Fegato
letteratura ed esperienza clinica

A Guarneri

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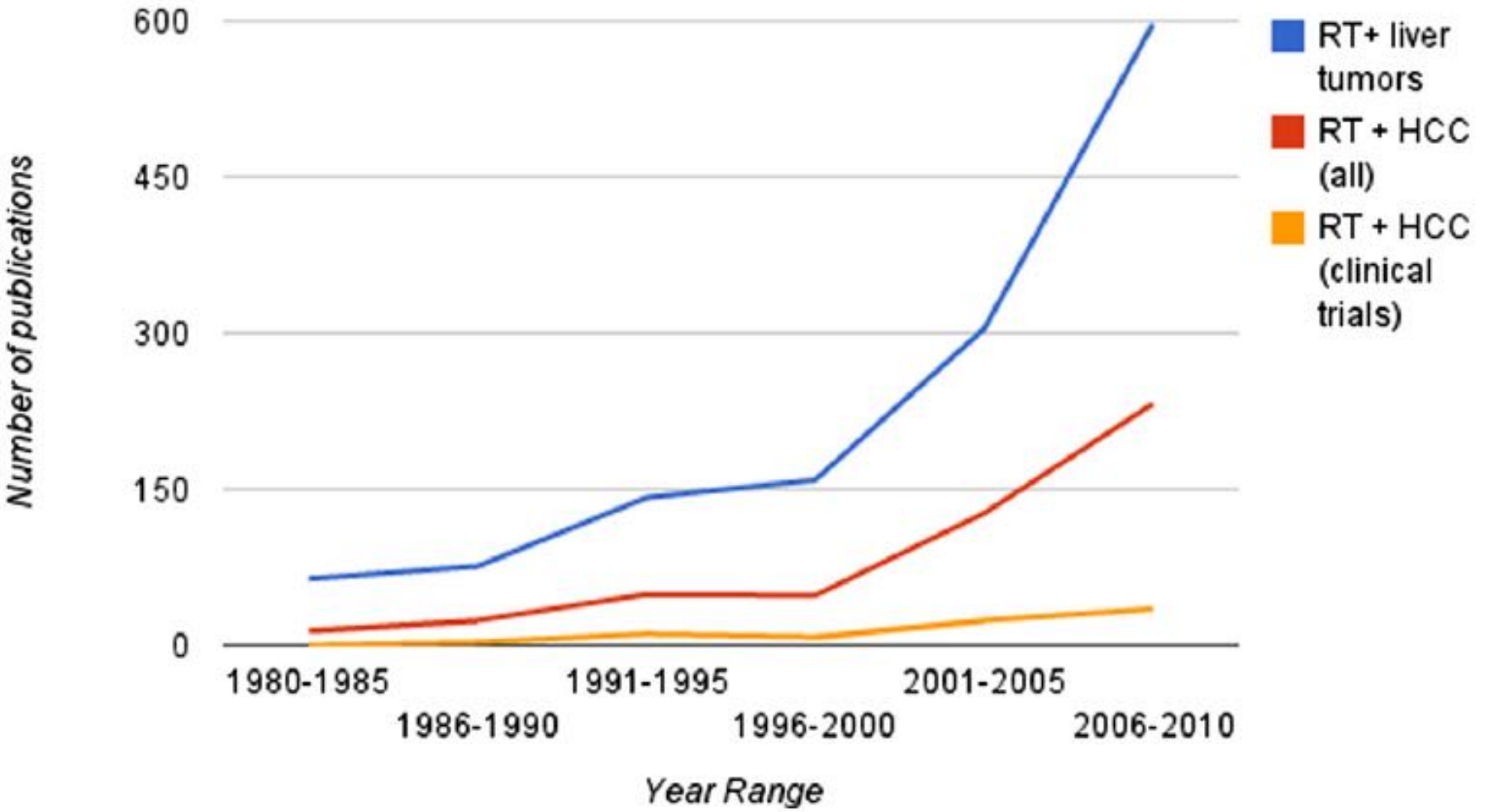
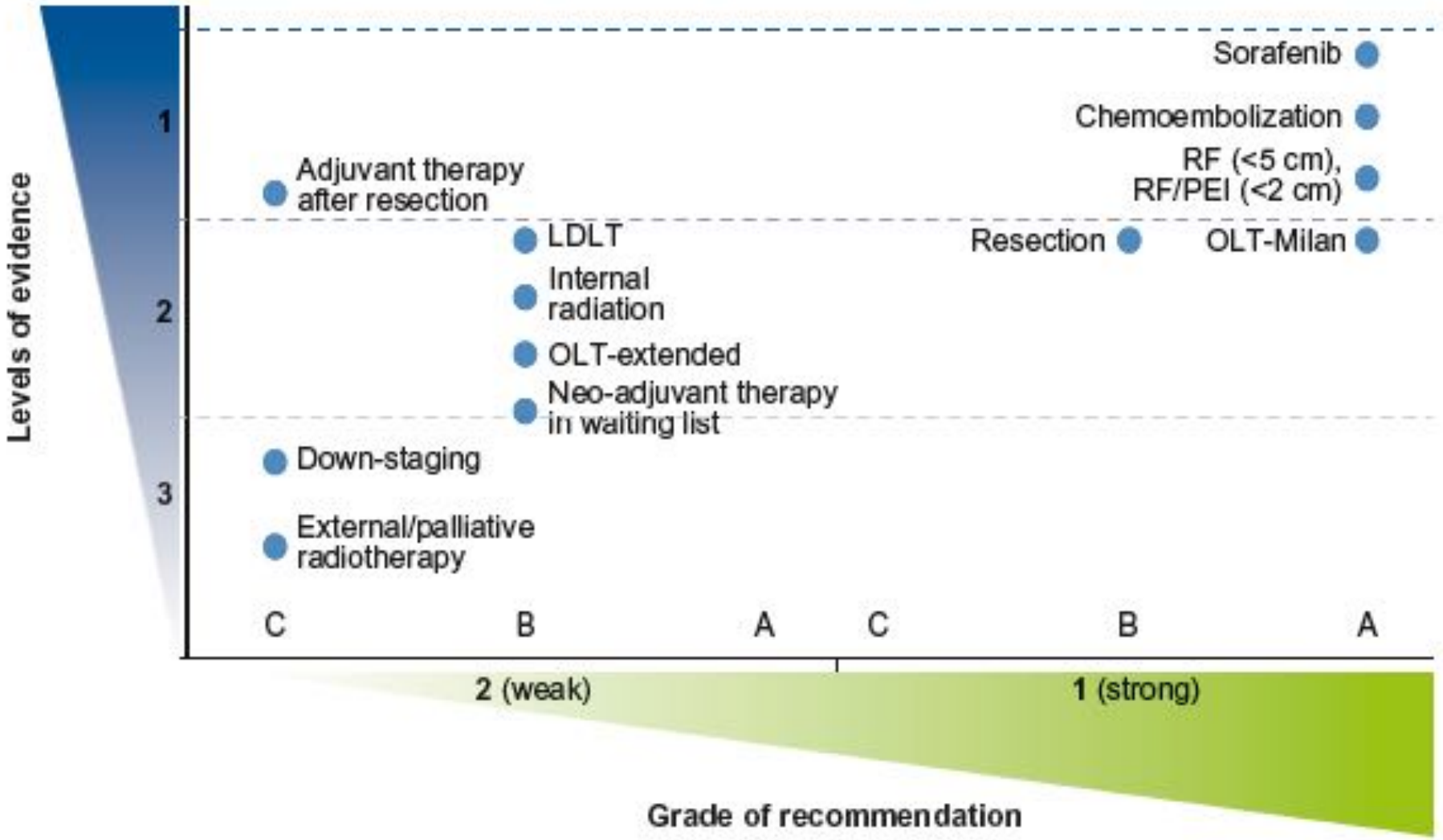

600
450
300
150
0
Number of publications
1980-1985
1986-1990
1991-1995
1996-2000
2001-2005
2006-2010
Year Range
RT+ liver tumors
RT + HCC (all)
RT + HCC (clinical trials)

HEPATOCELLULAR CARCINOMA



EASL–EORTC Clinical Practice Guidelines *J Hepatology 2012*

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RADIATION-ASSOCIATED LIVER INJURY

CHARLIE C. PAN, M.D.,* BRIAN D. KAVANAGH, M.D., M.P.H.,† LAURA A. DAWSON, M.D.,‡
X. ALLEN LI, PH.D.,§ SHIVA K. DAS, PH.D.,‖ MOYED MIFTEN, PH.D.,†
AND RANDALL K. TEN HAKEN, PH.D.*

Classic Radiation-Induced Liver Disease (RILD)

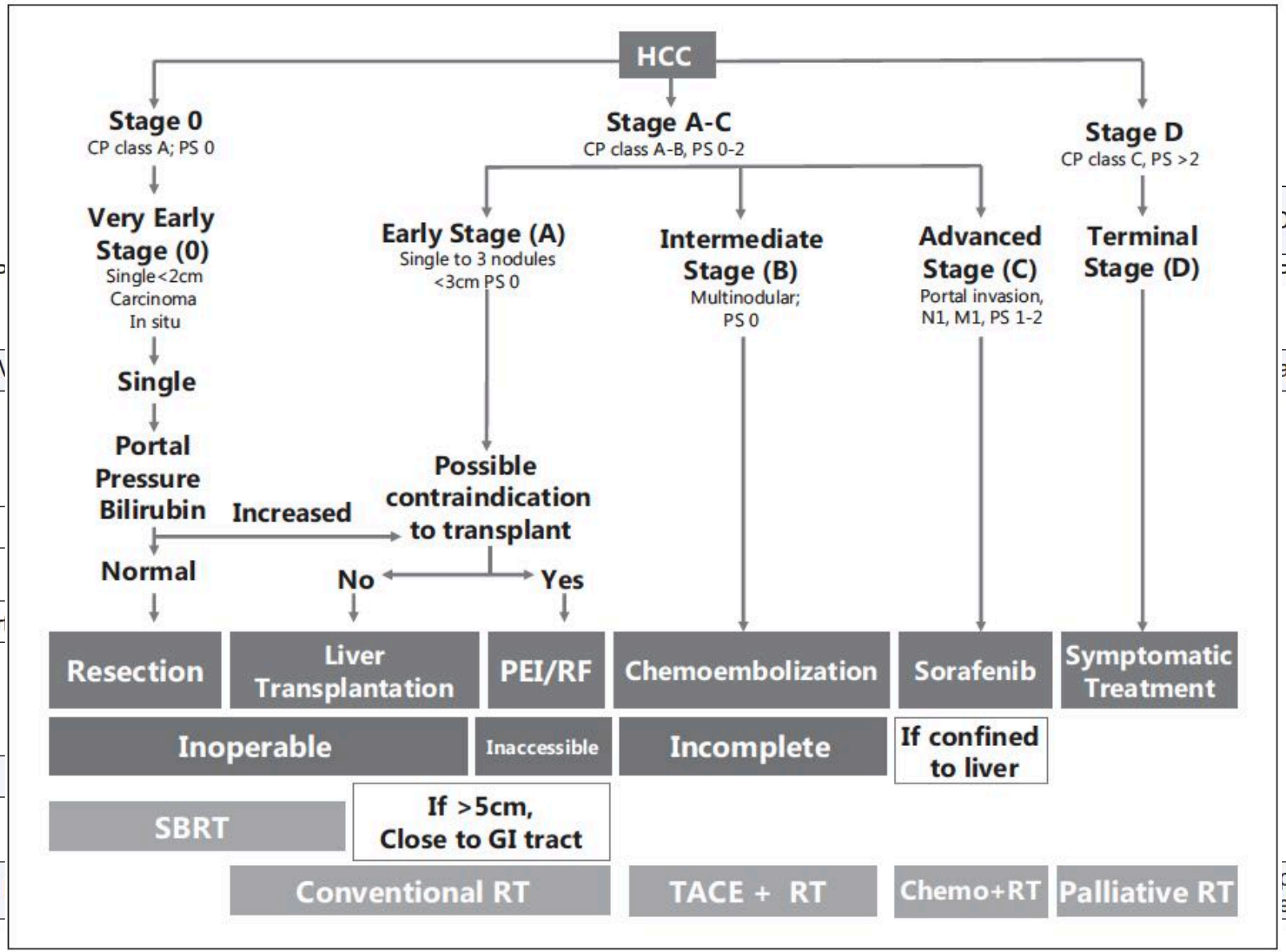
Clinical syndrome of anicteric hepatomegaly, ascites and elevated liver enzymes (more than twice the upper limit of normal or baseline value) typically occuring between 2 weeks to 3 months after therapy

Nonclassic Radiation-Induced Liver Disease (RILD)

typically occuring between 1 weeks to 3 months after therapy, involves elevated liver transaminases more than five times the upper limit of normal or decline in liver function

A confounder of RILD, especially in population with pre-existing liver dysfunction, is the baseline rate of morbidity within this population due to their preexisting liver disease

Int. J. Radiation Oncology Biol. Phys., Vol. 76, No. 3, Supplement, pp. S94–S100, 2010



EASL-EORTC Clinical Practice Guidelines: Management of hepatocellular carcinoma. J Hepatol 2012

Radiol med (2016) 121:735–743
DOI 10.1007/s11547-016-0650-5

RADIOTHERAPY

Radiotherapy in the multidisciplinary treatment of liver cancer: a survey on behalf of the Italian Association of Radiation Oncology

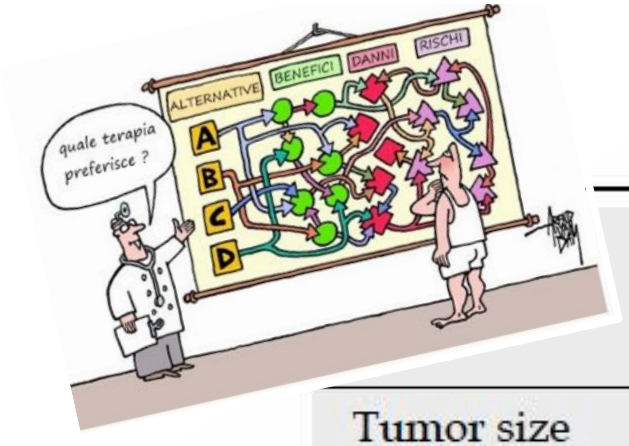
Francesco Dionisi[1] · Alessia Guarneri[2] · Veronica Dell'Acqua[3] · Mariacristina Leonardi[3] · Rita Niespolo[4] · Gabriella Macchia[6] · Tiziana Comito[5] · Maurizio Amichetti[1] · Pierfrancesco Franco[2] · Savino Cilla[7] · Luciana Caravatta[8] · Filippo Alongi[9] · Giovanna Mantello[10]

Centers	HCC			Liver metastases		
	Year of starting HCC irradiation	Irradiated patients since the starting	Irradiated patients in 2014	Year of starting liver metastases irradiation	Irradiated patients since the starting	Irradiated patients in 2014
1	–	–	–	2012	<20	<5
2	2006	<20	<5	2002	>30 ≤ 50	<5
3	–	–	–	2007	>20 ≤ 30	>5 ≤ 10
4	2013	<20	<5	2012	<20	>5 ≤ 10
5	–	–	–	2012	<20	<5
6	2011	<20	<5	2011	>20 ≤ 30	>5 ≤ 10
7	2014	<20	<5	2014	<20	<5
8	2002	<20	<5	2002	>50	>10 ≤ 20
9	2013	<20	<5	2006	>30 ≤ 50	>5 ≤ 10
10	2011	<20	<5	2007	>30 ≤ 50	>10 ≤ 20
11	2013	<5	<5	2012	<20	>5 ≤ 10
12	2012	>50	>30	2003	>30 ≤ 50	>10 ≤ 20
13	1995	>50	<5	1995	>50	>10 ≤ 20
14	–	–	–	2014	–	<5
15	2013	<20	<5	2013	<20	<5
16	2006	>20 ≤ 30	>5 ≤ 10	2006	>50	>30
17	2009	>50	>10 ≤ 20	2009	>50	>30
18	2005	>20 ≤ 30	<5	2005	>50	>20 ≤ 30

Stereotactic body radiation therapy in hepatocellular carcinoma: Optimal treatment strategies based on liver segmentation and functional hepatic reserve

Po-Ming Wang[a], *Na-Na Chung*[a], *Wei-Chung Hsu*[a,b,*], *Feng-Ling Chang*[a], *Chin-Jyh Jang*[a], *Marta Scorsetti*[c]

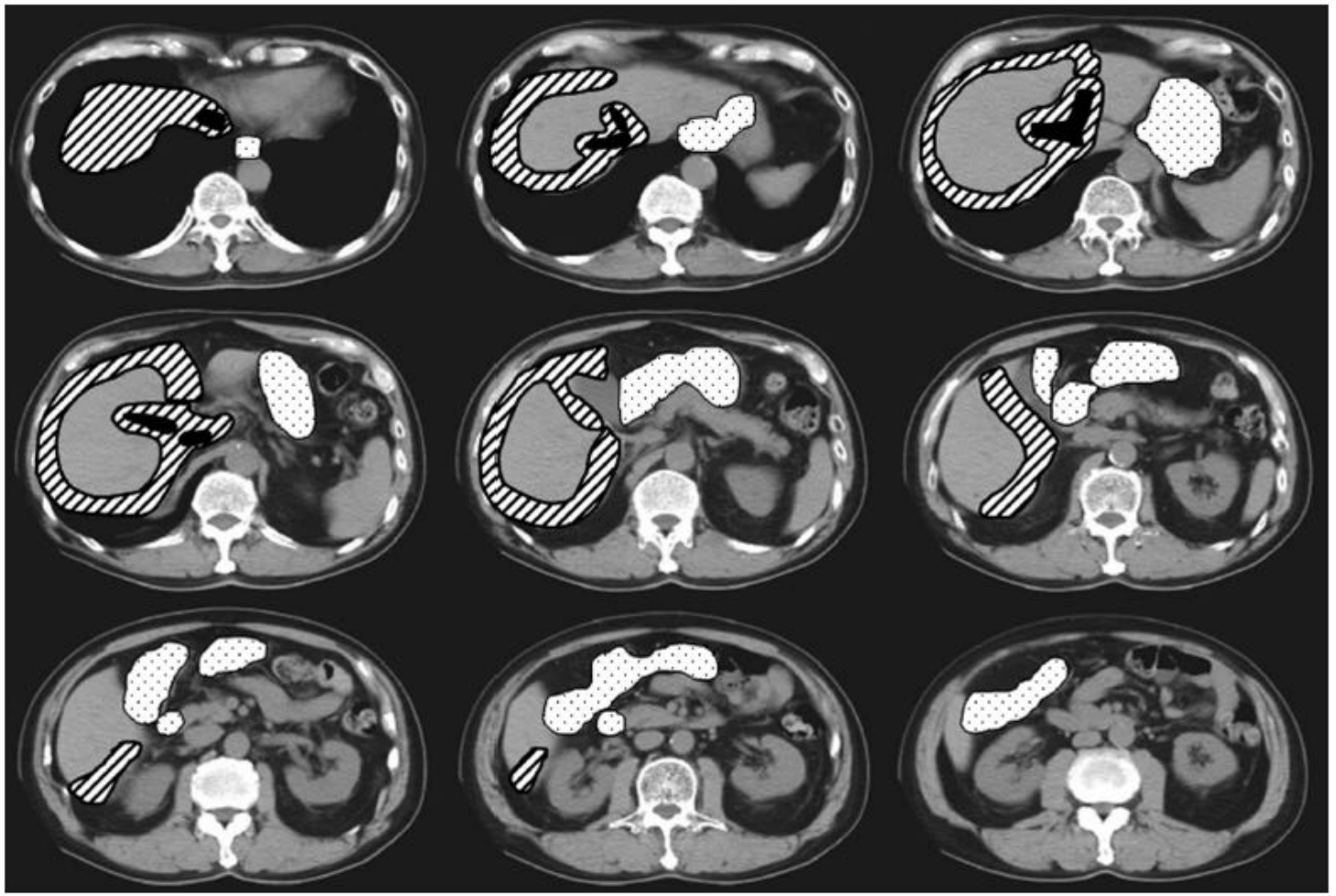
Author, year	Pt No.	CP B (%)	PVT (%)	Tumor size (cm or mL)	Dose(Gy)/fractions	1 y survival	Toxicity (Gr ≥ 3)
Sanuki, 2014	185	15	0	1.5–65.3 mL, 7.2 mL (med)	CPA: 40/5 CPB: 35/5	70% (3 y)	RILD 13%
Wang, 2014	32	6	28	6–848 mL, 86 mL (med)	<3 cm: 45/3 3–5 cm: 50/5 >5 cm: 50/10	74% (0.5 y)	RILD 5%; GI 0%
Bujoild, 2013	102	0	55	1.3–1913 mL, 117 mL (med)	24–54/6	87%	30%; 7%(Gr5)
Huang, 2012	36	29[a]	NA	1.1–12.3 cm, 4.4 cm (med)	25–48/4–5	73% (2 y)	RILD 7%; GI 3%
Kang, 2012	47	13	11	1.3–7.8 cm, 2.9 cm (med)	42–60/3 (by SLTD)	69% (2 y)	RILD 13%; GI 11%
Andolino, 2011	60	40	NA	1–6.5 cm, 3.1 cm (med)	CPA: 30–48/3 CPB: 24–48/5	67% (2 y)	37%; RILD: 16%
Cardenes, 2010	17	NA	18	8–95 mL, 34 mL (med)	CPA: 36–48/3 CPB: 40/5	75%	RILD 18%
Kwon, 2010	42	10	0	≤100 mL	<30 mL: 39/3 ≥30 mL: 30–36/3	93%	RILD 2%
Iwata, 2010	18[b]	6	NA	19–101 mL, 42 mL (med)	CPA: 55/10 CPB: 50/10	94%	RILD 0%; GI 0%
Mendez-Romero, 2006	8	25	25	0.5–6.1 cm, 4.5 cm (med)	<4 cm: 37.5/4 ≥4 cm: 25/5;	75%	RILD 13% (Gr 5)



WHAT IS THE ROLE OF RT IN HCC?

	Surgery	Percutaneous ablative therapy	TACE	SBRT
Tumor size	< 5 cm (or more)	< 3 cm	> 3-5 cm	4 (or 5) cm
Number of tumors	< 3	Depends on location	1-multiple (> 4)	< 1-3
Location or characteristics	Depends on liver function	Away from large vessels or biliary system	Hypervascular lesions	Away from bowels
Local control (2 yr)	> 90%	> 90%	< 65%	> 90%
Level of evidence	High	Intermediate-high	Intermediate-high	Low
Invasiveness	High	Less	Less	None
Damage to the liver	High	Low	Low-moderate	Low-moderate

SABR FOR HCC



Typical liver locations for which SBRT can be safely delivered

Typical liver locations for which SBRT is not easily suitable

World J Gastroenterol 2014 March 28; 20(12): 3100-3111

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Eligibility Criteria
Appropriate Patient selection

1. Histological or radiological confirmation of HCC
2. Single lesion with/without satellite nodules
3. Multiple lesions: number ≤3, diameter ≤6 cm
4. Child-Pugh A-B7
5. No extrahepatic disease (N1-M1)
6. Tumor vascular thrombosis (TVT)
7. PS ECOG 0-1

Med Oncol (2016)33:104
DOI 10.1007/s12032-016-0823-z

ORIGINAL PAPER

Stereotactic ablative radiotherapy in the treatment of hepatocellular carcinoma >3 cm

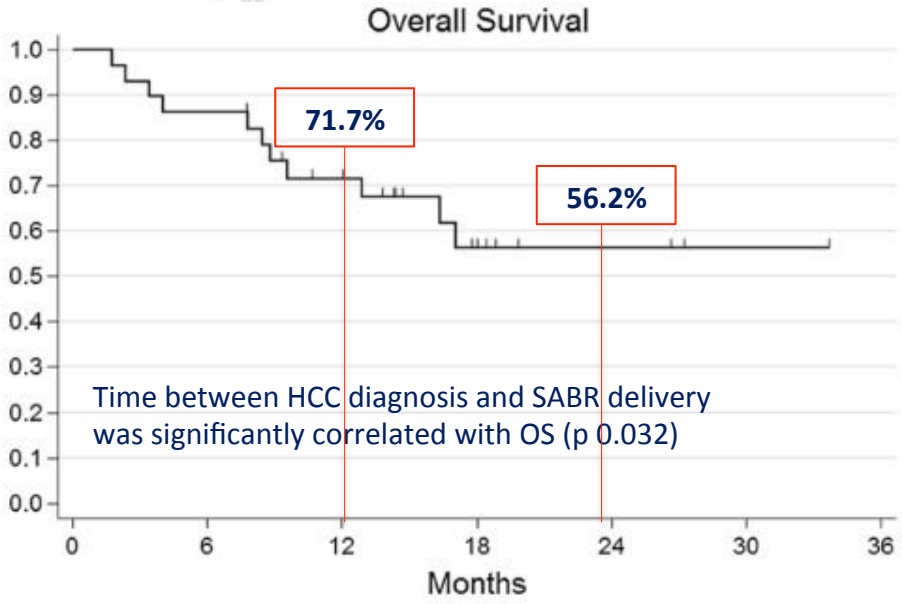
Alessia Guarneri[1] · Pierfrancesco Franco[2] · Elisabetta Trino[2] · Daniela Campion[3] · Riccardo Faletti[4] · Stefano Mirabella[5] · Silvia Gaia[6] · Riccardo Ragona[2] · Margherita Diotallevi[3] · Giorgio Saracco[3] · Mauro Salizzoni[5] · Umberto Ricardi[2] · Patrizia Carucci[6]

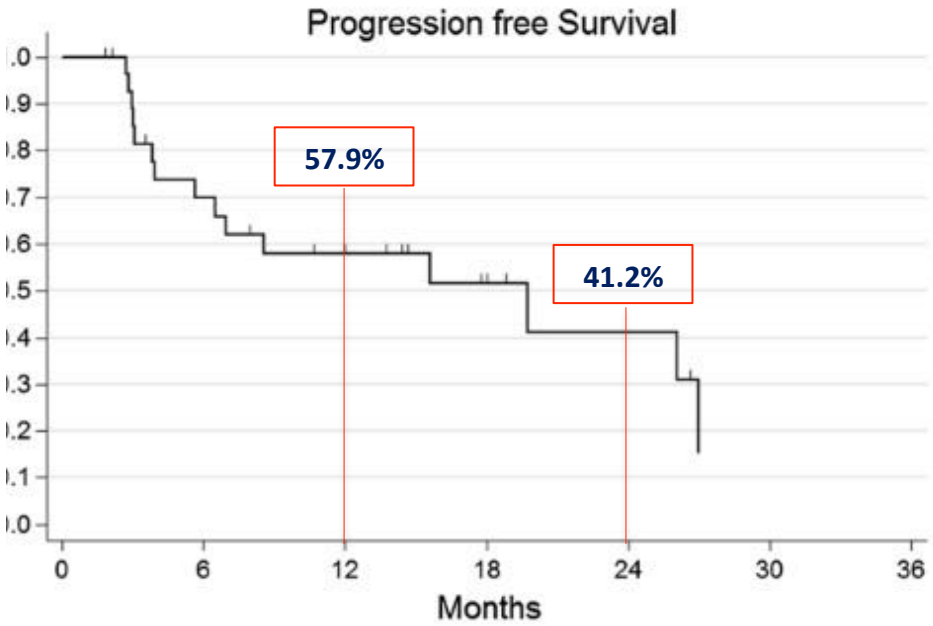
29 patients with at least one lesion >3 cm

Lesion size: range 31-120 mm, median 47 mm

Median follow-up time of 18 months

No local failure was observed





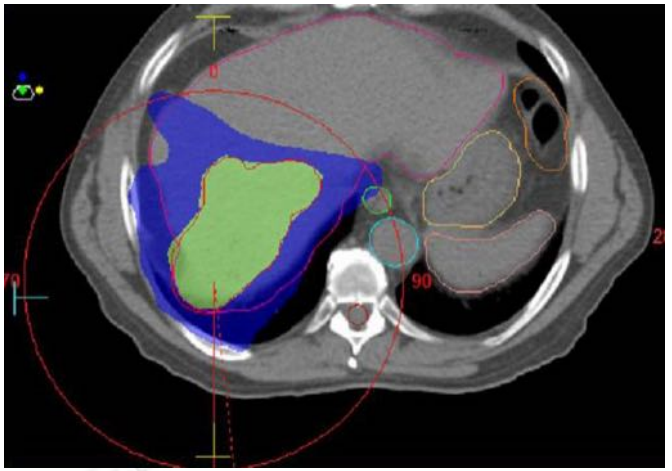
SABR provided LC and survival rates comparable to other local therapies for patients with HCC lesion sized >3 cm, with acceptable toxicity profile (RILD 6%)

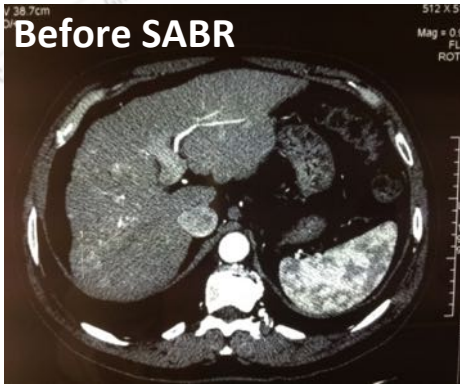
Stereotactic body radiotherapy combined with transarterial chemoembolization for hepatocellular carcinoma with portal vein tumor thrombosis

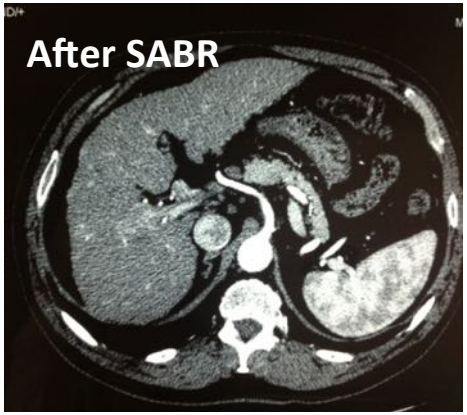
JINGBO KANG , QING NIE, RUI DU, LIPING ZHANG, JUN ZHANG, QILIANG LI, JIANGUO LI and WENJIE QI

Effectiveness of Stereotactic Body Radiotherapy for Hepatocellular Carcinoma with Portal Vein and/or Inferior Vena Cava Tumor Thrombosis

Mian Xi, Li Zhang, Lei Zhao, Qiao-Qiao Li, Su-Ping Guo, Zi-Zhen Feng, Xiao-Wu Deng, Xiao-Yan Huang, Meng-Zhong Liu*







PORTAL VEIN THROMBOSIS

- PTV is a poor prognostic factor (precludes surgery and arterial-directed therapies)
- RT has been used with PVT. Recanalization occurs in 30-80% post RT
- However it is a slow process (median time to maximal response 6 months)

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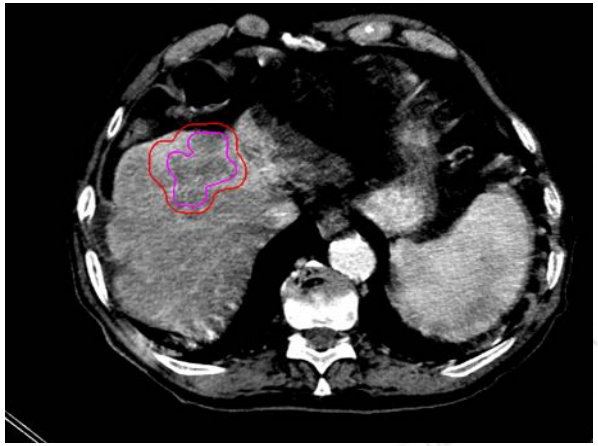
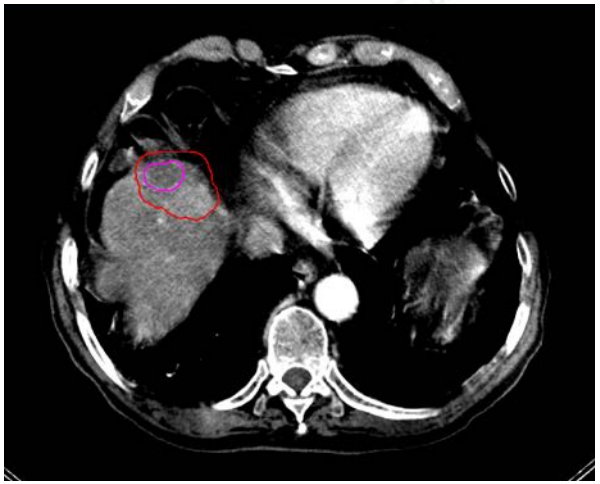
Clinical Indications

1. Surgery and loco-regional treatment contraindicated or refused
2. Recurrent HCC after loco-regional treatment
3. HCC BCLC B in association with loco-regional treatment (e.g TACE)
4. As a bridge to liver trasplantation
5. Neoadjuvant to liver trasplantation or local treatment (downstaging)



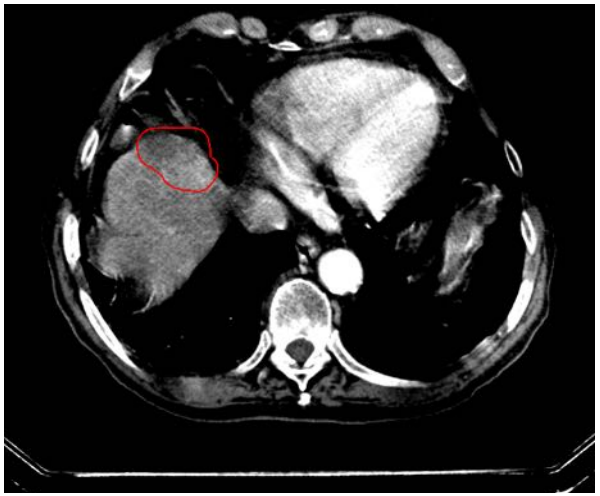
Stereotactic Body Radiation Therapy in Recurrent Hepatocellular Carcinoma

Wen-Yen Huang, M.D.,* Yee-Min Jen, M.D., Ph.D.,* Meei-Shyuan Lee, Ph.D.,† Li-Ping Chang, M.D., Ph.D.,‡ Chang-Ming Chen, M.D.,* Kai-Hsiung Ko, M.D.,§ Kuen-Tze Lin, M.D.,* Jang-Chun Lin, M.D.,* Hsing-Lung Chao, M.D.,* Chun-Shu Lin, M.D.,* Yu-Fu Su, M.D.,* Chao-Yueh Fan, M.D.,* and Yao-Wen Chang, M.D.*



Salvage Treatment With Hypofractionated Radiotherapy in Patients With Recurrent Small Hepatocellular Carcinoma

Sun Hyun Bae, M.D.,* Hee Chul Park, M.D., Ph.D.,* Do Hoon Lim, M.D., Ph.D.,* Jung Ae Lee, M.D.,* Geum Yeon Gwak, M.D., Ph.D.,† Moon Seok Choi, M.D., Ph.D.,† Joon Hyoek Lee, M.D., Ph.D.,† Kwang Cheol Koh, M.D., Ph.D.,† Seung Woon Paik, M.D., Ph.D.,† and Byung Chul Yoo, M.D., Ph.D.†



Stereotactic Body Radiation Therapy for Inoperable Hepatocellular Carcinoma as a Local Salvage Treatment After Incomplete Transarterial Chemoembolization

Jin-Kyu Kang, MD[1]; Mi-Sook Kim, MD, PhD[1]; Chul Koo Cho, MD, PhD[1]; Kwang Mo Yang, MD, PhD[1]; Hyung Jun Yoo, MD[1]; Jin Ho Kim, MD[1]; Sun Hyun Bae, MD[1]; Da Hoon Jung, MD[1]; Kum Bae Kim,[1]; Dong Han Lee, PhD[2]; Chul Ju Han, MD[3]; Jin Kim, MD[3]; Su Cheol Park, MD[3]; and Young Han Kim, MD[4]

Clinical Investigation: Gastrointestinal Cancer

Stereotactic Hypofractionated Radiation Therapy as a Bridge to Transplantation for Hepatocellular Carcinoma: Clinical Outcome and Pathologic Correlation

Alan W. Katz, M.D., M.P.H.,* Sheema Chawla, M.D.,* Zhenhong Qu, M.D., Ph.D.,¶ Randeep Kashyap, M.D.,† Michael T. Milano, M.D., Ph.D.,* and Aram F. Hezel, M.D.‡

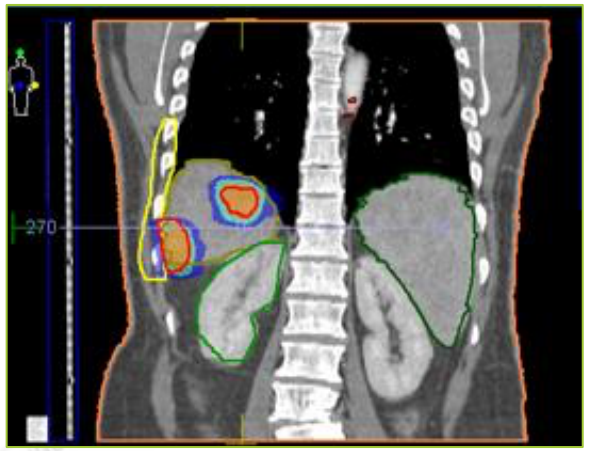


Table 4 Summary of published studies of radiation therapy as a bridge to transplant in HCC

Study, year (ref.)	No. of patients/no. of lesions	Median dose (Gy)/no. of fractions	BED (Gy_{10})	Median no. of months to transplant	Previous treatment (TACE/RFA)	Median tumor size	Local control rate (%)	Follow-up (months)
O'Connor *et al.*, 2008 (21)	5/6	48/3	124.8	13	No	3.2 cm	83	3.7 (mean)
Sandroussi *et al.*, 2010 (22)	10/10	33/1–6	15.7–86.4	5	Yes (n = 5)	79 cc	100	6 (median)
Andolino *et al.*, 2010 (23)	21/NK	48/3	124.8	7	0	3 cm	100†	22* (median)
Present series	10/12	50/10	75	6	Yes (n = 3)	3.6 cm	100	19.6 (median)

Abbreviations: NK = not known; RFA = radiofrequency ablation; TACE = transcatheter arterial embolization.
* Included patients who were not transplanted.
† Three regional failures.

No differences in operative (intra- peri-operative) morbidities or hospitalization

Int J Radiation Oncol Biol Phys, Vol. 83, No. 3, pp. 895–900, 2012

Radiol med
DOI 10.1007/s11547-016-0670-1

RADIOTHERAPY

Stereotactic ablative radiation therapy prior to liver transplantation in hepatocellular carcinoma

Alessia Guarneri[1] · Pierfrancesco Franco[1] · Renato Romagnoli[2] · Elisabetta Trino[1] · Stefano Mirabella[2] · Luca Molinaro[3] · Giorgia Rizza[2] · Andrea Riccardo Filippi[1] · Patrizia Carucci[4] · Mauro Salizzoni[2] · Umberto Ricardi[1]

Toxicity profile was acceptable with only one patient who experienced a category shift in terms of liver function and surgical procedures which were not consistently affected by prior SABR (only one case of surgical technique modification)

Local control was excellent

Patients	SBRT toxicity (CTACE v 4.02)	LT complication	ΔChild-Pugh class	ΔMELD score	Radiological response (mRECIST v4)	Pathological response	Status
1	G2 GGT elevation (3 months)	Sclerotic retraction of the retrohepatic region involving inferior vena cava	0	0	CR (CT) 2 months	CR	NED
2	Non-classic RILD (1 month)	None	3	+8	SD (MR) 1 month	Minimal pathologic response (two lesions)	NED
3	None	Sclerotic retraction of the retrohepatic region involving inferior vena cava	0	0	SD (CT) 3 months	CR (two lesions)	NED
4	G1 bilirubin elevation (10 days)	None	1	+3	NA	Significant pathologic response	NED
5	G1 asthenia (1–3 months), G1 bilirubin elevation (15 days)	Sclerotic retraction of the retrohepatic region involving inferior vena cava and hepatic hilar region with hepatic artery parietal fibrosis	1	+10	SD (CT) 2 months	CR	NED
6	G1 transaminase	None	1	−1	NA	SD (two lesions)	Died of multi-organ failure 24 days after LT
7	G2 GGT elevation (1 month)	None	1	+2	CR (MR) 3 months	CR	NED
8	None	None	0	0	NA	CR (three lesions)	NED

SABR @ Turin University – Follow up

Revue générale

Suivi après radiothérapie stéréotaxique des tumeurs hépatiques : revue de la littérature et recommandations

Follow-up after stereotactic body radiation therapy for liver tumours: A review of the literature and recommendations

G. Janoray[a,*], F. Mornex[b,c]

Target lesions		
Response category	RECIST	mRECIST
CR	Disappearance of all target lesions	Disappearance of any intratumoral arterial enhancement in all target lesions
PR	At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum of the diameters of target lesions	At least a 30% decrease in the sum of the diameters of viable (enhancement in the arterial phase) target lesions, taking as reference the baseline sum of the diameters of target lesions
SD	Any cases that do not qualify for either PR or PD	Any cases that do not qualify for either PR or PD
PD	An increase of at least 20% in the sum of the diameters of target lesions, taking as reference the smallest sum of the diameters of target lesions recorded since treatment started	An increase of at least 20% in the sum of the diameters of viable (enhancing) target lesions, taking as reference the smallest sum of the diameters of viable (enhancing) target lesions recorded since treatment started
Non-target lesions		
Response category	RECIST	mRECIST
CR	Disappearance of all non-target lesions	Disappearance of any intratumoral arterial enhancement in all target lesions
IR/SD	Persistence of one or more non-target lesions	Persistence of intratumoral arterial enhancement in one or more non-target lesions
PD	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions
mRECIST recommendations		
Pleural effusion and ascites	Cytopathologic confirmation of the neoplastic nature of any effusion that appears or worsens during treatment is required to declare PD.	
Porta hepatis lymph node	Lymph nodes detected at the porta hepatis can be considered malignant if the lymph node short axis is at least 2 cm.	
Portal vein thrombosis	Malignant portal vein thrombosis should be considered as a non-measurable lesion and thus included in the non-target lesion group.	
New lesion	A new lesion can be classified as HCC if its longest diameter is at least 1 cm and the enhancement pattern is typical for HCC. A lesion with atypical radiological pattern can be diagnosed as HCC by evidence of at least 1 cm interval growth.	

RECIST, Response Evaluation Criteria In Solid Tumors; mRECIST, modified Response Evaluation Criteria In Solid Tumors; CR, complete response; PR, partial response; IR, incomplete response; SD, stable disease; PD, progressive disease.
*Adapted from Llovet *et al.* [149] and Lencioni and Llovet [100].

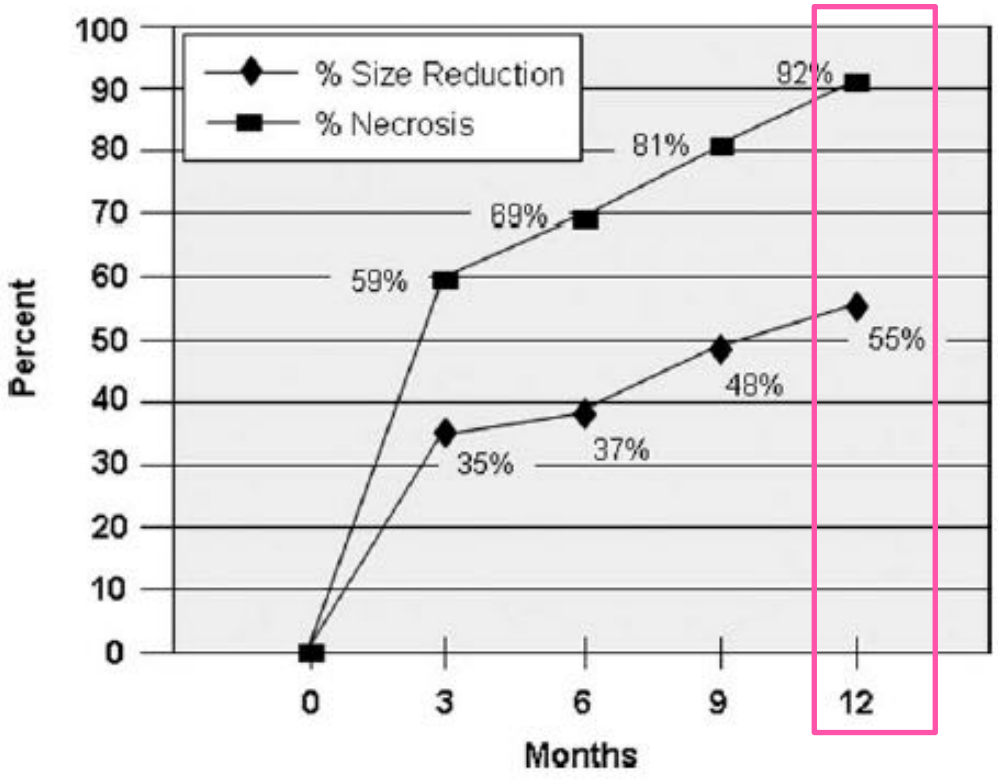
mRECIST

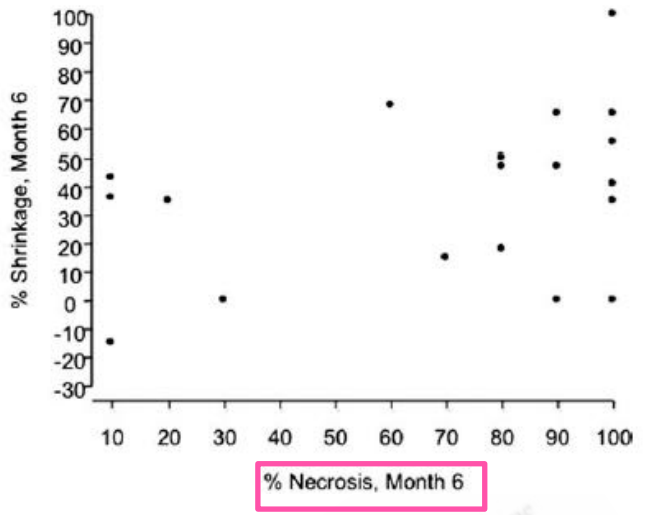
Recommandations concernant le suivi après radiothérapie stéréotaxique hépatique.

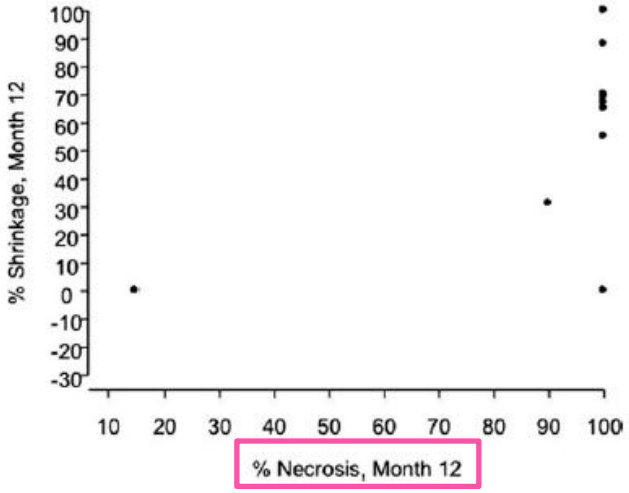
	Avant le traitement	1 fois par semaine pendant le traitement	À la fin du traitement	3 à 4 semaines	Tous les mois pendant 3 mois	À 3 mois	Tous les 3 mois pendant 2 ans	Tous les 6 mois ensuite
Examen clinique	X	X		X		X	X	X
Examen biologique	X	X		X	X	X	X	X
Examen radiologique	Tomodensitométrie ou IRM					Tomodensitométrie ou IRM	Tomodensitométrie ou IRM	Tomodensitométrie ou IRM
Évaluation de la toxicité	X	X		X		X	X	X
Assurance qualité	X		X					

Evaluation of Response After Stereotactic Body Radiotherapy for Hepatocellular Carcinoma*

Tracy R. Price, MD[1]; Susan M. Perkins, PhD[2]; Kumar Sandrasegaran, MBm, ChB[3]; Mark A. Henderson, MD[1]; Mary A. Maluccio, MD[4]; Jennifer E. Zook, MD[1]; A. Joseph Tector, MD, PhD[4]; Rodrigo M. Vianna, MD[4]; Peter A.S. Johnstone, MD[1]; and Higinia R. Cardenes, MD, PhD[1]







Percentage necrosis was greater than percentage size reduction at each point in time and the magnitude of difference increased at each point.

Cancer 2012;118:3191-8.

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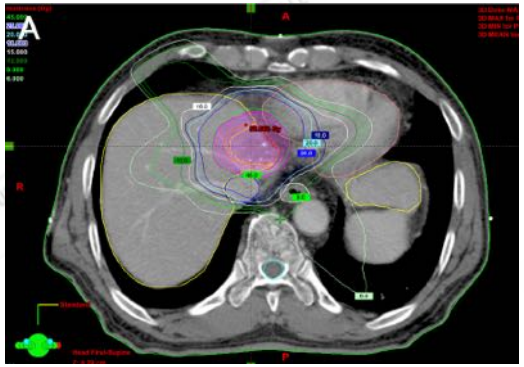
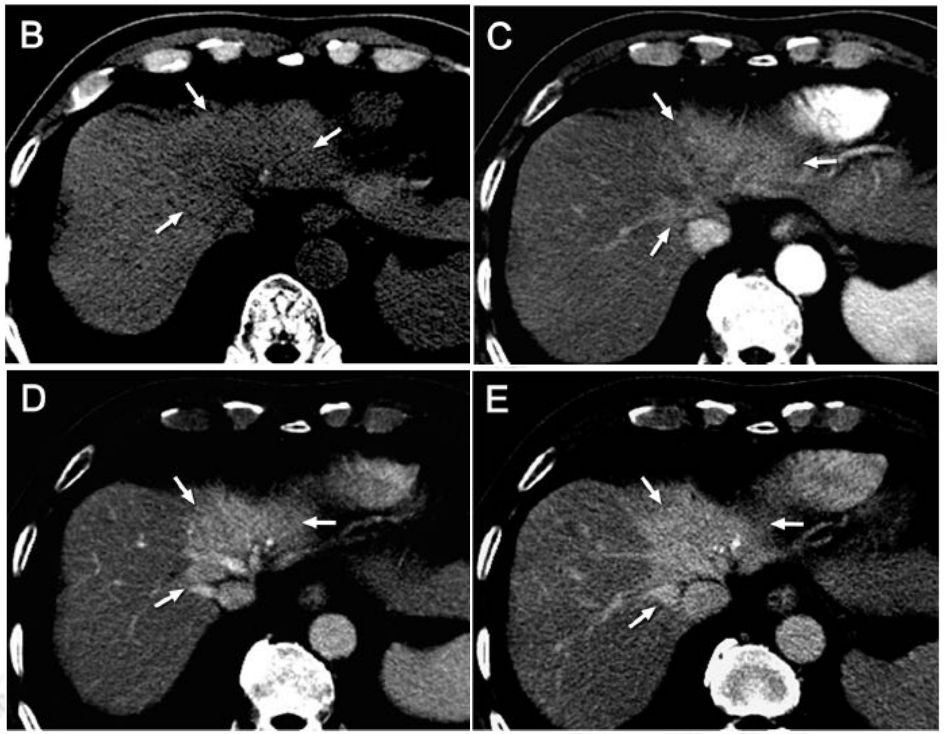
PLOS ONE | www.plosone.org February 2014

Stereotactic Body Radiotherapy-Induced Arterial Hypervascularity of Non-Tumorous Hepatic Parenchyma in Patients with Hepatocellular Carcinoma: Potential Pitfalls in Tumor Response Evaluation on Multiphase Computed Tomography

Mee Jin Park[1¤], So Yeon Kim[1]*, Sang Min Yoon[2], Jong Hoon Kim[2], Seong Ho Park[1], Seung Soo Lee[1], Yedaun Lee[1], Moon-Gyu Lee[1]





AJR:202, January 2014

Added Value of Diffusion-Weighted MRI for Evaluating Viable Tumor of Hepatocellular Carcinomas Treated With Radiotherapy in Patients With Chronic Liver Disease

Hyun Jeong Park[1,2]
Seong Hyun Kim[1]
Kyung Mi Jang[1]
Sanghyeok Lim[1]
Tae Wook Kang[1]
Hee Chul Park[3]
Dongil Choi[1]

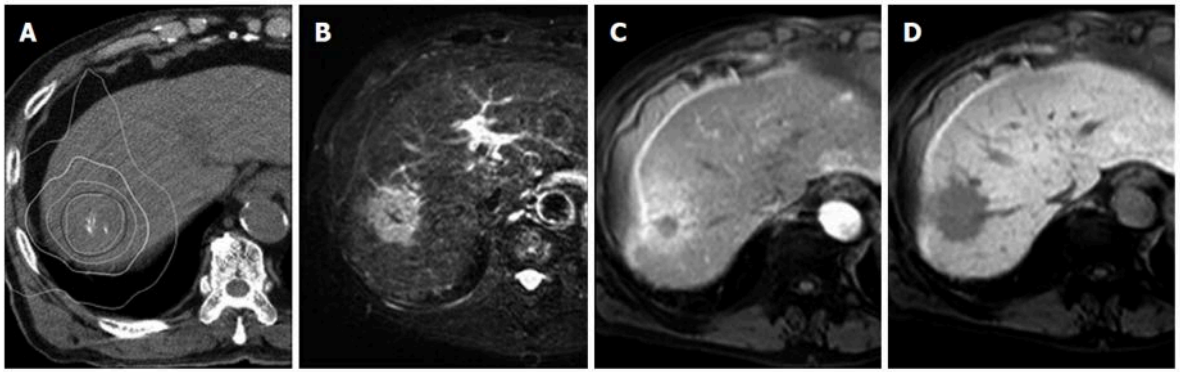


Figure 7 Typical focal liver reaction 4 mo after stereotactic body radiation therapy seen on gadoxetate acid-enhanced magnetic resonance imaging. An axial view of radiation dose distribution (A). The isodose lines (white lines) from inner to outer represent 40, 30, 20, and 10 Gy, respectively. A T2-weighted image shows a high-intensity area corresponding to a high-dose area (B), which is seen as an enhanced area in early phase after injection of gadoxetate acid (C). The hepatobiliary phase shows a well-demarcated low-intensity area (D).

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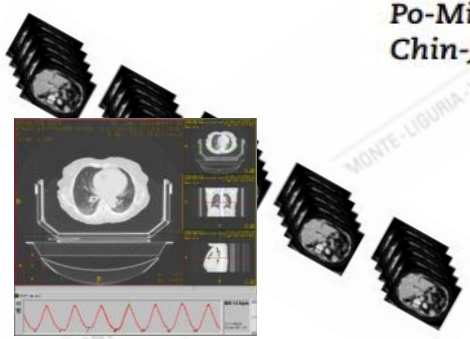
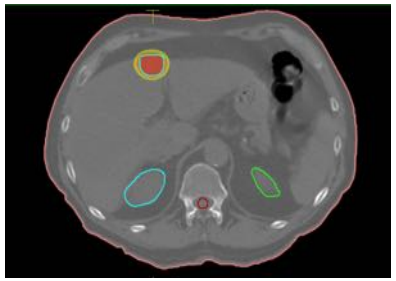
Stereotactic body radiation therapy in hepatocellular carcinoma: Optimal treatment strategies based on liver segmentation and functional hepatic reserve

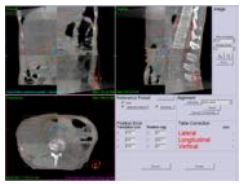
Po-Ming Wang[a], *Na-Na Chung*[a], *Wei-Chung Hsu*[a,b,*], *Feng-Ling Chang*[a], *Chin-Jyh Jang*[a], *Marta Scorsetti*[c]



- Tri-phase four-dimensional CT (4D CT)
- Incorporation of MRI in planning for a more precise target delineation

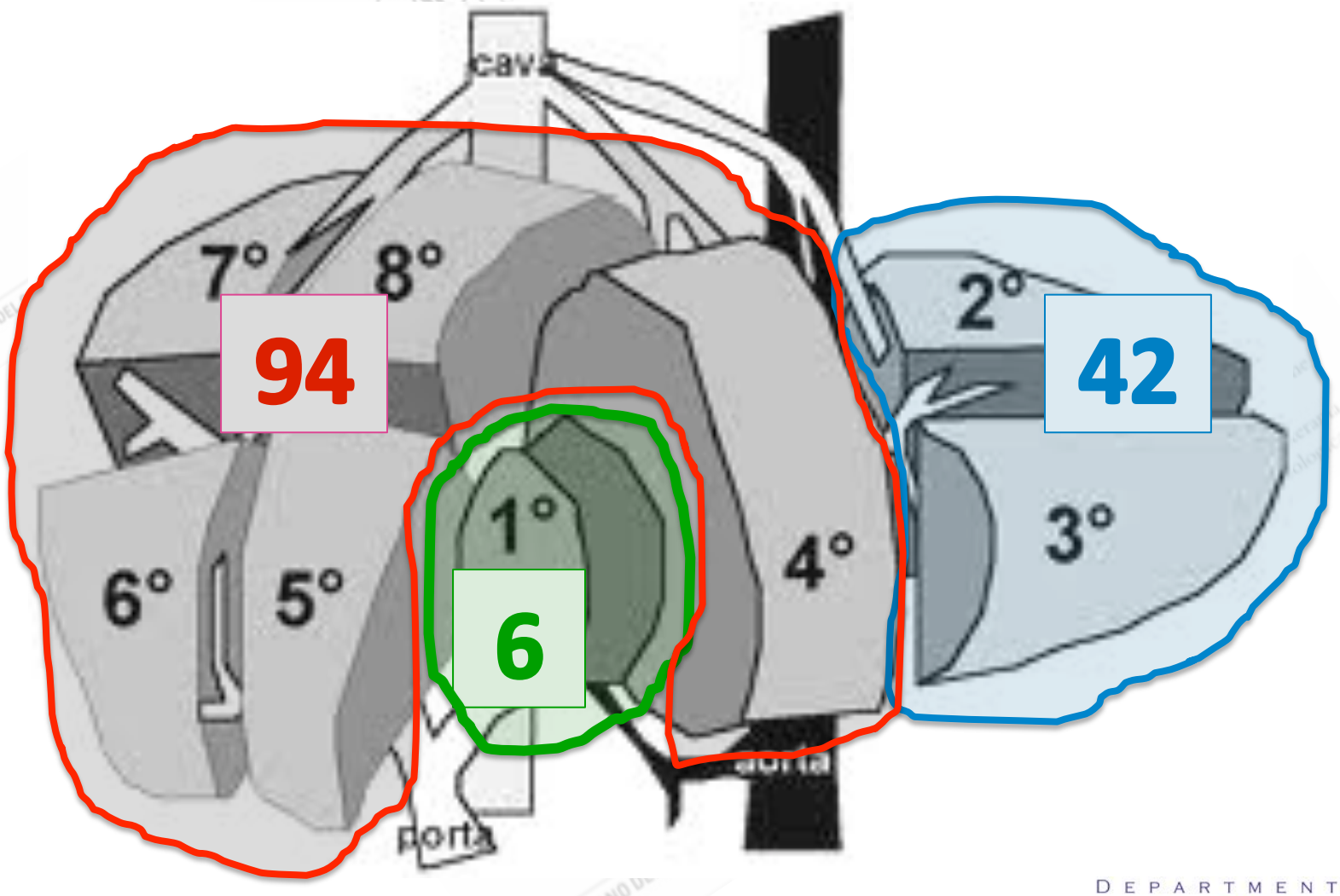


- GTV is defined as a primary tumor plus abnormal portal areas
- CTV defined as GTV plus a 0.5-1 cm margin for subclinical disease
- ITV is defined as the envelope of all CTVs from the different respiratory phases (as equivalent of the PTV)



- Single or multiple, coplanar or non-coplanar, moni-isocentric arcs
- Daily Cone beam CT acquisition

Site of The Tumor (142 lesions)



Future developments

- Little is known about the tolerance of the liver to re-irradiation

- Integration of an MRI scanner with a linea accelerator (MRI linac)

Apr 8, 2014

Installation begins on first MRI-linac

The clinical realization of MR-guided radiotherapy could represent the ultimate breakthrough in real-time image guidance – offering soft-tissue-based imaging throughout beam delivery. As such, researchers at the University Medical Center (UMC) Utrecht in the Netherlands have been working for more than a decade to overcome the not-insubstantial technical obstacles required to integrate an MRI scanner with a linear accelerator. They may finally be about to reap the rewards of their efforts.

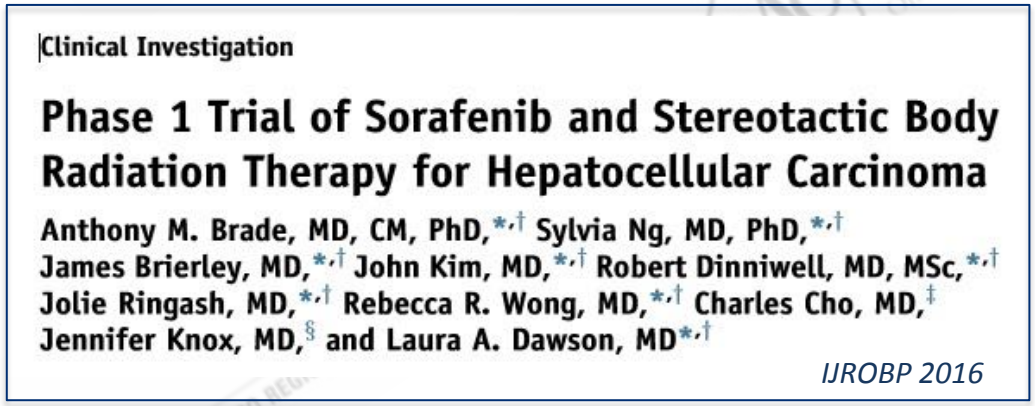
Installation begins

Future developments

Randomized trials have been development for HCC and are currently accruing patient

- **NTC02470533** *PI Mendez Romero* Phase II randomized trial comparing TACE with drug-eluting beads and SBRT in patients with Child Pugh grade A cirrhosis who are inelegible for resection and RFA.
- **NTC 01730937** *PI Dawson* is an international phase III randomized study between sorafenib alone and SBRT followed by sorafenib in patients with Child Pugh grade A cirrhosis
- **NTC02182687** *PI Nugent* is randomizing patients between TACE and SBRT as a bridge to liver transplant Patient should fulfill the Milan criteria Child Pugh grade A or B >7 are allowed
- **NTC02323360** is a phase III randomized trial for patients with incomplete response after TACE or TAE followed or not followed by SBRT
- **NTC 02513199** *PI Buckstein* the combination of chemoembolization abs SBRT in unresecetable HCC is being tested, but not in a randomized setting

The optimal combination of systemic and SABR is yet to be determined



Clinical Investigation

Phase 1 Trial of Sorafenib and Stereotactic Body Radiation Therapy for Hepatocellular Carcinoma

Anthony M. Brade, MD, CM, PhD,*,† Sylvia Ng, MD, PhD,*,† James Brierley, MD,*,† John Kim, MD,*,† Robert Dinniwell, MD, MSc,*,† Jolie Ringash, MD,*,† Rebecca R. Wong, MD,*,† Charles Cho, MD,‡ Jennifer Knox, MD,§ and Laura A. Dawson, MD*,†

IJROBP 2016

The combination of sorafenib and SBRT to patients with locally advanced HCC and Child Pugh A liver function resulted in unacceptably high rates of serious toxicity.

Take home messages

There is a growing clinical experience in HCC RT with promising clinical outcomes

SAFE

high doses well tolerated in patients with normal underlying liver function

EFFECTIVE

recent prospective studies of more focal RT for liver tumors suggest that higher doses associated with good local control

CAUTION

SABR may not be appropriate in patients with underlying liver dysfunction

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“Better is possible. It does not take genius.It takes moral clarity. It takes ingenuity. And above all, it takes a willingness to try”

Atul Gawande

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