

SBRT für HCC und CCC DEGRO AG Stereotaxie

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Thomas Brunner



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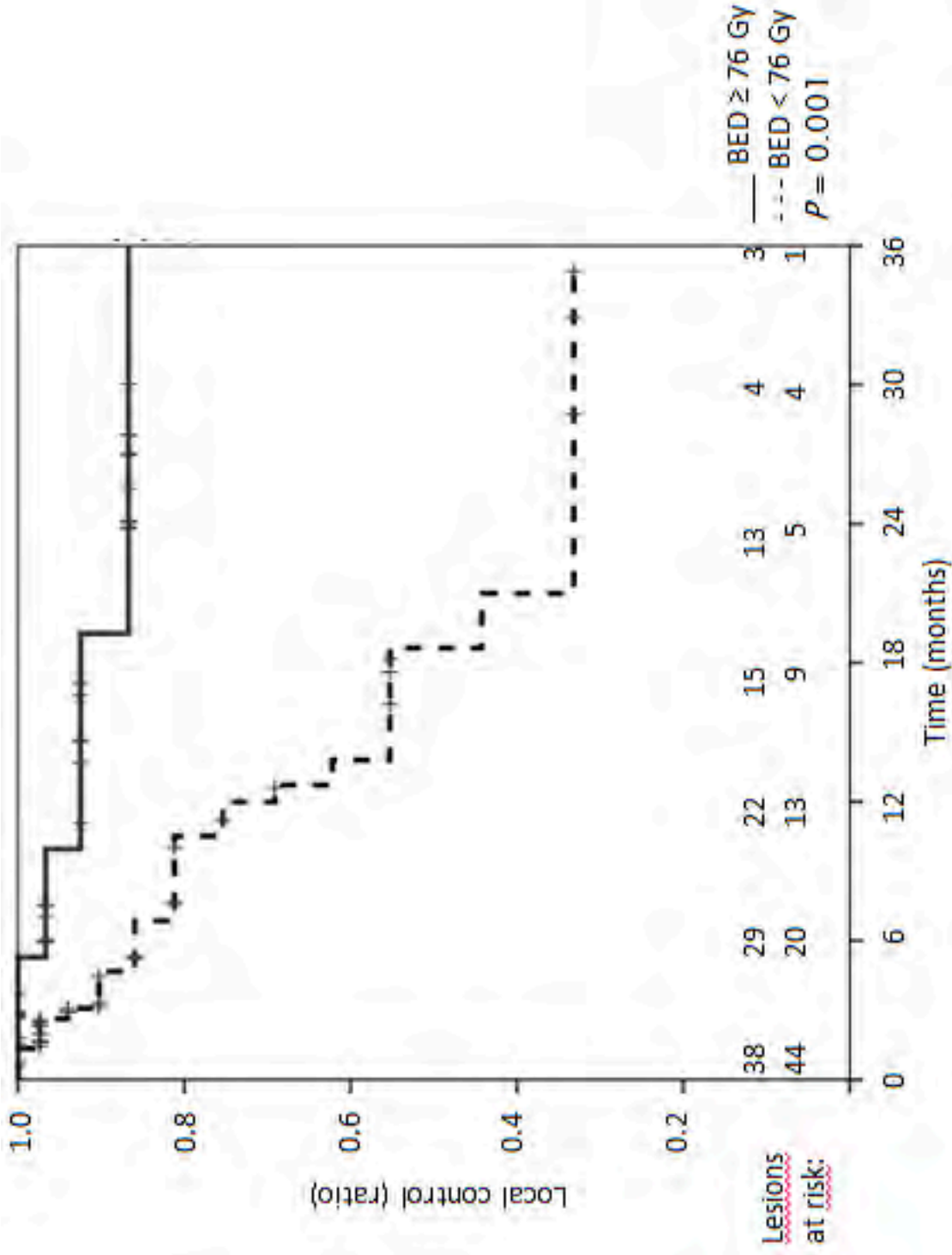
CHOLANGIOZELLULÄRES KARZINOM (CCC)



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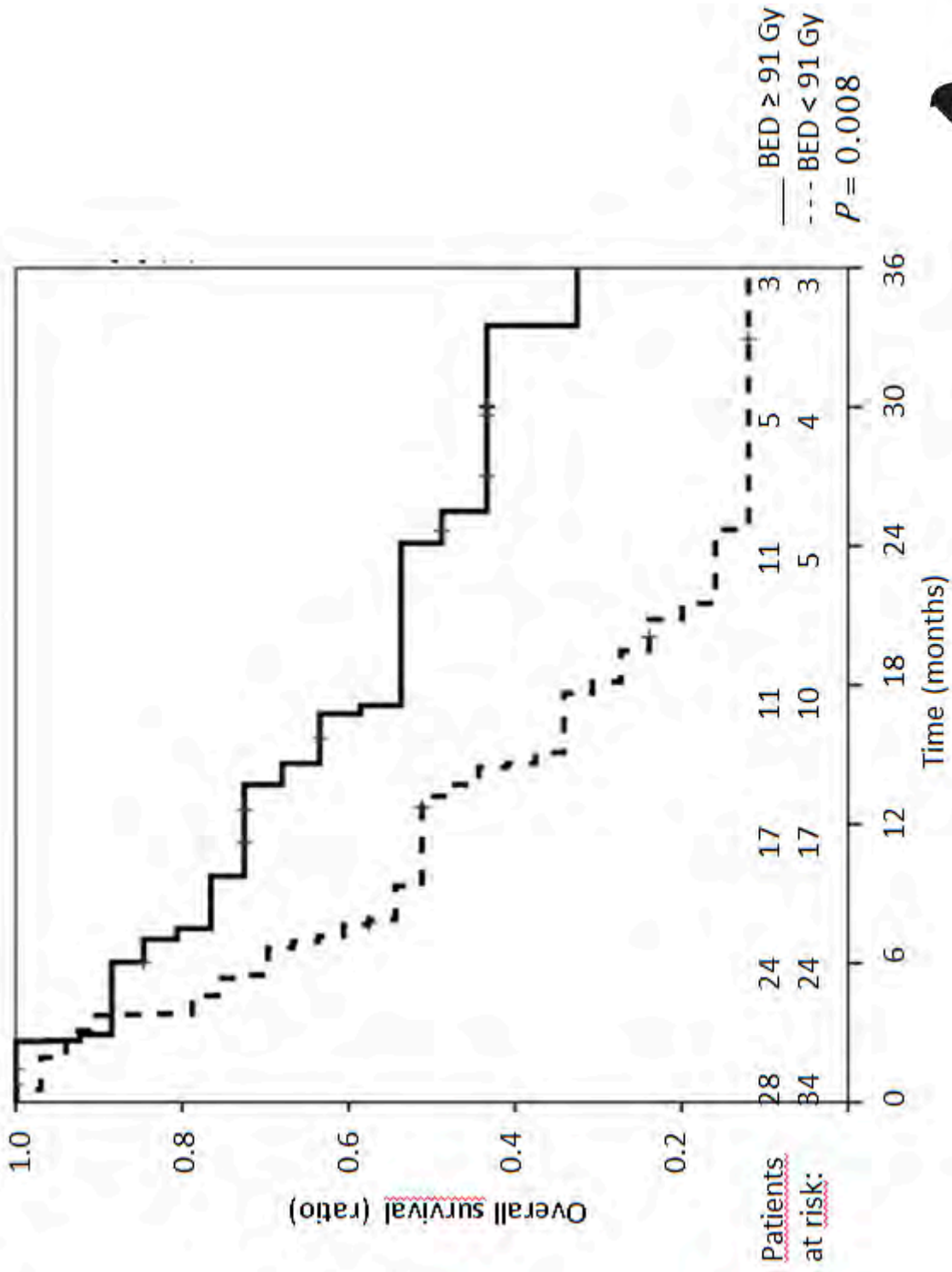
CCC: Local control by BED D_{median}



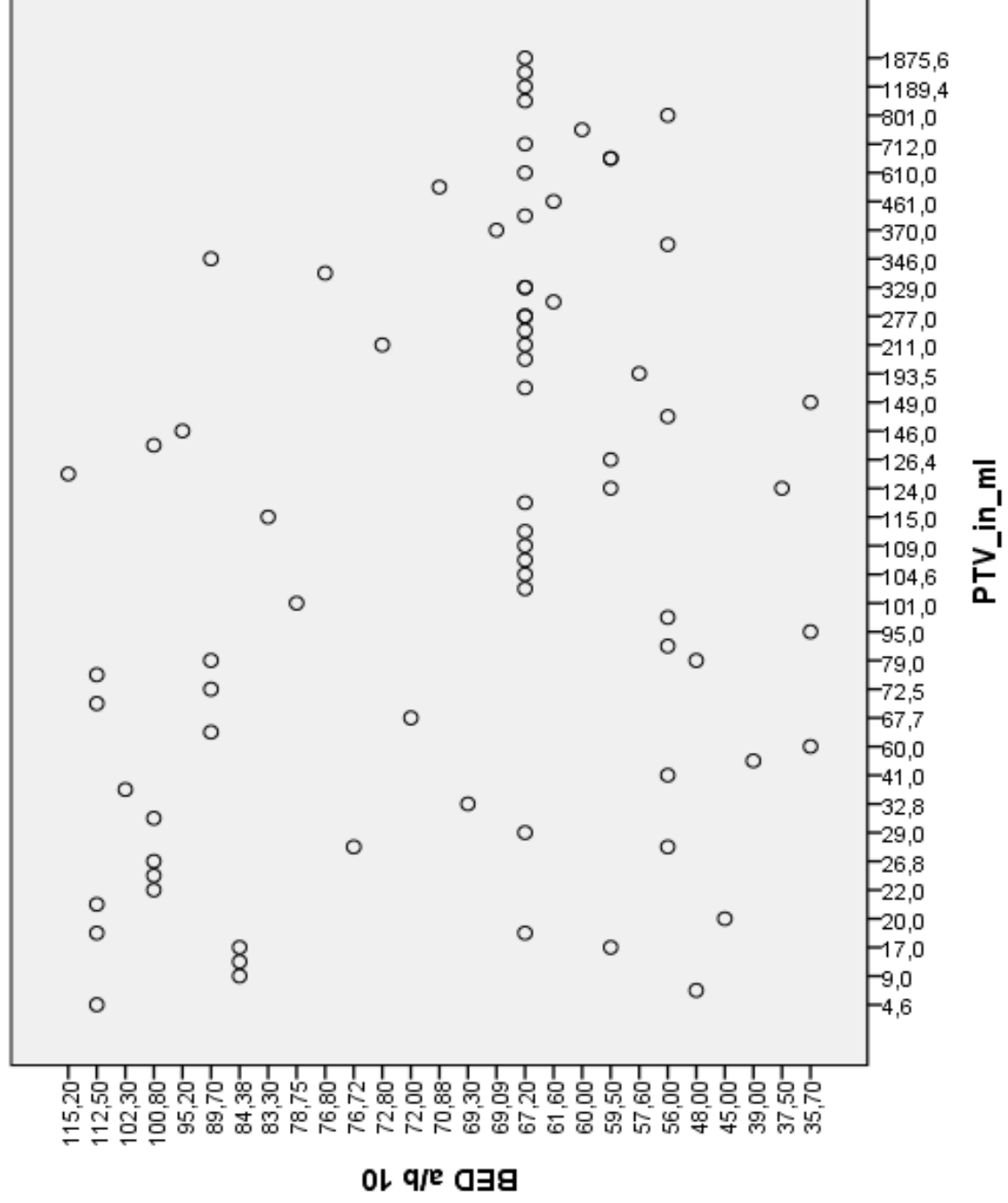
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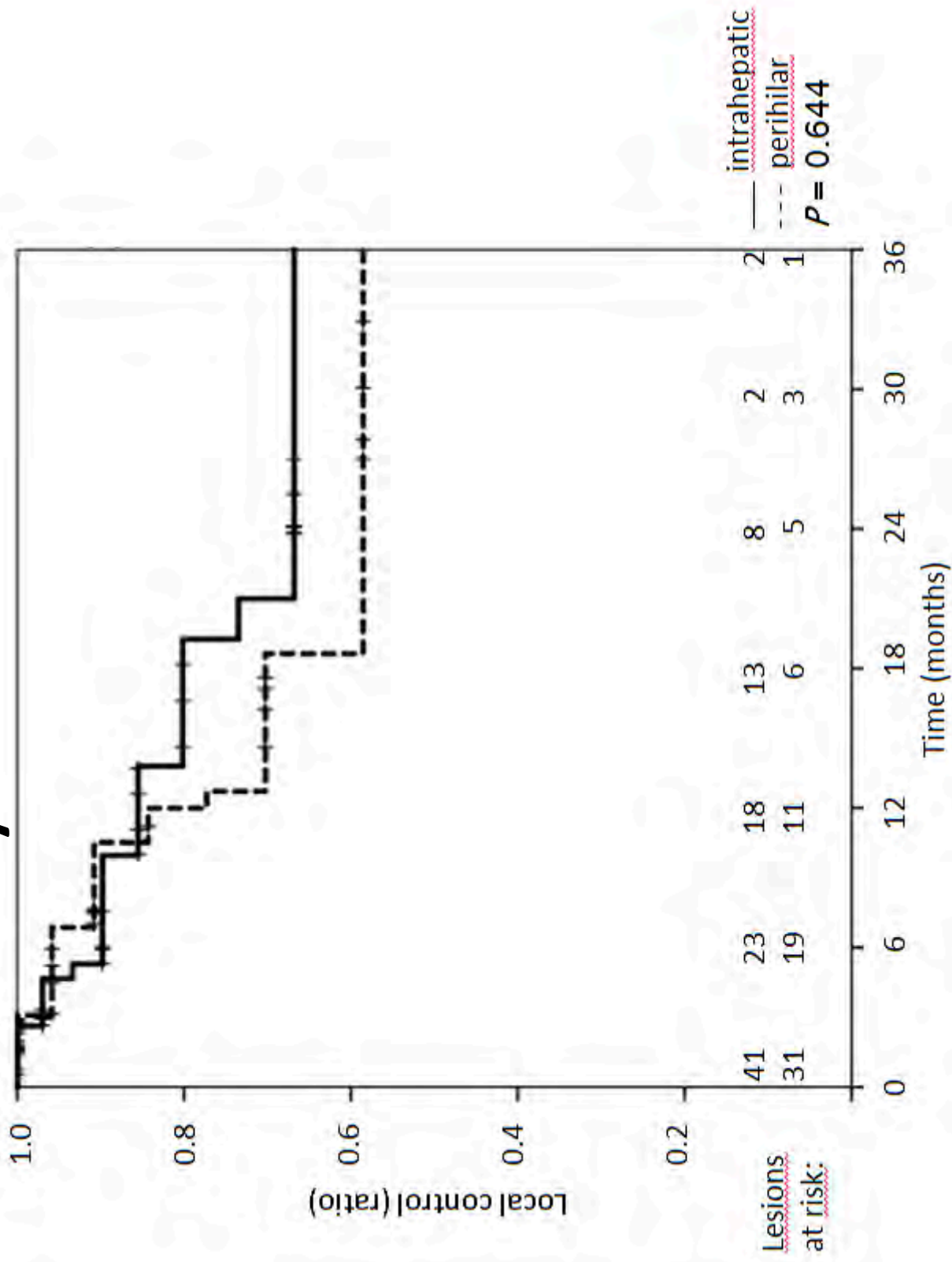
CCC: Overall survival by BED D_{max}



BED and PTV



LC by location of CCC



HEPATOZELLULÄRES KARZINOM (CCC)



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Original Paper

Stereotactic Body Radiation Therapy as an Alternative Treatment for Patients with Hepatocellular Carcinoma Compared to Sorafenib: A Propensity Score Analysis



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Non-DEGRO-AG centres

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- Imperial College London, Hammersmith Hospital, London, UK;
- Medical Oncology and Hematology Unit, Humanitas Cancer Center, Humanitas Clinical and Research Center, Milan, Italy;
- Department of Translational Medicine, Università degli Studi del Piemonte Orientale “A. Avogadro,” Novara, Italy;
- Department of Gastroenterology and Hepatology, Kindai University School of Medicine, Osakasayama, Japan
- Center for Liver Cancer, National Cancer Center Hospital, Goyang, South Korea;



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Baseline characteristics in the **unmatched cohort**

Table 1. Baseline characteristics of study patients and lesions treated

Characteristics	Sorafenib (n = 901)	SBRT (n = 122)	p value	Mean standardized difference
Gender			0.627	0.049
Male	729 (80.9)	101 (82.8)		
Female	172 (19.1)	21 (17.2)		
Age, years	66.7±11.7	67.2±8.5	0.988	0.050
ECOG				
0	595 (66.0)	75 (61.5)	0.361	0.094
1	186 (20.6)	46 (37.7)	<0.001	0.383
2	120 (13.3)	1 (0.8)	<0.001	0.504
Child score	6.1±1.1	5.9±1.2	0.027	0.166
Child A	544 (60.4)	79 (64.8)	0.375	0.091
Child B	354 (39.3)	37 (30.3)	0.060	0.199
Child C	3 (0.3)	6 (4.9)	<0.001	0.292



Previous treatment ^a					
Surgery	163 (18.1)	21 (17.2)	0.900	0.024	
Radiofrequency ablation	184 (20.4)	6 (4.9)	<0.001	0.480	
TACE	485 (53.8)	51 (41.8)	0.016	0.242	
Intrahepatic tumor expansion	<i>n</i> = 719		<0.001	0.646	
Oligonodular	168 (23.4)				
Multifocal	551 (76.6)				
BCLC					
A	41 (4.6)	6 (4.9)	0.999	0.014	
B	242 (26.9)	69 (56.6)	<0.001	0.632	
C	618 (68.6)	47 (38.5)	<0.001	0.633	
Largest tumor diameter, cm	5.9±4.1	5.6±3.4	0.836	0.080	
PVT	306 (34.0)	22 (18.0)	<0.001	0.371	
Extrahepatic metastases	322 (35.7)	16 (13.1)	<0.001	0.545	
Laboratory					
AST, U/L	87±80	94±67	0.358	0.094	
ALT, U/L	61±58	57±42	0.813	0.089	
Bilirubin, mg/dL	1.1±0.8	1.2±2.2	0.257	0.036	
Albumin, g/dL	3.7±0.5	3.5±0.7	0.045	0.329	
AFP, ng/mL	12,959.5±61,182.5	2,174.9±9,637.4	0.001	0.246	
Treatment characteristics of SBRT patients					
TD, Gy	44 (21–66)				
BED _{10,TD} , Gy	84.4 (36–180)				
D _{max} , Gy	58 (26–72)				
BED _{10,maxo} , Gy	119 (40–272)				

Incidence of treatment-associated adverse events in the **unmatched** cohort

	Any grade	Grade 1	Grade 2	Grade 3	Grade 4
<i>Adverse events in patients treated with sorafenib</i>					
Hand-foot skin reaction	281 (31.2)	102 (36.3) ^a	104 (37.0)	73 (26.0)	2 (0.7)
Diarrhea	354 (39.3)	143 (40.4)	102 (28.8)	99 (27.9)	10 (2.9)
Obstipation	16 (1.8)	11 (68.8)	5 (31.3)	0	0
Fatigue	264 (29.3)	104 (39.4)	96 (36.4)	59 (22.3)	5 (1.9)
Weight loss	171 (19.0)	98 (57.3)	54 (31.6)	14 (8.2)	5 (2.9)
Hypertension	120 (13.3)	53 (44.2)	50 (41.7)	17 (14.2)	0
Mucositis	42 (4.7)	18 (42.9)	18 (42.9)	6 (14.3)	0
Nausea and vomiting	68 (7.5)	37 (54.4)	26 (38.2)	5 (7.4)	0
<i>Adverse events in patients treated with SBRT</i>					
Fatigue	1 (1.0)	1 (100)	0	0	0
Increase in aminotransferases	0	0	0	0	0
Increase in bilirubin	9 (7.4)	0	2 (22.2)	7 (77.8)	0
Increase in alkaline phosphatase	2 (1.6)	0	2 (100)	0	0
Increase in γ -glutamyl transferase	3 (2.5)	0	2 (66.7)	1 (33.3)	0
Duodenitis/gastrointestinal bleeding	3 (2.5)	0	2 (66.7)	1 (33.3)	0
Liver-associated toxicity					
Liver abscess	1 (0.8)	0	0	0	1 (100)
Radiation-induced liver disease	1 (0.8)	0	0	1 (100) ^b	0
Hepatic decompensation	3 (2.5)	0	0	2 (66.7) ^b	1 (33.3)
Cholangitis	1 (0.8)	0	0	1 (100)	0

^a Relative frequencies refer to any grade of the reported adverse event. ^b One of the patients with hepatic decompensation developed radiation-induced liver disease.



Baseline characteristics of patients after propensity score matching

Characteristics	Sorafenib (n = 95)	SBRT (n = 95)	p value	Mean standardized difference
Gender				
Male	78 (82.1)	79 (83.2)	0.999	0.029
Female	17 (17.9)	16 (16.8)		
Age, years	66.9±12.5	66.7±8.9	0.472	0.018
ECOG				
0	63 (66.3)	71 (74.7)	0.265	0.018
1	31 (32.6)	23 (24.2)	0.260	0.187
2	1 (1.1)	1 (1.1)	0.999	0
Child score	5.8±0.9	5.9±1.2	0.629	0.094
Child A	70 (73.7)	67 (71.3)	0.426	0.054
Child B	25 (26.3)	28 (29.5)	0.999	0.071



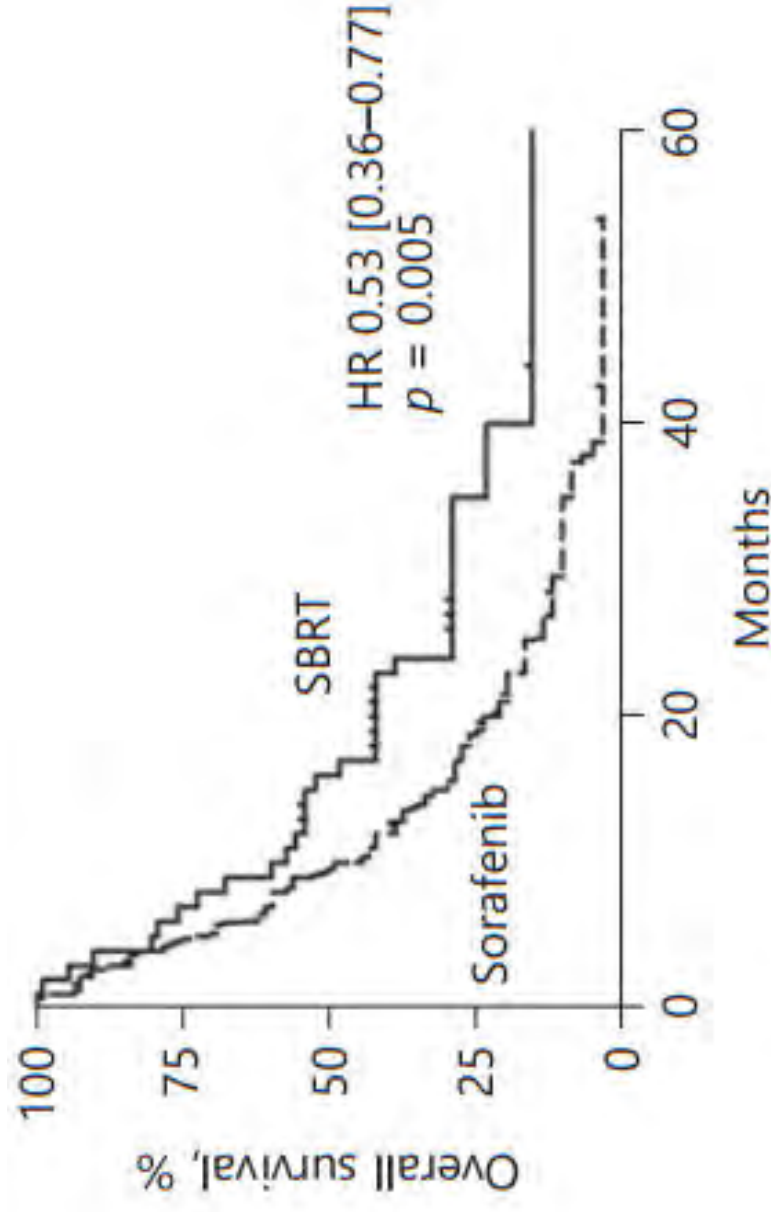
Baseline characteristics of patients after propensity score matching

Previous treatment ^a	Sorafenib	SBRT	p-value	mSD
Surgery	18 (18.9)	16 (16.8)	0.850	0.054
Radiofrequency ablation	4 (4.2)	5 (5.3)	0.999	0.052
TACE	47 (49.5)	48 (50.5)	0.999	0.020
Intrahepatic tumor expansion			0.999	0.020
Oligonodular	39 (41.1)	40 (42.1)		
Multifocal	56 (58.9)	55 (57.9)		
BCLC				
A	5 (5.3)	4 (4.2)	0.999	0.051
B	42 (44.2)	48 (50.5)	0.468	0.116
C	48 (50.5)	43 (45.3)	0.561	0.104
Largest tumor diameter, cm	6.5±4.1	6.2±3.6	0.495	0.008
PVT	20 (21.1)	21 (22.1)	0.999	0.024
Extrahepatic metastases	24 (25.3)	16 (16.8)	0.213	0.102
Laboratory				
AST, U/L	100±128	93±70	0.385	0.066
ALT, U/L	65±81	58±44	0.810	0.107
Bilirubin, mg/dL	1.1±0.7	1.7±1.4	0.023	0.041
Albumin, g/dL	3.6±0.5	3.5±0.5	0.321	0.021
AFP, ng/mL	16,100±69,008.7	22,611±10,016.1	0.016	0.322

Data are presented as *n* (%) or mean ± SD. ECOG, Eastern Cooperative Oncology Group; BCLC, Barcelona Clinic Liver Cancer; PVT, portal vein thrombosis; SBRT, stereotactic body radiation therapy; AST, aspartate aminotransferase; ALT, alanine aminotransferase; AFP, alpha-fetoprotein.^a Patients may have received more than one treatment.



Patients treated with SBRT had significantly improved overall survival compared to patients treated with sorafenib in the matched cohort (9.6 vs. 16.0 months).



No. at risk	SBRT: 95	17	4	2
	Sorafenib: 95	18	3	-

a



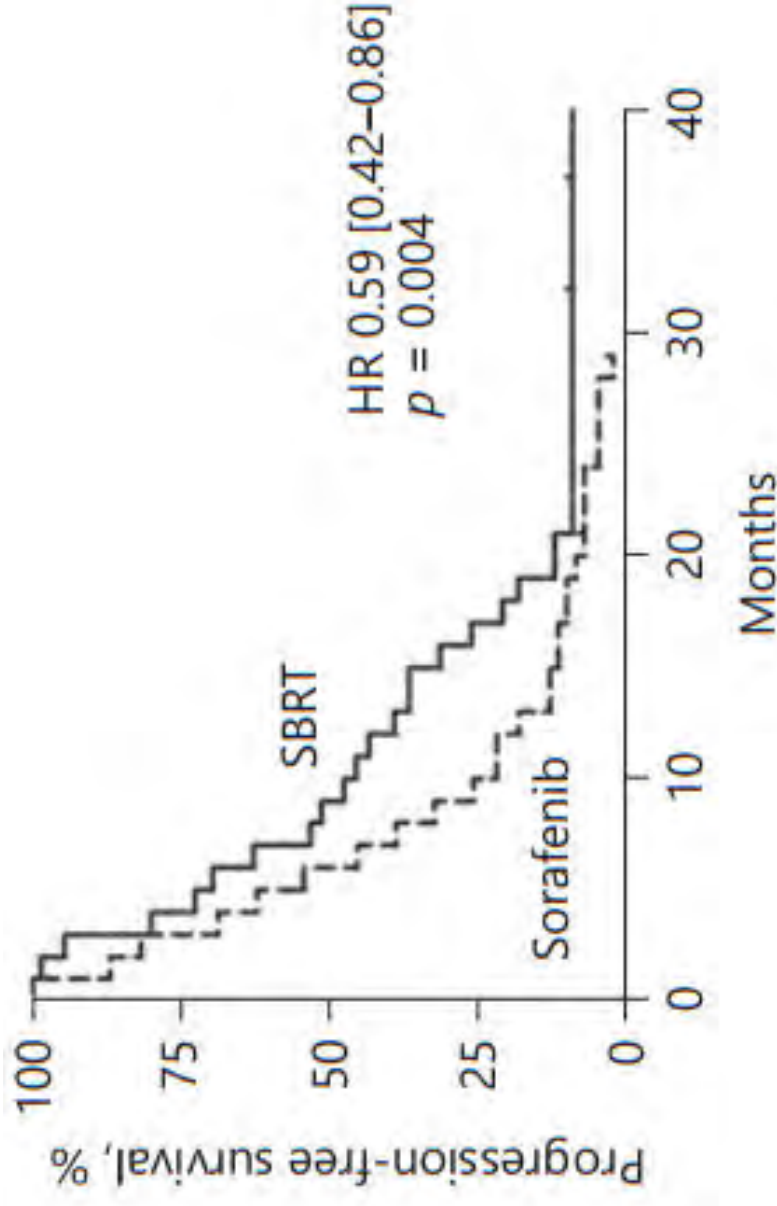
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Patients treated with SBRT also had an improved PFS compared to sorafenib patients (9.0 vs. 6.0 months).

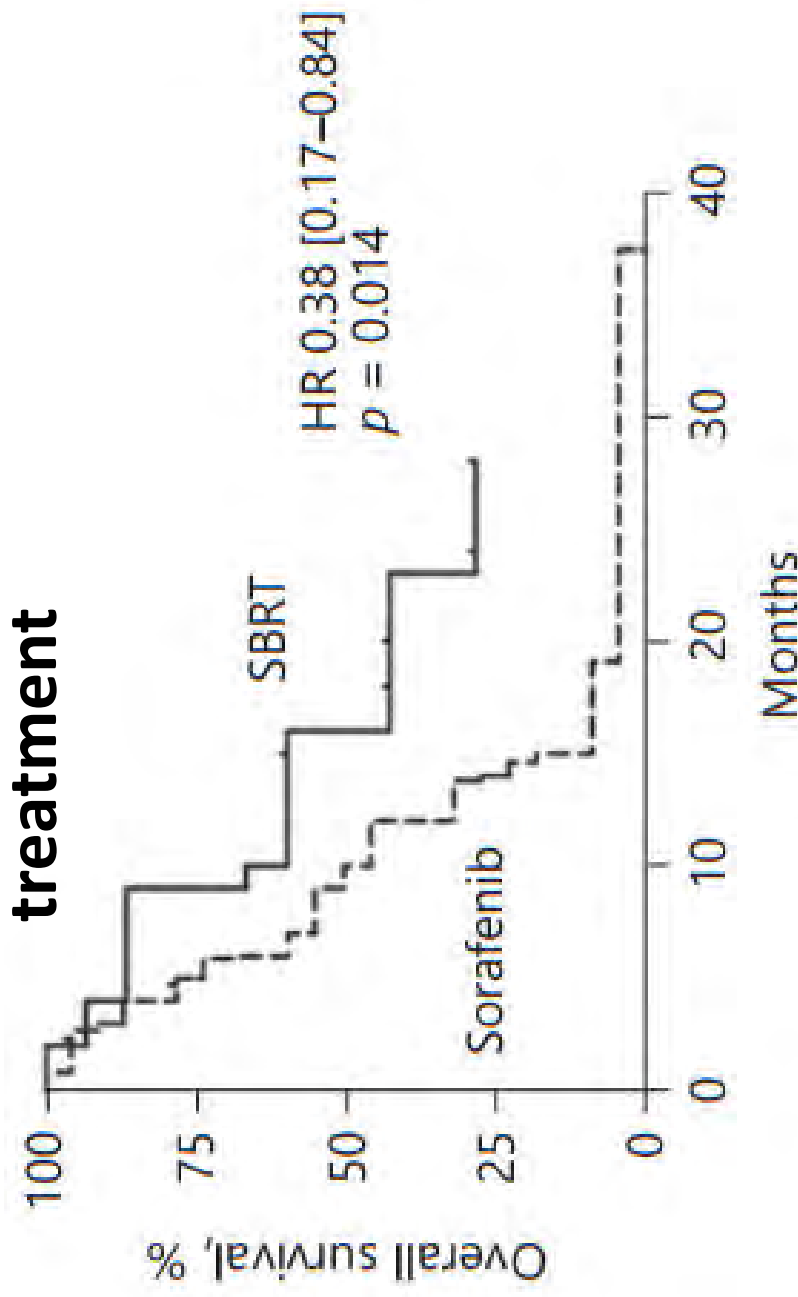


No. at risk	SBRT: 83	23	6	4	2
Sorafenib: 79	20	6	-	-	-

b



Patients with extrahepatic metastases treated with SBRT had improved overall survival compared to sorafenib



No. at risk SBRT: 16

11

5

1

-

Sorafenib: 24

11

2

2

-

a



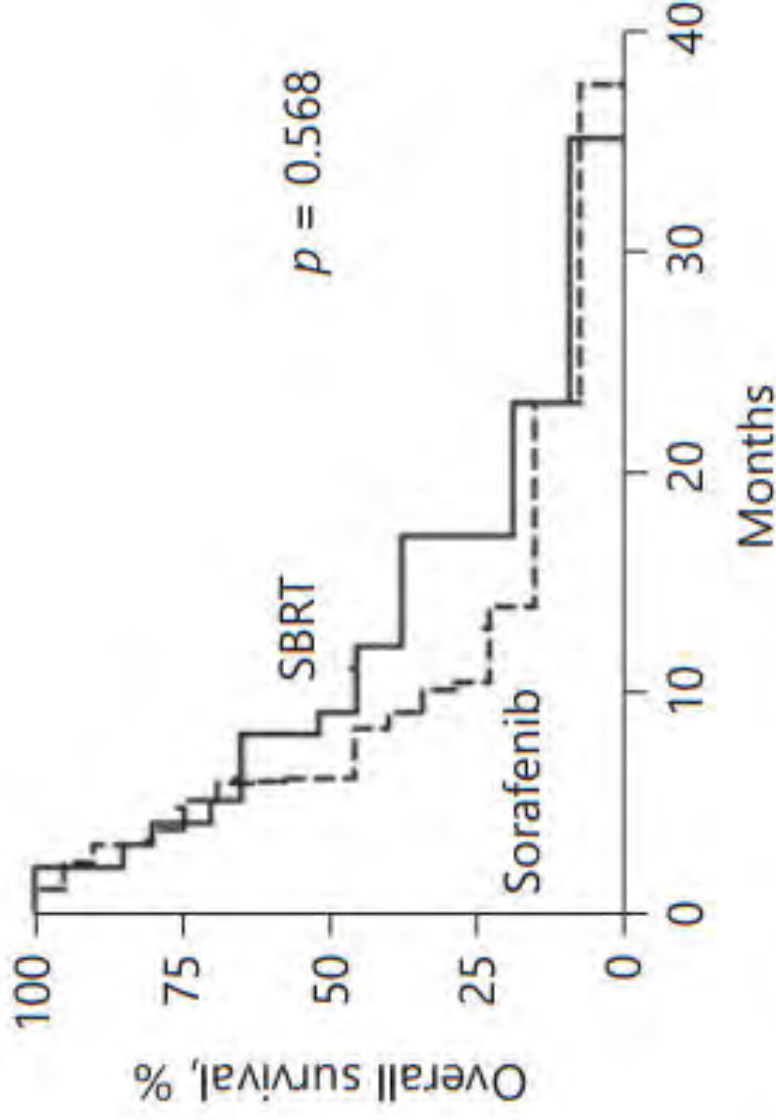
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In patients with PVT, SBRT was not associated with longer overall survival compared to sorafenib treatment.



No. at risk	SBRT: 20	6	3	2	-
Sorafenib: 21	8	4	2	2	-

b



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Univariable and multivariable Cox regression model in the matched cohort of patients

Variable	Univariable Cox regression		Multivariable Cox regression	
	HR	95% CI	HR	95% CI
Age	0.99	0.97-1.00		
Gender (female vs. male)	1.15	0.74-1.80		
Child score	1.23	1.05-1.45	1.39	1.16-1.66
				<0.001
Previous treatment				
Surgery	0.99	0.65-1.54		
Radiofrequency ablation	0.80	0.33-1.96		
TACE	1.26	0.89-1.79		
Intrahepatic tumor expansion (olignodular vs. multifocal)	1.51	1.05-2.16		
BCLC				
A	1		1	
B	1.82	0.66-5.06	1.58	0.55-4.48
C	3.40	1.23-9.41	3.21	1.12-9.22
Largest tumor diameter	1.09	1.05-1.14	1.07	1.02-1.12
PVT	1.77	1.18-2.65		
Extrahepatic metastases	1.26	0.84-1.90		
Treatment (sorafenib vs. SBRT)	0.57	0.40-0.81	0.53	0.36-0.77
				0.001



Radiofrequency Ablation Versus Stereotactic Body Radiotherapy for Localized Hepatocellular Carcinoma in Nonsurgically Managed Patients: Analysis of the National Cancer Database

Devalkumar J. Rajyaguru, Andrew J. Borgert, Angela L. Smith, Reggie M. Thomas, Patrick D. Conway, Thorvardur R. Halfdanarson, Mark J. Truty, A. Nicholas Kurup, and Ronald S. Go

Gundersen Health System,
Mail Stop EB2-001, 1900 South Ave,
La Crosse, WI



Rajyaguru DJ et al. JCO 2018



Methods

- observational study to compare the effectiveness of RFA versus SBRT in nonsurgically managed patients with stage I or II HCC (National Cancer Database).
- OS compared by propensity score–weighted and propensity score–matched analyses based on
 - patient-, facility-, and tumor-level characteristics.
- sensitivity analysis was performed to evaluate the effect of severe fibrosis/cirrhosis.
- In addition, we performed exploratory analyses to determine the effectiveness of RFA and SBRT in clinically relevant patient subsets.



National Cancer Database hepatocarcinoma,
hepatocellular cancer, pleomorphic, and
undifferentiated carcinoma
2004-2013
(N = 119,933)

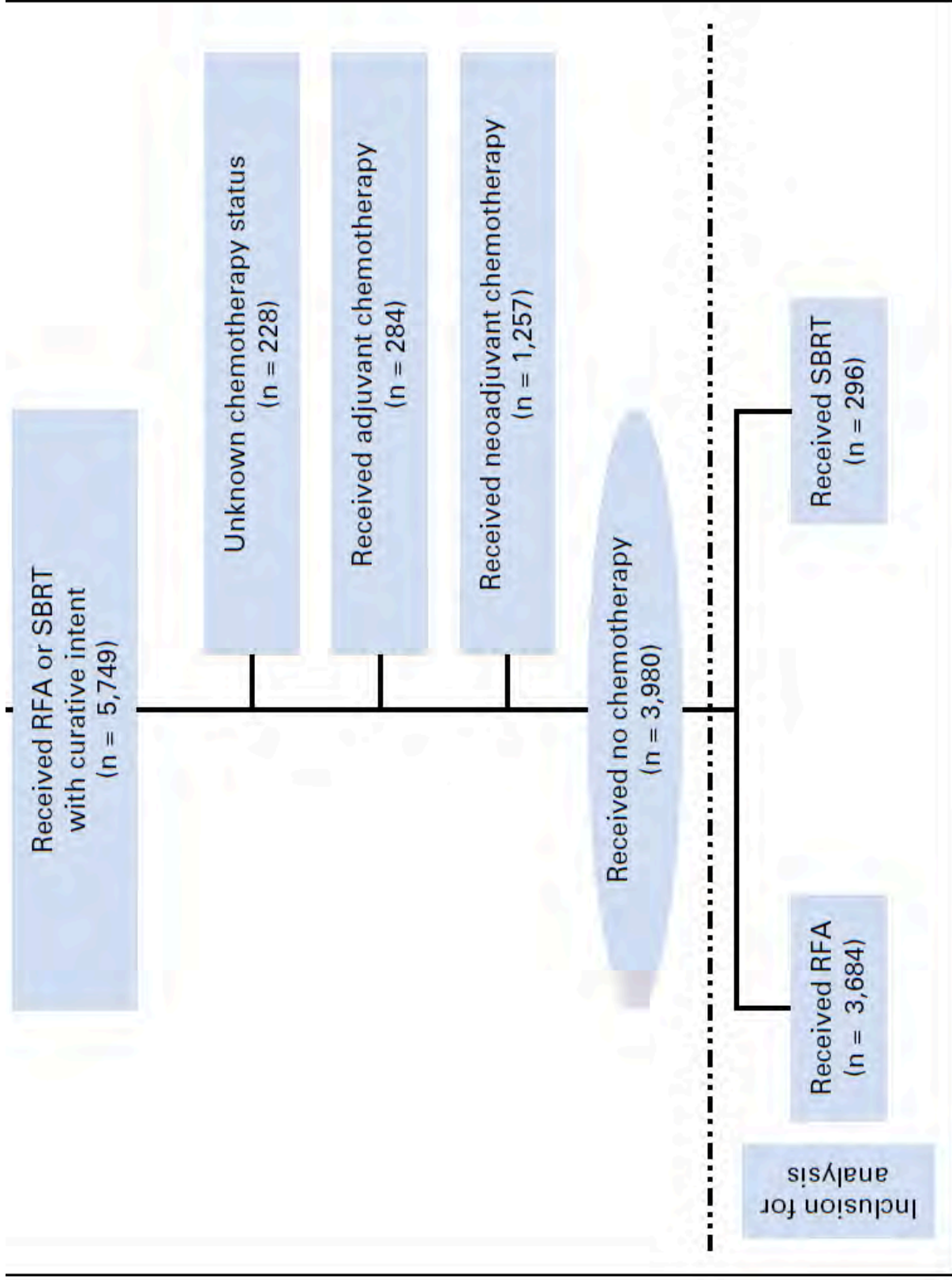
Advanced clinical stage at diagnosis
(n = 72,299)

Patients with clinical T stage I and II,
no positive nodes, and non-metastatic
(n = 47,634)

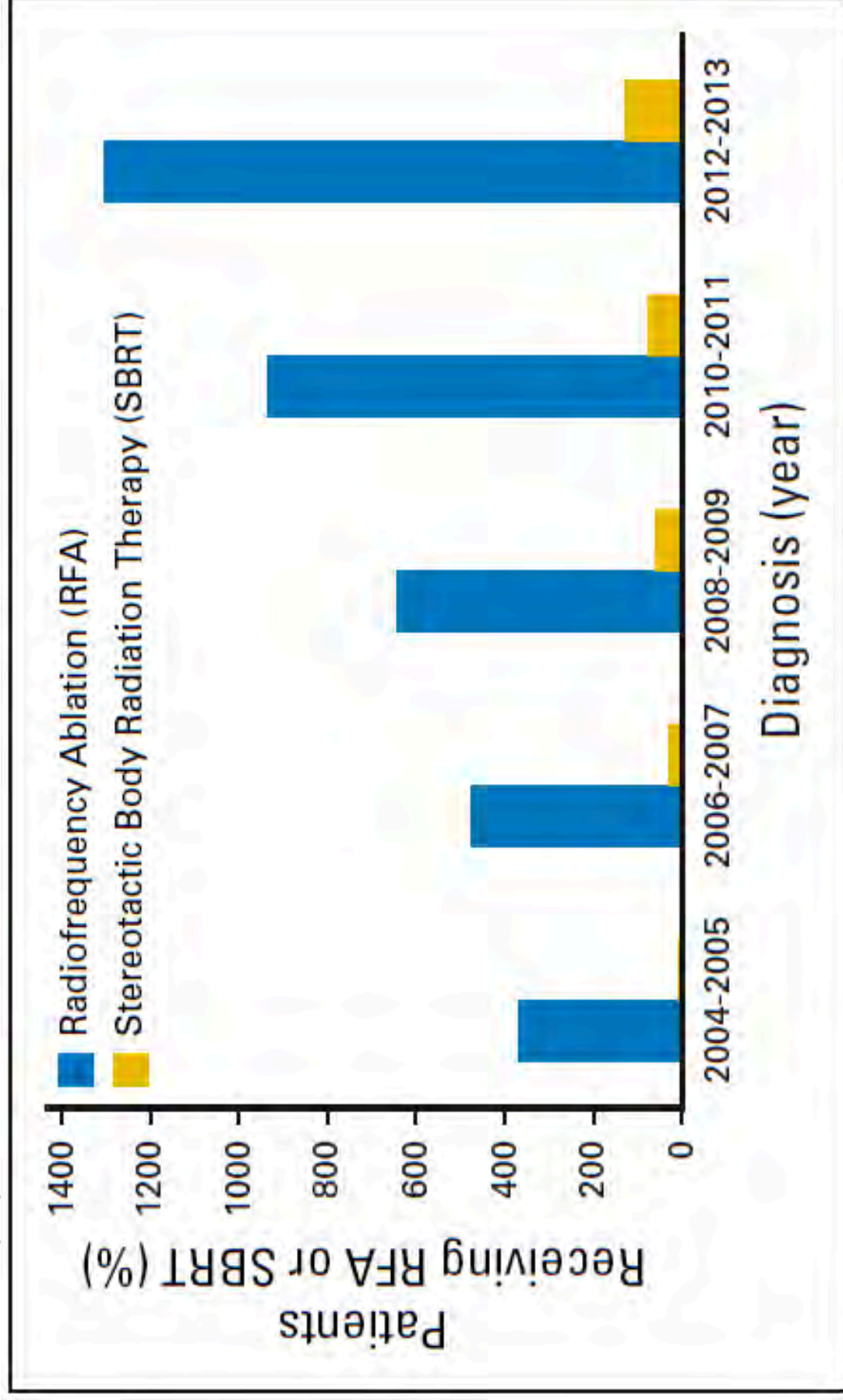
Tumor size > 5cm or no tumor size reported
(n = 12,682)

Patients with tumor size \leq 5 cm
(n = 34,952)





Use of RFA vs SBRT for stage I and II HCC over time in the unmatched study population from the National Cancer Center Database, 2004-2013.



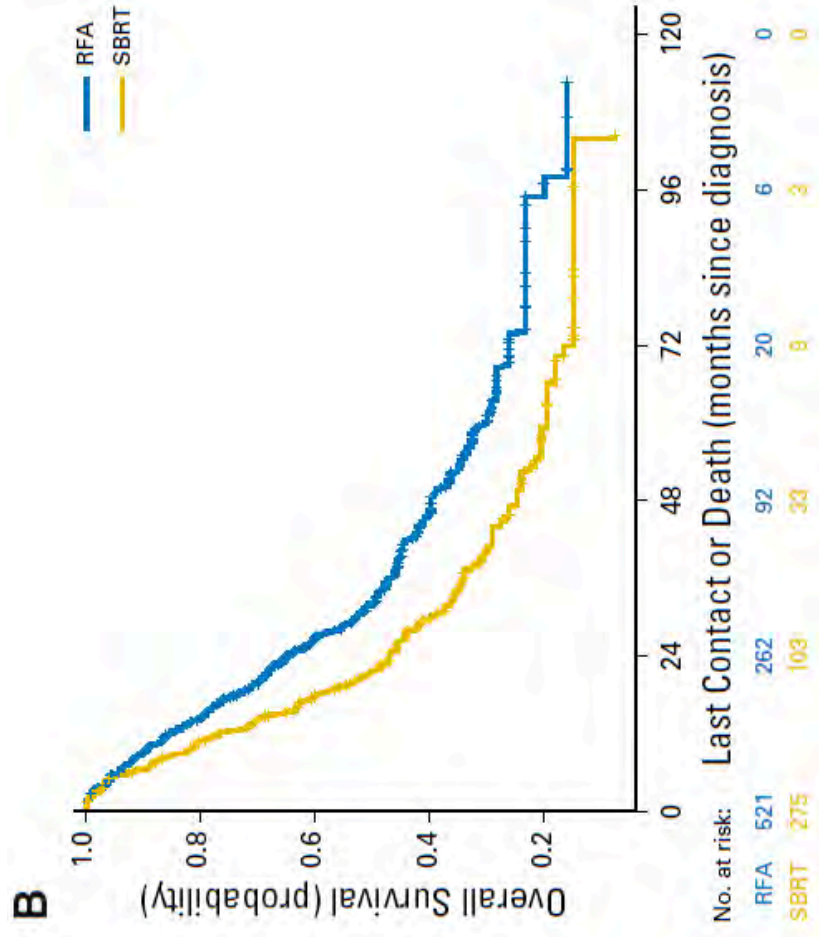
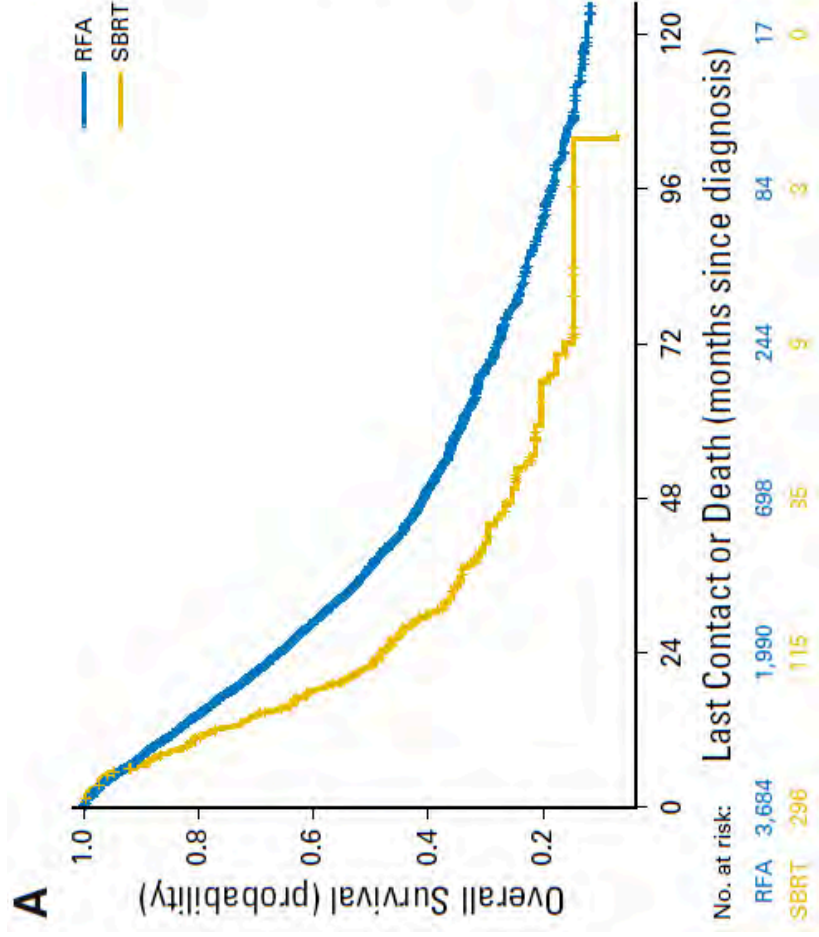
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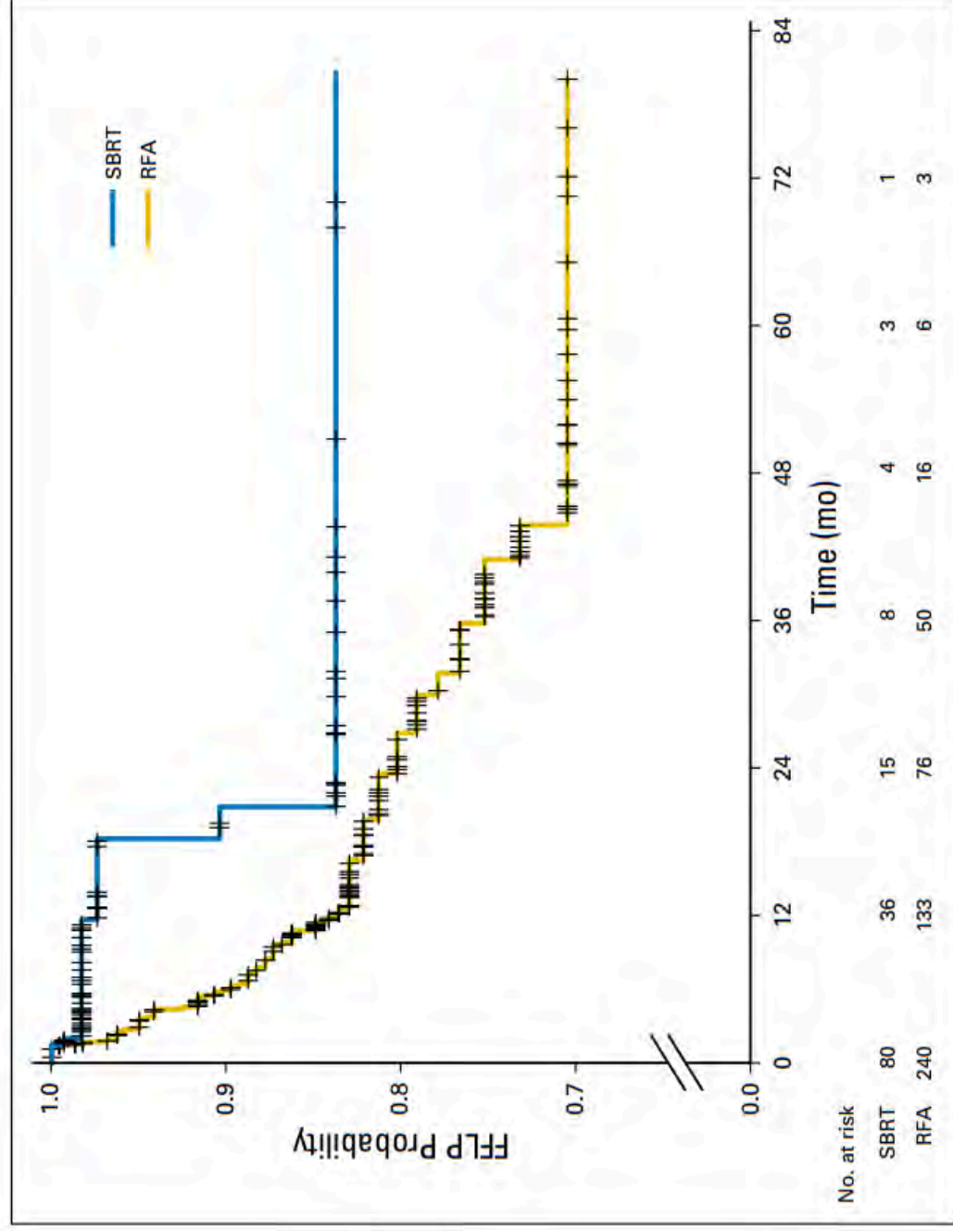
Overall survival in (A) the unmatched, (B) the propensity score matched



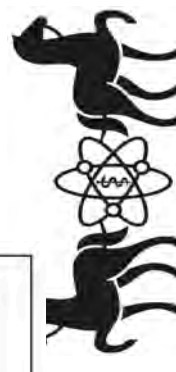
Rajyaguru DJ et al. JCO 2018



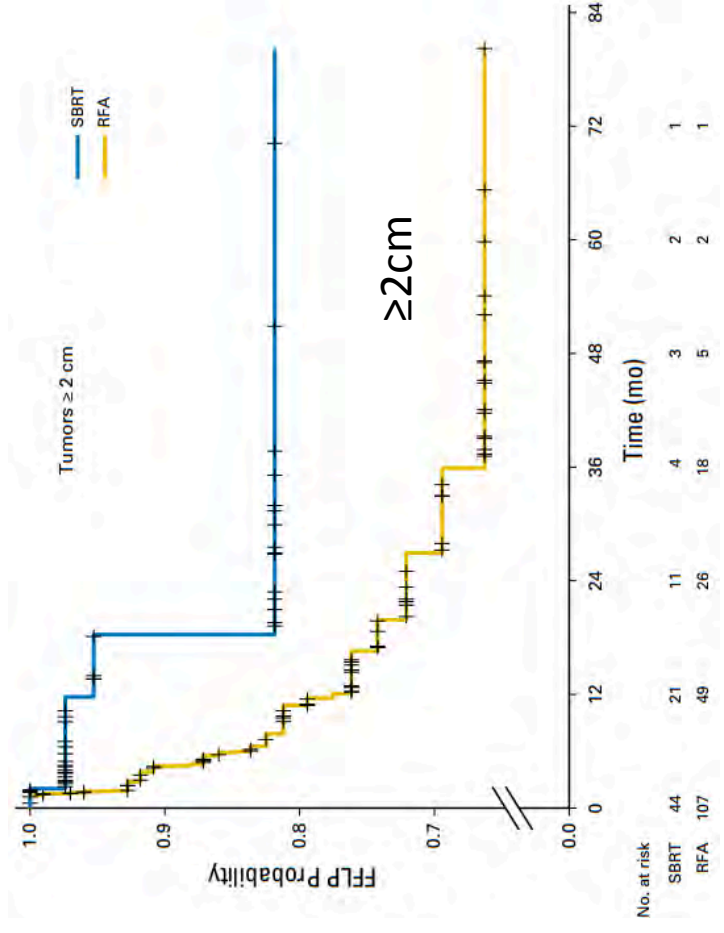
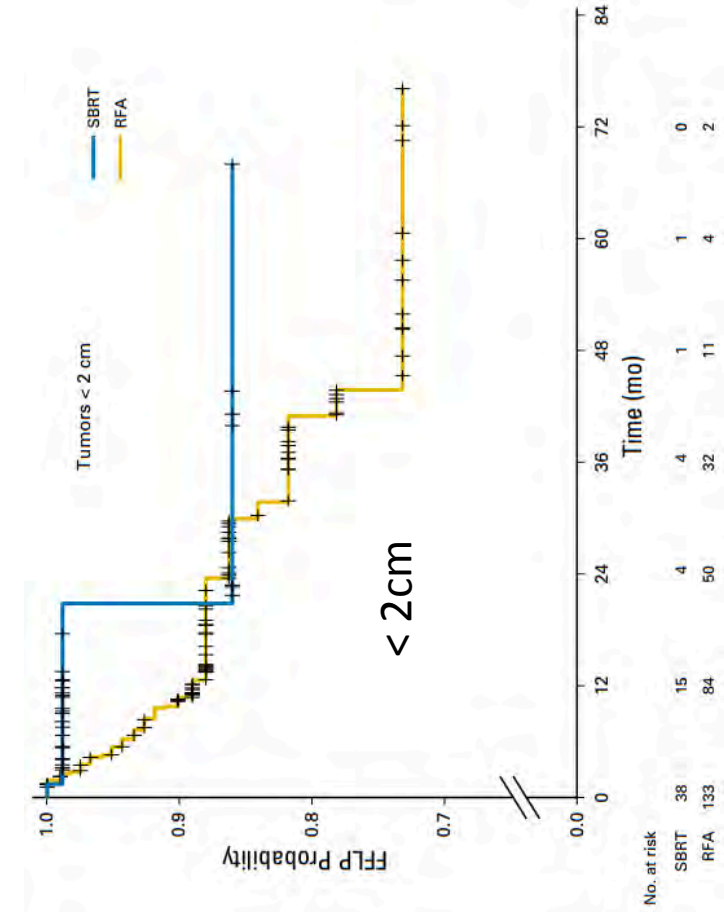
Freedom from local progression by treatment modality. RFA vs SBRT



Wahl D et al. JCO 2016



Freedom from local progression by treatment modality. RFA vs SBRT



Wahl D et al. JCO 2016



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.



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Correspondence on Rajyaguru et al

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Boda-Heggemann, Gkika et al. JCO 2018



Weaknesses of Rajaguru et al.

- No Information on the liver function of patients is missing (ie, **Child-Turcotte-Pugh [CTP]** score, which is the predominant prognostic factor). The majority of patients die as a result of ascites, portal hypertension, and/or hepatic encephalopathy and
- No data on the presence of portal vein invasion.
- **the difference in survival reported is a result of selection bias**
- The authors attempt to compensate for missing CTP score by providing the **Ishak fibrosis score**, although this information is available for few patients (SBRT, 16%; RFA, 29%).



Weaknesses of Rajaguru et al.

- Analysis excludes patients receiving any form of adjuvant or neoadjuvant therapy
- or other forms of local ablative therapies.
- But: typical course of the disease requires further treatment
- does not reflect common practice.



Weaknesses of Rajaguru et al.

- One has to assume that only patients who were not candidates for other treatment options were referred for SBRT.
 - patients receiving RFA were more likely to have private insurance, and they were younger compared with patients receiving SBRT.
- > direct impact on survival.



Weaknesses of Rajaguru et al.

- no data on LC are reported
- years 2003 – 2014: SBRT at that time (2003 to 2010) was in the early phase of development and optimization



Eleni Gkika, Oliver Blanck,
Christos Moustakis, Thomas Brunner

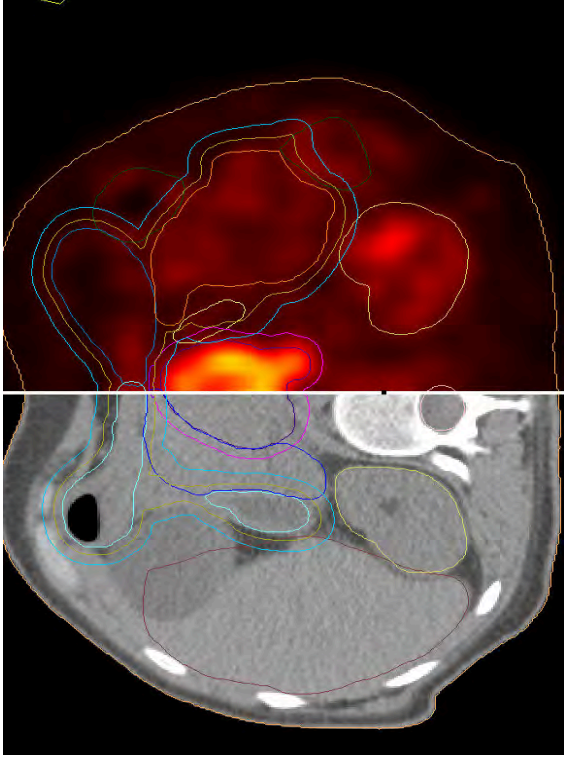
PLANUNGSSTUDIE PANKREAS- KARZINOM (CCC)



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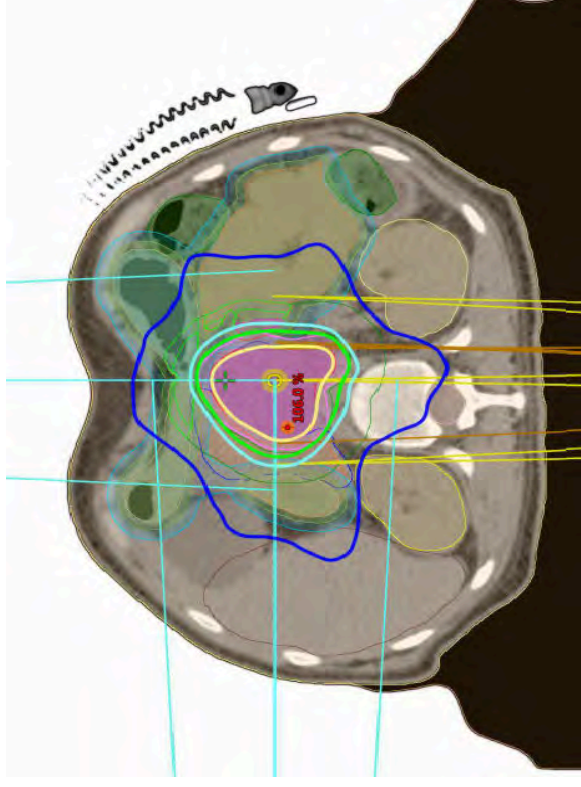


Pankreaskarzinom: Konturierungs und Planungs-Studie



Phase 1:

- ✓ Berechnung der **Interobserver Variabilität** bei der **Konturierung** mit der Hilfe eines 4D Planungs-PET CTs + MRT oder 3D CTs + PET CT + MRT



Phase 2:

- ✓ Berechnung der **Variabilität** bei der **Planung** unter Angabe der Dosis/Fraktionierung und Constraints

Bei Interesse: T. Brunner kontaktieren

Fallvignetten sind begleitend zu den Bildern vorhanden

Patient:

Männlich, 53 Jahre

Diagnose:

Progredientes, funktionell inoperables Pankreaskopfkarzinomrezidiv am Truncus coeliacus mit Ummauerung von Truncus, A.hepatica com. Und Kontakt zur A. mesenterica sup.

Histologie: Adenokarzinom G2

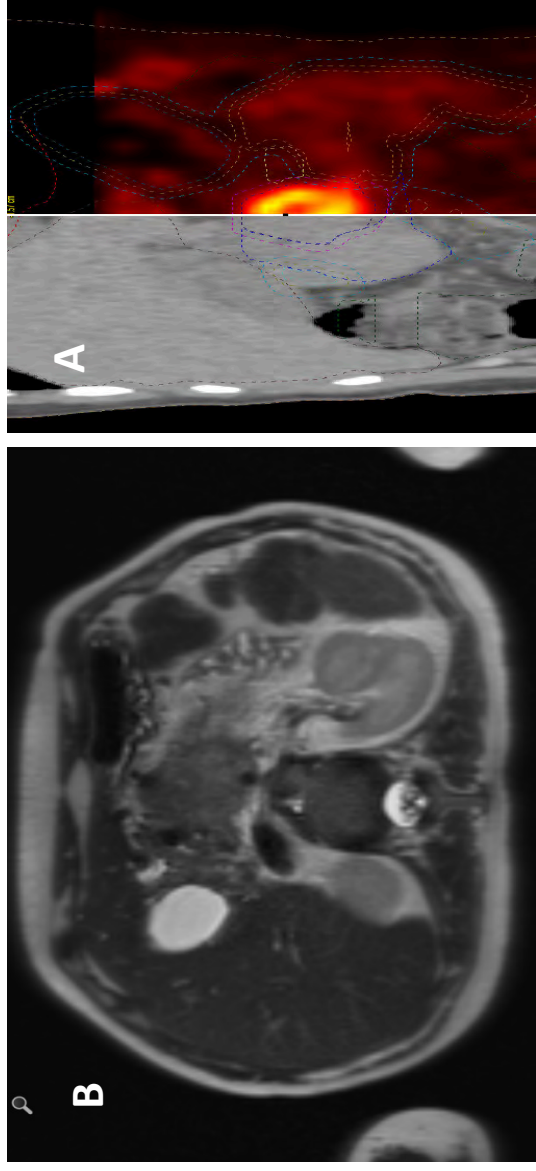
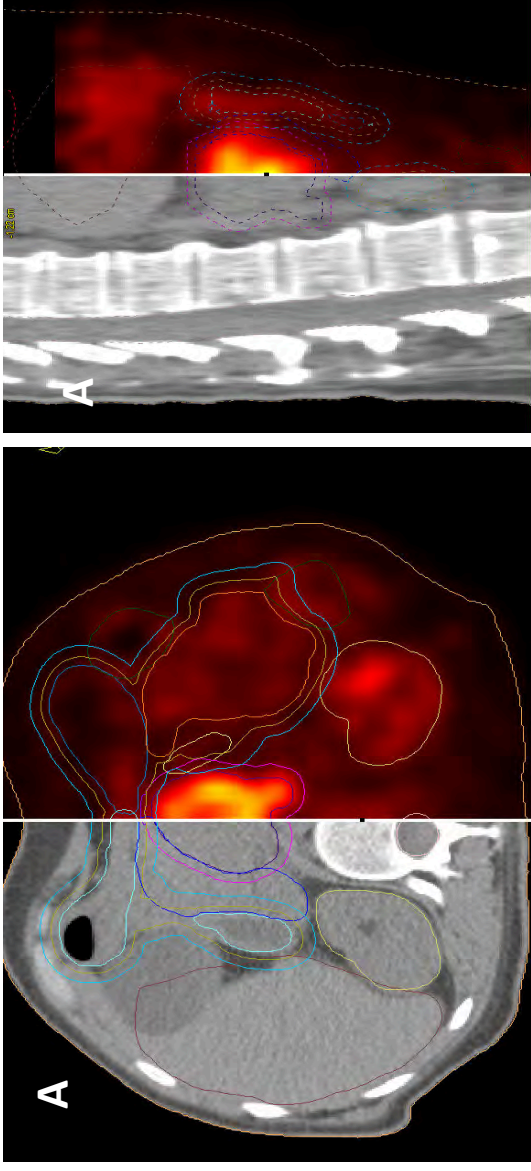
Erstdiagnose: 01/2012

Bisheriger Verlauf:

--02/2012 Anlage biliodigestiver Anastomose mit Y-Roux-Rekonstruktion mit Cholezystektomie und Probeexzision bei inoperablem Pankreaskopfkarzinom; cT4 cN1 cM0 G2

--03/2012 bis 11/2012 Palliative Chemotherapie mit FOLFORINOX und Gemcitabin

Pankreaskarzinom: Konturierungs und Planungs-Studie



Fall 1:

Histologisch gesichertes
inoperables
PankreaskorpusCa

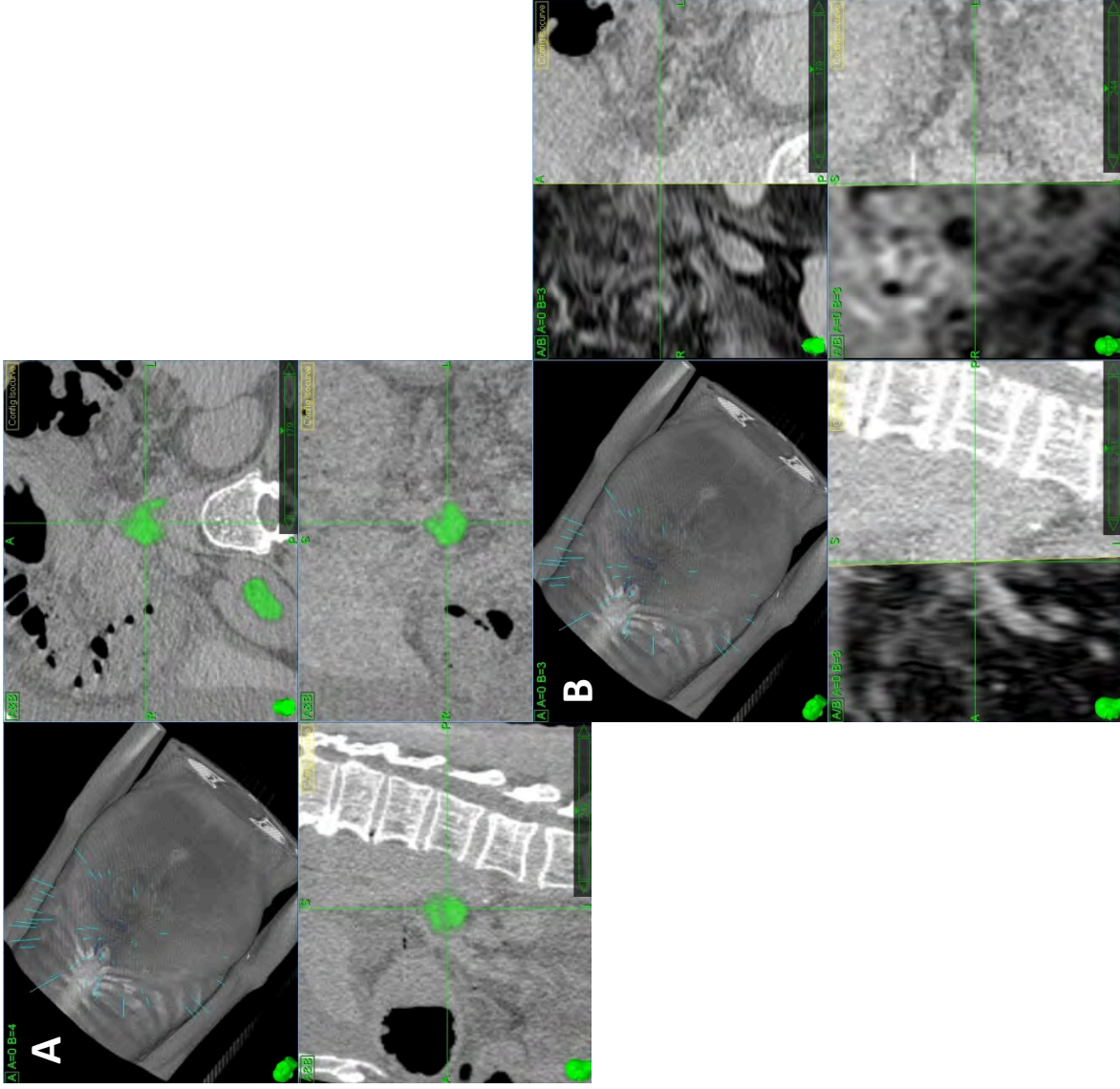
Zn. 3 Zyklen Chemotherapie

Abbruch bei
Unverträglichkeit

Planung: SBRT

- A. 4D PET/CT in
Bestrahlungsposition
- B. MRT

Pankreaskarzinom: Konturierungs- und Planungs-Studie



Fall 2:

Progredientes, funktionell inoperables Pankreaskopfkarzinomrezidiv

Zn. Neo-Adjuvante und Adjuvante Chemotherapie bei primärer Radio-Chemotherapie mit 45Gy (1,8 Gy EHD)

Planung: SBRT bei Vorbelastung

- A. 4D PET/CT in Bestrahlungsposition
- B. MRT

Einige wenige Details

- Target Structures:
 - GTV,
 - CTV
 - PTV
- Organs at Risk:
 - Duodenum, stomach
 - Other bowel structures (≤ 3 cm)
 - Spinal cord
 - Kidneys, liver

Dose Prescription & Reporting (ICRU 91)

Körperregion	Verschreibungsvolumen nach Art des Hauses, aber bitte angeben:				Conformity index	Homogeneity index	Gradient index
Generelle Prinzipien	D_(near) Min ICRU 91	D_(near) Max ICRU 91	D50%	D0.1cc (! Zentral im ITV)	CI einfach	CI invers Paddick	GI ICRU91
	D95% PTV	D05	D50% PTV	D0,1 ml (! zentral im ITV)	PIV / PTV	PTV*PI V / (PTV Ω PIV) ²	V50% / V 100%
Pankreas					D95% ITV		
					<1.2	≤1.25	≤ 2,5 (4.0)
						= 1,25	

Ablauf

- Einreichung aller Strukturen
- Planung auf die jeweiligen Strukturen
- Erste Analyserunde
- Re-Planung auf ein ausgewähltes Structure Set
- Zweite Analyserunde