

# Stereotactic Body Radiation Therapy: A New Strategy for Loco-Regional Treatment for Hepatocellular Carcinoma While Awaiting Liver Transplantation

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## Abstract

**Background** Trans-arterial chemoembolization and radiofrequency ablation are commonly used for control of hepatocellular carcinoma (HCC) on liver transplant (LTx) waiting list. Stereotactic body radiation therapy (SBRT) was introduced to our institution for HCC as a bridging or downsizing therapy to LTx.

**Patients and methods** Twenty-five HCC lesions in 22 patients were treated with SBRT while waiting for LTx from January 2010 to December 2015. Nineteen of these patients received deceased donor LTx. SBRT was defined as 40–50 Gy delivered in 4–6 fractions. Pre- and post-liver transplant outcome were analyzed in addition to the dropout rate and tumor response to SBRT.

**Results** Median size of original tumors was 3.2 cm (2.0–8.9), and median size of tumor after SBRT was significantly smaller at 0.9 cm (0–3.2) in the explanted livers ( $p < 0.01$ ). The dropout rate was 9%, and they were only downsized patients outside of Milan criteria. Liver disease did not progress between pre- and post-SBRT except one patient. Twenty-eight percent of treated HCCs showed complete pathologic response, and 22% had extensive partial response with some residual tumor. No HCC recurrence was experienced after LTx.

**Conclusion** SBRT is indicated to be safe, effective treatment for HCC on LTx waiting list, and it leads to satisfactory post-liver transplant outcomes.

## Abbreviations

TACE Trans-arterial chemoembolization  
HCC Hepatocellular carcinoma  
SBRT Stereotactic body radiation therapy

RFA Radiofrequency ablation  
RILD Radiation induced liver disease  
MELD Model for end-stage liver disease  
PTV Planned target volume  
AFP Alpha fetoprotein

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## Introduction

In the USA, hepatocellular carcinoma (HCC) accounts for approximately 16,000 deaths annually. It is one of the few cancers with increasing frequency and mortality nationwide [1]. Liver transplantation is one of the best treatments for HCC in liver cirrhosis and provides excellent oncological outcomes while curing liver cirrhosis. Given the

high risk of recurrence of HCC and the limited organs available, strict selection with Milan criteria has been applied to identify patients with HCC most likely to benefit from transplantation [2]. However, patients with HCC in liver cirrhosis face major challenges, as their disease must be under control, while they are waiting for liver transplantation. As loco-regional therapy for HCC, trans-arterial chemotherapy embolization (TACE) and/or radiofrequency ablation (RFA) are used nationwide. TACE may have worse outcome with serum bilirubin > 2 mg/dl or patients with Child class B and C [3, 4]. RFA also has some technical limitations. It is generally unable to achieve full ablation in lesions larger than 4 cm, and there is a potential loss of heat energy with reduced treatment effect if large blood vessels are near the treatment zone [5]. It is also reported that 0–35% of patients with bridging therapy of Milan criteria dropped out from liver transplant list because of tumor progression [6]. Furthermore, the new UNOS policy of HCC does not grant exception points until stable control of tumors is confirmed for 6 months [7]. Therefore, control of HCC is even more important for patients on the waiting list to successfully reach liver transplant.

Over the past decade, stereotactic body radiation therapy (SBRT) has emerged as a noninvasive, safe and effective therapy for liver tumors that is delivered in 5 or fewer fractions [8–13]. Promising clinical data from multiple studies suggest that HCCs are radiosensitive tumors. Image-guided SBRT for unresectable HCCs sustained local control rates ranging from 70 to 100% in prospective phase I/II clinical trials [8–13]. Furthermore, an impressive 5-year survival rate of 53.5% has been achieved in 50 patients with solitary tumors and Child–Pugh class A cirrhosis in the absence of significant toxicity utilizing SBRT [14]. Kirichenko et al. also reported outcomes of eight patients who completed hepatic resections in combination with planned SBRT for unresectable hepatic tumors. Two-year local control was 96% for hepatoma and 93.8% for metastases; it was 100% for lesions  $\leq$  4 cm. Two-year overall survival was 82.3% (hepatoma) and 64.3% (metastases) [15].

Three-dimensional computed tomography (3D-CT) and hepatic single-emission computed tomography (SPECT) fusion were used in this study to facilitate functional treatment planning with conformal avoidance of best functional hepatic parenchyma from the high-dose irradiation. We herein report our initial experience with SBRT for HCC as a bridging or downsizing therapy in patients on the liver transplant waiting list, and demonstrate this new strategy for loco-regional therapy of HCC and the associated liver transplant outcomes.

## Patients and methods

Demographic, diagnostic, and treatment-related data were obtained from a prospectively maintained database of liver transplant recipients at the Allegheny General Hospital, Pittsburgh, PA. Patients who received SBRT for HCC as bridging or downsizing therapy prior to liver transplant were included in this study. In our institution, SBRT was the first choice for bridging or downsizing therapy of HCC prior to liver transplant. Institutional review board approval was obtained (IRB RC5406) at Allegheny General Hospital, Pittsburgh, PA. Twenty-five HCC lesions in 22 patients were treated with SBRT from Jan 2010 to Dec 2015. Three patients had multiple lesions, and those lesions bigger than 2.0 cm were treated with simultaneously or subsequently treated based on functional scan. Three patients were outside of Milan criteria, and 19 patients were within Milan criteria. SBRT was defined as 40–50 Gy delivered in 4–6 fractions. Multiphase contrast CT and MRI images were routinely acquired in patients every 3 months post-completion of SBRT up until the time of transplant. Radiation-induced liver disease (RILD) was objectively monitored by checking blood work (liver function tests, coagulation profile, complete blood count), recalculating Child–Pugh scores and grading the laboratory abnormalities according to version 4.0 of the common terminology criteria for adverse events (CTCAE v4.0) [16]. These studies were acquired beginning 1 month after treatment and every month. Acute and long-term toxicities were also graded according to CTCAE v4.0 [16]. The model for end-stage liver Disease (MELD) score was shown as a calculated number according to the previously described model without UNOS HCC exception [17]. All imaging studies were reviewed by liver specialized radiologists, and local control was defined as the absence of tumor radiographic progression within or at the PTV margin. New liver lesions arising outside the planned target volume (PTV) were identified as intrahepatic progression.

## SBRT planning and delivery

The detailed description of functional radiotherapy planning for liver SBRT in cirrhotic patients has been previously published [15, 18]. Briefly, each patient in this study was positioned on a custom-molded VacLoc<sup>®</sup> vacuum cushion for immobilization (Bionix, Toledo, OH) and a contrast-enhanced treatment planning CT was obtained to outline the gross tumor volume (GTV). This was immediately followed by a 4D-CT to obtain the internal target volume (ITV) capturing respiratory-induced tumor motion. A planning target volume (PTV) was then constructed by adding an additional 0.3–0.5 cm margin to the ITV to

account for setup error uncertainties. Image-guided radiation therapy (IGRT) using cone-beam CT was used before each daily treatment session to reduce setup uncertainties. SBRT dose was prescribed to the isodose line encompassing the PTV.

All patients in this study underwent 3D-CT/SPECT with  $^{99m}\text{Tc}$ -sulfur colloid for identification and subsequent conformal avoidance of well-perfused, functionally active hepatic parenchyma during SBRT. Details of SPECT/CT co-registration and treatment planning methodology have been previously reported [15, 18]. Liver dose constraints were imposed exclusively on residual functional liver volumes obtained from 3D-CT/SPECT with calculation of predicted functional liver volume (pFLV) from an equation used in transplant surgery and  $^{90}\text{Y}$  radioembolization dosimetry; ( $pFLV = -794.41 + 1268.28 \times \text{body surface area}$ ) [19, 20]. Next, we specified that at least 35% of pFLV from treatment planning 3D-CT/SPECT should receive no more than 16 Gy (4 fraction SBRT) or 18 Gy (5–6 fraction SBRT). Thirty-five percent of residual functional liver to be avoided from threshold irradiation corresponds to a conservative estimate of normal liver volume to be spared from hepatic resection [21]. These dose constraints are biologically equivalent to the dose limits (threshold dose) the entire liver can safely tolerate [22, 23] and which were also used in other liver SBRT trials [9, 24]. Additional constraints included stomach  $V_{25} < 10$  cc (maximum  $< 30$  Gy) and small bowel  $V_{20} < 20$  cc (maximum  $< 30$  Gy) where  $V_{25}$  and  $V_{20}$  are the corresponding organ volumes receiving at least 25 or 20 Gy, respectively.

## Pathological examination

Hematoxylin and eosin-stained 5- $\mu\text{m}$  sections from formalin-fixed paraffin-embedded samples of the native explants were reviewed by a dedicated pathologist (MB). Complete response was considered as the absence of residual tumor, and partial response was defined as 30–99% necrosis, as outlined in a previous report [25].

## Statistical analysis

Data are presented as median (minimum–maximum). Nonparametric comparisons between two groups were conducted by the Wilcoxon test. Parametric comparisons between two groups were conducted by *t* test. Survival curve was evaluated with the Kaplan–Meier Method. Spearman correlation was used to analyze the correlation between tumors size on CT/MRI scan and pathological size in the explanted livers. Data were analyzed using JMP 10.0.2 (SAS Institute, Cary, NC).

## Results

The patient demographics are shown in Table 1. Median initial tumor size on CT or MRI was 3.2 cm (2.0–8.9). Median radiation dose was 45 Gy (36–50 Gy). SBRT was well tolerated, and there was no acute toxicity grade 3 or above. There was no incidence of grade  $> 2$  RILD. Only 1 patient had progression of Child–Pugh score from A to B at 6 months post-SBRT (Table 1). Alpha fetoprotein (AFP) was monitored as a HCC tumor marker before and after SBRT. AFP-level post-SBRT was 12.5 ng/mL (1.5–278.9 ng/mL) and significantly lower than the pre-SBRT level of 28.1 ng/mL (3.5–727.8 ng/mL) ( $p < 0.05$ ) (Table 1). Median MELD score before SBRT was 11 (6–19), and median MELD score on the date of liver transplant was 12.5 (7–35). There was no significant difference in MELD score before and after SBRT (at time of liver transplant) (Fig. 1).

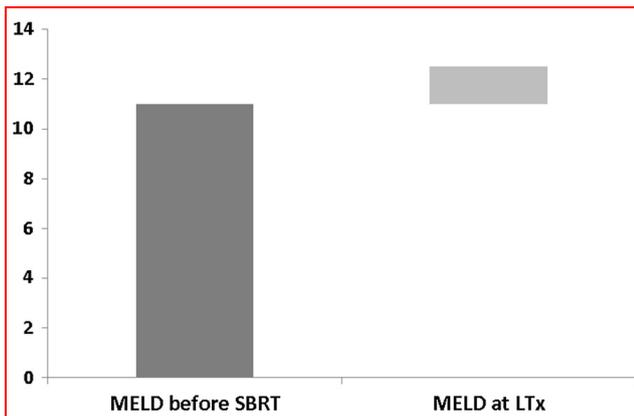
Median wait time for liver transplant was 237 days (55–1083 days). Median length of follow-up after liver transplant was 883 days (81–2314 days).

Two patients dropped off of the liver transplant waiting list due to de novo lesions. Both of these patients were initially outside of Milan criteria with downsized tumors. A third patient was delisted due to well-controlled HCC and advanced age. Nineteen patients underwent deceased donor liver transplants including one patient with downsized disease initially outside Milan criteria. Patient survival is shown in Fig. 1. One-year and 3-year actuarial survival rate were 88% and 81%, respectively (Fig. 2). No patient had recurrence of HCC after liver transplant during this study period.

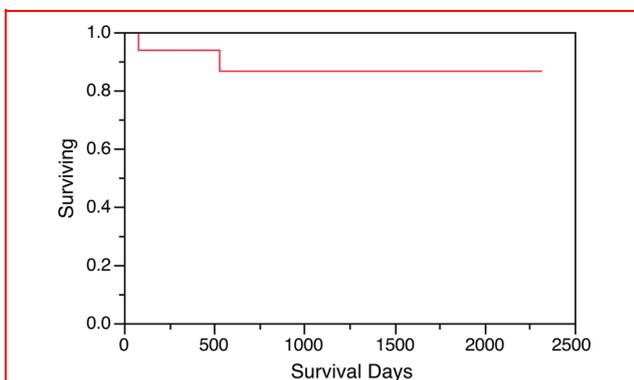
On examination of the explanted livers, 5 cases showed complete response (27.8%). In these cases, no residual HCC was detected, the tumor bed showing only sclerotic collagen or cirrhosis. Two showed partial response: one with extensive coagulative necrosis (Fig. 3a) and another

**Table 1** Demographics of liver transplant recipients

Age	58 (52–71)
Sex (male:female)	20 patients:2 patients
Liver disease	15HCV, 4ETOH, 3NASH
Child–Pugh (pre-SBRT)	A: 11 cases, B: 9 cases, C: 2 cases
Child–Pugh (post-SBRT)	A: 10 cases, B: 10 cases, C: 2 cases
Initial tumor size	3.2 cm (2.0–8.9 cm)
Radiation dose	45 Gy (36–50 Gy)
Fraction	5 (4–6)
MELD (pre-SBRT)	11 (6–19)
MELD (at LTx)	12.5 (7–35)
AFP (pre-SBRT)	28.1 ng/mL (3.5–727.8 ng/mL)
AFP (post-SBRT)	12.5 ng/mL (1.5–278.9 ng/mL)



**Fig. 1** MELD score change before SBRT and at the time of liver transplant



**Fig. 2** Patient survival of liver transplant for HCC post-SBRT

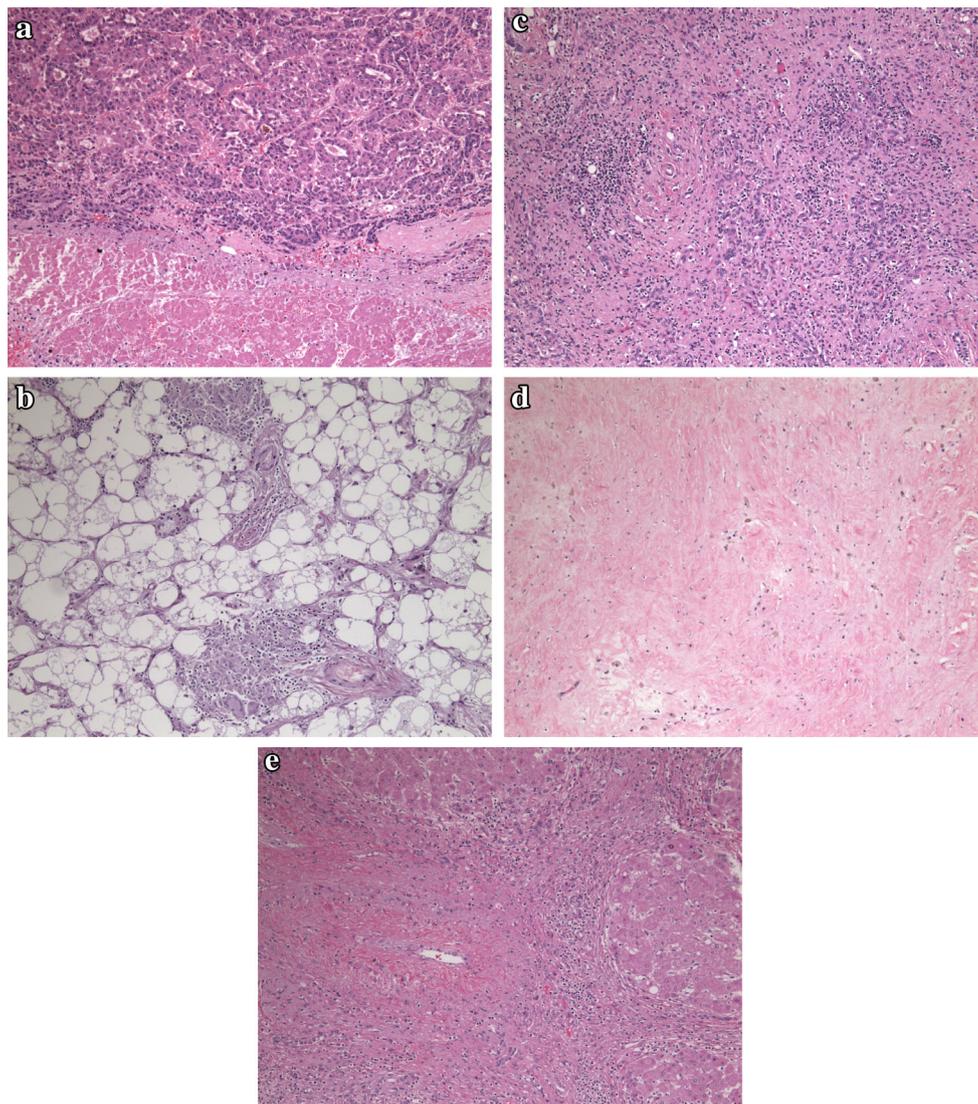
with extensive degenerated clear cells, CD68 positive macrophages and epithelioid granulomas (Fig. 3b). Three cases showed minor coagulative necrosis, and 8 cases showed no necrosis; in all these cases, the tumor bed showed changes which varied from extensive ductular reaction (Fig. 3c), to sclerotic collagen (Fig. 3d), to micronodular cirrhosis only (Fig. 3e). The median viable tumor size in explanted livers was 0.9 cm (0–3.2 cm), significantly smaller than original tumor size ( $p < 0.01$ ) (Fig. 4).

The length of time between SBRT and liver transplant was compared in the two groups, those with complete pathological response and those without complete response. There was no significant difference in response between the two groups (Fig. 5). Furthermore, we analyzed tumor size measured on CT or MRI compared to tumor size in explanted livers. CT or MRI images from before liver transplant were used. There is a significant correlation between tumor size on scans and in explanted livers (Spearman  $\rho = 0.617$ ,  $p = 0.006$ ) (Fig. 6).

## Discussion

SBRT has emerged as a minimally invasive local therapy in the management of primary liver tumors. Multiple retrospective and prospective studies of SBRT onto HCC have shown the safety and efficacy in Phase I and II trials, although there have been no prospective randomized trials of SBRT. Keane et al. reported that local control of HCC ranges rate of 64–100% at 1 year, and overall survival ranges from 48 to 100% [26]. The effects of SBRT were particularly impressive in patients with small tumors, with 1-year local control rates of 95–100% and 1-year overall survival rates of 99–100% seen in two series of SBRT for tumors measuring 1–5 cm [27, 28]. In addition, SBRT was a well-tolerable procedure with assessing quality-of-life metrics [29]. In this study, we achieved excellent local control of HCC in patients who were waiting for liver transplant. It should be noted that more than half of the tumors were larger than 3 cm, and some of them were in proximity to major blood vessels or biliary systems, or next to the diaphragm or liver capsule. Those lesions could be challenging for treatment with RFA or TACE. In addition, one half of patients had advanced liver cirrhosis (Child–Pugh B or C), but they tolerated SBRT well with minimal side effects in contrary to other reports [30–32]. It has to be noted that all our patients completed functional treatment planning with  $^{99m}\text{Tc}$ -sulfur colloid 3D-CT/SPECT which allowed accurate delineation of residual functionally active hepatic parenchyma during 3D-conformal radiotherapy planning. We postulate that tailoring hepatic dose-volume constraints to residual functionally active liver parenchyma, with its subsequent conformal avoidance from high-dose irradiation during SBRT, may contribute to reduction in hepatic toxicity in patients with advanced hepatic cirrhosis. After SBRT treatment, patients were routinely followed with MRI or CT imaging. Findings on MRI or CT in terms of tumor size were well correlated with pathological findings of explanted tumors. These results suggest that MRI or CT can appropriately follow tumors after SBRT. In our study, SBRT was the first choice for local control of HCC. Recently, a study of SBRT as a bridge to liver transplant comparing TACE and RFA was reported [33]. The study showed drop rate, complication rate and actuarial survival were similar between SBRT, TACE and RFA groups. It also supported that SBRT could be an alternative to conventional bridge therapies to liver transplant.

Several studies have reported the actual incidence of recurrent HCC after transplantation. The HCC recurrence rate after liver transplantation varies from 6.4 to 40% previously [6]. Less than 15% recurrence of HCC rate was reported within Milan criteria without local therapies. [34].

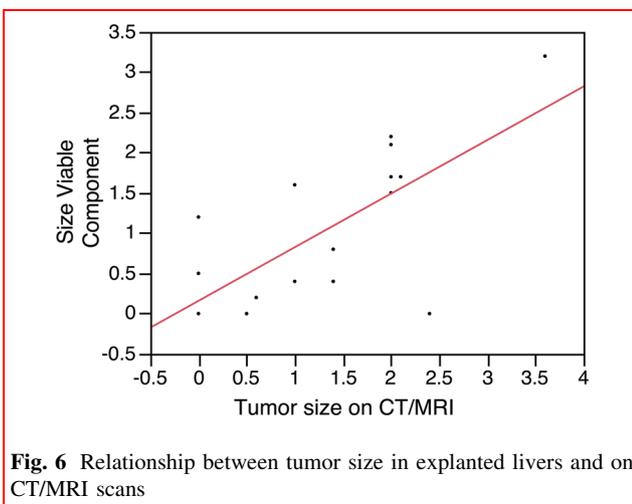
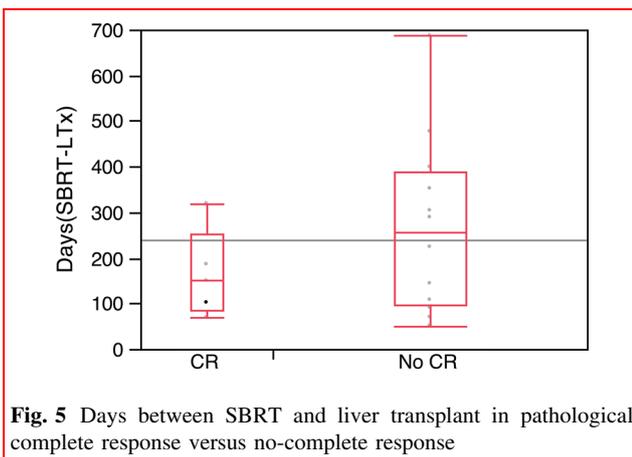
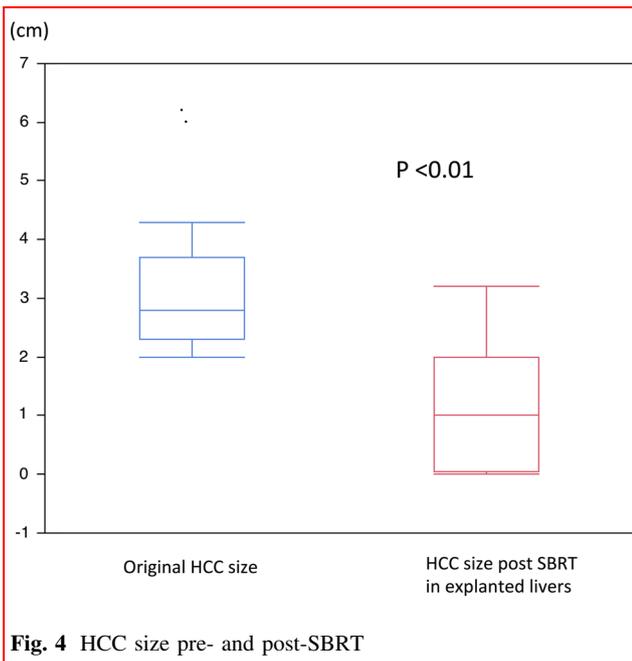


**Fig. 3** **a** Coagulative necrosis. Residual viable hepatocellular carcinoma with pseudoglands is seen in the upper portion. Trabecular architecture is still recognizable in the coagulative necrosis in the lower portion. **b** Clear cell degeneration. Hepatocyte cytoplasm is replaced by clear spaces and wispy material. Two epithelioid granulomas are seen in the upper and lower central portions.

**c** Ductular reaction. Hepatocytes are lost, leaving residual bile ductules, lymphocytes and small vessels. **d** Sclerosis. The hepatic parenchyma is replaced by dense collagen with scattered siderophages. **e** Cirrhosis. At left is a sclerosed vessel, which is surrounded by fibrous septa, ductular reaction and regenerative hepatocyte nodules

It is controversial whether bridging therapies can reduce recurrence rate of HCC while waiting for liver transplant. Regarding TACE, it is reported that recurrence rates of HCC were 7.6% and 10.7% in two large series within the Milan criteria who were treated with TACE before liver transplantation [35, 36]. Millonig et al. also observed that patients with complete response experienced longer free recurrence rate than patients with viable tumor in explanted livers [35]. There is another study of 150 patients with HCC within Milan criteria who underwent liver transplant by Tsochatzis et al. [37]. In the study, 45% of patients received trans-arterial embolization (TAE) with polyvinyl alcohol particles or TACE before liver transplantation, and

remaining 55% of patients did not receive any treatment for HCC before liver transplant. HCC recurrence after liver transplantation was significantly lower in the TAE-TACE group (6%) than in no treatment group (18.1%). On the other hand, 7 studies were reported about RFA for HCC as a bridging treatment to liver transplant. [34]. A total of 231 patients were studied over follow-up periods of 15–41 months (mean 28 months). Only 8 patients were found to have HCC recurrence after liver transplant (3.5%), and the rate of recurrence ranged between 0% and 13%. There was no recurrence of HCC after liver transplantation in our study, although we have midterm follow-up. These results also suggest that SBRT pre-liver transplant can



reduce recurrence after liver transplantation. Regarding pathologic response in the explanted livers, our study yielded 28% (5/18) complete response, similar to the 27% (3/11) of the previous SBRT report of O'Connor et al. [38] and higher than the 14% (3/22) found by Facciuto et al. [25]. As previously noted [38], this could potentially be explained by the higher SBRT doses used in the 2 more recent studies: 45 Gy (30–60 Gy, our study), 51 Gy (33–54 Gy, O'Connor) versus 24–36 Gy (Facciuto).

High AFP levels are predictive of a high risk of recurrence after liver transplantation. AFP has been reported to reflect malignant biology in early HCCs. It is associated with vascular invasion and intrahepatic metastases and is not expressed in well-differentiated HCC [39]. Pretransplant AFP levels higher than 1000 ng/mL [40] or 300–400 ng/mL [41, 42] have been associated with reduced post-transplantation survival. AFP was significantly decreased after SBRT in this study, and our results suggest that SBRT is effective at controlling aspect of tumor biology as well.

There are several limitations on this study including small number of patients and no direct comparison of other loco-regional modalities. We also recognize that SBRT, like other modalities, has its own limitations: loss of functional liver volume in patients with advanced cirrhosis and the tumor's proximity to adjacent organs (i.e., stomach, duodenum and colon). However, our data suggest that SBRT in selected patients can be an equal or more effective modality to control HCC, while waiting for liver transplant based on our experience of minimal dropout rate from the list and no recurrence of HCC after liver transplant.

#### Compliance with ethical standards

**Conflict of interest** The authors who have taken part in this study declared that they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

#### References

1. El-Serag HB, Mason AC (1999) Rising incidence of hepatocellular carcinoma in the United States. *N Engl J Med* 340:745–750
2. Mazzaferro V, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F et al (1996) Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med* 334:693–699
3. Abdelmaksoud AH, Mandooh S, Nabeel MM, Elbaz TM, Shousha HI, Monier A et al (2017) Portal vein thrombosis in unresectable Hcc cases: a single center study of prognostic factors and management in 140 patients. *Asian Pac J Cancer Prev* 18(1):183–188
4. Sellers MT, Huggins S, Kegley K, Pollinger HS, Shrestha R, Johnson MW et al (2013) Multivariate analysis of prognostic factors for survival following doxorubicin-eluting

- bead transarterial chemoembolization for hepatocellular carcinoma. *J Vasc Interv Radiol* 24(5):647–654
5. Lopez PM, Villanueva A, Llovet JM (2006) Systematic review: evidence-based management of hepatocellular carcinoma—an updated analysis of randomized controlled trials. *Aliment Pharmacol Ther* 23:1535–1547
  6. Pompili M, Francica G, Ponziani FR, Iezzi R, Avolio AW (2013) Bridging and downstaging treatments for hepatocellular carcinoma in patients on the waiting list for liver transplantation. *World J Gastroenterol* 19(43):7515–7530
  7. [https://optn.transplant.hrsa.gov/media/1140/policy\\_notice\\_12-2014.pdf](https://optn.transplant.hrsa.gov/media/1140/policy_notice_12-2014.pdf)
  8. Herfarth KK, Debus J, Lohr F, Bahner ML, Rhein B, Fritz P et al (2001) Stereotactic single dose radiation therapy of liver tumors: results of a phase I/II trial. *J Clin Oncol* 19:164–170
  9. Rusthoven KE, Kavanagh BD, Cardenes H, Stieber VW, Burri SH, Feigenberg SJ et al (2009) Multi-institutional phase I/II trial of stereotactic body radiation therapy for liver metastases. *J Clin Oncol* 27:1572–1578
  10. Hoyer M, Roed H, Traberg Hansen A, Ohlhuis L, Petersen J, Nellesmann H et al (2006) Phase II study on stereotactic body radiotherapy of colorectal metastases. *Acta Oncol* 45:823–830
  11. Wulf J, Hädinger U, Oppitz U, Thiele W, Ness-Dourdoumas R, Flentje M (2001) Stereotactic radiotherapy of targets in the lung and liver. *Strahlenther Onkol* 177:645–655
  12. Méndez Romero A, Wunderink W, Hussain SM, De Pooter JA, Heijmen BJ, Nowak PC 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
  13. Méndez Romero A, Wunderink W, van Os RM, Nowak PJ, Heijmen BJ, Nuytens JJ et al (2008) Quality of life after stereotactic body radiation therapy for primary and metastatic liver tumors. *Int J Radiat Oncol Biol Phys* 70:1447–1452
  14. Chiba T, Tokuuye K, Matsuzaki Y, Sugahara S, Chuganji Y, Kagei K et al (2005) Proton beam therapy for hepatocellular carcinoma: a retrospective review of 162 patients. *Clin Cancer Res* 11:3799–3805
  15. Kirichenko A, Gayou O, Parda D, Kudithipudi V, Tom K, Khan A et al (2016) Stereotactic body radiotherapy (SBRT) with or without surgery for primary and metastatic liver tumors. *HPB (Oxford)* 18:88–97
  16. Cancer Therapy Evaluation Program, Common Terminology Criteria for Adverse Events, Version 4.0, (<http://ctep.cancer.gov>), Publish Date: May 28, 2009
  17. Kamath PS, Wiesner RH, Malincho M, Kremers W, Therneau TM, Kosberg CL et al (2001) A model to predict survival in patients with end-stage liver disease. *Hepatology* 33:464–470
  18. Gayou O, Day E, Kirichenko A (2012) A method for registration of single photon emission computed tomography (SPECT) and computed tomography (CT) images for liver stereotactic radiotherapy (SRT). *Med Phys* 39:7398–7401
  19. Urata K, Kawasaki S, Matsunami H, Hashikura Y, Ikegami T, Ishizone S et al (1995) Calculation of child and adult standard liver volume for liver transplantation. *Hepatology* 21:1317–1321
  20. Kennedy A, Nag S, Salem R, Murthy R, McEwan AJ, Nutting C et al (2007) Recommendations for radioembolization of hepatic malignancies using yttrium-90 microsphere brachytherapy: a consensus panel report from the radioembolization brachytherapy oncology consortium. *Int J Radiat Oncol Biol Phys* 68:13–23
  21. Penna C, Nordlinger B (2002) Colorectal metastasis (liver and lung). *Surg Clin North Am* 82:1075–1090
  22. Leibel SA, Pajak TF, Massullo V, Order SE, Komaki RU, Chang CH (1987) A comparison of misonidazole sensitized radiation therapy to radiation therapy alone for the palliation of hepatic metastases: results of a Radiation Therapy Oncology Group randomized prospective trial. *Int J Radiat Oncol Biol Phys* 13:1057–1064
  23. Russell AH, Clyde C, Wasserman TH, Turner SS, Rotman M (1993) Accelerated hyperfractionated hepatic irradiation in the management of patients with liver metastases: results of the RTOG dose escalating protocol. *Int J Radiat Oncol Biol Phys* 27:117–123
  24. Goodman KA, Wiegner EA, Maturen KE, Zhang Z, Mo Q, Yang G (2010) Dose-escalation study of single-fraction stereotactic body radiotherapy for liver malignancies. *Int J Radiat Oncol Biol Phys* 78:486–493
  25. Facciuto ME, Singh MK, Rochon C, Sharma J, Gimenez C, Katta U et al (2012) Stereotactic body radiation therapy in hepatocellular carcinoma and cirrhosis: evaluation of radiological and pathological response. *J Surg Oncol* 105:692–698
  26. Keane FK, Wo JY, Zhu AX, Hong TS (2016) Liver-directed radiotherapy for hepatocellular carcinoma. *Liver Cancer* 5:198–209
  27. Sanuki N, Takeda A, Oku Y, Mizuno T, Aoki Y, Eriguchi T et al (2014) Stereotactic body radiotherapy for small hepatocellular carcinoma: a retrospective outcome analysis in 185 patients. *Acta Oncol* 53:399–404
  28. Honda Y, Kimura T, Aikata H, Kobayashi T, Fukuhara T, Masaki K et al (2013) Stereotactic body radiation therapy combined with transcatheter arterial chemoembolization for small hepatocellular carcinoma. *J Gastroenterol Hepatol* 28:530–536
  29. Klein J, Dawson LA, Jiang H, Kim J, Dinniwel R, Brierley J et al (2015) Prospective longitudinal assessment of quality of life for liver cancer patients treated with stereotactic body radiation therapy. *Int J Radiat Oncol Biol Phys* 93:16–25
  30. Cheng JC, Wu JK, Huang CM, Liu HS, Huang DY, Cheng SH et al (2002) Radiation-induced liver disease after three-dimensional conformal radiotherapy for patients with hepatocellular carcinoma: Dosimetric analysis and implication. *Int J Radiat Oncol Biol Phys* 54:156–162
  31. Cheng JC, Wu JK, Lee PC, Liu HS, Jian JJ, Lin YM et al (2004) Biologic susceptibility of hepatocellular carcinoma in patients treated with radiotherapy to radiation induced liver disease. *Int J Radiat Oncol Biol Phys* 60:1502–1509
  32. Liang SX, Zhu XD, Xu ZY, Zhu J, Zhao JD, Lu HJ et al (2006) Radiation-induced liver disease in three-dimensional conformal radiation therapy for primary liver carcinoma: the risk factors and hepatic radiation tolerance. *Int J Radiat Oncol Biol Phys* 65:426–434
  33. Sapisochin G, Barry A, Doherty M, Fischer S, Goldaracena N, Rosales R et al (2017) Stereotactic body radiotherapy vs. TACE or RFA as a bridge to transplant in patients with hepatocellular carcinoma. An intention-to-treat analysis. *J Hepatol* 67(1):92–99
  34. Llovet JM, Burroughs A, Bruix J (2003) Hepatocellular carcinoma. *Lancet* 362:1907–1917
  35. Millonig G, Graziadei IW, Freund MC, Jaschke W, Stadlmann S, Ladurner R et al (2007) Response to preoperative chemoembolization correlates with outcome after liver transplantation in patients with hepatocellular carcinoma. *Liver Transpl* 13:272–279
  36. Alba E, Valls C, Dominguez J, Martinez L, Escalante E, Lladó L, Serrano T (2008) Transcatheter arterial chemoembolization in patients with hepatocellular carcinoma on the waiting list for orthotopic liver transplantation. *AJR Am J Roentgenol* 190:1341–1348
  37. Tsochatzis E, Garcovich M, Marelli L, Papastergiou V, Fatourou E, Rodriguez-Peralvarez ML et al (2013) Transarterial embolization as neo-adjuvant therapy pretransplantation in patients with hepatocellular carcinoma. *Liver Int* 33:944–949
  38. 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
39. Fujioka M, Nakashima Y, Nakashima O, Kojiro M (2001) Immunohistologic study on the expressions of alpha-fetoprotein and protein induced by vitamin K absence or antagonist II in surgically resected small hepatocellular carcinoma. *Hepatology* 34:1128–1134
  40. Yao FY, Ferrell L, Bass NM, Watson JJ, Bacchetti P, Venook A et al (2001) Liver transplantation for hepatocellular carcinoma: expansion of the tumor size limits does not adversely impact survival. *Hepatology* 33:1394–1403
  41. Toso C, Asthana S, Bigam DL, Shapiro AM, Kneteman NM (2009) Reassessing selection criteria prior to liver transplantation for hepatocellular carcinoma utilizing the Scientific Registry of Transplant Recipients database. *Hepatology* 49:832–838
  42. Zheng SS, Xu X, Wu J, Chen J, Wang WL, Zhang M et al (2008) Liver transplantation for hepatocellular carcinoma: Hangzhou experiences. *Transplantation* 85:1726–1732