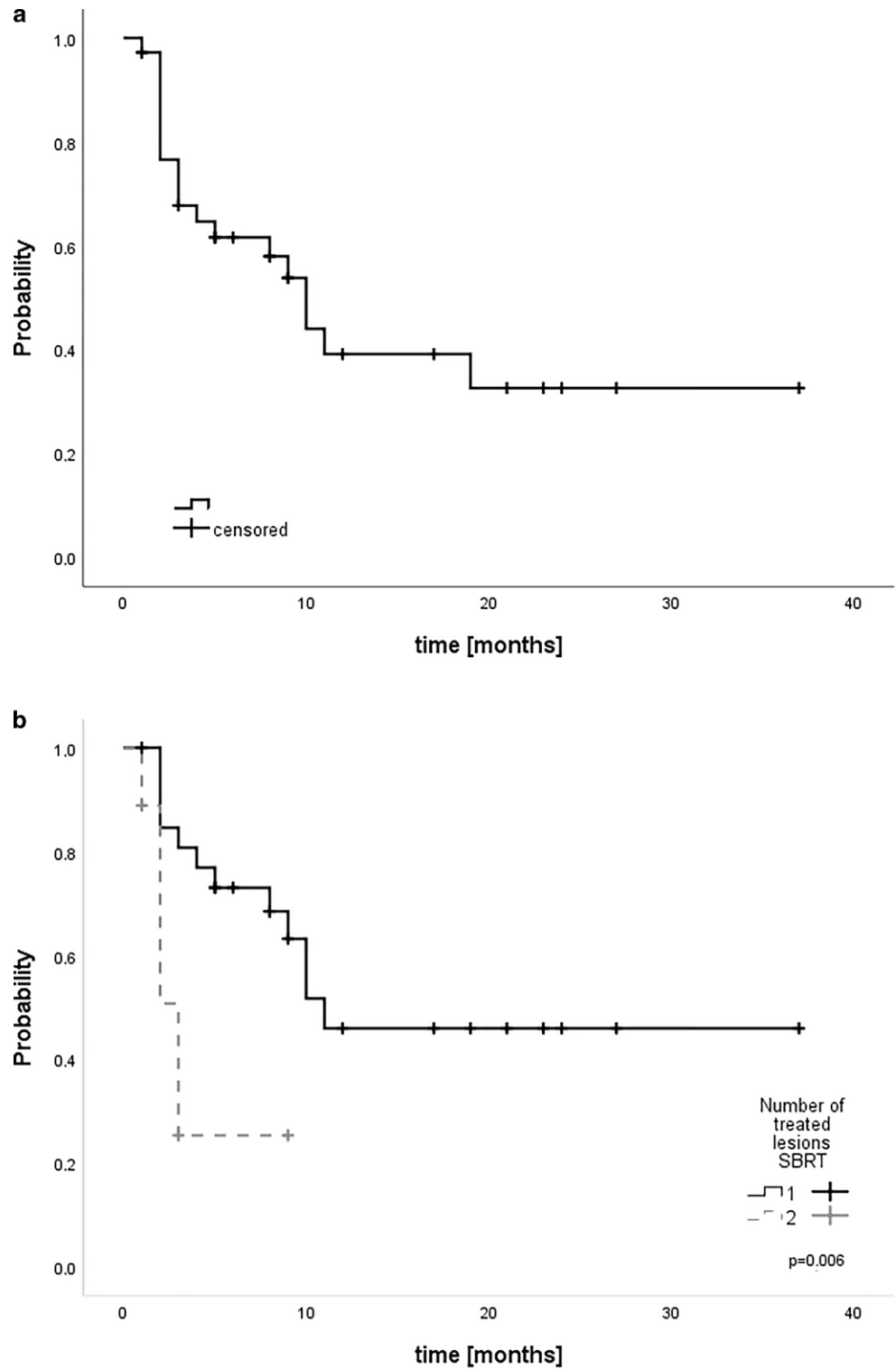


**Table 2** Univariate analysis for LC, FFHF, and OS

	LC		FFHF		OS	
	1-year rate in %	<i>p</i> -value	1-year rate in %	<i>p</i> -value	1-year rate in %	<i>p</i> -value
<b>Gender</b>						
Male	93	0.820	43	0.434	69	0.367
Female	92		0		47	
<b>Age</b>						
≤median (63 years)	95	0.668	34	0.861	63	0.577
>median	91		41		67	
<b>AFP</b>						
≤10	100	0.067	41	0.926	83	0.496
>10	83		42		49	
<b>KPS</b>						
≤70	100	0.436	42	0.508	71	0.989
>70	91		36		63	
<b>Liver function</b>						
CP A	94	0.440	42	0.539	70	0.043
CP B	88		0		33	
<b>GTV</b>						
≤ median (6.7 ccm)	100	0.088	27	0.221	77	0.806
>median	86		56		60	
<b>Abdominal compression</b>						
Yes	100	0.027	39	0.582	67	0.431
No	82		38		61	
<b>SBRT lesions</b>						
Single	–	–	46	0.006	81	<0.001
Multiple	–		0		22	
<b>Total treated lesions</b>						
SBRT only (1 lesion)	–	–	48	0.004	78	0.021
Local treatments > 1 lesion	–		25		47	
<b>SBRT ± TACE</b>						
Yes	96	0.361	41	0.601	55	0.316
No	88		33		78	
<b>Any pretreatment</b>						
Yes	–	–	28	0.064	61	0.804
No	–		77		74	
<b>BED</b>						
≤100 Gy	93	0.984	45	0.883	62	0.896
>100 Gy	93		31		69	
<b>BCLC stage</b>						
Stage A	100	0.345	56	0.353	100	0.041
Stage B/C	91		33		54	

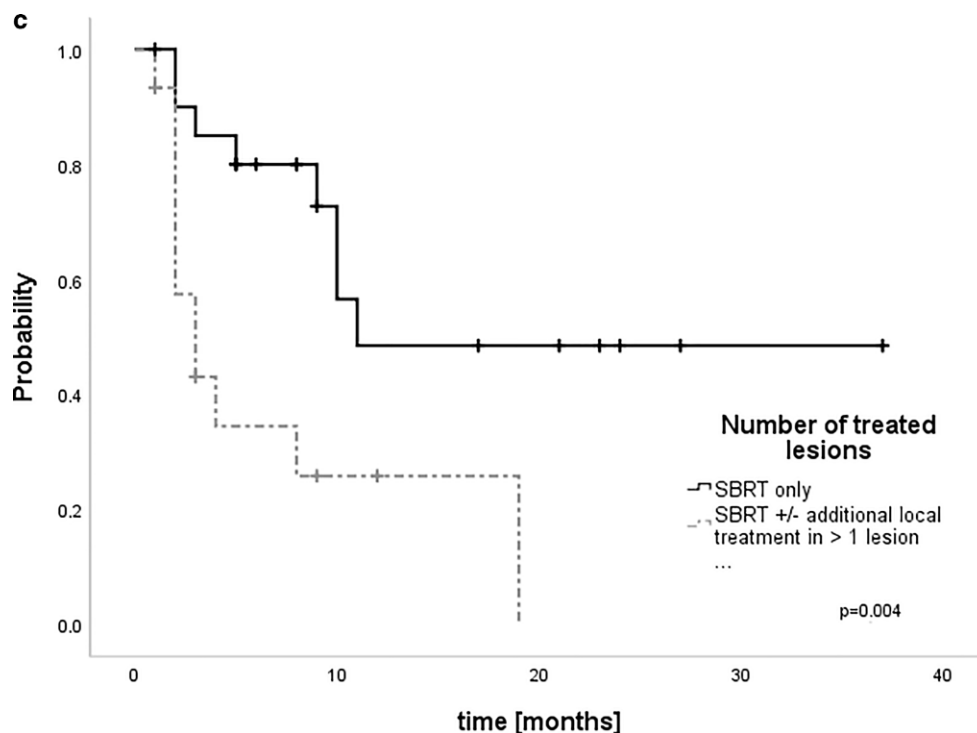
LC local control (per lesion), FFHF freedom-from-hepatic-failure, OS overall survival, yrs years, KPS Karnofsky performance score, CP A/CP B Child–Pugh class A/Child–Pugh class B, GTV gross tumor volume (measured per patient on free-breathing CT), ccm cubic centimeters, AFP serum alpha-fetoprotein [U/ml], SBRT stereotactic body radiation therapy, TACE transarterial chemoembolization, BED biologically effective dose, BCLC Barcelona Clinical Liver Cancer  
*p*-values indicating statistical significance in italics

**Fig. 3** Freedom-from-hepatic-failure (a: entire cohort, b: according to the number of irradiated lesions)





**Fig. 3** (continued) Freedom-from-hepatic-failure (c: according to the number of actually overall treated lesions)



SBRT ± TACE only in one lesion (1- and 2-year FFHF single lesion 48% [1- and 2-year] vs. 25% and 0% for multiple lesions,  $p=0.004$  [Fig. 3c]). Regarding the number of local liver-directed pretreatments, there was a trend toward improved FFHF in patients without any pretreatment (1-year FFHF and 2-year FFHF without pretreatment 77% vs. 28% with pretreatments;  $p=0.064$ ). No significant association between BED and FFHF was observed, see Table 2.

### Overall survival

So far, 16 patients (44%) have died, translating into an estimated median survival of 22 months with 1- and 2-year OS rates of 64% and 41%, respectively (Fig. 4a) regarding all patients. The number of irradiated lesions was significantly predictive for OS (1-year OS single 81% vs. 22% multiple,  $p<0.001$ ; 2-year OS 63% vs. 0%,  $p<0.001$  [Fig. 4d]). Patients with multiple lesions—regardless of the type of current treatment (two lesions with SBRT ± TACE or one with SBRT ± TACE and one with RFA/TACE)—also showed a significantly decreased OS (1-year OS single 78% vs. 47% multiple, 2-year OS 59% vs. 18%,  $p=0.021$  [Fig. 4e]). Child–Pugh class (CP class) prior to SBRT was also predictive for OS (1-year OS CP A 70% vs. 33% CP B, 2-year OS 45% vs. 0%,  $p=0.043$  [Fig. 4b]). BCLC score was also predictive for OS after 1 and 2 years ( $p=0.041$  [Fig. 4c]). No significant association between BED and overall survival was observed (Table 2). Similar results

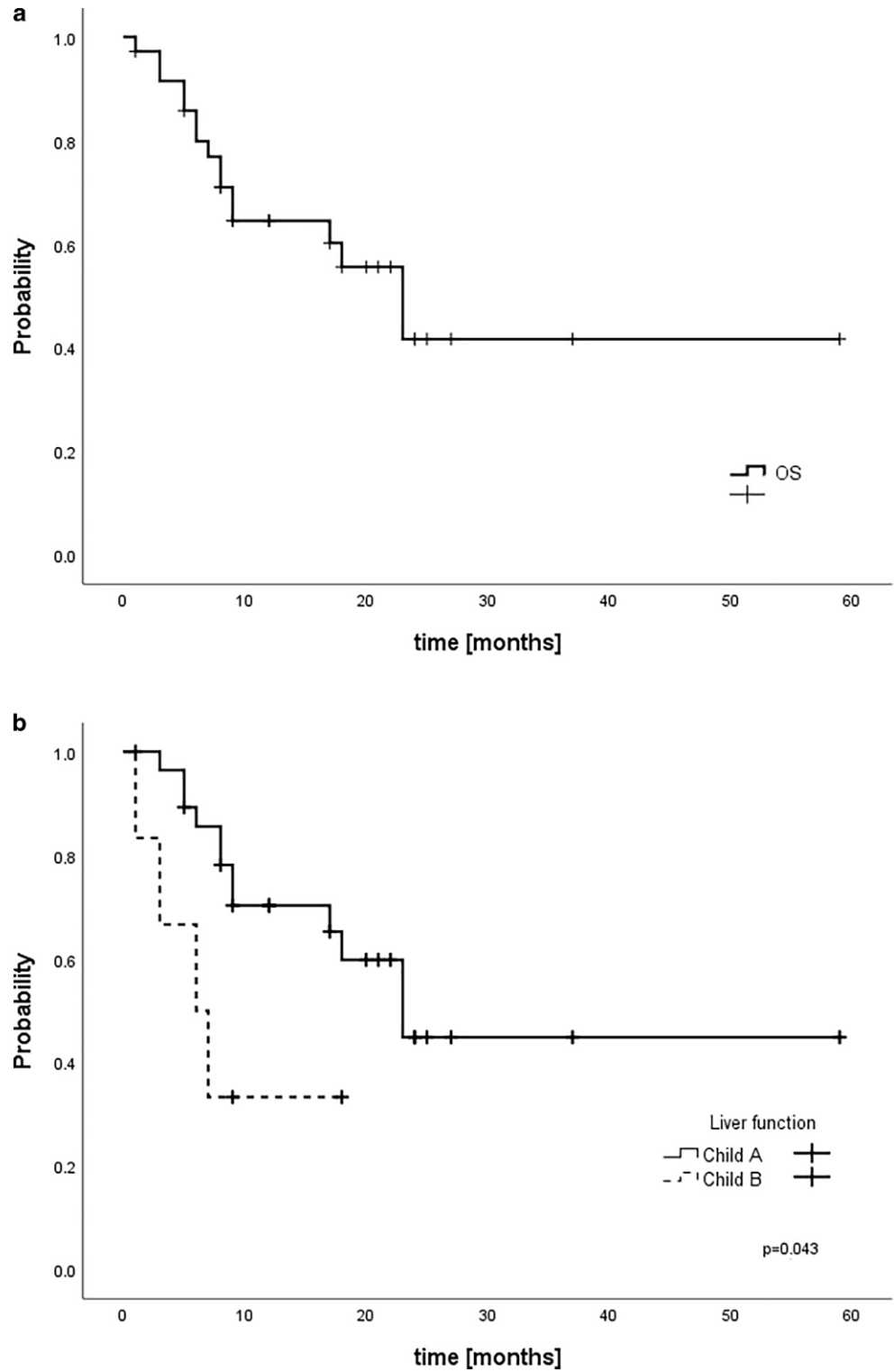
were obtained if the 6 patients with OLT were excluded from analysis (data not shown).

### Toxicity

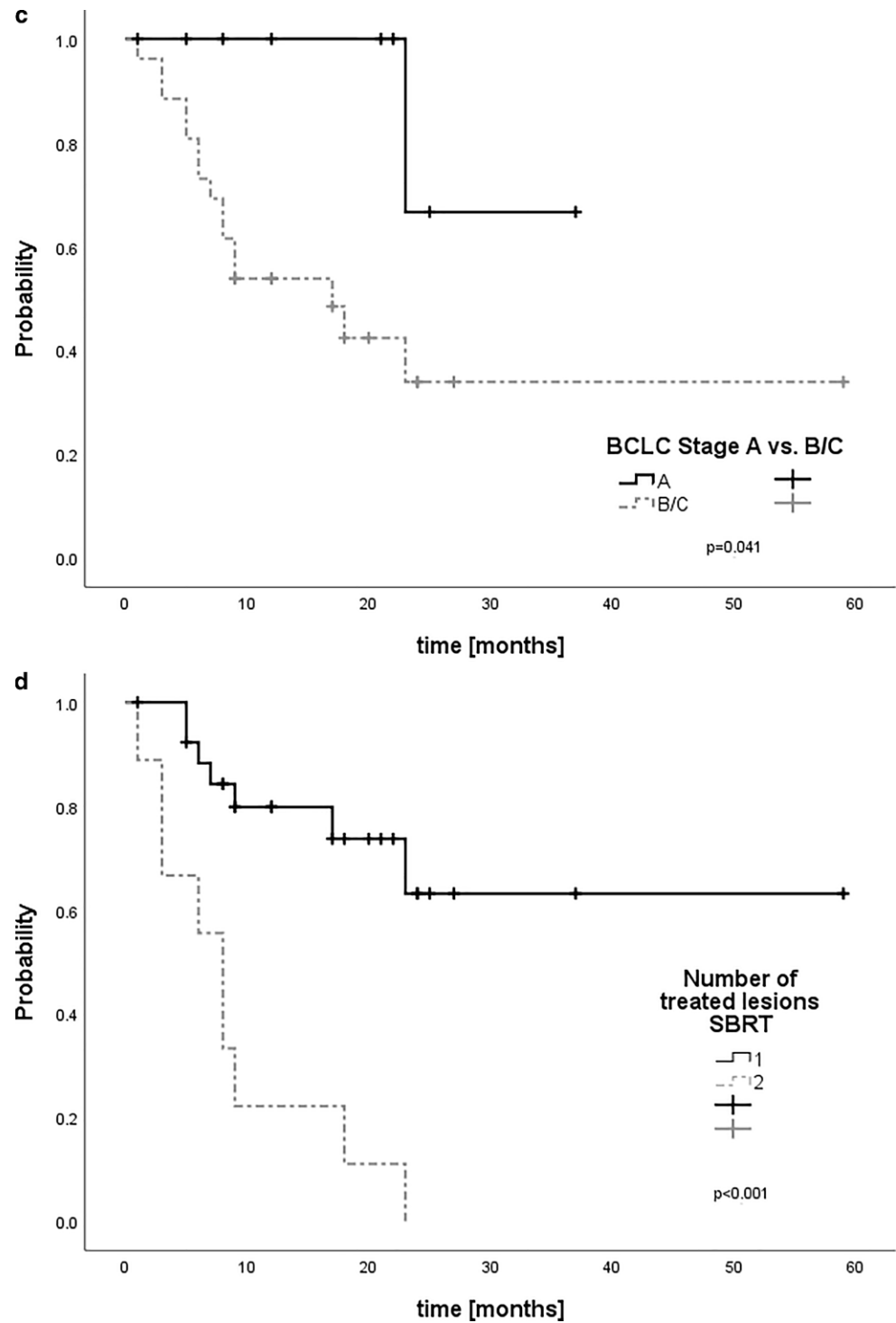
CT-guided fiducial placement was feasible without any severe acute complications. In two patients, one of the fiducials was dislocated into the vascular system, both remained asymptomatic. SBRT was well tolerated in general. Aside from mild side effects of grade 1 in 14% and grade 2 in 8% (mainly fatigue and gastrointestinal symptoms like nausea or abdominal pain), only one patient (3%) developed a severe acute toxicity. This patient already suffered from CP C cirrhosis prior to SBRT and developed acute hepatic failure (grade 4) after SBRT which was ultimately salvaged by OLT. This patient was still alive at last follow-up. No grade 5 toxicities attributable to SBRT were observed.

Late toxicity possibly related to SBRT was also generally mild. Only three patients (8%) developed grade 3 late toxicities. Two showed marked deterioration of liver function, with a decline in CP class from A (6 points) to class B (8 points) scored as grade 3; one of them also showed symptoms of fatigue, ascites, and abdominal pain clinically consistent with RILD symptoms, scored as grade 3. Mean liver dose was 12 and 15 Gy, although the second patient had the largest GTV (249 ccm) of all patients. However, our predefined dose constraints (defined as mean liver dose minus GTV < 18 Gy and > 700 ml of liver receiving less than 15 Gy) were met in both patients. The third patient suffering from

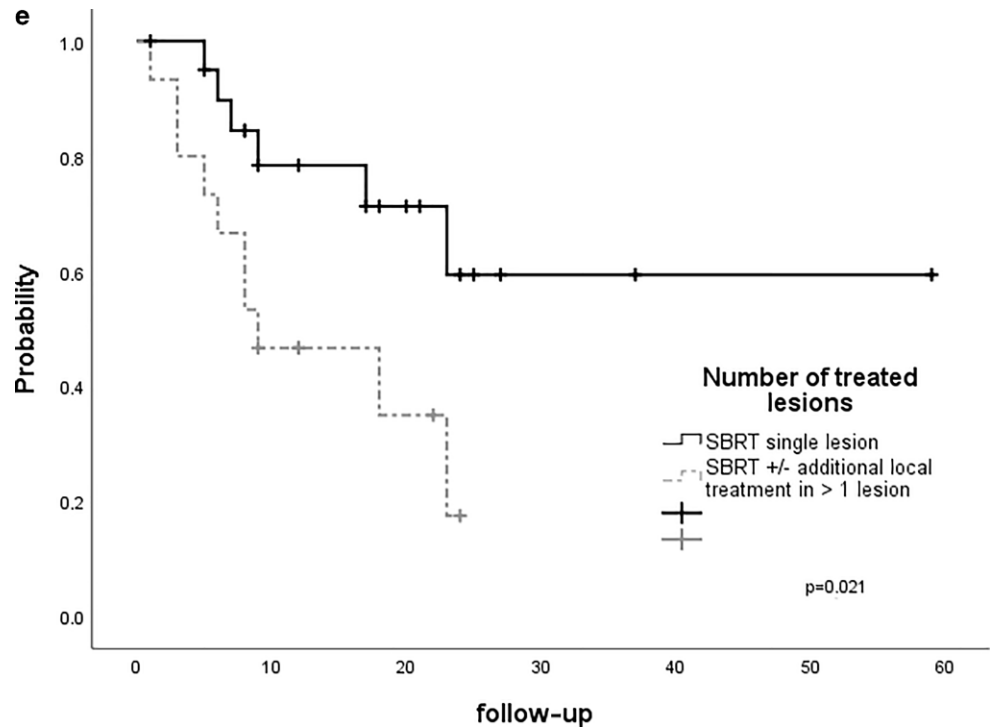
**Fig. 4** Overall survival (**a**: entire cohort, **b**: according to Child Pugh class)



**Fig. 4** (continued) Overall survival (**c**: according to BCLC stage, **d**: according to the number of irradiated lesions)



**Fig. 4** (continued) Overall survival (e: according to the number of actually overall treated lesions)



a centrally located large HCC developed cholangitis and a stricture of the proximal common hepatic bile duct. He was treated by antibiotics and repeated stent placement, but this side effect finally resolved (toxicity scored as grade 3). Maximum dose to the central biliary tract was 37.5 Gy in 3 fractions in this patient. No grade 4/5 late toxicities attributable to SBRT were observed.

### SBRT ± TACE

Additional TACE to the same lesion within 6 weeks before SBRT was performed in 21 patients. In 11 of these patients, no fiducial markers were necessary because of sufficient lipiodol enhancement.

No significant differences were found for the addition of TACE compared to SBRT alone in any of the endpoints, see Table 2.

### SBRT as bridging prior to OLT

SBRT was performed as bridging to transplant in 6 patients with 7 lesions. Three of them had liver cirrhosis CP A, 2 of them CP B, and one had CP C. Causes of the underlying liver cirrhosis were alcohol related in 2 patients, infectious (hepatitis B/C) in 2 patients, and the remaining 2 patients had autoimmune hepatitis. All patients fulfilled EASL criteria for diagnosis and Milan criteria for OLT eligibility. OLT was performed after a median interval of 6 months (range 1–8 months) from SBRT. Median follow-up from

SBRT was 18 months (range 7–73) in those patients. All patients remained locally and distantly controlled until OLT. In 5/6 patients and 6/7 lesions, no residual HCC (pathologic complete response) was found in the explanted liver. The only patient with residual disease had been treated with SBRT only and received OLT early (1 month) after SBRT. No severe acute toxicity from SBRT was observed, except deterioration of liver function in the CP C patient (grade 4) salvaged by OLT, who is still alive. One patient died shortly after OLT due to postoperative complications (septic shock) and one due to distant failure 9 months after OLT, resulting in 1- and 2-year OS rates of 66%. Comparing the OLT group with the non-OLT patients, the OLT group showed similar OS after 1 year (both 66%) but an increased OS rate after 2 years (66 vs. 43% in patients without OLT), but this difference did not reach statistical significance ( $p=0.49$ ).

## Discussion

### SBRT outcome

We observed encouraging 1- and 2-year LC rates of 93% in our cohort of patients treated with SBRT for HCC. These results are in line with other series reporting 1-year LC rates of 65–100% using similar SBRT approaches [9, 16–32]. For example, Bujold et al. [24] observed a 1-year LC control rate of 87% in the largest published prospective (phase I/II) trial including 102 HCC patients, which showed similar

patient characteristics to our cohort with regard to lesion size and number. Nabavizadeh et al. [30] and Jeong et al. [31] recently published large retrospective series and found even higher 1-year LC rates of 97% and 99%. Based on those and our results, SBRT seems to be very effective in controlling disease at least locally. The high (so-called ablative) doses used within this approach seem to effectively destroy all malignant cells in the vast majority of the treated lesions, as shown by the high pathological complete response rate of 86% achieved in our patients who received OLT later on. Interestingly, we identified the use of an abdominal compression device as the only significant predictive factor for LC. Abdominal compression has been shown to reduce respiratory motion of the liver [33], thus resulting in smaller ITV and PTV volumes, which might have prompted a more adequate target volume coverage. However, this finding should be regarded very cautiously given the low number of events in our study. In contrast, we could not confirm the prognostic value of several factors described by others like dose, fractionation, and lesion size [9, 21, 23], probably again due to the small sample size and the low number of events.

Regarding OS, we observed 1- and 2-year rates of 64% and 41%. These findings are in the range of published series describing 1-year survival rates of 32–94% [9, 16–31], although the wide range clearly indicates the inclusion of inhomogeneous patient groups in the published reports. We identified the number of treated lesions as well as CP class and BCLC stage prior to SBRT as predictive factors for OS in our cohort. Surprisingly, the number of lesions has been evaluated with regard to OS in only very few of the studies including patients with multiple lesions. Bujold et al. [24] reported on 102 patients enrolled in two prospective phase II trials and did not find a correlation of OS with the number of lesions. Su et al. [27] analyzed 132 Chinese patients retrospectively and reported a non-significant but remarkable decrease in 2-year OS of 85%, 77%, and 63% in patients with 1, 2, or 3 lesions. Moreover, the number of lesions was predictive for progression-free survival (PFS) in their study. Scorsetti et al. [9] did not directly evaluate the number of lesions as a prognostic factor. However, they included only patients with up to three lesions with a single diameter <6 cm and reported a significant decrease in OS for patients with a cumulative GTV diameter of >5 cm, indicating that patients with more than one lesion may be at a higher risk for death. In contrast, many groups have consistently reported CP class as a prognostic factor for OS [9, 17, 20, 23, 31]. For example, Lasley et al. [17] described a median OS of 45 months in CP A versus 17 months in CP B patients in their prospective trial. Huang et al. [23] retrospectively analyzed 119 patients and reported a significantly decreased 3-year OS of 62% in CP B patients compared to 86% in CP A patients. CP class was also con-

firmed as an independent prognostic factor in their multivariate analysis. Moreover, CP B patients seem to be at a higher risk for severe toxicities [17, 20] and thus might be not ideal candidates for SBRT or should at least be selected very carefully. A similar or even higher prognostic value has been reported for BCLC stage. For example, Marrero et al. [34] analyzed 239 patients and found that BCLC stage had the best prognostic stratification compared to several other commonly used staging systems.

In contrast to the encouraging results with regard to LC and OS, we observed a high number of liver outfield failures translating into rather poor 1- and 2-year FFHF rates of 39% and 32%, respectively. The only factor with a significant impact on FFHF was the number of treated lesions. Similar results have been described by others in comparable patient cohorts. For example, Takeda et al. [28] enrolled 101 patients in a phase II trial combining TACE and SBRT and found a 3-year intrahepatic-failure-free rate of only 34%, although only patients with a single lesion were eligible. Bujold et al. [24] described 11 infield but 61 outfield intrahepatic failures in their series of 102 patients and Huang et al. [23] also identified outfield intrahepatic failure as the main pattern of recurrence. This may implicate that patients with multiple lesions detected on imaging have a higher risk for further subclinical disease in general and might not be ideal candidates for SBRT or other local treatments. However, most of our patients had already been treated with other local treatments and received SBRT only because they were deemed ineligible for other treatments except TACE or systemic agents. In this heavily pretreated cohort, the risk for developing further recurrences might be simply increased compared to treatment-naïve patients due to selection of an unfavorable biology.

## Toxicity

With the possibility of outfield failures and the need for salvage treatments after locally ablative therapies, preservation of liver function and toxicity issues gain importance in the decision process for specific treatments. With SBRT, we observed a high treatment compliance with generally mild side effects in the majority of patients. Severe acute and late toxicities were only observed in 3% and 8% of our patients, respectively. These results compare favorably with other series, which reported acute grade 3+ side effects in 5–37% including up to 7% deaths [1], mainly in CP B patients. The main severe side effect regardless of its onset in our series was deterioration of liver function in 8% of our patients. Distinctly higher rates (13–29%) of a decline in CP class after SBRT have been reported by others [18, 24, 35], although some authors described a marked recovery over time [24]. However, some of these series included a higher percentage of CP B patients and treated larger le-

sions resulting in more dose to normal liver tissue. Both factors have been shown to be associated with toxicity [17, 35]. For example, Lasley et al. [17] observed severe liver toxicity of 38% in CP B compared to 11% in CP A patients and described several dose–volume factors associated with increased liver toxicity, especially in CP B patients. Culleton et al. [25] evaluated specifically patients with CP B/C and observed a decline of  $\geq 2$  points in 63% after 3 months. Therefore, SBRT should be used with caution in patients with impaired pretreatment liver function (CP B), while it seems to be generally well tolerated in CP A patients. Moreover, a recent systematic review demonstrated well-preserved quality of life after SBRT at least similar or even favorable compared to other approaches [36].

### SBRT as bridging to transplant

OLT is the most effective treatment for HCC with underlying cirrhosis [37]. However, the availability of OLT may be limited by donor organ shortages resulting in prolonged waiting times [37]. Therefore, effective treatments have to be offered in between to maintain disease control until availability of a donor organ (so-called bridging) [37]. Similarly to definitive treatment, different methods—including RFA, TACE, SIRT, and SBRT—are currently in use, depending on the location and size of the lesion and patients' comorbidities [37]. In our cohort, we observed a pathological complete response (pCR) in the explanted liver in 5/6 (83%) patients treated with OLT after SBRT at a median interval of 6 months. These results compare favorably with the (rare) evidence published in the literature. For example, Uemura et al. [38] reported 28% pCR and 22% extensive pathological partial responses (pPR) after SBRT with 40–50 Gy in 4–6 fractions followed by OLT in 11 patients. O'Connor et al. [39] found a pCR rate of 27% in 10 patients treated with SBRT (51 Gy in 3 fractions) followed by OLT and Moore et al. [40] observed 27% pCR and 55% pPR in a series of 11 patients treated by SBRT with 30–54 Gy in 3–5 fractions. This difference cannot be easily attributed to different doses, as BEDs in all studies were at least similar and considered ablative. A longer time interval from SBRT to OLT may theoretically also result in higher pCR rates; however, our median interval (6 months) was in the range of the mentioned studies (4–8 months) [38–40]. However, in contrast to the mentioned studies, SBRT was preceded by TACE within 6 weeks in 4 of 5 patients with pCR in our cohort. TACE alone has been reported to result in 30–44% complete tumor necrosis in explanted livers [37]. Therefore, one may speculate that the combination of TACE and SBRT in the majority of transplanted patients has contributed to the higher pCR rate. However, given the small number of patients, it cannot be fully ruled out that the difference occurred simply by chance or was triggered by other factors.

Nevertheless, based on the data from our and other studies, SBRT seems to be a suitable method for bridging patients waiting for OLT.

### Limitations

Our study has some limitations, especially its retrospective nature, the rather short follow-up, and the limited number of patients. However, in the absence of randomized trials and with limited data from prospective studies, retrospective evaluation seems a suitable way to gain more information in a heterogeneous patient group treated with a variety of slightly different approaches.

### Conclusion

SBRT in highly pretreated patients with HCC resulted in excellent LC and acceptable OS with low toxicity. OS was predicted by pretreatment number of lesions and pretreatment CP class. However, especially patients with multiple lesions were at a high risk for outfield intrahepatic failures indicating a possible need for improved patient selection and/or additional therapies. SBRT can be used as definitive treatment or as bridging to OLT.

**Author Contribution** SG performed data acquisition and participated in patient treatment, statistical analysis, and in drafting the manuscript. CH participated in treatment of the patients and statistical analysis. FW, PP, ED treated the patients and participated in data acquisition. CB revised the manuscript critically. FR participated in data acquisition, statistical analysis, treatment of the patients, drafting the manuscript and critically reviewed the data and the manuscript.

### Compliance with ethical guidelines

**Conflict of interest** S. Gerum, C. Heinz, C. Belka, F. Walter, P.M. Pappotzka, E.N. De Toni, and F. Röder declare that they have no competing interests.

**Ethical standards** The study was approved by the Ethics committee of the University of Munich (LMU), reference number 617-16. Informed consent was obtained from all individual participants included in the study.

### References

1. Murray LJ, Dawson LA (2017) Advances in stereotactic body radiation therapy for hepatocellular carcinoma. *Semin Radiat Oncol* 27:247–255
2. Waller LP, Deshpande V, Pyrsopoulos N et al (2015) Hepatocellular carcinoma: a comprehensive review. *World J Hepatol* 7:2648–2663
3. Delis SG, Dervenis C (2008) Selection criteria for liver resection in patients with hepatocellular carcinoma and chronic liver disease. *World J Gastroenterol* 14:3452–3460
4. NCCN Clinical Practice Guidelines in Oncology—hepatobiliary cancers version 2/2019. [https://www.nccn.org/professionals/physician\\_gls/pdf/hepatobiliary.pdf](https://www.nccn.org/professionals/physician_gls/pdf/hepatobiliary.pdf)

5. Kalogeridi MA, Zygogianni A, Kyrgias G et al (2015) Role of radiotherapy in the management of hepatocellular carcinoma: a systematic review. *World J Hepatol* 7:101–112
6. Gerum S, Heinz C, Belka C et al (2018) Stereotactic body radiation therapy (SBRT) in patients with hepatocellular carcinoma and oligometastatic disease. *Radiat Oncol* 13:100
7. Lawrence TS, Robertson JM, Anscher MS et al (1995) Hepatic toxicity resulting from cancer treatment. *Int J Radiat Oncol Biol Phys* 31:1237–1248
8. Dawson LA, Normolle D, Balter JM et al (2002) Analysis of radiation-induced liver disease using the Lyman NTCP model. *Int J Radiat Oncol Biol Phys* 53:810–821
9. Scorsetti M, Comito T, Cozzi L et al (2015) The challenge of inoperable hepatocellular carcinoma (HCC): results of a single-institutional experience on stereotactic body radiation therapy (SBRT). *J Cancer Res Clin Oncol* 141:1301–1309
10. Boda-Heggemann J, Jahnke A, Chan MK et al (2018) Direct dose correlation of MRI morphological alterations of healthy liver tissue after robotic liver surgery. *Strahlenther Onkol* 194:414–424
11. Fleckenstein J, Boda-Heggemann J, Siebelist K et al (2018) Non-coplanar VMAT combined with non-uniform dose prescription markedly reduces lung dose in breath-hold lung SBRT. *Strahlenther Onkol* 194:815–823
12. Moustakis C, Blanck O, Ebrahimi Tazehmahalleh F et al (2017) Planning benchmark study for SBRT of early stage NSCLC—results of the DERO working group stereotactic radiotherapy. *Strahlenther Onkol* 193:780–790
13. Gkika E, Adebahr S, Kirste S et al (2017) Stereotactic body radiotherapy (SBRT) in recurrent or oligometastatic pancreatic cancer. *Strahlenther Onkol* 193:433–443
14. Chang JY, Senan S, Paul MA et al (2015) Stereotactic ablative radiotherapy versus lobectomy for operable stage I non-small-cell lung cancer: a pooled analysis of two randomised trials. *Lancet Oncol* 16:630–637
15. Blomgren H, Lax I, Näslund I et al (1995) Stereotactic high dose fraction radiation therapy of extracranial tumors using an accelerator. Clinical experience of the first thirty-one patients. *Acta Oncol* 34:861–870
16. Gerum S, Roeder F (2019) Stereotactic body radiation therapy (SBRT) in patients with hepatocellular carcinoma (HCC): a mini-review. *World J Gastrointest Oncol* 11:367–376
17. Lasley FD, Maninna EM, Johnson CS et al (2015) Treatment variables related to liver toxicity in patients with hepatocellular carcinoma, Child-Pugh class A and B enrolled in a phase 1–2 trial of stereotactic body radiation therapy. *Pract Radiat Oncol* 5:e443–449
18. Mendez-Romero A, Wunderink W, Hussain SM et al (2006) Stereotactic body radiation therapy for primary and metastatic liver tumors: a single institution phase I–II study. *Acta Oncol* 45:831–837
19. Tse RV, Hawkins M, Lockwood G et al (2008) Phase I Study of individualized stereotactic body radiotherapy for hepatocellular carcinoma and intrahepatic cholangiocarcinoma. *J Clin Oncol* 26:657–664
20. Cardenes HR, Price TR, Perkins SM et al (2010) Phase I feasibility trial of stereotactic body radiation therapy for primary hepatocellular carcinoma. *Clin Transl Oncol* 12:218–225
21. Kang JK, Kim MS, Cho CK et al (2012) Stereotactic body radiation therapy for inoperable hepatocellular carcinoma as a local salvage treatment after incomplete transarterial chemoembolization. *Cancer* 118:5424–5431
22. Price TR, Perkins SM, Sandrasegaran K et al (2012) Evaluation of response after stereotactic body radiotherapy for hepatocellular carcinoma. *Cancer* 118:3191–3198
23. Huang WY, Jen YM, Lee MS et al (2012) Stereotactic body radiation therapy in recurrent hepatocellular carcinoma. *Int J Radiat Oncol Biol Phys* 84:355–361
24. Bujold A, Massey CA, Kim JJ et al (2013) Sequential phase I and II trials of stereotactic body radiotherapy for locally advanced hepatocellular carcinoma. *J Clin Oncol* 31:1631–1639
25. Culleton S, Jiang H, Haddad CR et al (2014) Outcomes following definitive stereotactic body radiotherapy for patients with Child-Pugh B or C hepatocellular carcinoma. *Radiother Oncol* 111:412–417
26. Sanuki N, Takeda A, Oku Y et al (2014) Stereotactic body radiotherapy for small hepatocellular carcinoma: a retrospective outcome analysis in 185 patients. *Acta Oncol* 53:399–404
27. Su TS, Liang P, Lu HZ et al (2016) Stereotactic body radiation therapy for small primary or recurrent hepatocellular carcinoma in 132 Chinese patients. *J Surg Oncol* 113:181–187
28. Takeda A, Sanuku N, Tsurugai Y et al (2016) Phase 2 Study of stereotactic body radiotherapy and optional transarterial chemoembolization for solitary hepatocellular carcinoma not amenable to resection and radiofrequency ablation. *Cancer* 122:2041–2049
29. Moon DH, Wang AZ, Tepper JE (2018) A prospective study of the safety and efficacy of liver stereotactic body radiotherapy in patients with and without prior liver-directed therapy. *Radiother Oncol* 126:527–533
30. Nabavizadeh N, Waller JG, Fain R et al (2018) Safety and efficacy of accelerated hypofractionation and stereotactic body radiation therapy for hepatocellular carcinoma patients with varying degrees of hepatic impairment. *Int J Radiat Oncol Biol Phys* 100:577–585
31. Jeong Y, Jung J, Cho B et al (2018) Stereotactic body radiation therapy using a respiratory-gated volumetric-modulated arc therapy technique for small hepatocellular carcinoma. *BMC Cancer* 18:416
32. Chiang CL, Chan MKH, Yeung CSY et al (2019) Combined stereotactic body radiotherapy and trans-arterial chemoembolization as initial treatment in BCLC stage B-C hepatocellular carcinoma. *Strahlenther Onkol* 195:254–264
33. Heinzerling JH, Anderson JF, Papiez L et al (2008) Four-dimensional computed tomography scan analysis of tumor and organ motion at varying levels of abdominal compression during stereotactic treatment of lung and liver. *Int J Radiat Oncol Biol Phys* 70:1571–1578
34. Marrero JA, Fontana RJ, Barrat A et al (2005) Prognosis of hepatocellular carcinoma: comparison of 7 staging systems in an American cohort. *Hepatology* 41:707–716
35. Andolino DL, Johnson CS, Maluccio M et al (2011) Stereotactic body radiotherapy for primary hepatocellular carcinoma. *Int J Radiat Oncol Biol Phys* 81:e447–e453
36. Mutsaers A, Greenspoon J, Walker-Dilks C et al (2017) Systematic review of patients reported quality of life following stereotactic ablative radiotherapy for primary and metastatic liver cancer. *Radiat Oncol* 12:110
37. Rubinstein MM, Kaubisch A, Kinkhabwala M, Reinus J, Liu Q, Chuy JW (2017) Bridging therapy effectiveness in the treatment of hepatocellular carcinoma prior to orthotopic liver transplantation. *J Gastrointest Oncol* 8:1051–1055
38. Uemura T, Kirichenko A, Bunker M, Vincent M, Machado L, Thai N (2019) Stereotactic body radiation therapy: a new strategy for locoregional treatment for hepatocellular carcinoma while awaiting liver transplantation. *World J Surg* 43:886–893
39. O'Connor JK, Trotter J, Davis GL, Dempster J, Klintmalm GB, Goldstein RM (2012) Long-term outcomes of stereotactic body radiation therapy in the treatment of hepatocellular cancer as a bridge to transplantation. *Liver Transpl* 18:949–954
40. Moore A, Cohen-Naftaly M, Tobar A, Kundel Y, Benjaminov O, Braun M, Issachar A, Mor E, Sarfaty M, Bragilovski D, Hur BR, Gordon N, Stemmer SM, Allen AM (2017) Stereotactic body radiation therapy (SBRT) for definitive treatment and as a bridge to liver transplantation in early stage inoperable hepatocellular carcinoma. *Radiat Oncol* 12:163