2024 Midwest Radiation Oncology Symposium

SBRT for Hepatocellular Carcinoma

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No conflict of interest

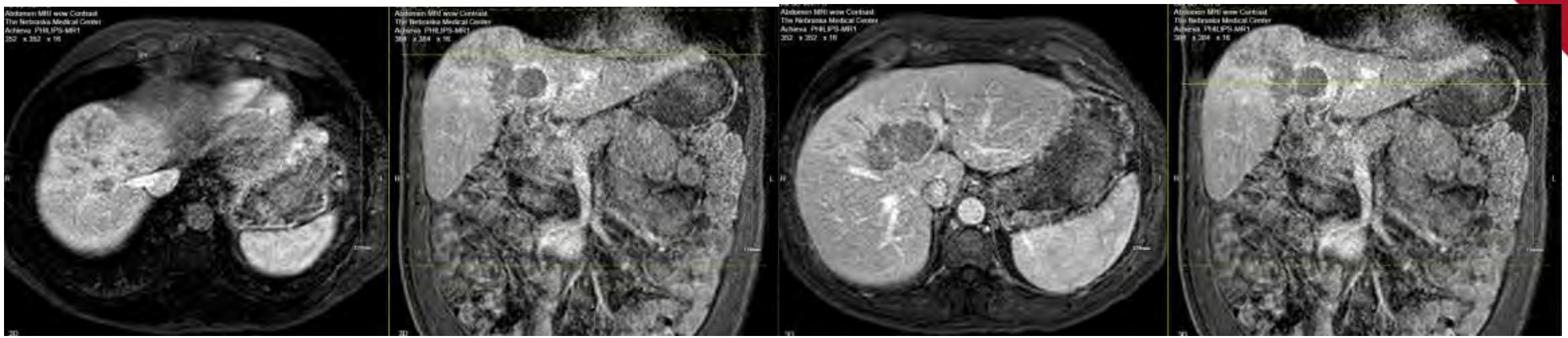
Introduction

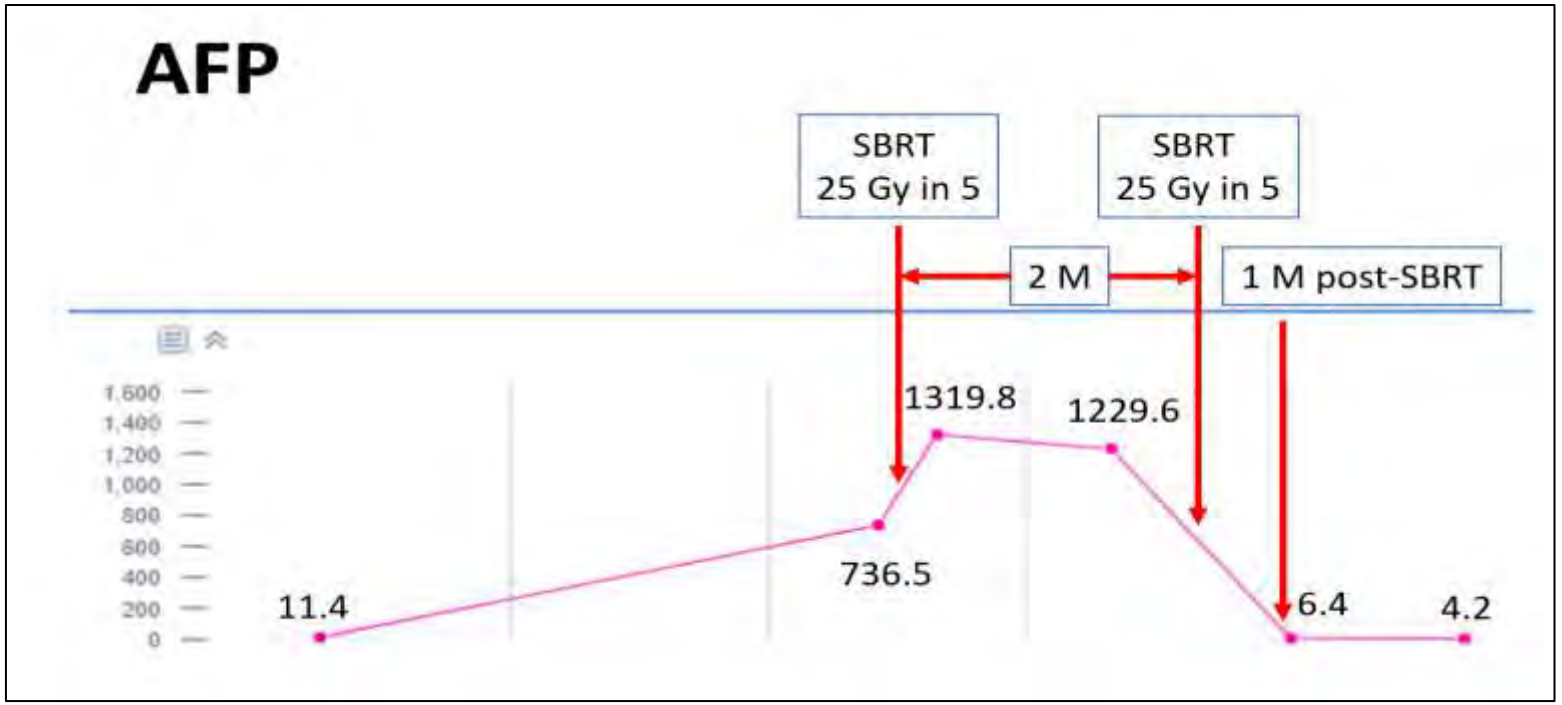
- HCC is a significant global health challenge.
- HCC is often presenting in the context of underlying chronic liver disease, such as cirrhosis caused by hepatitis B or hepatitis C infection, which complicates treatment options.
- HCC accounts for about 85% to 90% of all primary liver cancers.

Learning Objectives

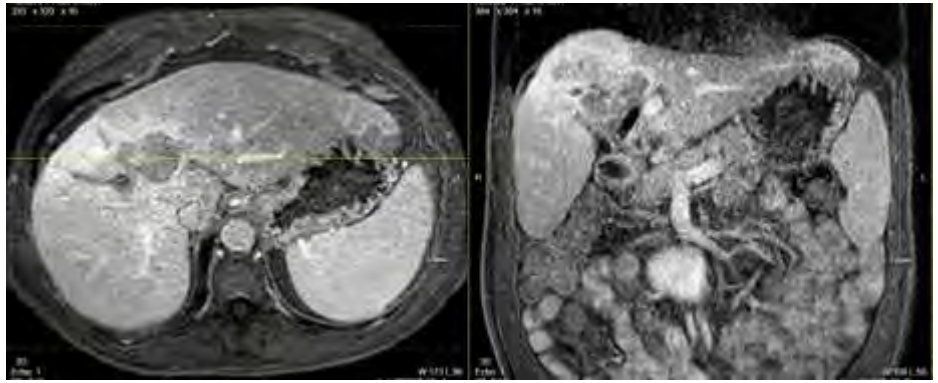
- Case presentation
- Common dose fractionations of SBRT
- Local control rates and failure patterns
- Radiologic and pathologic response rates
- Factors associated with local control and survival
- SBRT-associated toxicities
- SBRT vs. RFAm SBRT vs. TACE-DEB
- SBRT for recurrent HCC
- SBRT as a bridging therapy for liver transplant

Initial presentation



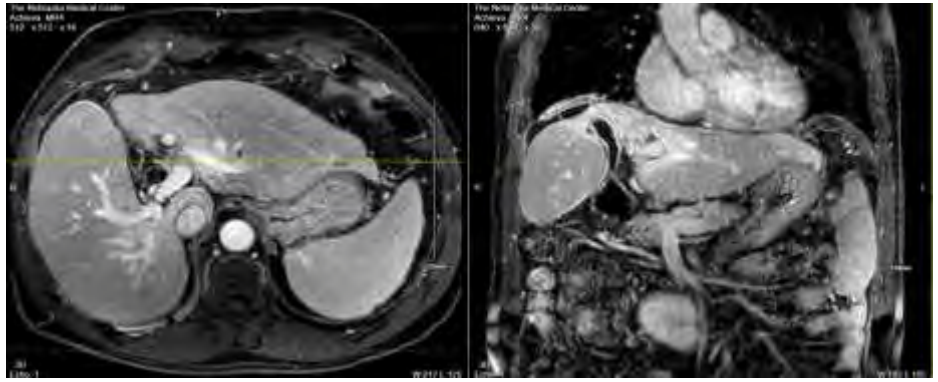


1 month after 1st course of 25 Gy in 5 SBRT

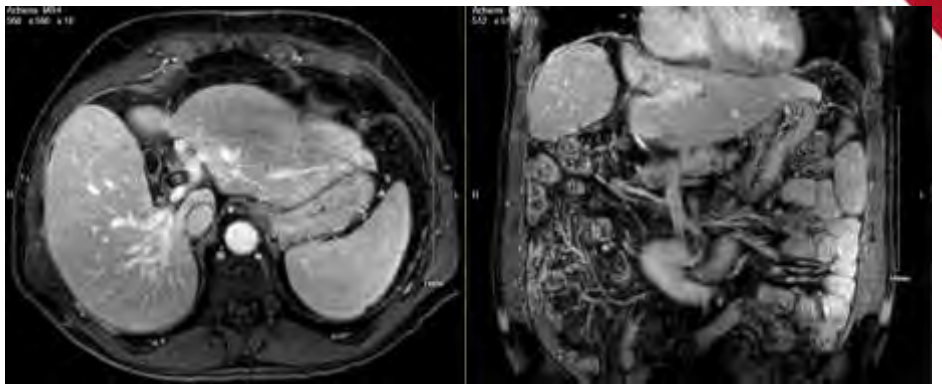


1.5 months after 2nd course of 25 Gy in 5 SBRT

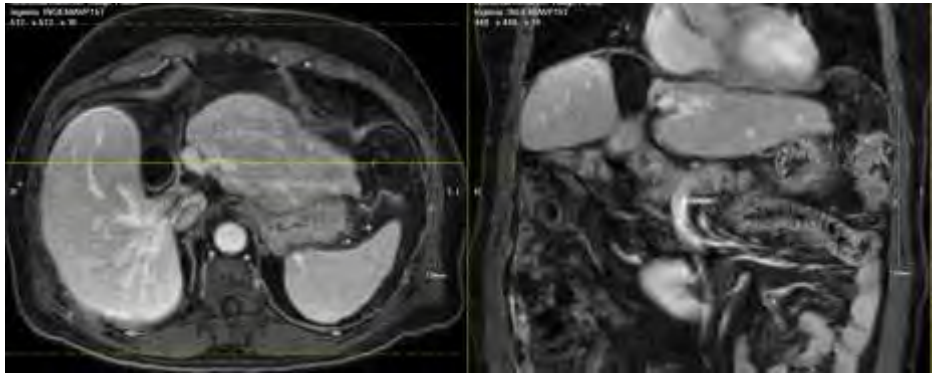
4 months after 2nd course of SBRT



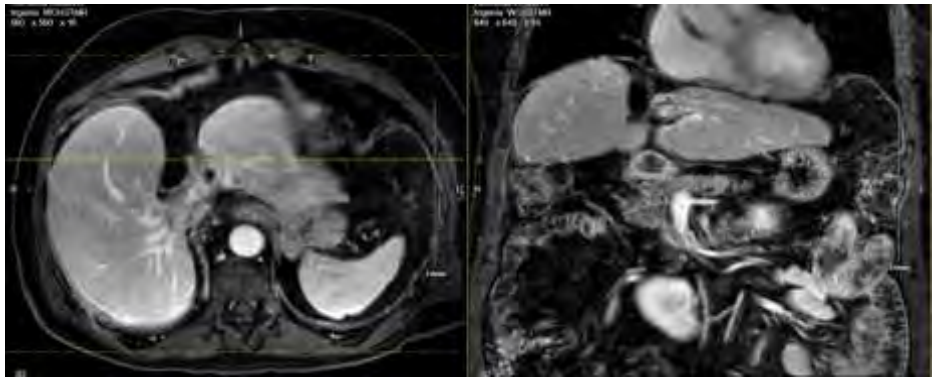
10 months after 2nd course of SBRT

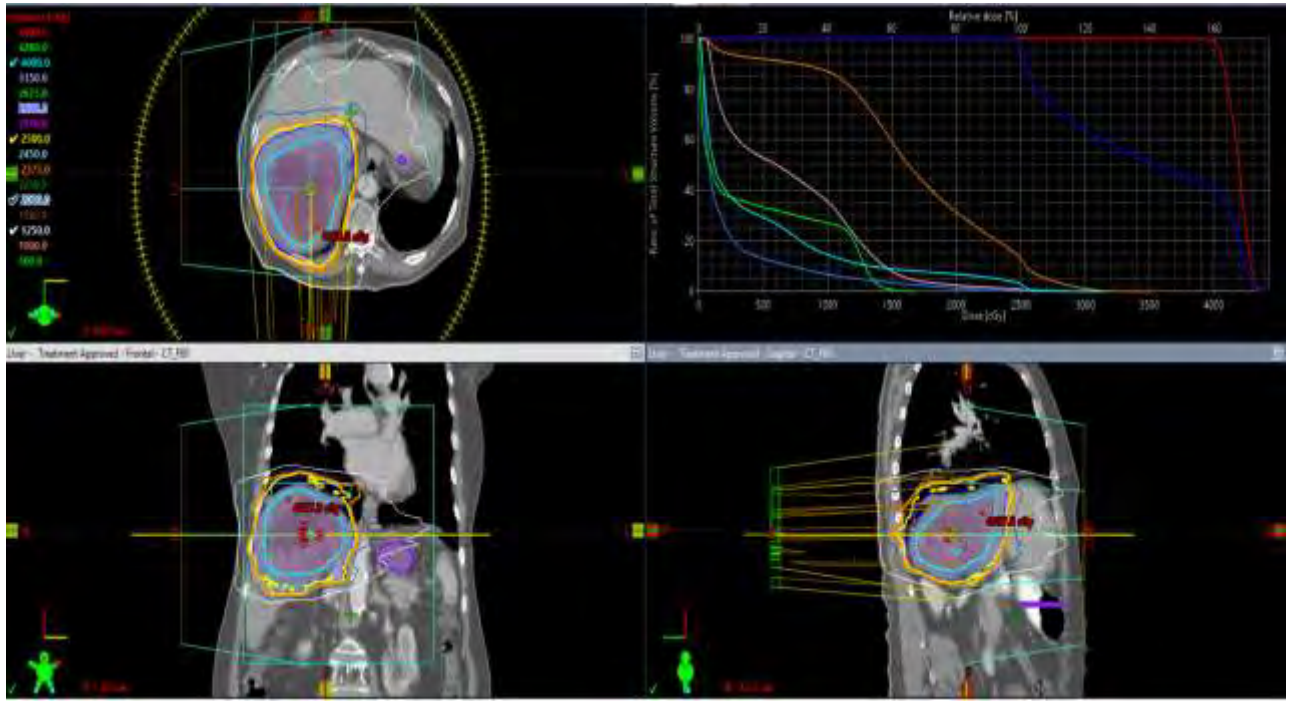


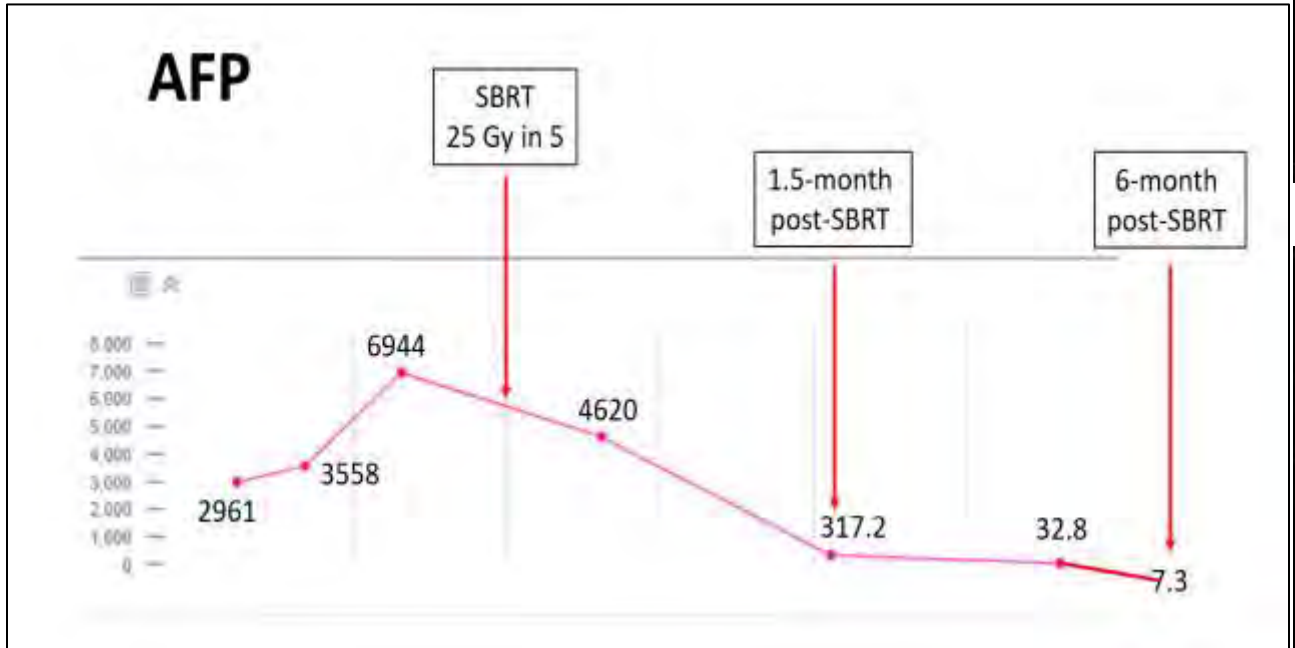
5 years after 2nd course of SBRT



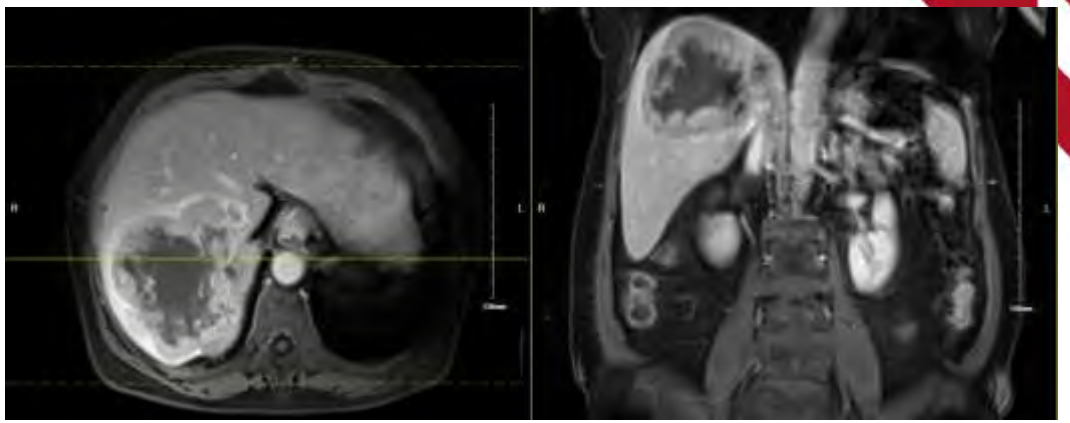
10 years after 2nd course of SBRT



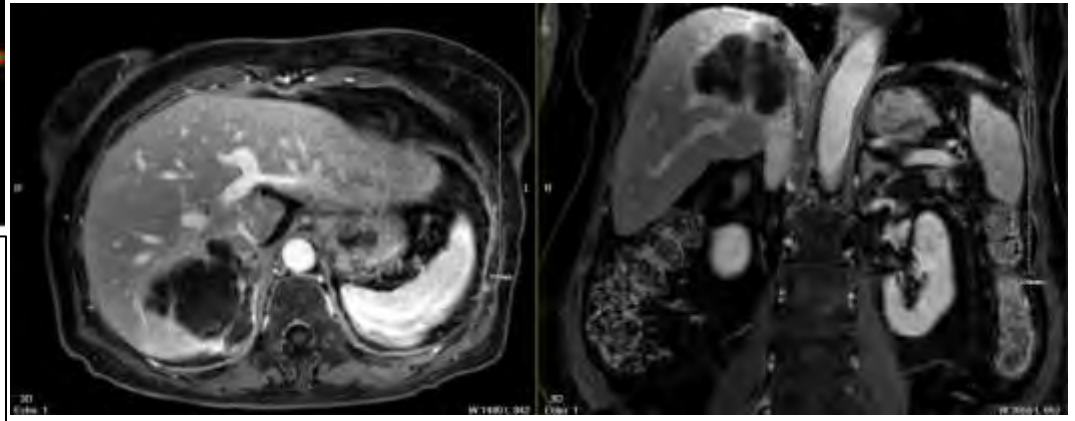




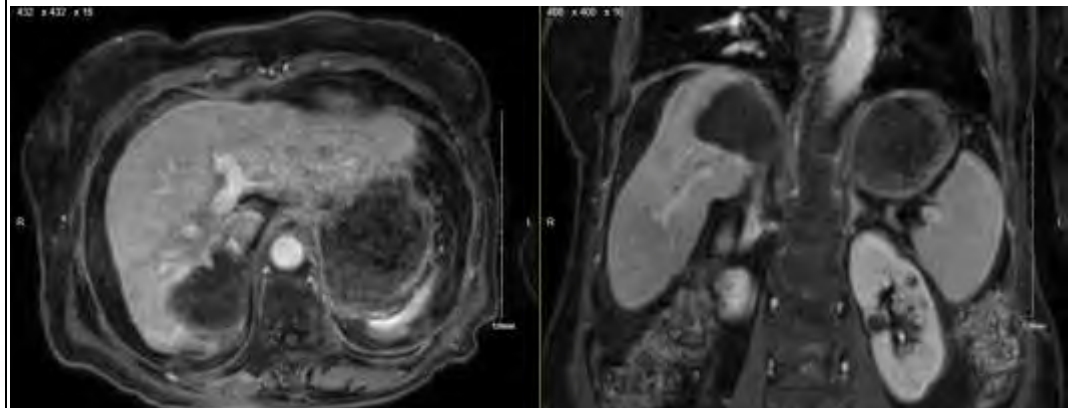
Initial presentation



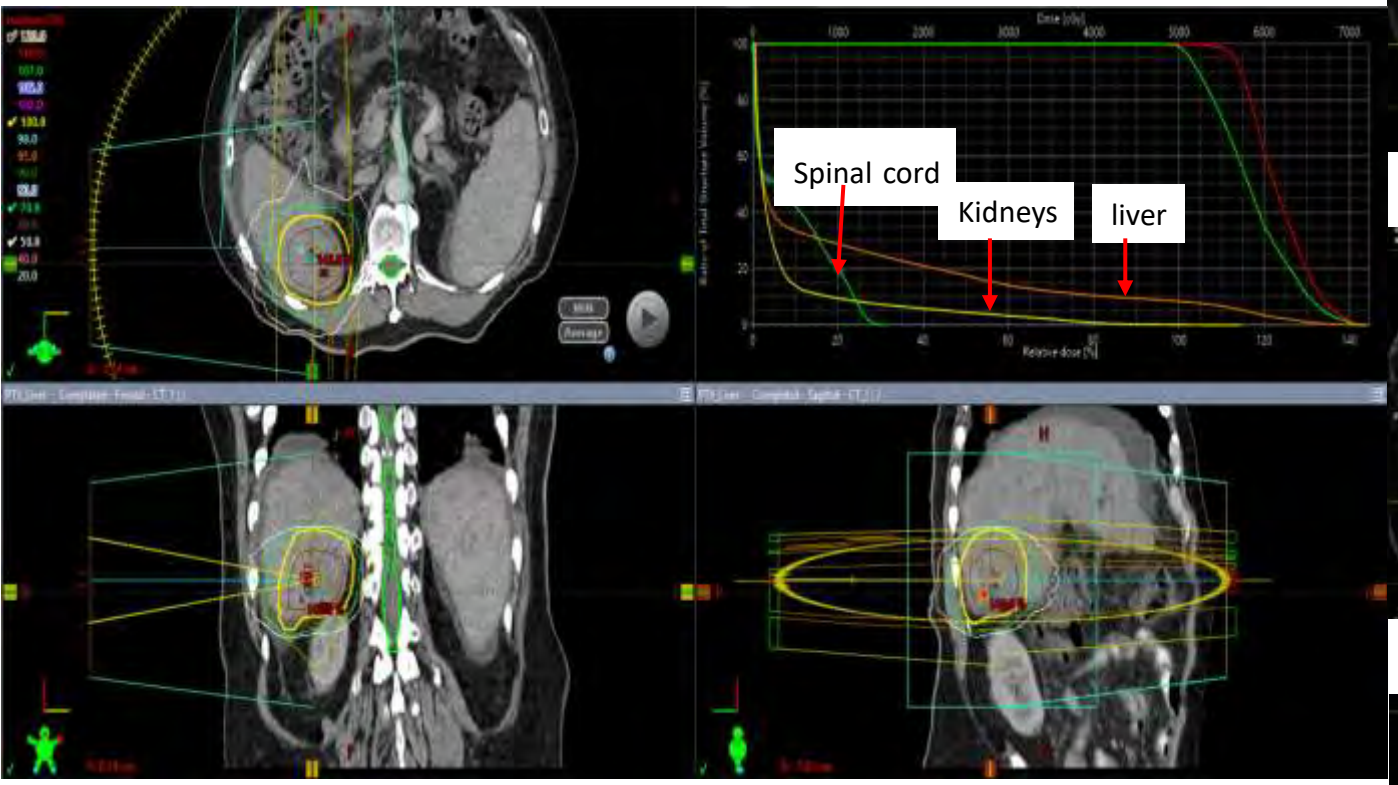
1-month post-SBRT



10-month post-SBRT



50 Gy in 5 fractions



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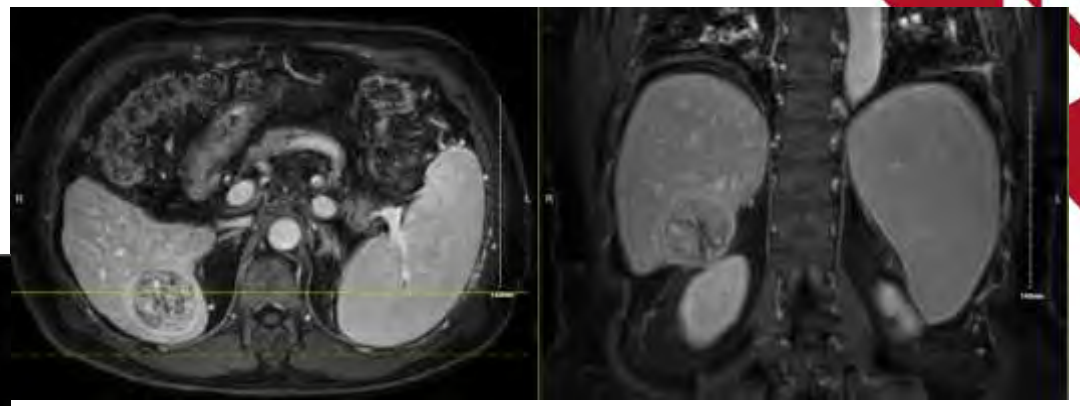
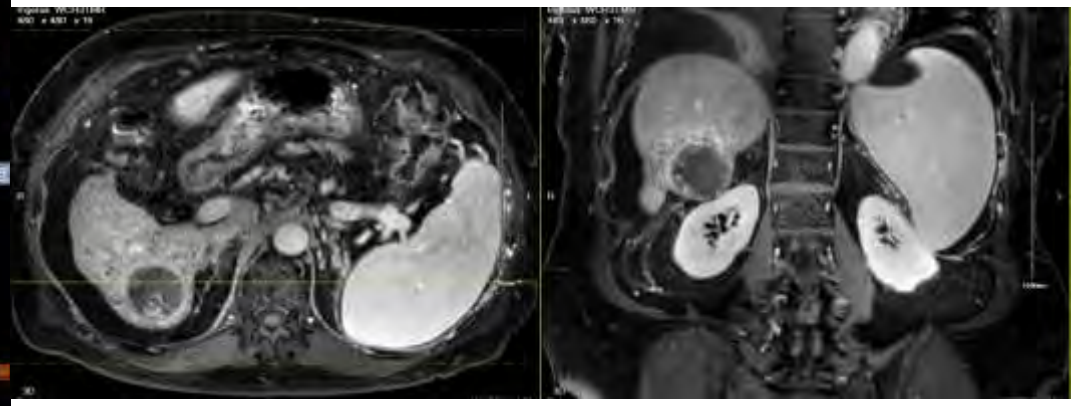
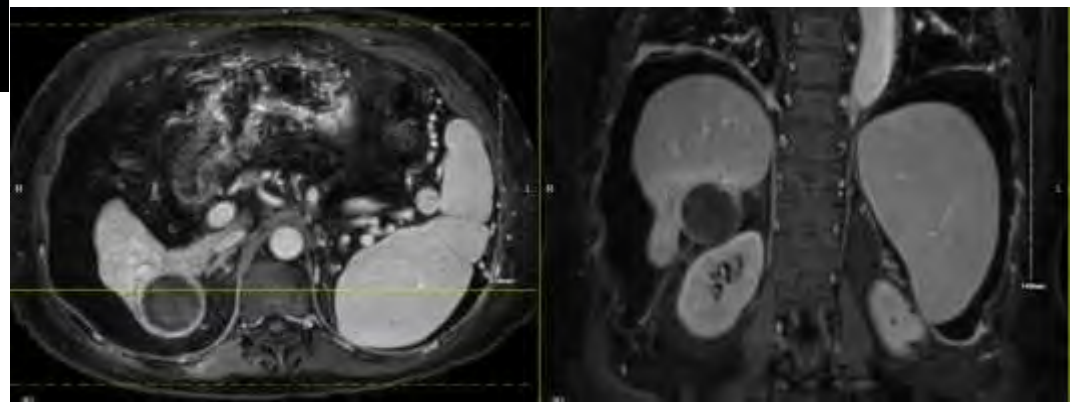


8-month post-SBRT



14-month post-SBRT



External Beam Radiation Therapy for Primary Liver Cancers: An ASTRO Clinical Practice Guideline

Table 6 Recommended EBRT doses and fractionation for HCC and IHC*

Fractionation Regimen	Total dose/fractionation	BED_{10}	References
	Noncirrhotic (primarily IHC): 4000-6000 cGy/3-5 fx	7200-18,000 cGy	110
Ultrahypofractionation	**CP class A: 4000-5000 cGy/3-5 fx**	7200-12,500 cGy	24,27,28,30,34,35, 44,61,86,101,111
	CP class B7: 3000-4000 cGy/5 fx	4800-7200 cGy	28,36,86,94,101
	4000-5400 cGy/6 fx	6700-10,300 cGy	85,94
	5000-6600 cGy/10 fx	7500-11,000 cGy	57,59,83,89,106,113
Moderate hypofractionation	4800 cGy/12 fx	6720 cGy	110
	4500-6750 cGy/15 fx	5900-9800 cGy	32,46,50,62,90,113,114
	6000 cGy/20 fx	7800 cGy	57
	6600-7200 cGy/22 fx	8600-9600 cGy	57,59,112
Standard fractionation	**5040 cGy/28 fx**‡	5947 cGy	114,115
	6000 cGy/30 fx	7200 cGy	114,115
	7700 cGy/35 fx	9400 cGy	9839

Abbreviations: BED_{10} = biologically effective dose assuming an $\alpha/\beta = 10$; CP = Child-Pugh; EBRT = external beam radiation therapy; fx = fractions; HCC = hepatocellular carcinoma; IHC = intrahepatic cholangiocarcinoma.

* Bolded regimens are the most common prescriptions used, based on consensus of the task force. Dose constraints in Table 7 pertain to these most common dose fractionations.

† Lower doses recommended for central lesions in which the maximum point dose to central bile duct(s) cannot be met.

‡ For IHC when combined with concurrent systemic therapy.

January–February 2022, Pages 28-51

Local Control After Stereotactic Body Radiation Therapy for Liver Tumors

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Summary

The authors quantitatively evaluated published experiences with hepatic SBRT to determine local control rates for primary and metastatic liver tumors and examined whether outcomes are affected by SBRT dosing regimen. For primary liver tumors, SBRT provides high rates of durable local control, with no clear evidence of a dose–response relationship for commonly utilized schedules; whereas for liver metastases after SBRT,

Purpose: To quantitatively evaluate published experiences with hepatic stereotactic body radiation therapy (SBRT), to determine local control rates after treatment of primary and metastatic liver tumors and to examine whether outcomes are affected by SBRT dosing regimen.

Methods and Materials: We identified published articles that reported local control rates after SBRT for primary or metastatic liver tumors. Biologically effective doses (BEDs) were calculated for each dosing regimen using the linear-quadratic equation. We excluded series in which a wide range of BEDs was used. Individual lesion data for local control were extracted from actuarial survival curves, and data were aggregated to form a single dataset. Actuarial local control curves were generated using the Kaplan-Meier method after grouping lesions by disease type and BED (<100 Gy_{10} vs >100 Gy_{10}). Comparisons were made using log–rank testing.

Results: Thirteen articles met all inclusion criteria and formed the dataset for this analysis. The 1-, 2-, and 3-year actuarial local control rates after SBRT for primary liver tumors (n = 431) were 93%, 89%, and 86%, respectively. Lower 1- (90%), 2- (79%), and 3-year (76%) actuarial local control rates were observed for liver metastases (n = 290, log–rank $P = .011$). Among patients treated with SBRT for primary liver tumors, there

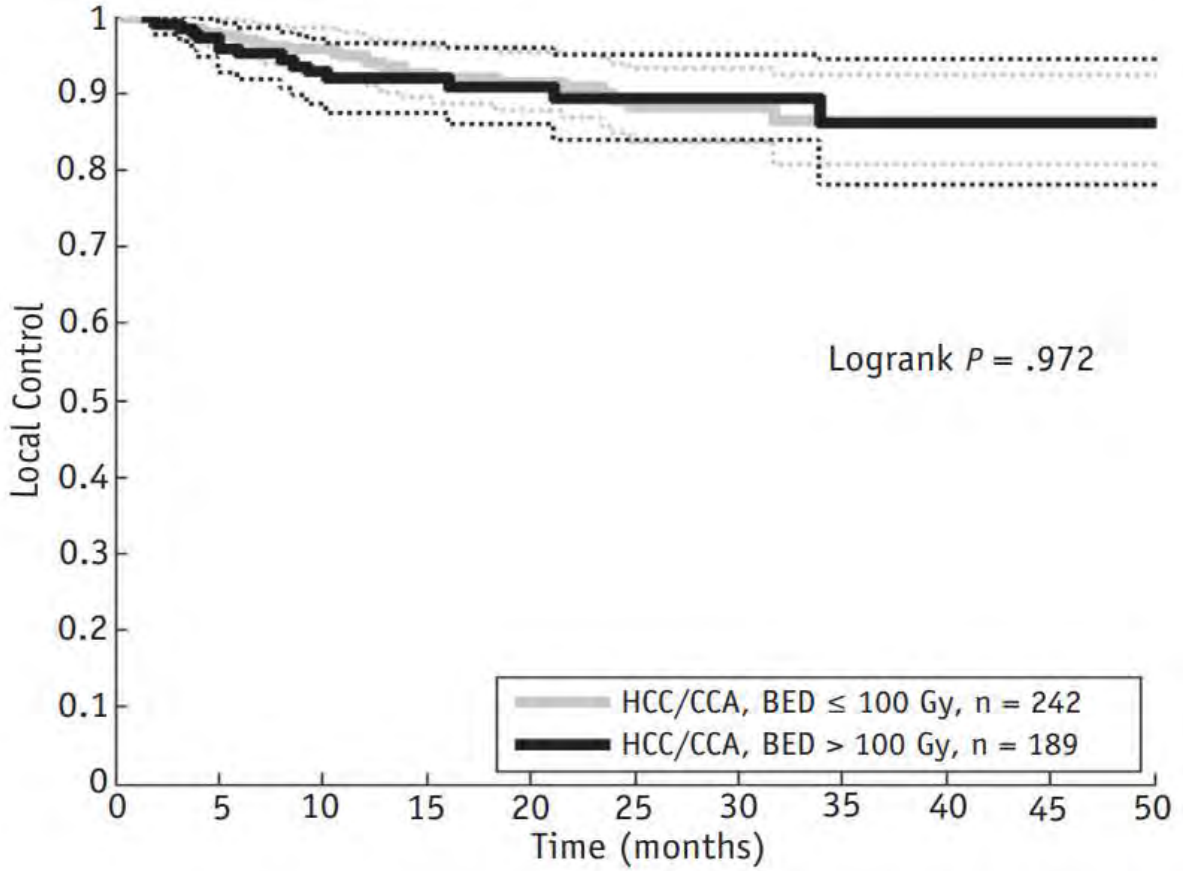

Fig. 2. Kaplan-Meier curves for local control of primary liver tumors after stereotactic body radiation therapy, after grouping patients by biologically effective dose (BED). *Abbreviations:* CCA = cholangiocarcinoma; HCC = hepatocellular carcinoma.

Stereotactic Body Radiation Therapy in Hepatocellular Carcinoma: Evaluation of Radiological and Pathological Response

TABLE II. Radiological and Pathological Response Per Lesion

Radiological response, N = 27		Pathological response, N = 22	
Complete response (CR)	8(30%)	Complete response (CR)	3(14%)
Partial response (PR)	2(7%)	Partial response (PR)	5(23%)
Stable disease (SD)	15(56%)	No response (NR)	14(63%)
Progressive disease (PD)	2(7%)	Pathological responders (CR + PR)	8(37%)
Radiological responders (CR + PR)	10(37%)		

Size of lesions (cm)		
Mean		2.01 ± 0.78
Radiation dose per patient	**BED10**	
2,400 cGy/2 fractions	**52.8 Gy**	8 (29%)
2,800 cGy/4 fractions	**47.6 Gy**	17 (63%)
3,200 cGy/2 fractions	**83.2 Gy**	1 (4%)
3,600 cGy/2 fractions	**100.8 Gy**	1 (4%)

Upon analysis of response time, the higher incidence of response peak for radiological evaluation post-SBRT treatment is at 3 months

Journal of Surgical Oncology 2012;105:692–698

Long-term effect of stereotactic body radiation therapy for primary hepatocellular carcinoma ineligible for local ablation therapy or surgical resection. Stereotactic radiotherapy for liver cancer

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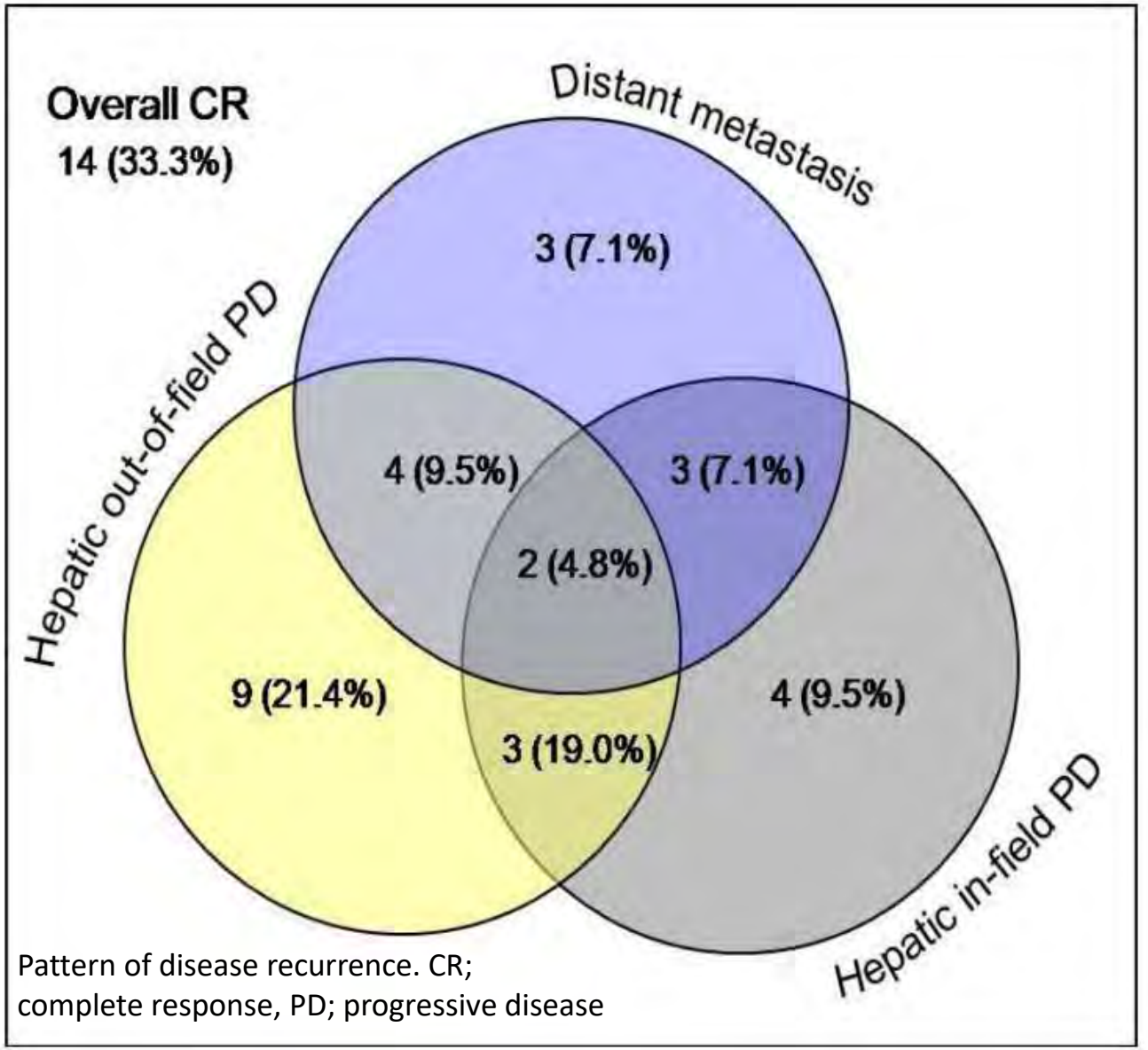
Abstract

Background: We evaluated the long-term effect of stereotactic body radiation therapy (SBRT) for primary small hepatocellular carcinoma (HCC) ineligible for local therapy or surgery.

Methods: Forty-two HCC patients with tumors ≤ 100 cc and ineligible for local ablation therapy or surgical resection were treated with SBRT: 30-39 Gy with a prescription isodose range of 70-85% (median 80%) was delivered daily in three fractions. Median tumor volume was 15.4 cc (3.0-81.8) and median follow-up duration 28.7 months (8.4-49.1).

Results: Complete response (CR) for the in-field lesion was initially achieved in 59.6% and partial response (PR) in 26.2% of patients. Hepatic out-of-field progression occurred in 18 patients (42.9%) and distant metastasis developed in 12 (28.6%) patients. Overall in-field CR and overall CR were achieved in 59.6% and 33.3%, respectively. Overall 1-year and 3-year survival rates were 92.9% and 58.6%, respectively. In-field progression-free survival at 1 and 3 years was 72.0% and 67.5%, respectively. Patients with smaller tumor had better in-field progression-free survival and overall survival rates (<32 cc vs. ≥32 cc, $P < 0.05$). No major toxicity was encountered but one patient died with extrahepatic metastasis and radiation-induced hepatic failure.

Conclusions: SBRT is a promising noninvasive-treatment for small HCC that is ineligible for local treatment or surgical resection.



Pattern of disease recurrence. CR; complete response, PD; progressive disease

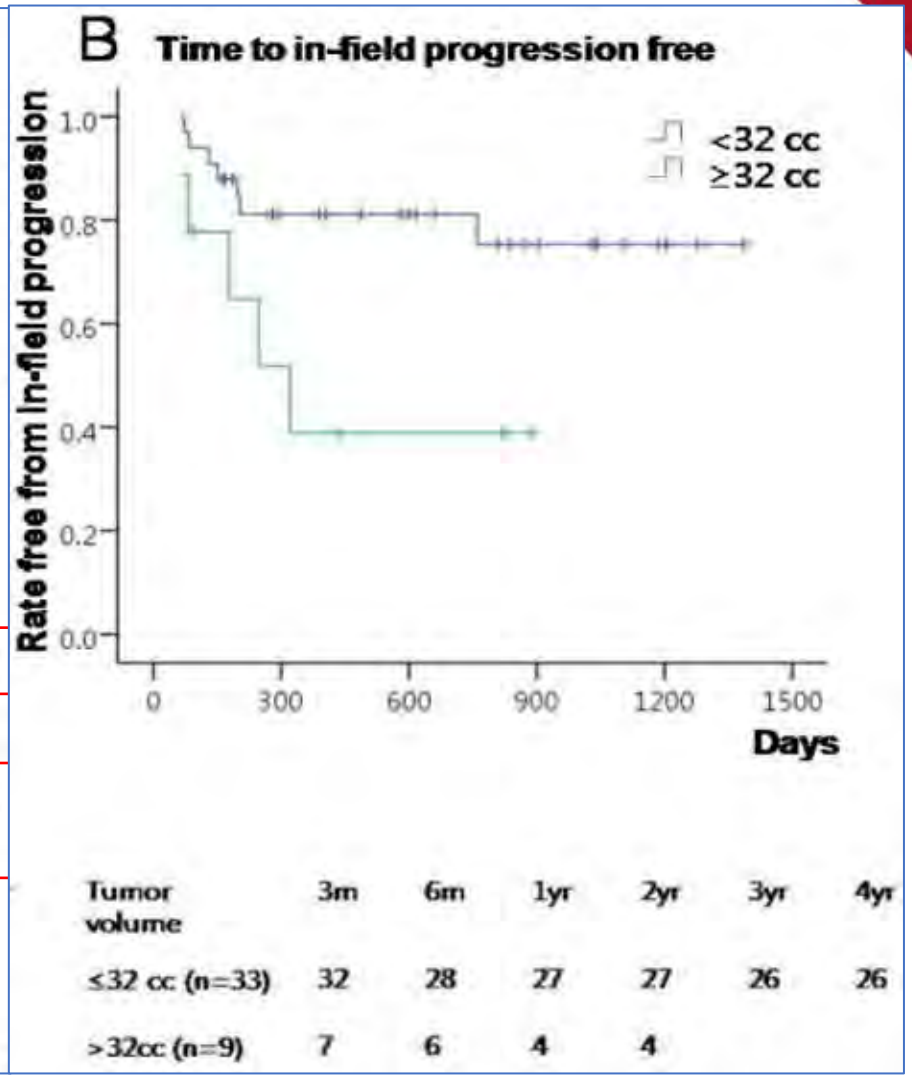
30-39 Gy in 3 fractions

70%:43-56Gy, BED10:103-160Gy
85%:35-46Gy, BED10:76-115Gy

Kwon et al. BMC Cancer 2010, 10:475

Table 3 Factors identified on univariate and multivariate analysis as influencing the survival

	Univariate analysis	Multivariate analysis	
	P	Hazard ratio (95% Confidence Interval)	P
Initial In-field response	0.003		
In-field progression	0.006		
Hepatic out-field recurrence	0.106		
Distant metastasis	0.167	15.495 (1.298-184.896)	0.030
Tumor stage	0.218		
Initial tumor volume 32 cc (< vs. ≥)	0.005	6.328 (1.126-35.574)	0.036
Child-Pugh classification score	0.023		
Age	0.822		



Kwon et al. BMC Cancer 2010, 10:475

A multicenter retrospective cohort study of practice patterns and clinical outcome on radiotherapy for hepatocellular carcinoma in Korea

Aim: To determine the national practice processes of care and outcomes of radiotherapy for hepatocellular carcinoma (HCC) in Korea. *Patients and Methods:* A national survey of 53 institutions nationwide was conducted by requesting data on their experience of radiotherapy for HCC. Among them, 10 institutions were selected for performing more detailed analysis, based on the radiotherapy experience of at least five HCC patients between 2004 and 2005. *Results:* This study covered the treatment of 398 HCC patients for 2 years. Most patients (78%) were in stage III or IV. Radiotherapy was chosen after the failure of other treatments, most frequently transarterial chemoembolization. Radiotherapy was performed predominantly using the three-dimensional conformal technique (3D-CRT, 81.9%) mostly with a total dose of $\geq$45 Gy. In 9.3% of the patients, radiotherapy was performed using radiosurgery. In a biologically effective dose (BED) with 10 Gy of α/β, 4.2–124.3 Gy_{10} was delivered. The median survival time was 12 months, and the 2-year overall survival rate was 27.9%. A tumour size $<$ 5 cm, a negative lymph node and BED $>$ 53.1 Gy_{10} were shown by multivariate analysis to be significant factors for a better prognosis. In a subset analysis for the 326 patients treated with 3D-CRT, better liver function with Child–Pugh class A was shown to be an additional factor for a better prognosis. *Conclusions:* Radiotherapy has been used to treat advanced HCC in various modes, but mostly as a salvage treatment. Although this study was retrospective, it indicates that radiotherapy is a quite effective modality for HCC patients.

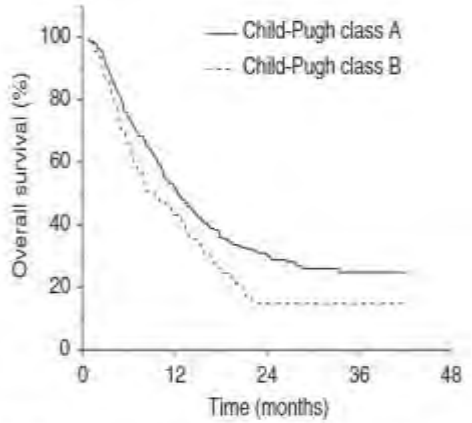


Fig. 1. Overall survival curve according to Child–Pugh class (A vs. B) in patients treated with three-dimensional conformal radiotherapy. Child–Pugh class B significantly reduced survival (P=0.03).

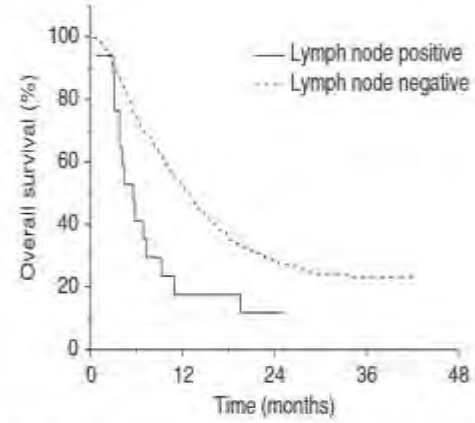


Fig. 3. Overall survival curve according to lymph node positivity (positive vs. negative) in patients treated with three-dimensional conformal radiotherapy. The patients with positive lymph node showed poor prognosis (P=0.003).

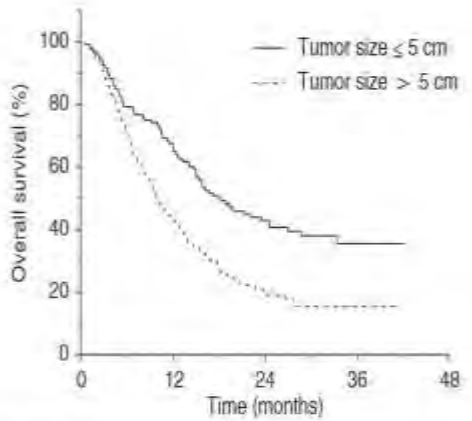


Fig. 2. Overall survival curve according to tumour size ($\leq$ 5 vs. $>$ 5 cm) in patients treated with three-dimensional conformal radiotherapy. More than 5 cm of tumour size was considered adverse factor for overall survival (P=0.000).

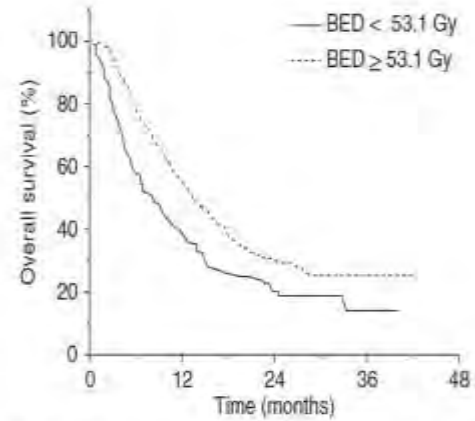


Fig. 4. Overall survival curve according to biological effective dose ($<$ 53.1 vs. $\geq$53.1 Gy_{10}) in patients treated with three-dimensional conformal radiotherapy. Overall survival was higher in patients treated with high dose ($\geq$53.1 Gy_{10}) radiation (P=0.003).

Liver International ISSN 1478-3223, p147-152, 2009

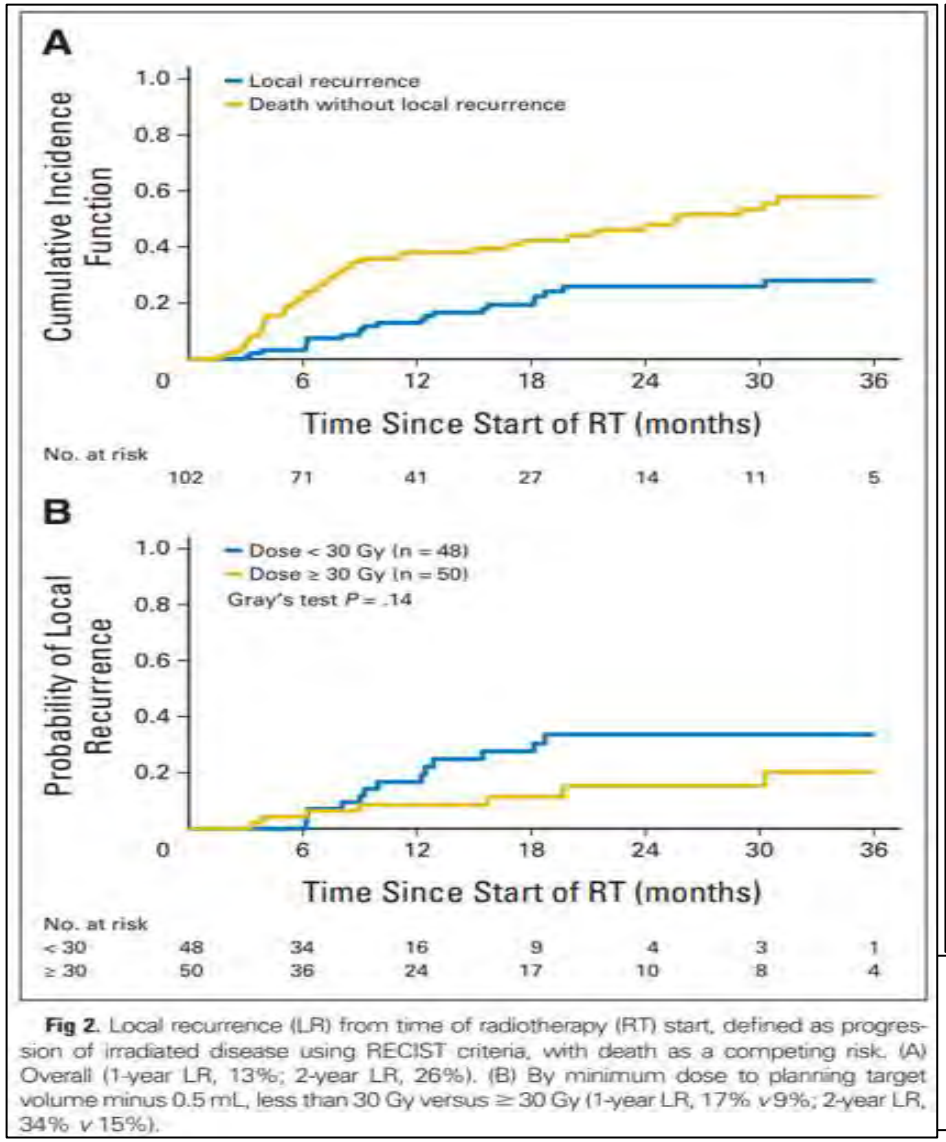


Fig 2. Local recurrence (LR) from time of radiotherapy (RT) start, defined as progression of irradiated disease using RECIST criteria, with death as a competing risk. (A) Overall (1-year LR, 13%; 2-year LR, 26%). (B) By minimum dose to planning target volume minus 0.5 mL, less than 30 Gy versus ≥ 30 Gy (1-year LR, 17% *v* 9%; 2-year LR, 34% *v* 15%).

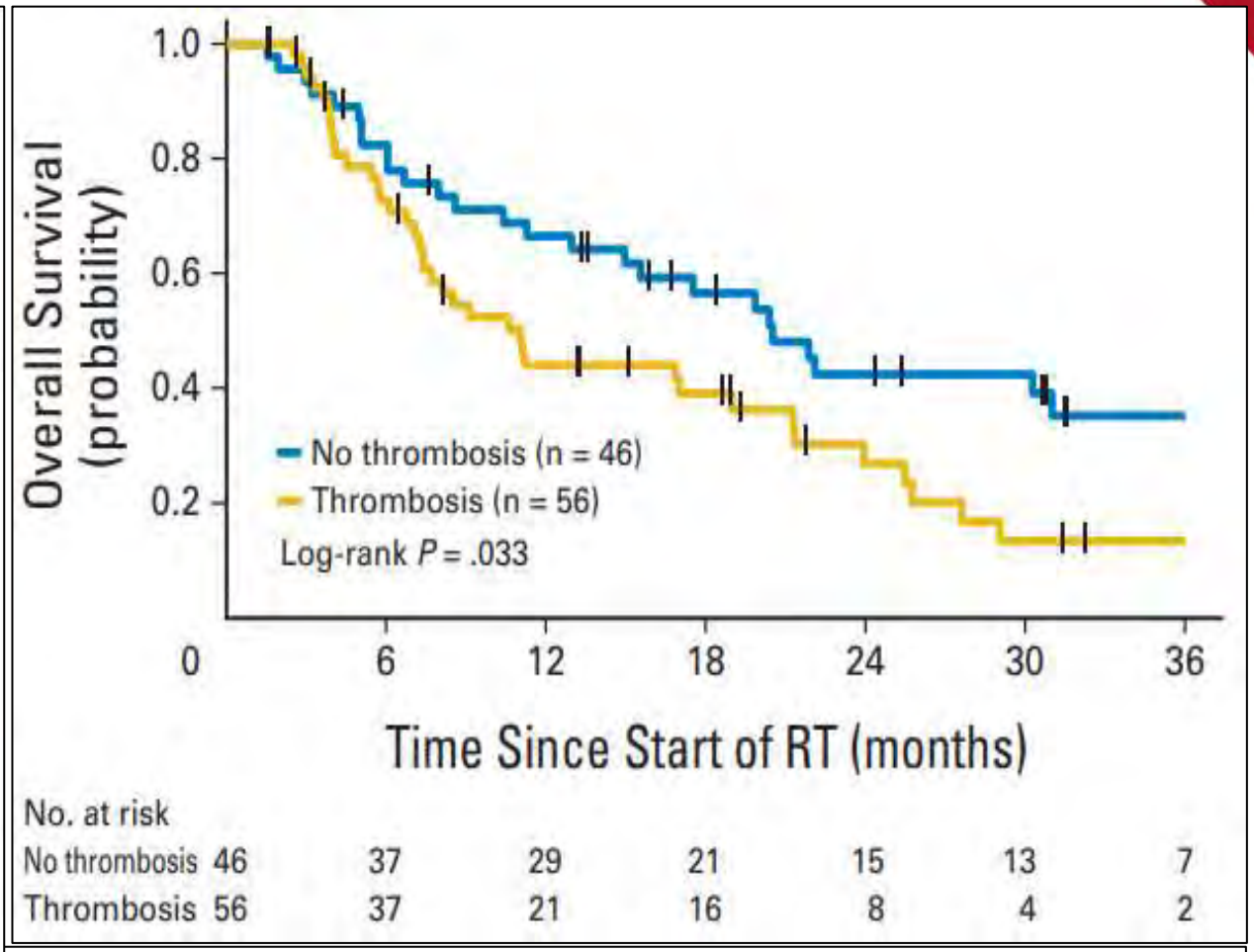


Fig 3. Overall survival (OS) from time of radiotherapy (RT) start by tumor vascular thrombosis presence at baseline
(1-year OS, 44% v 67%; 2-year OS, 27% v 42%).

Child-Pugh class vs. OS/PFS

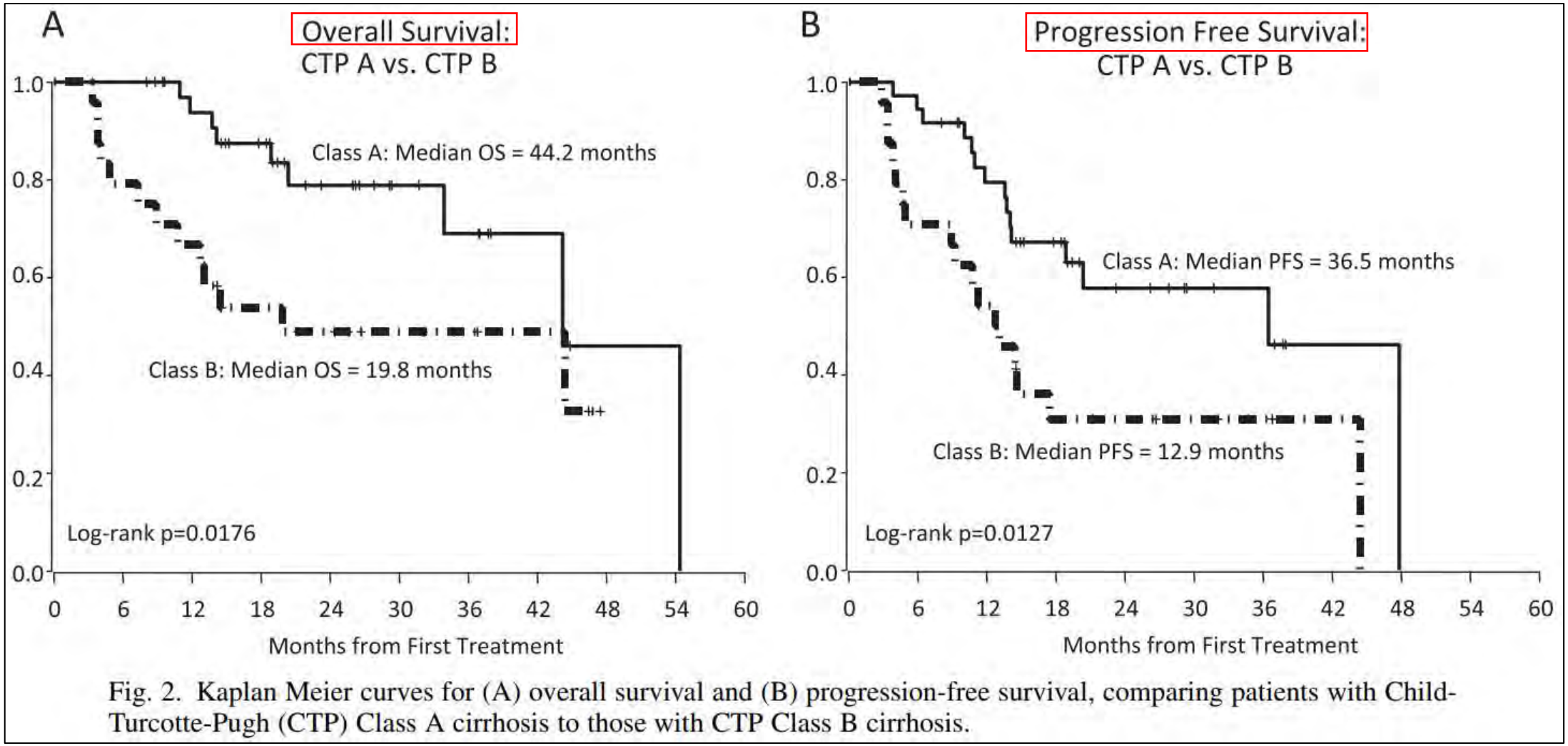


Fig. 2. Kaplan Meier curves for (A) overall survival and (B) progression-free survival, comparing patients with Child-Turcotte-Pugh (CTP) Class A cirrhosis to those with CTP Class B cirrhosis.

CP A: 14 Gy x 3; CP B: 8 Gy x 5

IROBP, 81 (4), e447-e453, 2011

SBRT for recurrent HCC

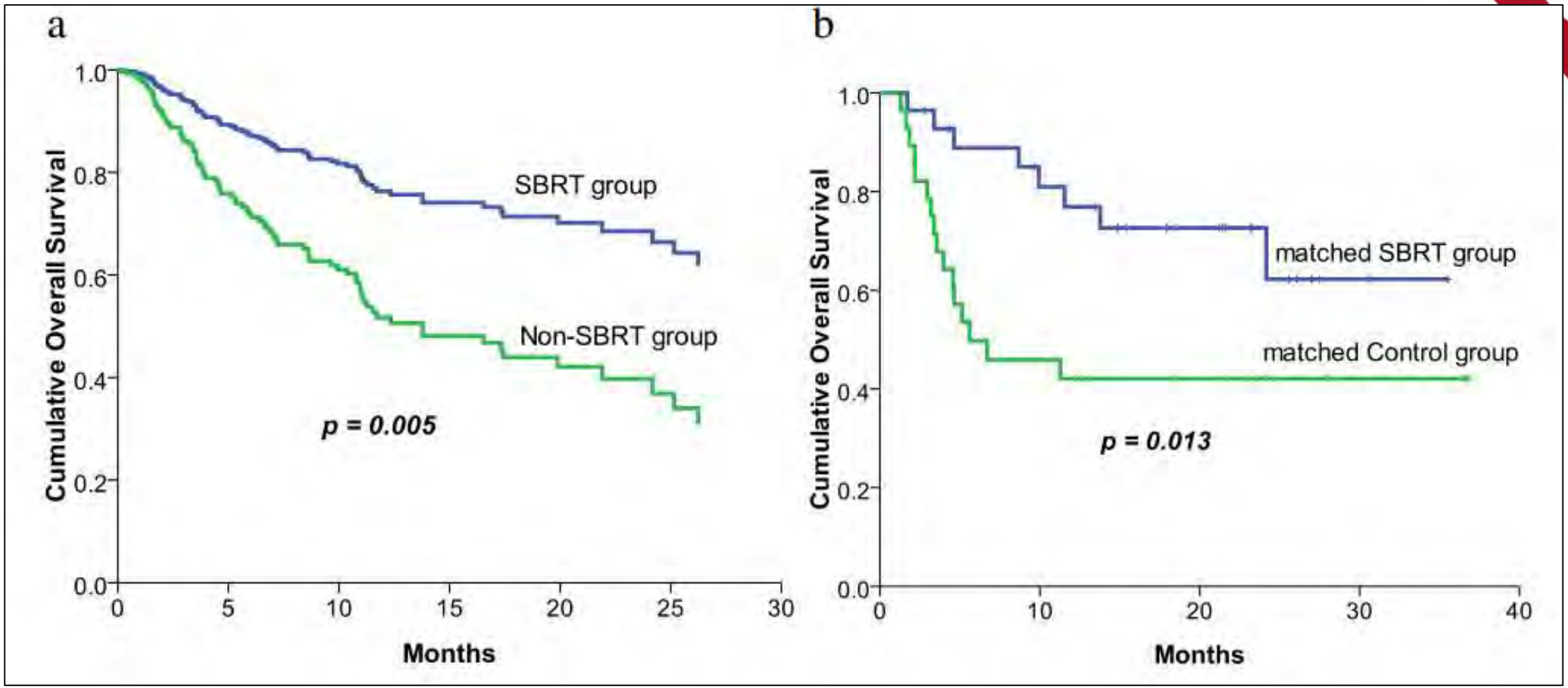
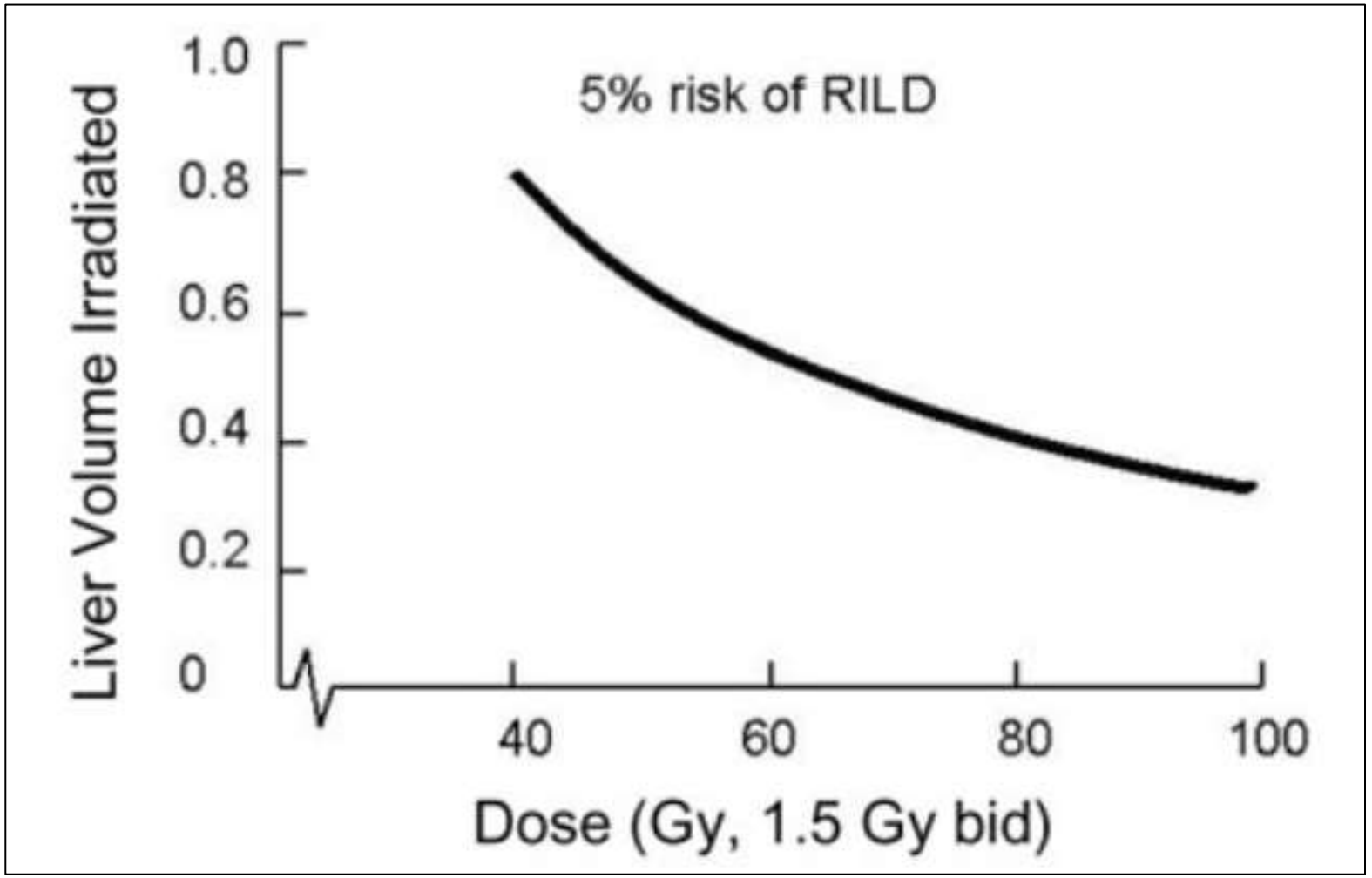


Fig. Comparison of OS curves. (a) SBRT (n Z 36) vs. non-SBRT group (n Z 138) after adjusting for potential prognostic factors using multivariable Cox regression hazard model (p Z 0.005; HR Z 2.44; 95% CI, 1.31e4.56). (b) Matched SBRT (n Z 28) vs. matched control group (n Z 28). The 2-year OS rates are 72.6% and 42.1%, respectively.

IJROBP, Vol. 84, No. 2, pp. 355e361, 2012

The relation of volume of liver irradiated and dose for a 5% risk of radiation induced liver disease



CANCER April 15, 2006 / Volume 106 / Number 8

Sequential Phase I and II Trials of Stereotactic Body Radiotherapy for Locally Advanced Hepatocellular Carcinoma

Alexis Bujold, Christine A. Massey, John J. Kim, James Brierley, Charles Cho, Rebecca K.S. Wong, Rob E. Dinniwell, Zahra Kassam, Jolie Ringash, Bernard Cummings, Jenna Sykes, Morris Sherman, Jennifer J. Knox, and Laura A. Dawson

See accompanying editorial on page 1619

A B S T R A C T

Purpose
To describe outcomes of prospective trials of stereotactic body radiotherapy (SBRT) for hepatocellular carcinoma (HCC).

Patients and Methods
Two trials of SBRT for patients with active HCC unsuitable for standard locoregional therapies were conducted from 2004 to 2010. All patients had Child-Turcotte-Pugh class A disease, with at least 700 mL of non-HCC liver. The SBRT dose range was 24 to 54 Gy in six fractions. Primary end points were toxicity and local control at 1 year (LC1y), defined as no progressive disease (PD) of irradiated HCC by RECIST (Response Evaluation Criteria in Solid Tumors).

Results
A total of 102 patients were evaluable (Trial 1, 2004 to 2007: n = 50; Trial 2, 2007 to 2010: n = 52). Underlying liver disease was hepatitis B in 38% of patients, hepatitis C in 38%, alcohol related in 25%, other in 14%, and none in 7%. Fifty-two percent received prior therapies (no prior sorafenib). TNM stage was III in 66%, and 61% had multiple lesions. Median gross tumor volume was 117.0 mL (range, 1.3 to 1,913.4 mL). Tumor vascular thrombosis (TVT) was present in 55%, and extrahepatic disease was present in 12%. LC1y was 87% (95% CI, 78% to 93%). SBRT dose (hazard ratio [HR] = 0.96; $P = .02$) and being in Trial 2 (HR = 0.38; $P = .03$) were associated with LC1y on univariate analysis. Toxicity ≥ grade 3 was seen in 30% of patients. In seven patients (two with TVT PD), death was possibly related to treatment (1.1 to 7.7 months after SBRT). Median overall survival was 17.0 months (95% CI, 10.4 to 21.3 months), for which only TVT (HR = 2.47; $P = .01$) and being in Trial 2 (HR = 0.49; $P = .01$) were significant on multivariate analysis.

Conclusion
These results provide strong rationale for studying SBRT for HCC in a randomized trial.

J Clin Oncol 31:1631-1639. © 2013 by American Society of Clinical Oncology

Table 2. Toxicity, CTCAE ≥ Grade 3

Toxicity	Grade 3 No.	Grade 3 %	Grade 4 No.	Grade 4 %	Grade 5 No.	Grade 5 %
All	27	26.5	3	2.9	7*	6.9
Fatigue	1	1.0	0	0.0	—	
Biochemical†						
Albumin	0	0.0	0	0.0	0	0.0
AST/ALT	11	10.9	0	0.0	—	
Bilirubin	3	3.0	2	2.0	—	
Creatinine	1	1.0	0	0.0	0	0.0
INR	0	0.0	—		—	
Hematologic†						
Hemoglobin	2	2.0	0	0.0	0	0.0
Leukocytes	1	1.0	0	0.0	0	0.0
Platelets	9	9.0	0	0.0	0	0.0
GI						
Cholangitis	0	0.0	0	0.0	1	1.0
Gastritis/GI bleed	1	1.0	0	0.0	1	1.0
Liver failure	1	1.0	1	1.0	5*	4.9
Nausea/vomiting	1	1.0	0	0.0	0	0.0
Pain (RUQ/chest wall)	1	1.0	0	0.0	—	
Proportion of patients with CTP deterioration, without progressive disease, %						
3 months						
Score			46			
Class			29			
12 months						
Score			17			
Class			6			

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; CTP, Child-Turcotte-Pugh liver function scale; INR, international normalized ratio; RUQ, Right upper quadrant.
*Includes two patients with tumor vascular thrombosis progressive disease probably contributory to liver function deterioration.
†Within first 3 months of treatment; not present at or worsening from baseline.

J Clin Oncol 31:1631-1639. © 2013

Table 4 Adverse events related to treatment

Toxicity	Acute (%)		Late (%)
grade	Grade 1	Grade 2	Grade 4
Constitutional symptoms	15	0	0
Leukopenia	5	3	0
Elevated liver enzyme	5	8	0
Elevated bilirubin and alkaline phosphatase	0	1	0
Liver failure	0	0	1
Other (target error)	0	1	0

30-39 Gy in 3 fractions

70%:43-56Gy, BED10:103-160Gy
85%:35-46Gy, BED10:76-115Gy

Kwon et al. BMC Cancer 2010, 10:475

Table 4. Hematologic and hepatic toxicity

Change in Common Toxicity Criteria grade, pre-SBRT grade → post-SBRT grade	*n* (60)
Liver enzymes	
No change	46
0 → 1	8
1 → 2	3
1 → 3	1
2 → 3	2
Albumin	
No change	43
0 → 1	2
1 → 2	8
2 → 3	7
Platelets	
No change	40
0 → 1	4
1 → 2	6
1 → 3	2
2 → 3	7
3 → 4	1
INR	
No change	50
0 → 1	4
1 → 2	4
1 → 3	1
2 → 3	1
Alkaline phosphatase	
No change	53
0 → 1	7
Bilirubin	
No change	31
0 → 1	7
0 → 2	4
1 → 2	10
2 → 3	7
1 → 4	1

Abbreviation: SBRT = stereotactic body radiation therapy.

Child Pugh A: 14 Gy x 3 = 44 Gy
Child Pugh B: 8 Gy x 5 = 40 Gy

IJROBP, 81 (4), e447-e453, 2011

Predictors of Liver Toxicity Following Stereotactic Body Radiation Therapy for Hepatocellular Carcinoma

Purpose: To identify risk factors associated with a decline in liver function after stereotactic body radiation therapy (SBRT) for hepatocellular carcinoma.

Methods and Materials: Data were analyzed from patients with hepatocellular carcinoma treated on clinical trials of 6-fraction SBRT. Liver toxicity was defined as an increase in Child-Pugh (CP) score ≥2 three months after SBRT. Clinical factors, SBRT details, and liver dose-volume histogram (DVH) parameters were tested for association with toxicity using logistic regression. CP class B patients were analyzed separately.

Results: Among CP class A patients, 101 were evaluable, with a baseline score of A5 (72%) or A6 (28%). Fifty-three percent had portal vein thrombus. The median liver volume was 1286 cc (range, 766-3967 cc), and the median prescribed dose was 36 Gy (range, 27-54 Gy). Toxicity was seen in 26 patients (26%). Thrombus, baseline CP of A6, and lower platelet count were associated with toxicity on univariate analysis, as were several liver DVH-based parameters. Absolute and spared liver volumes were not significant. On multivariate analysis for CP class A patients, significant associations were found for baseline CP score of A6 (odds ratio [OR], 4.85), lower platelet count (OR, 0.90; median, 108 × 10^9/L vs 150 × 10^9/L), higher mean liver dose (OR, 1.33; median, 16.9 Gy vs 14.7 Gy), and higher dose to 800 cc of liver (OR, 1.11; median, 14.3 Gy vs 6.0 Gy). With 13 CP-B7 patients included or when dose to 800 cc of liver was replaced with other DVH parameters (eg, dose to 700 or 900 cc of liver) in the multivariate analysis, effective volume and portal vein thrombus were associated with an increased risk.

Conclusions: Baseline CP scores and higher liver doses (eg, mean dose, effective volume, doses to 700-900 cc) were strongly associated with liver function decline 3 months after SBRT. A lower baseline platelet count and portal vein thrombus were also associated with an increased risk.

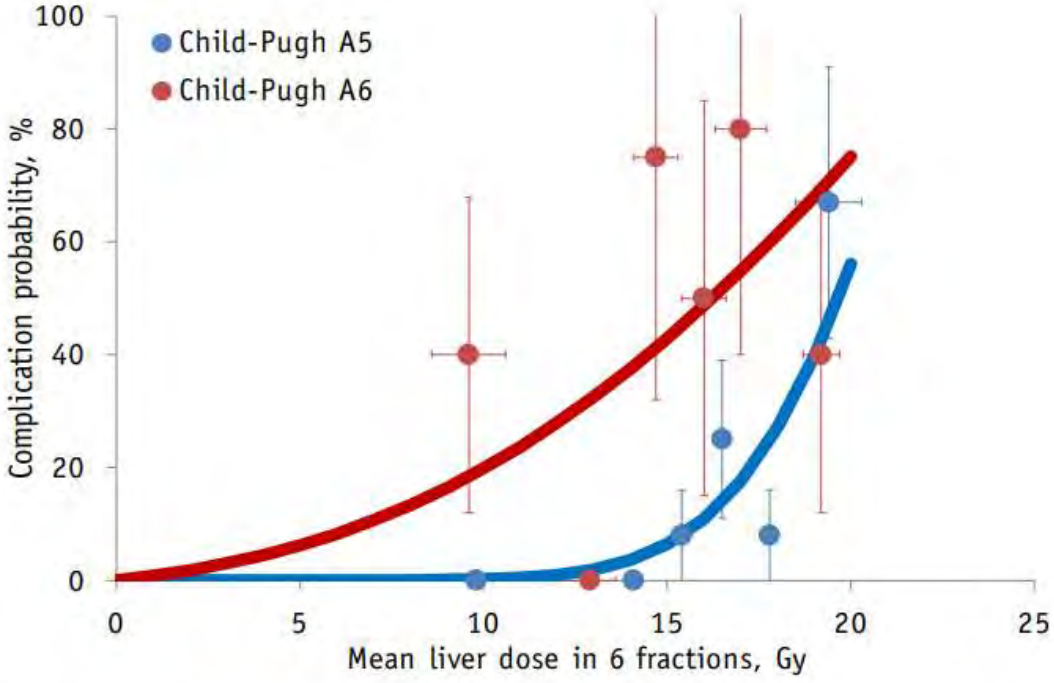


Fig. 2. Dose complication response by baseline liver function for 6-fraction stereotactic body radiation therapy. The liver excludes gross tumor volumes. Error bars indicate the standard error of the mean.

JROBP, Vol. 97, No. 5, pp. 939e946, 2017

Table 3 Parameters associated with toxicity, including both CP class A (n = 101) and B (n = 13) patients

Parameter	UVA		MVA	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Gender (male vs female)		.328		
Total GTV volume		.543		
Liver – GTV volume		.188		
Portal vein thrombus (present vs absent)		.108		
Baseline CP score		.003*		.022
6 vs 5	4.00 (1.54-10.39)		4.77 (1.47-15.50)	
7 vs 5	5.39 (1.55-18.69)		4.09 (0.92-18.18)	
Baseline platelet count (per 10×10^9/L increase)	0.90 (0.84-0.97)	.007*	0.89 (0.81-0.97)	.019
Underlying liver disease		.609		
Hepatitis C vs hepatitis B				
Any vs hepatitis B				
Prescribed dose	0.94 (0.88-1)	.052*		
Mean liver dose	1.23 (1.05-1.44)	.010*		
V_{eff} (per 0.1 increase)	1.66 (1.19-2.31)	.003*	1.83 (1.19-2.80)	.006
Physical NTCP		.341		
Biological NTCP	1.08 (1-1.17)	.054*		
D800cc (per 0.1-Gy increase)	1.10 (1.04-1.17)	.001*	1.10 (1.02-1.19)	.016

Abbreviations: CI = confidence interval; CP = Child-Pugh; D800cc = dose to 800 cc of liver; GTV = gross tumor volume; MVA = multivariate analysis; NTCP = normal tissue complication probability; OR = odds ratio; UVA = univariate analysis; V_{eff} = effective liver volume.

* Parameters with $P<.1$ on UVA were entered into MVA.

CP A5		Mean Liver Dose (Gy)						
		≤ 15	≤ 16	≤ 17	≤ 18	≤ 19	≤ 20	≤ 21
D800cc (Gy)	≤ 5	0% (0/17)	0% (0/22)	0% (0/25)	3% (1/29)	6% (2/31)	6% (2/31)	6% (2/32)
	≤ 10	0 % (0/22)	0% (0/30)	0% (0/36)	5% (2/43)	7% (3/45)	7% (3/45)	7% (3/45)
	≤ 15	0% (0/24)	3% (1/34)	2% (1/41)	6% (3/51)	7% (4/56)	7% (4/57)	7% (4/57)
	≤ 20	0% (0/24)	3% (1/35)	5% (2/43)	8% (4/53)	10% (6/60)	11% (7/62)	13% (8/63)
	≤ 25	0% (0/24)	3% (1/35)	7% (3/45)	9% (5/55)	11% (7/63)	12% (8/65)	16% (11/68)
	≤ 30	0% (0/24)	3% (1/35)	7% (3/45)	9% (5/55)	11% (7/64)	13% (9/67)	18% (13/71)

Fig. 3. Proportion of Child-Pugh class A5 patients meeting the given dosimetric thresholds with liver toxicity following 6-fraction stereotactic body radiation therapy. The green region indicates the dose range without observed toxicity, with a color continuum through increasing risk progression. *Abbreviation:* D800cc = dose to 800 cc of liver. (A color version of this figure is available at www.redjournal.org.)

JROBP, Vol. 97, No. 5, pp. 939e946, 2017

Patients and Methods

From 2004 to 2012, 224 patients with inoperable, nonmetastatic HCC underwent RFA (n = 161) to 249 tumors or image-guided SBRT (n = 63) to 83 tumors.

We applied inverse probability of treatment weighting to adjust for imbalances in treatment assignment.

Freedom from local progression (FFLP) and toxicity were retrospectively analyzed.

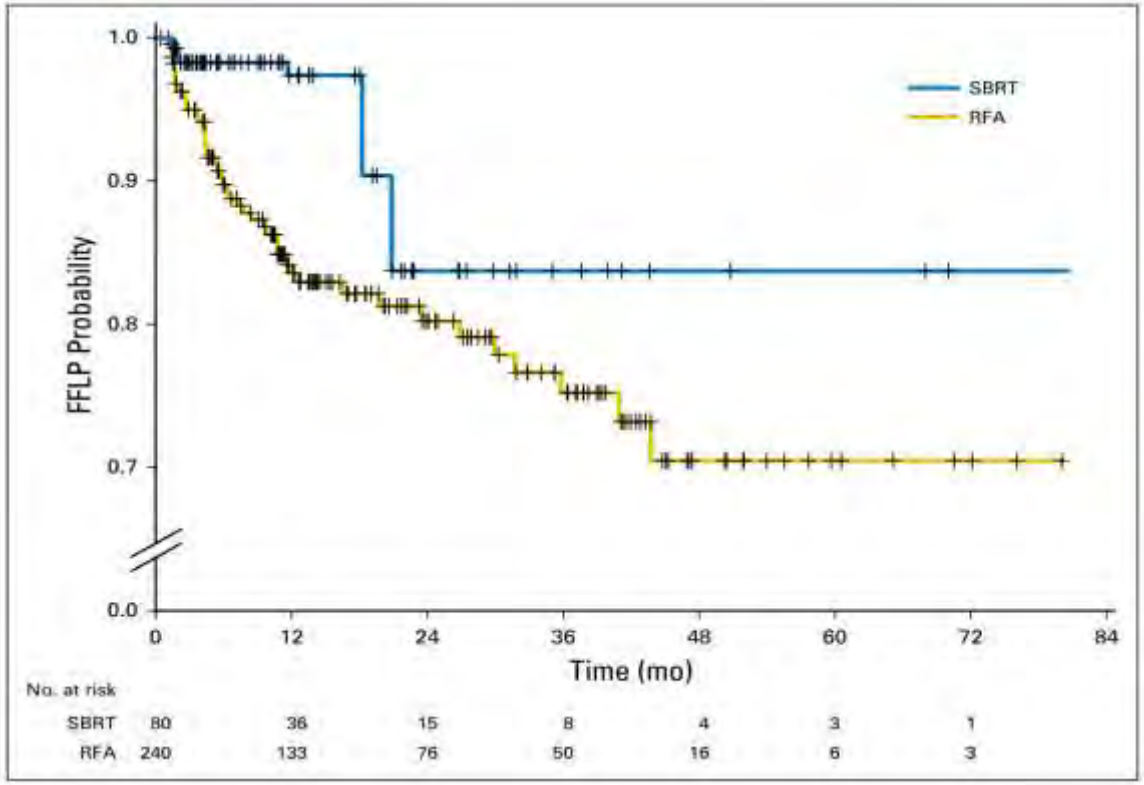
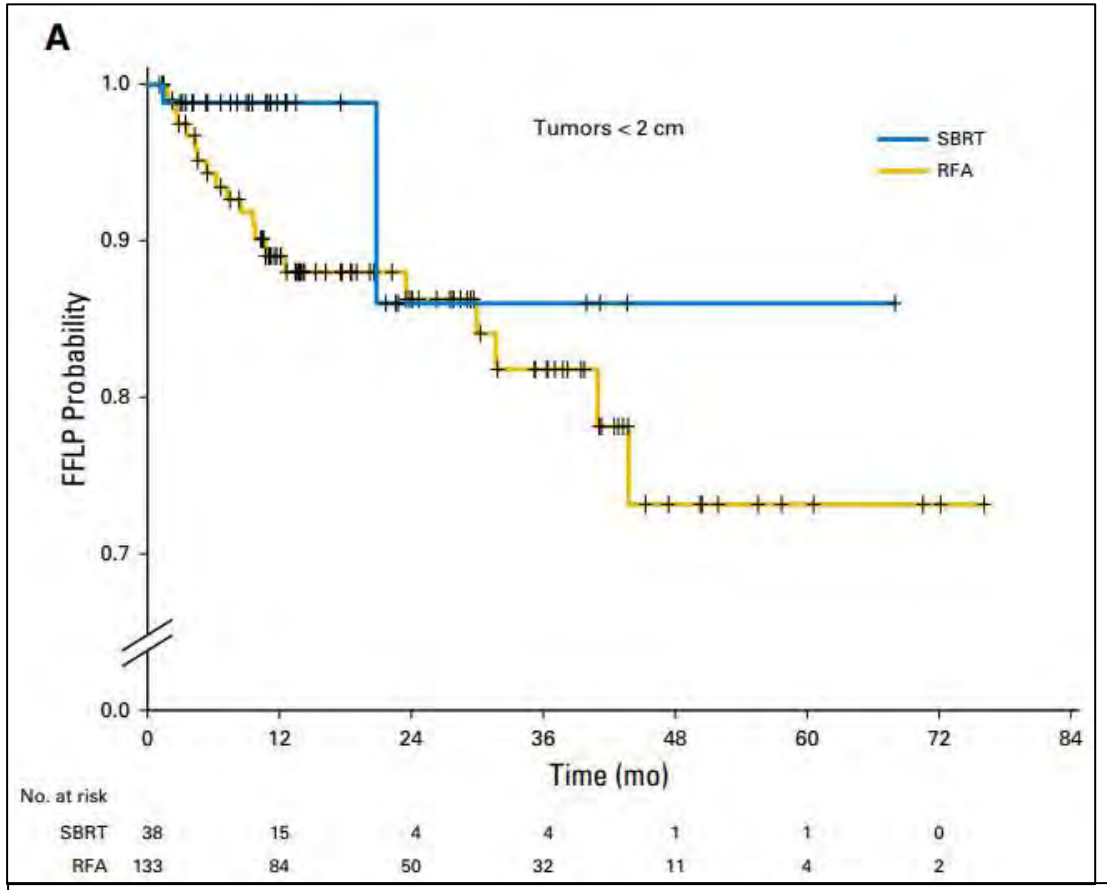


Fig 1. Freedom from local progression (FFLP) by treatment modality. RFA, radiofrequency ablation; SBRT, stereotactic body radiotherapy.

J Clin Oncol 2016, 34:452-459.



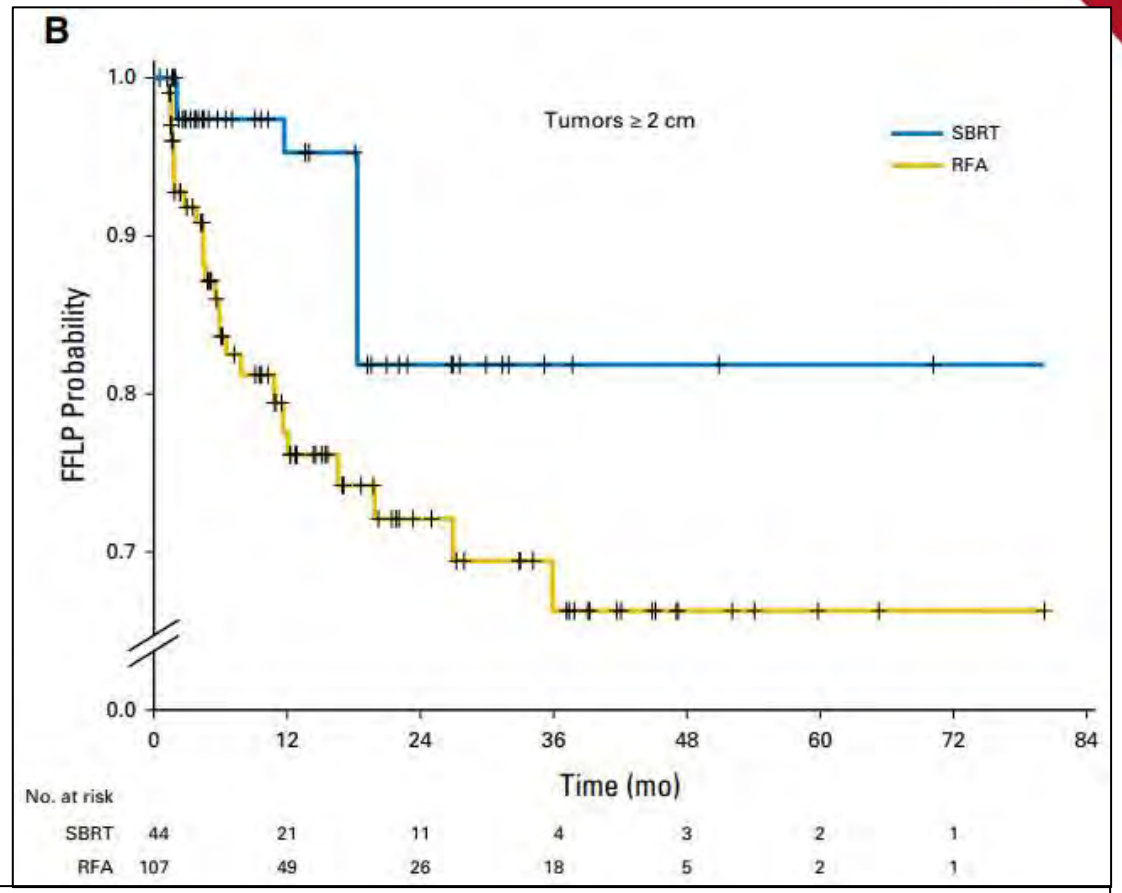


Fig 3. (A) Freedom from local progression (FFLP) for tumors smaller than 2 cm by treatment modality. (B) FFLP for tumors $ 2 cm by treatment modality. RFA, radiofrequency ablation; SBRT, stereotactic body radiotherapy.

J Clin Oncol 2016, 34:452-459.

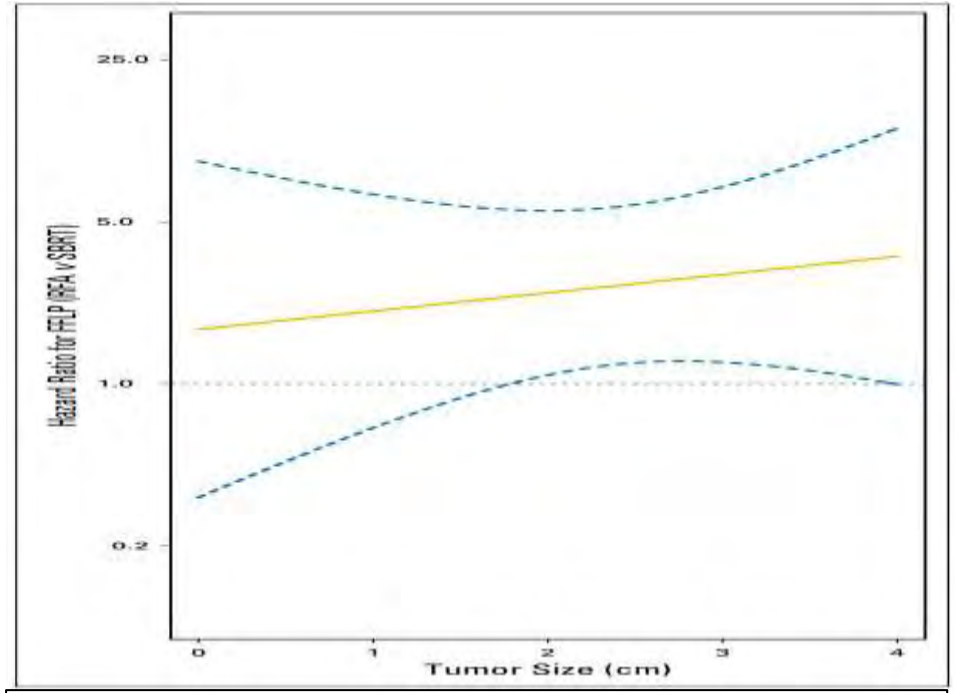


Fig 2. Freedom from local progression (FFLP) by treatment modality by tumor size. Solid line represents hazard ratio estimate, and dashed lines represent 95% CIs. y-axis is plotted on a logarithmic scale (base = 5).
RFA, radiofrequency ablation;
SBRT, stereotactic body radiotherapy

Table 3. Multivariate Cox Proportional Hazards Analysis of Factors Associated With Local Progression

	HR	95% CI	*P*
Treatment			
RFA *v* SBRT	3.84	1.62 to 9.09	.002
Age	1.01	0.97 to 1.06	.514
Tumor size	1.35	0.99 to 1.84	.055
Child-Pugh score	0.95	0.74 to 1.22	.703
AFP	1.12	0.97 to 1.30	.130
No. prior treatments	1.25	1.00 to 1.56	.055

NOTE. Age (per year), tumor size (per cm), Child-Pugh score (per point), AFP (per doubling) and No. prior treatments (per treatment) were treated as continuous variables.

Abbreviations: AFP, alpha-fetoprotein; HR, hazard ratio; RFA, radiofrequency ablation; SBRT, stereotactic body radiation therapy.

J Clin Oncol 2016, 34:452-459.

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Brief Report

Transarterial chemoembolization with drug-eluting beads vs. stereotactic body radiation therapy for hepatocellular carcinoma: Outcomes from a multicenter randomized phase II trial (The TRENDY trial): Short running title: TACE-DEB vs. SBRT for hepatocellular carcinoma

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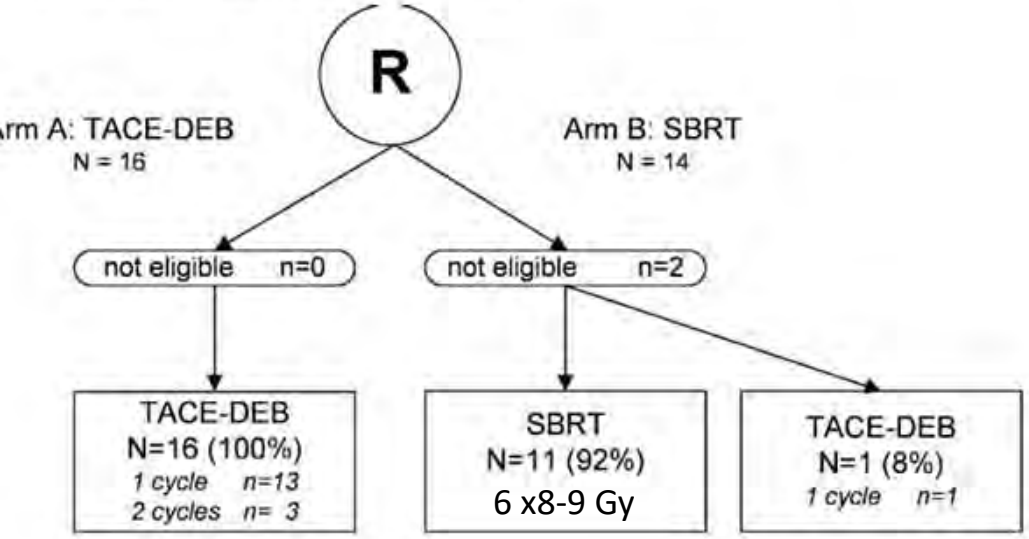
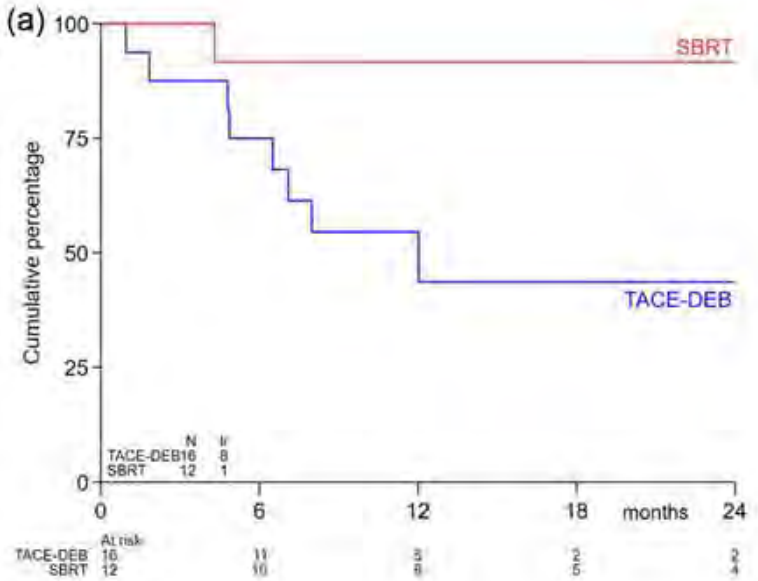
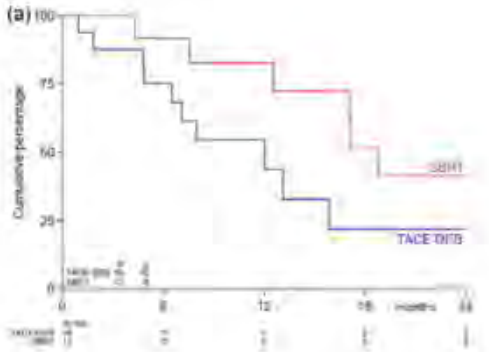




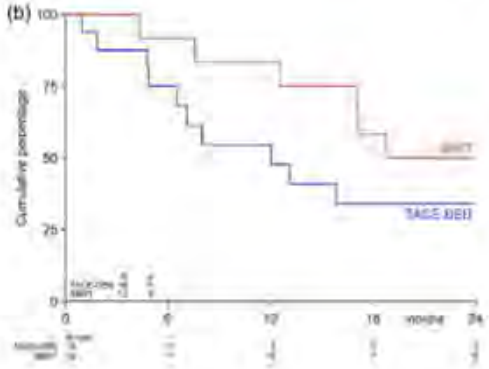
Median TTP was 12 months for TACEDEB and 19 months for SBRT (p=0.15). Median LC was 12 months for TACE-DEB and >40 months (not reached) for SBRT (p=0.075). Median OS was 36.8 months for TACEDEB and 44.1 months for SBRT (p=0.36).

Figure: Time to progression by randomization arm.

2a. Original analysis, with censoring at liver transplantation.



2b. Post-hoc analysis, without censoring at liver transplantation.



N indicates the number of patients; p, number of progressions

Methods and Materials:
Between August 2007 and January 2009, 18 patients with 21 lesions received SHORT. A median total dose of 50 Gy was delivered in 10 fractions. Three patients underwent either chemoembolization (n Z 1) or radiofrequency ablation (n Z 2) prior to SHORT. Radiographic response was based on computed tomography evaluation at 3 months after SHORT. Histological response as a percentage of tumor necrosis was assessed by a quantitative morphometric method.

Table 2 Treatment characteristics

Characteristic	Outcome or value
Median normal liver volume (cc)	1552.5
Total number of lesions	21
Median lesion diameter (cm) (range)	4 (1.2–6.5 cm)
Median lesion volume (cc) (range)	63 (31–137 cc)
Median prescribed dose (Gy)	50
Median fraction size (Gy)	5
Median cc of liver receiving >20 Gy (range)	293 (114–446 cc)
Mean liver dose (Gy) (range)	8.5 (1–15.6 Gy)

Table 3 Histological response

Patient	Child-Pugh class	Age	Tumor site (no.of lesions)	Tumor size (cm)	Total dose (Gy)	No. of fractions (*n*)	% of necrosis
1	A	45	Right lobe (1)	7.2	50	10	78
2	B	54	Right lobe (1)	1.9	50	10	57
3	C	61	Right lobe (2)	5.1, 3.7	50, 50	10, 10	14, 0
4	C	53	Right lobe (1)	3	55	10	10
5	B	57	Right lobe (1)	1.7	50	10	27
6	NK	58	Right lobe (1)	4.6	50	10	100
7	C	52	Right lobe (1)	3	50	10	8
8	C	63	Right lobe (1)	3.8	50	10	75
9	NK	67	Central (1)	6	50	10	100
10	B	58	Right lobe (1)	1.2	50	10	0
11	NK	52	Dome (1)	4.0	50	10	NK
12	B	58	Right lobe (1), dome (1)	2.4, 1	50, 50	10, 10	NK

Abbreviation: NK = not known.

From April 2005 to August 2010, 10 patients with 11 HCCs were treated with SBRT as a bridge to transplantation. All patients were evaluated by a liver transplant surgeon before radiosurgery. SBRT was delivered with the Cyber Knife robotic radiosurgery system. After SBRT, all patients underwent orthotopic liver transplantation. The tumor response was determined by explant pathology.

TABLE 3. Toxicity After SBRT for HCC as a Bridge to Liver Transplantation

	Grade 1	Grade 2	Grades 3-5
Nausea/vomiting [n/N (%)]	1/10 (10)	1/10 (10)	—
Fatigue [n/N (%)]	1/10 (10)	—	—
Abdominal pain [n/N (%)]	1/10 (10)	—	—

TABLE 2. Tumor and Treatment Characteristics for Patients With HCC Treated With SBRT as a Bridge to Liver Transplantation

Patient	Pre-SBRT Treatment	Tumor Diameter (cm)	SBRT Dose (Gy)*	Time From SBRT to Liver Transplantation (Days)	Explant Pathology/ Tumor Size	Follow-Up After SBRT (Months)	Disease Status
1	None	5.5	33	8	Residual HCC/5 cm	60	NED
2	None	3.4	39	48	Residual HCC/3.4 cm	74	NED
3	None	3.0	42	113	Residual HCC/millimetric	67	NED
4	TACE × 1	2.5	42	794	Residual HCC/millimetric	64	NED
5	None	4.3	51	209	Residual HCC/4.3 cm	63	NED
6	TACE × 1	3.8	51	330	Residual HCC/3.0 cm	64	NED
7	None	3.0	54	38	No viable tumor	57	NED
8a	None	4.5	54	67	No viable tumor	50	NED
8b	None	2.5	54	67	No viable tumor	50	NED
9	TACE × 2	2.9	54	185	Residual HCC/1.2 cm	57	NED
10	TACE × 2	2.8	54	112	Residual HCC/millimetric	17	NED

*Three fractions.

LIVER TRANSPLANTATION 18:949-954, 2012

HEPATOLOGY
AASLD
HEPATOLOGY, VOL. 74, NO. 5, 2021

Prospective Study of Stereotactic Body Radiation Therapy for Hepatocellular Carcinoma on Waitlist for Liver Transplant

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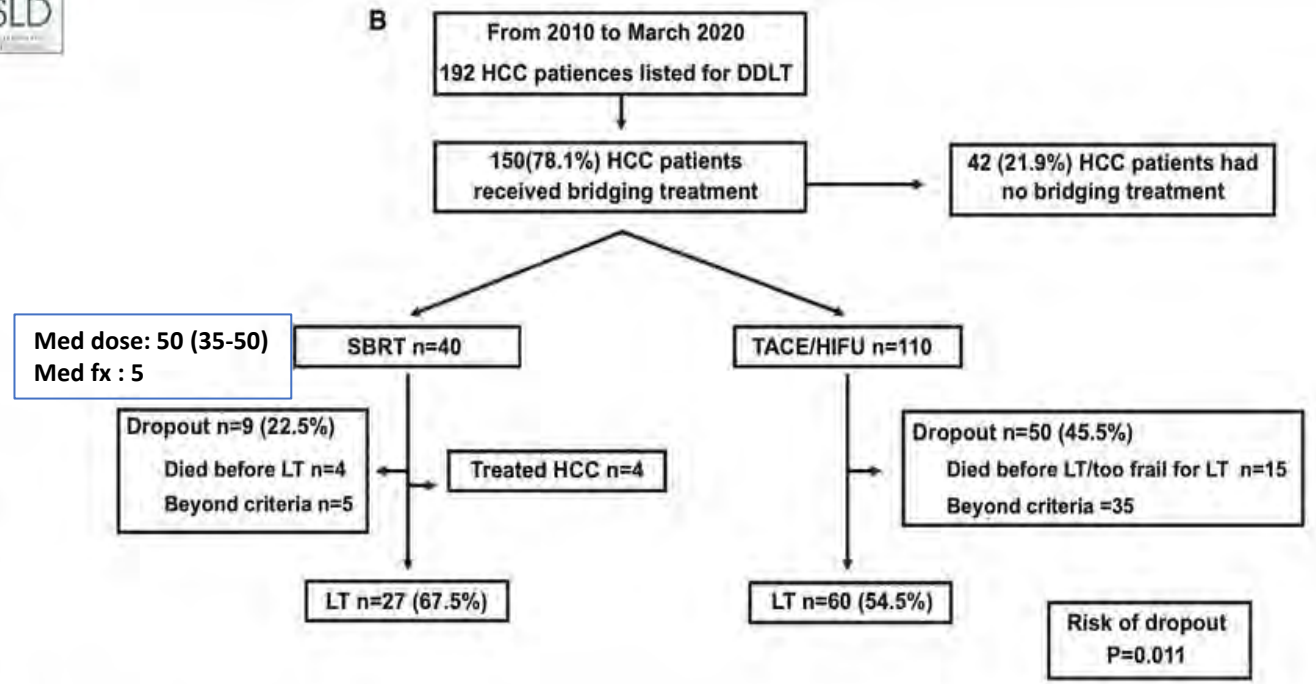
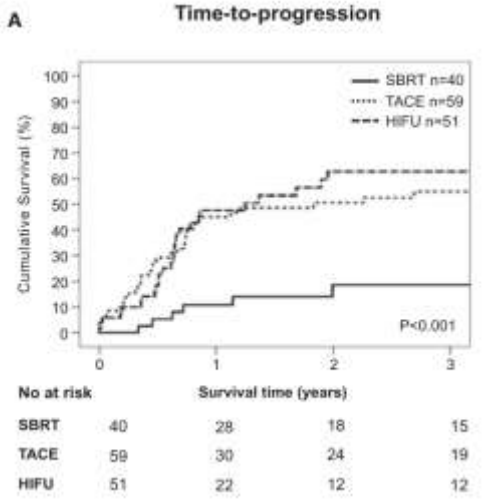


- SBRT showed a better radiological tumor control when compared with other bridging therapies at every time point after treatment
- SBRT was associated with a lower risk of dropout
- SBRT demonstrated a higher rate of pCR in explant histopathology when compared with TACE and HIFU (High-intensity focused ultrasound)



In summary, SBRT represents a powerful tool in the management of hepatocellular carcinoma, offering high rates of local control with a favorable toxicity profile. Its role extends beyond primary treatment, providing options for recurrent disease management and bridging therapy in liver transplantation.