

The Role of Radiation Oncologist: Hi-Tech Treatments for Liver Tumors

Marta Scorsetti M.D.

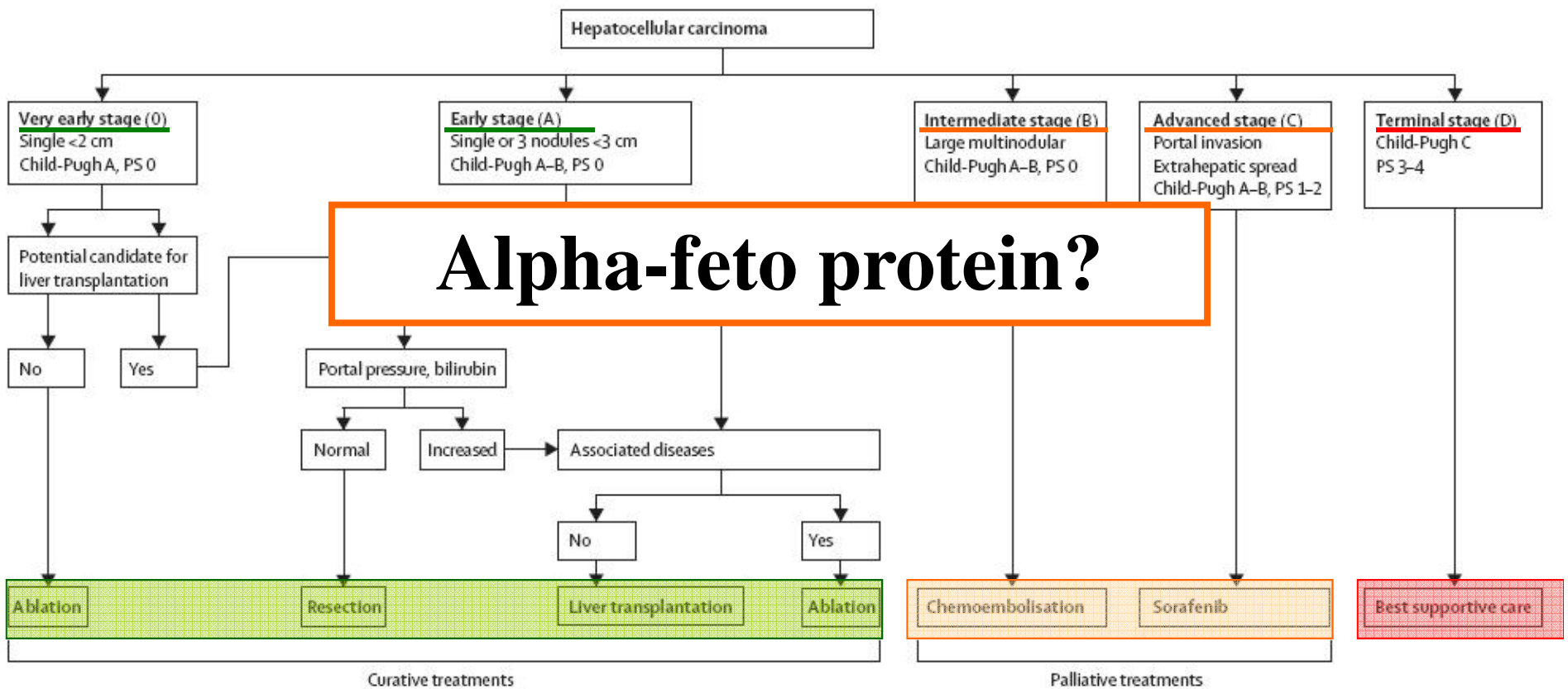
Radiotherapy and Radiosurgery Dpt.

Istituto Clinico Humanitas, Milan, Italy.



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BCLC 2012



The value of the Barcelona Clinic Liver Cancer and alpha-fetoprotein in the prognosis of hepatocellular carcinoma

Rafael Gómez-Rodríguez¹, Marta Romero-Gutiérrez¹, Tomás Artaza-Varasa¹,
Concepción González-Frutos¹, Juan José Ciampi-Dopazo², Gema-de-la-Cruz-Pérez¹
and Juan José Sánchez-Ruano¹

2012

The value of alpha-fetoprotein (AFP) has not been properly defined. **The aim of this study was to evaluate the BCLC classification in our clinical practice and to know what the prognostic value of AFP is.**

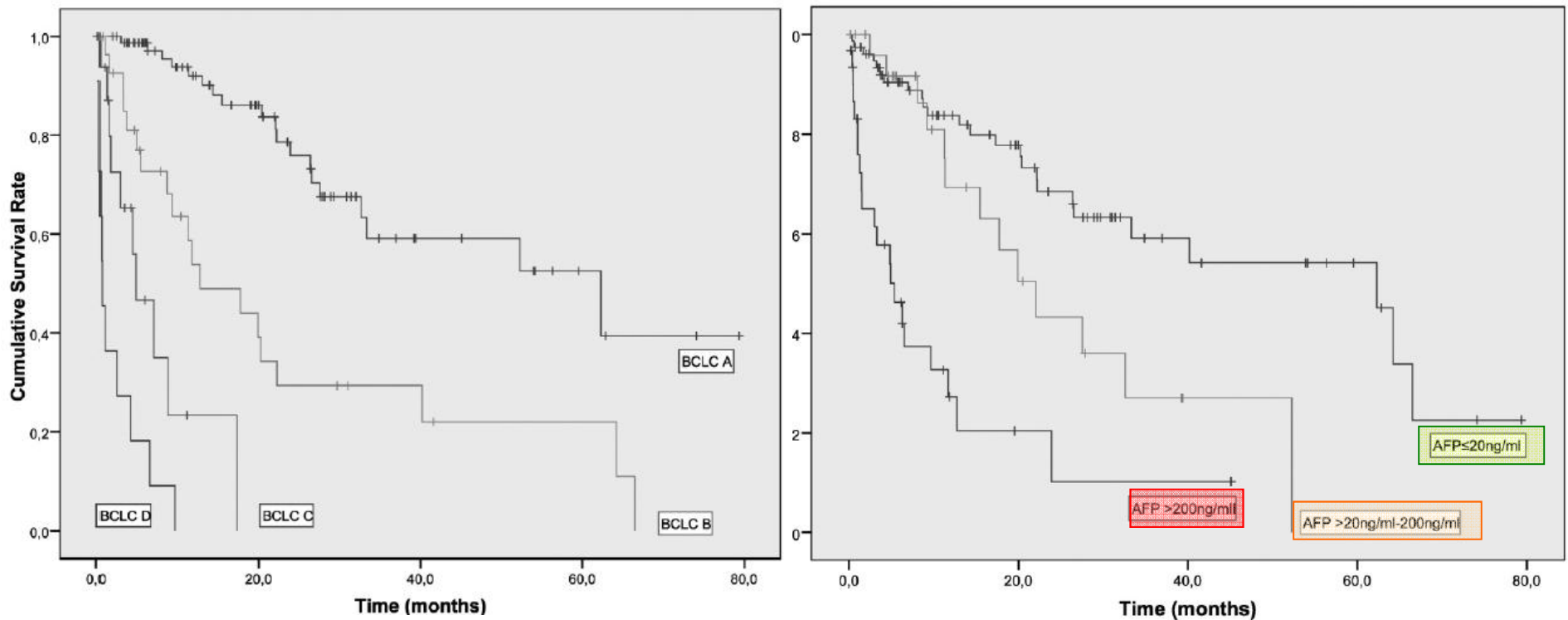
136 consecutive HCC patients were prospectively included in this study. The patients were studied and managed according to usual clinical practice.

Conclusions: our results confirm that the BCLC is a good prognostic system. The AFP has prognosis value in HCC patients. The addition of AFP could improve the BCLC system.

The value of the Barcelona Clinic Liver Cancer and alpha-fetoprotein in the prognosis of hepatocellular carcinoma

Rafael Gómez-Rodríguez¹, Marta Romero-Gutiérrez¹, Tomás Artaza-Varasa¹,
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2012

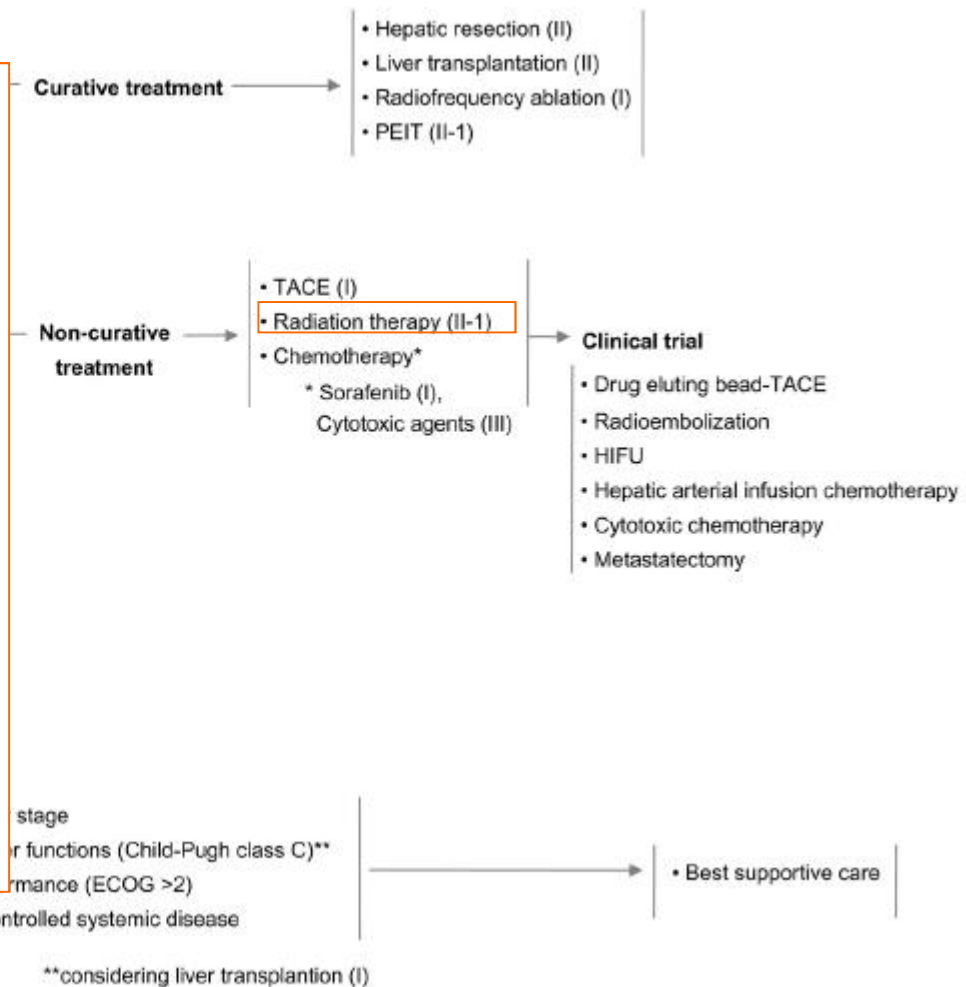


2009 Practice Guidelines for the Management of Hepatocellular Carcinoma

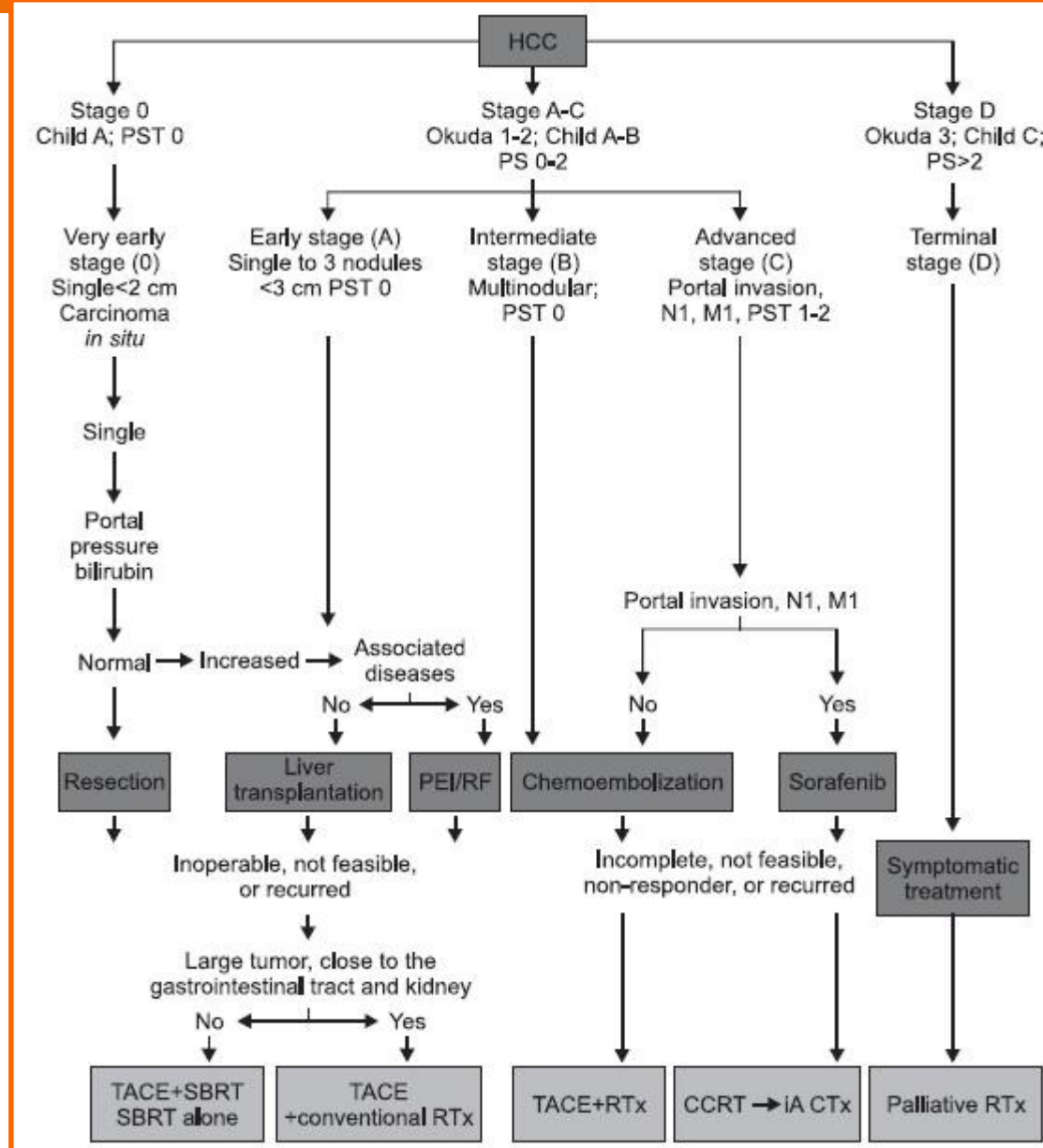
[1] RT can be offered for patients with HCC if the liver functions are **Child-Pugh class A or superb B**, and the tumor takes up 2/3 or less of the total liver volume (evidence level II-3).

[2] RT can be considered for HCC with **portal vein tumor thrombosis** (evidence level II-1).

[3] RT can be effective to **relieve the symptoms** caused by HCC and its metastases (evidence level II-2).



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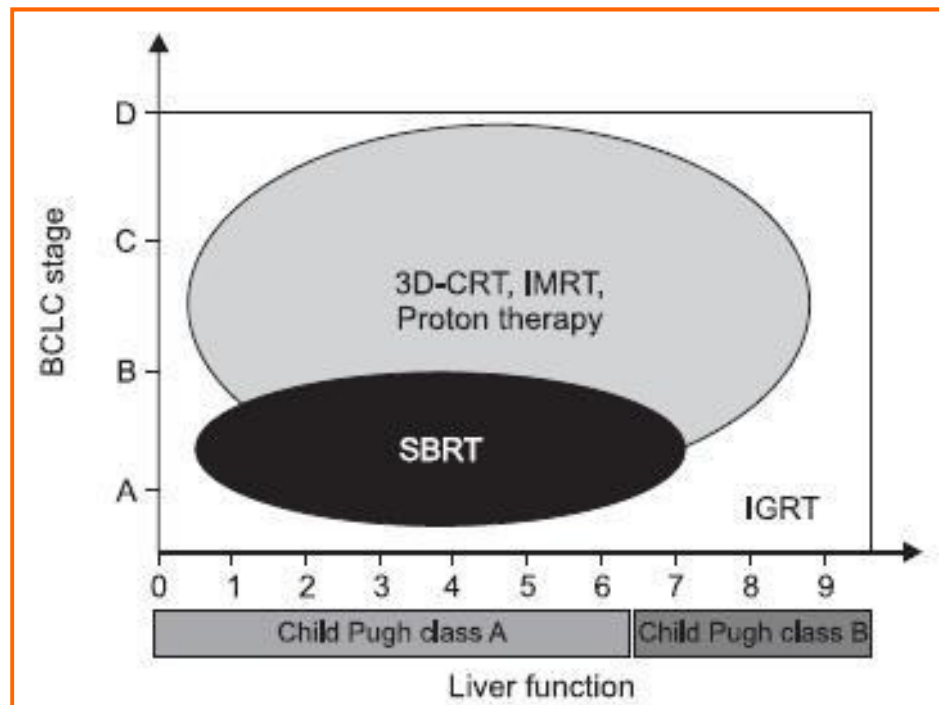
Lee IJ, Seong J.
Gut Liver. 2012
Apr;6(2):139-48.

REVIEW

The Optimal Selection of Radiotherapy Treatment for Hepatocellular Carcinoma

Ik Jae Lee and Jinsil Seong

Department of Radiation Oncology, Yonsei Liver Cancer Clinic, Yonsei University College of Medicine, Seoul, Korea



There are several strategies that may be used to deliver radiation to HCC. Currently, a variety of RT modes are available:

1. INTERNAL RT
2. PROTON THERAPY
3. 3D-CRT
4. IMRT
5. SBRT

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CLINICAL INVESTIGATION

Liver



REPEATED PROTON BEAM THERAPY FOR HEPATOCELLULAR CARCINOMA

TAKAYUKI HASHIMOTO, M.D.,*† KOICHI TOKUUYE, M.D.,*† NOBUYOSHI FUKUMITSU, M.D.,*†
HIROSHI IGAKI, M.D.,*† MASAHARU HATA, M.D.,*† KENJI KAGEI, M.D.,*† SHINJI SUGAHARA, M.D.,†
KIYOSHI OHARA, M.D.,† YASUSHI MATSUZAKI, M.D.,‡ AND YASUYUKI AKINE, M.D.*†

CLINICAL INVESTIGATION

Liver



PROTON BEAM THERAPY FOR AGED PATIENTS WITH HEPATOCELLULAR CARCINOMA

MASAHARU HATA, M.D.,*†|| KOICHI TOKUUYE, M.D.,*† SHINJI SUGAHARA, M.D.,†
ERIKO TOHNO, M.D.,‡ HIDETSUGU NAKAYAMA, M.D.,*† NOBUYOSHI FUKUMITSU, M.D.,*†
MASASHI MIZUMOTO, M.D.,† MASATO ABEI, M.D.,§ JUNICHI SHODA, M.D.,§
MANABU MINAMI, M.D.,‡ AND YASUYUKI AKINE, M.D.*†

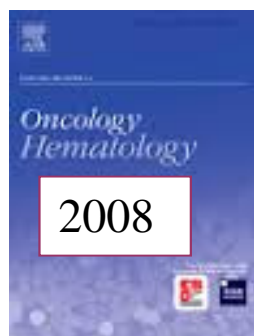
EXTERNAL RT:

3D-CRT Several factors should be considered when treating liver tumors with RT.

First, the **proximity of the liver to other radiosensitive organs** should be considered, such as the duodenum, colon, small intestines, and kidneys

The second factor involves the **liver and tumor movement along with respiration**. Reducing respiratory motion can be attempted by **abdominal compression** which can decrease the target margins.

Toxicity : nausea and vomiting, gastro-duodenal side effects, subacute colitis, RILD (radiation-induced liver disease)



Conformal radiotherapy for hepatocellular carcinoma

R.V. Tse^a, Chandan Guha^b, L.A. Dawson^{a,*}

Selected trials of conformal radiotherapy for HCC

Study	No. of HCC patients	Liver function	Radiotherapy dose (dose/fraction daily)	Objective response rate	Median survival (months)	1-year survival
Ben-Josef et al. [22,41]	35	Child A INR <1.2	90 Gy (1.5 Gy twice daily fractions)	40%	15.2	57%
Mornex et al. [43]	27	Child A 16, Child B 11	66 Gy (2 Gy)	92%, CR 80%	–	–
Seong et al. [47]	303	Child A 246, Child B 58, Child C 1	25–60 Gy (1.8 Gy)	–	11	45%
Park et al. [48]	59	Child A or no cirrhosis 56, Child B 3	33–55 Gy (2–3 Gy)	66%	–	2-year 47%
Liu et al. [49]	44	Child A 32, Child B 12	39.6–60 Gy (1.8 Gy)	61%, CR 14%	15.2	60.5%
Kim et al. [50]	70	Child A 56, Child B 14	44–54 Gy (2–3 Gy)	55%, CR 6%	10.8	43%

EXTERNAL RT:

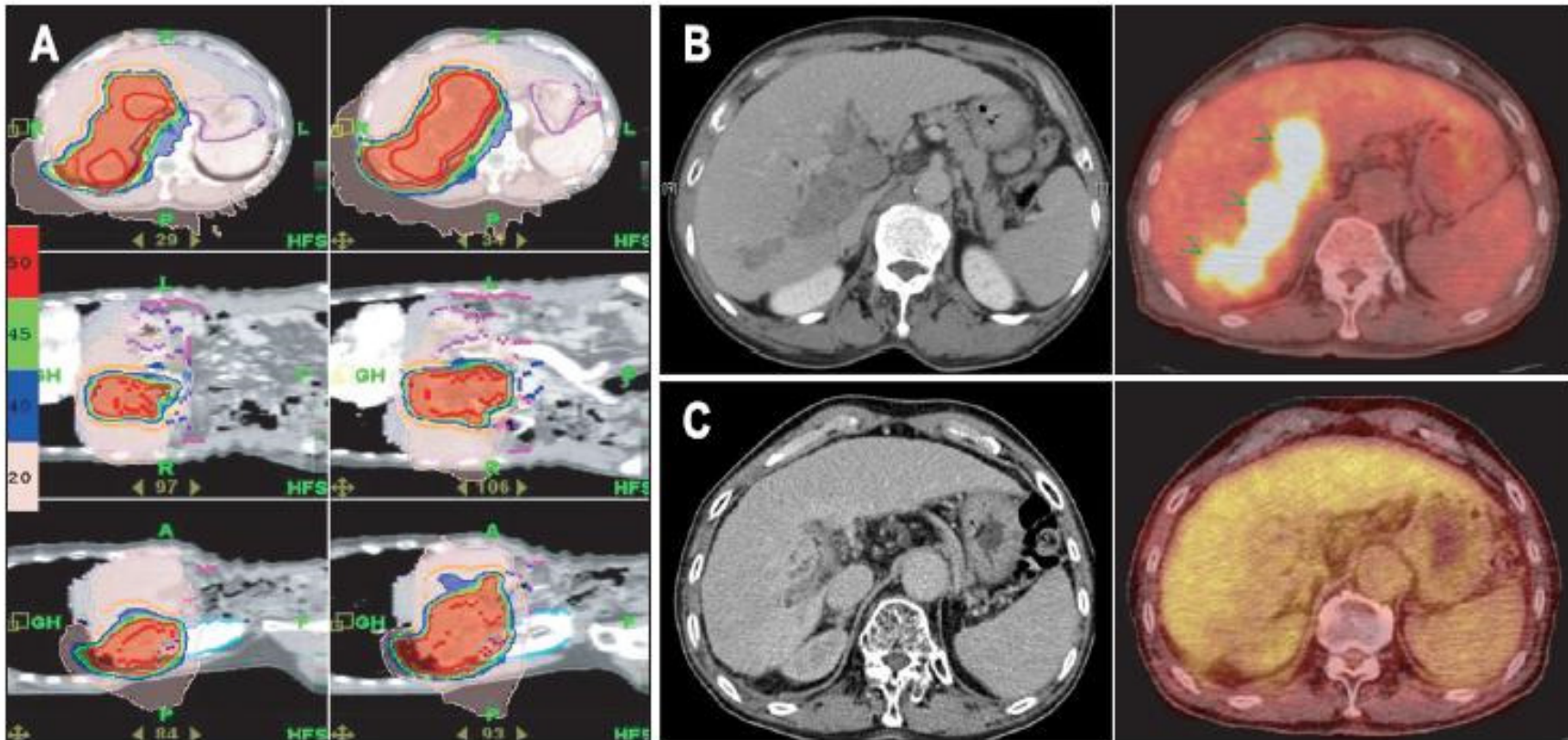
IMRT an advanced 3D-CRT, uses non-uniform beam intensity patterns with computer-aided optimization to **achieve superior dose distribution**. It allows **greater control of dose distribution** and improves the ability to **cover the treatment volume to concave tumor shapes**.

IMRT achieved a large **dose reduction in the spinal cord and spared the kidneys and stomach**. Cheng et al IJROBP 2003

Helical Tomotherapy (HT) provides better dose coverage for tumors and reduce the dose to normal structures. Widesott et al IJROBP 2008, Lee et al Jpn J clin Oncol 2011

VMAT (RapidArc) volumetric modulated arc therapy achieves better planning target volume (PTV) coverage and better protection of normal tissue and improves treatment efficiency. Gong et al Strahlenther Onkol 2012, Park et al The British Journal of Radiology 2012

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The case of a 51-year-old man diagnosed with a **huge left hepatocellular carcinoma (15 cm) and portal vein thrombosis**. He was treated with **concurrent intra-arterial chemoradiotherapy (50Gy/20fr)** and received **6 cycles of intra-arterial chemotherapy**. The patient underwent a **left lobectomy 15 months after treatment and showed complete pathologic remission**. (A) The computed tomography images at the initial presentation, (B) after 1 month, and (C) showing a partial response after 15 months.

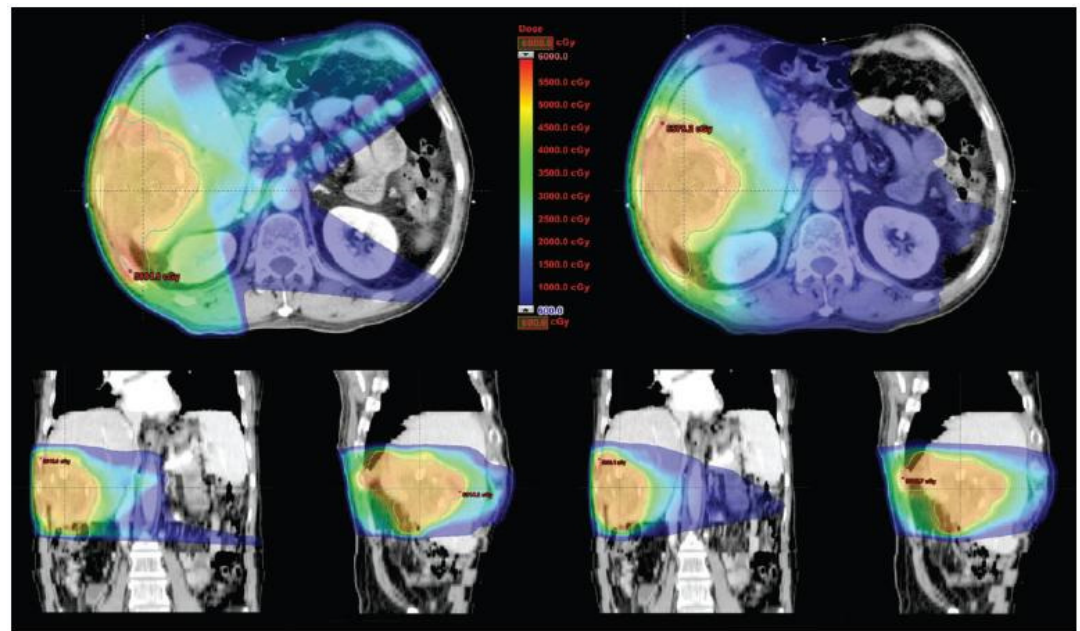
The British Journal of Radiology, 85 (2012), e323–e329

RapidArc[®] vs intensity-modulated radiation therapy for hepatocellular carcinoma: a comparative planning study

^{1,2}J M PARK, BS, ¹K KIM, MD, ¹E K CHIE, MD, ¹C H CHOI, BS, ¹S J YE, PhD and ^{1,3}S W HA, MD

The dose-volumetric results of RA vs IMRT were different according to the different target location within the liver. RA tended to be **more effective in the sparing** of non-liver organs at risk such as duodenum, kidney, and/or spinal cord.

Moreover, **RA was more efficient in the treatment delivery** than IMRT in terms of total monitor unit used.



EXTERNAL RT:

SBRT is a technique designed to **very precisely deliver radiation** to tumors anywhere in the body. It allows the delivery of **higher doses of radiation**, thus potentially improving the likelihood of **killing cancer cells** of a tumor in less time. The precision associated with SBRT simultaneously helps **reduce the dose of radiation to normal tissue** around a tumor, thus helping to **reduce side effects** for patients.

Treatment requires **less time**; typically SBRT consist of **3-5 fractions**

Non invasive technique



CyberKnife



TrueBeam STX



TomoTherapy



Review

Stereotactic radiation therapy and selective internal radiation therapy for hepatocellular carcinoma

Radiothérapie stéréotaxique et radiothérapie interne sélective du carcinome hépatocellulaire

A. Bujold, L.A. Dawson*

Stereotactic body radiation therapy phase I-II studies, hepatocellular carcinoma alone.

Authors	n	Tumor size	Patient characteristics (%)			Treatment (dose/number of fractions)	Outcome at 1 y (%)		Toxicity grade 3 or worse (n)
			CPB	EHD	PVT		Local control	Survival	
Mendez Romero et al. [43]	8	0.5–7.2 cm	25	0	25	< 4 cm 37.5 Gy/3 fractions > 4 cm 25 Gy/5 fractions or 30 Gy/3 fractions	75	75	1 RILD grade 5
Tse et al. [45]	31	9–1913 ml	0	10	45	24–54 Gy/6 fractions	65	48	7 CP progression 2 GI grade 5
Cardenes et al. [47]	17	2–6 cm	65	0	18	CPA 36–48 Gy/3 fractions CPB 36–42 Gy/3 fractions, or 40 Gy/5 fractions	100	75	3 RILD grade 3–4

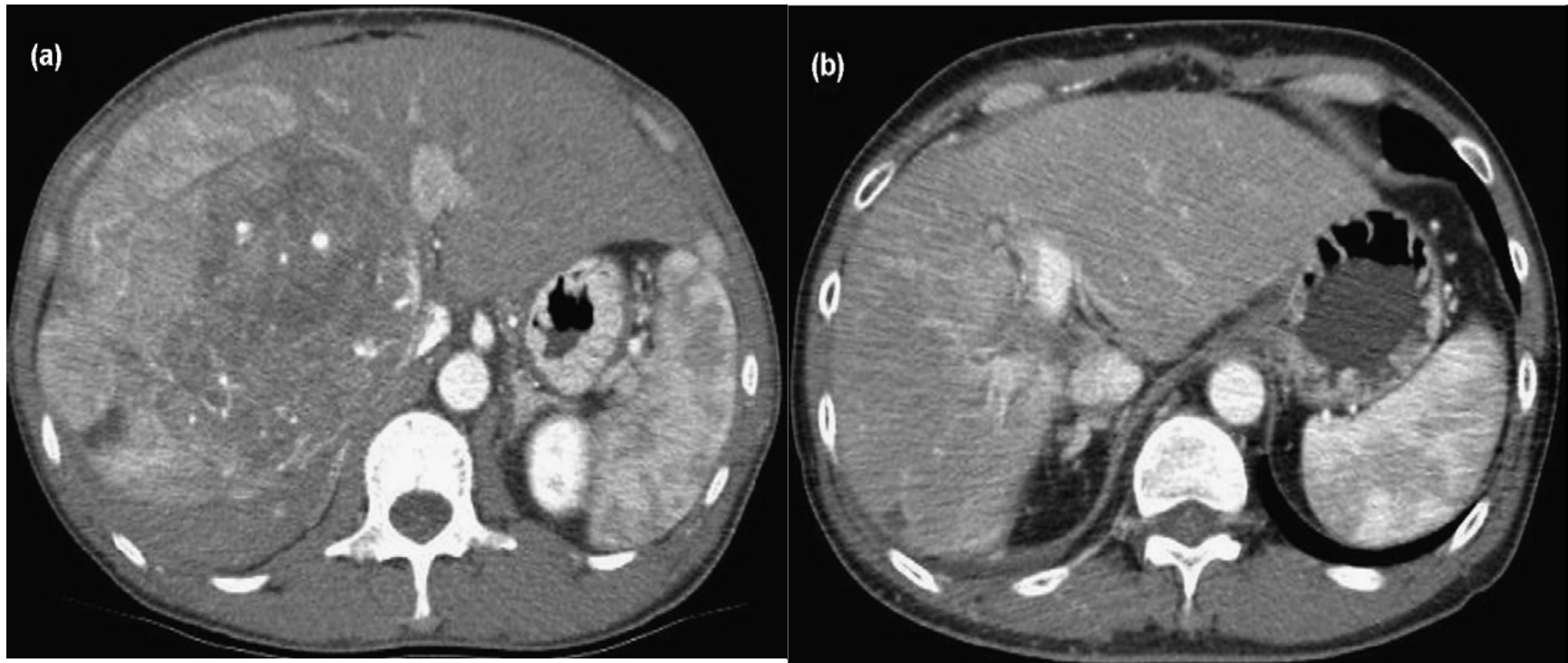
CP: Child-Turcotte-Pugh Cirrhosis Scale; EHD: extrahepatic disease; HCC: hepatocellular carcinoma; PVT: portal vein thrombus.

Phase I Study of Individualized Stereotactic Body
Radiotherapy for Hepatocellular Carcinoma and
Intrahepatic Cholangiocarcinoma

*Regina V. Tse, Maria Hawkins, Gina Lockwood, John J. Kim, Bernard Cummings, Jennifer Knox,
Morris Sherman, and Laura A. Dawson*

- Patients with **unresectable HCC or IHC**, and who are not suitable for standard therapies, were eligible for **six-fraction SBRT during 2 weeks**.
- **Forty-one patients** with unresectable **Child-Pugh A HCC** (n = 31) or IHC (n = 10) completed **six-fraction SBRT**. Five patients (12%) had grade 3 liver enzymes at baseline.
- The median tumor size was 173 mL (9 to 1,913 mL). **The median dose was 36.0 Gy (24.0 to 54.0 Gy)**.
- Median survival of HCC and IHC patients was 11.7 months (95% CI, 9.2 to 21.6 months) and 15.0 months (95% CI, 6.5 to 29.0 months), respectively.
- **No radiation-induced liver disease or treatment-related grade 4/5 toxicity was seen within 3 months after SBRT. Individualized SBRT is a safe treatment for unresectable HCC-IHC**

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Example of treatment response.

(A) Axial CT scan of **patient with HCC**, pre-treatment. (B) Corresponding axial CT scan of same HCC patient, 10 months after **receiving stereotactic radiotherapy** to the tumor (total dose **34.2 Gy in six fractions**, alternate days). The inferior vena cava is no longer compressed.



STEREOTACTIC BODY RADIOTHERAPY FOR PRIMARY HEPATOCELLULAR
CARCINOMA

DAVID L. ANDOLINO, M.D.,* CYNTHIA S. JOHNSON, M.S.,† MARY MALUCCIO, M.D.,‡ PAUL KWO, M.D.,§
A. JOSEPH TECTOR, M.D.,‡ JENNIFER ZOOK, M.D.,* PETER A. S. JOHNSTONE, M.D.,*
AND HIGINIA R. CARDENES, M.D., PH.D.*

Methods and Materials: From 2005 to 2009, **60 patients** with liver-confined HCC were treated with SBRT: 36 Child-Turcotte-Pugh (CTP) Class A and 24 CTP Class B.

The median number of fractions, dose per fraction, and **total dose**, was 3, 14 Gy, and **44 Gy**, respectively, for those with **CTP Class A** cirrhosis and 5, 8 Gy, and **40 Gy**, respectively, for those with **CTP Class B**.

Results: The median follow-up time was 27 months, and the median tumor diameter was 3.2 cm. The 2-year **LC, PFS, and OS** were **90%, 48%, and 67%**, respectively, with median TTP of 47.8 months.

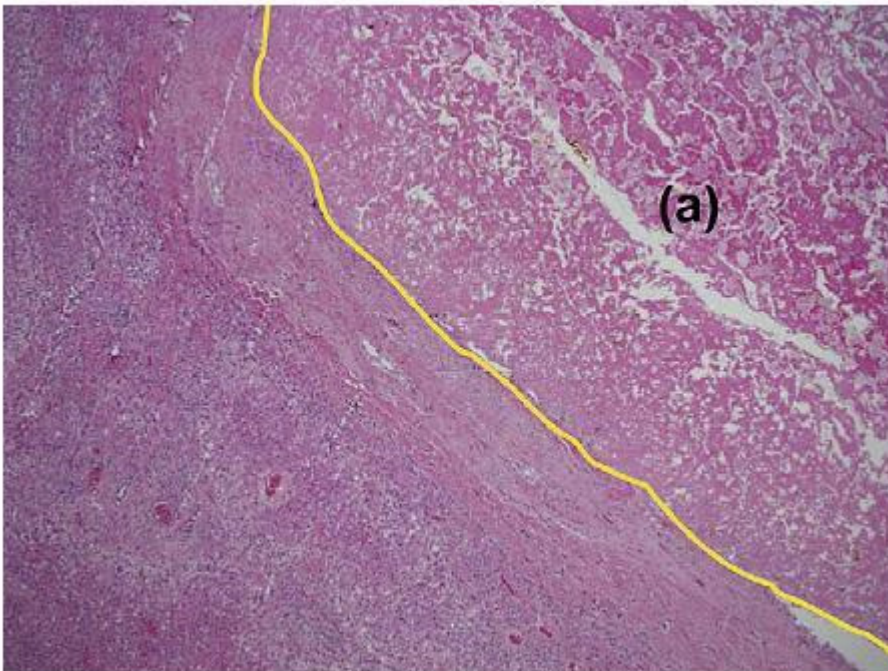
Conclusions: SBRT is a **safe, effective, noninvasive option for patients with HCC ≤ 6 cm**. As such, SBRT should be considered when **bridging to transplant** or as **definitive therapy** for those **ineligible for transplant**.

Clinical Investigation: Gastrointestinal Cancer

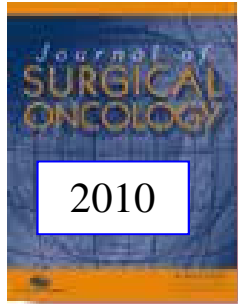


Stereotactic Hypofractionated Radiation Therapy as a Bridge to Transplantation for Hepatocellular Carcinoma: Clinical Outcome and Pathologic Correlation

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.[‡]



Hematoxylin-eosin-stained tissue sample (original magnification 125) showing **100% pathological response (a)** in a patient who underwent **SHORT (50Gy/10 fr)** alone as a bridge therapy, followed by liver **transplantation at 11 months**.



Preliminary Result of Stereotactic Body Radiotherapy as a Local Salvage Treatment for Inoperable Hepatocellular Carcinoma

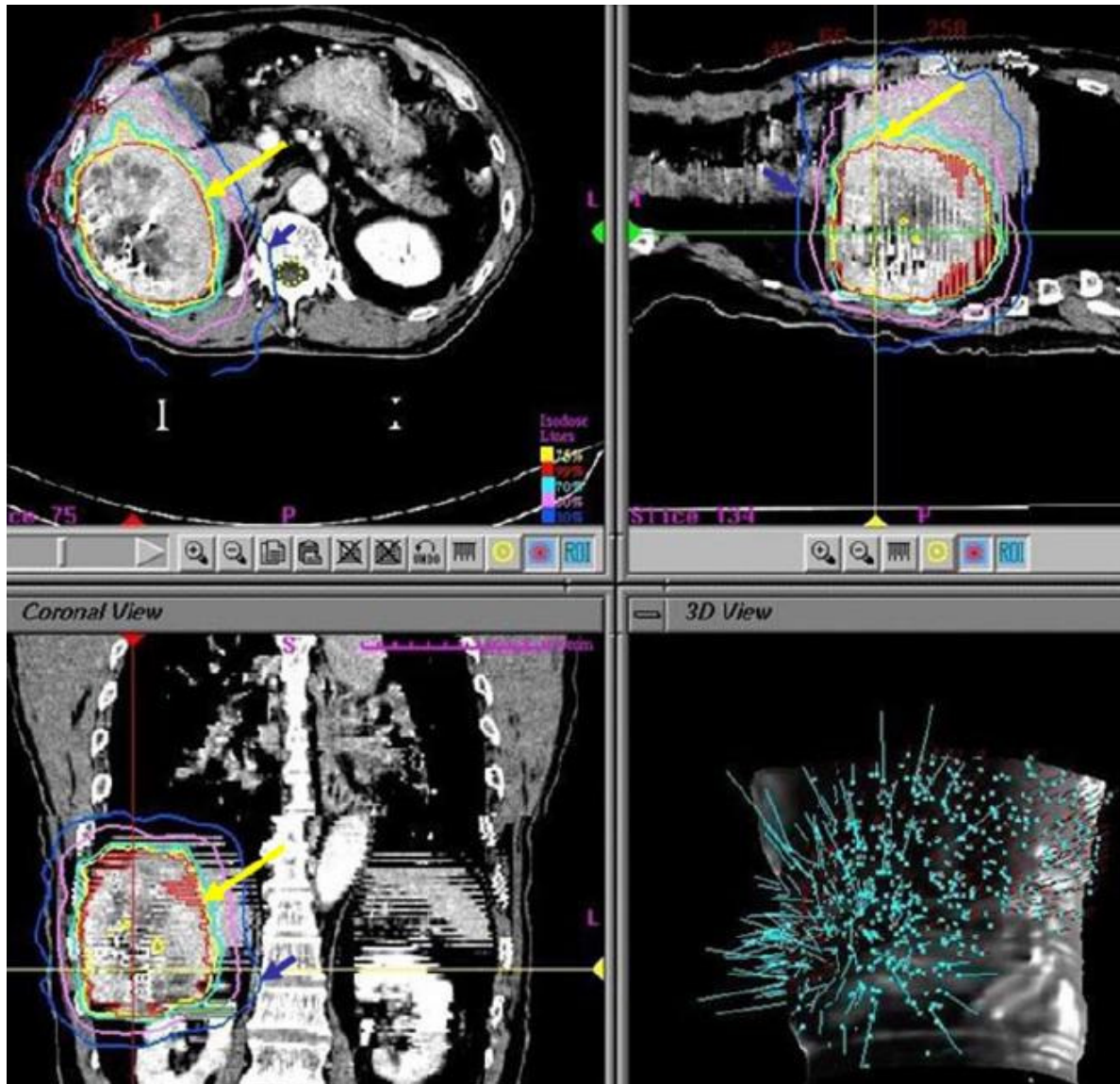
YOUNG SEOK SEO,¹ MI-SOOK KIM, MD,^{1*} SUNG YUL YOO,¹ CHUL KOO CHO,¹ CHUL WON CHOI,¹
JIN HO KIM,¹ CHUL JU HAN,² SU CHEOL PARK,² BYUNG HEE LEE,³
YOUNG HAN KIM,³ AND DONG HAN LEE⁴

Objectives: To evaluate the toxicity and efficacy of stereotactic body radiotherapy (SBRT) for the treatment of localized HCC in the absence of another standard treatment option.

Methods: The authors reviewed the details of **38 patients** with inoperable HCC (diameter <10 cm) treated by **SBRT with CyberKnife** in a prospectively registered database at their institution. **All patients had been treated by transcatheter arterial chemoembolization before SBRT, which had been finally deemed ineffective. SBRT dosages (33–57Gy in three or four fractions)** were administered according to tumor volumes, which ranged from 11 to 464 ml (median, 40.5 ml).

Results: **Two-year overall survival and local progression-free survival rates were 61.4% and 66.4%**, respectively. The **local response rate was 63%** at 3 months after SBRT. A high radiation dose was found to be independently related to survival. A decline in liver function was observed in six patients (16%) and Grade 3 musculoskeletal toxicity in one patient (2.7%).

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Conclusions: This study showed that **SBRT can be safely administered to select HCC patients**, and these results suggest that this technique should be considered a salvage treatment. A further well-controlled large-scale study and longer follow-up are needed to **determine optimal dose-fraction schedules** and characterize late complications.

Seo et al, JSO 2010

Hepatology Research 2008; 38: 60–69

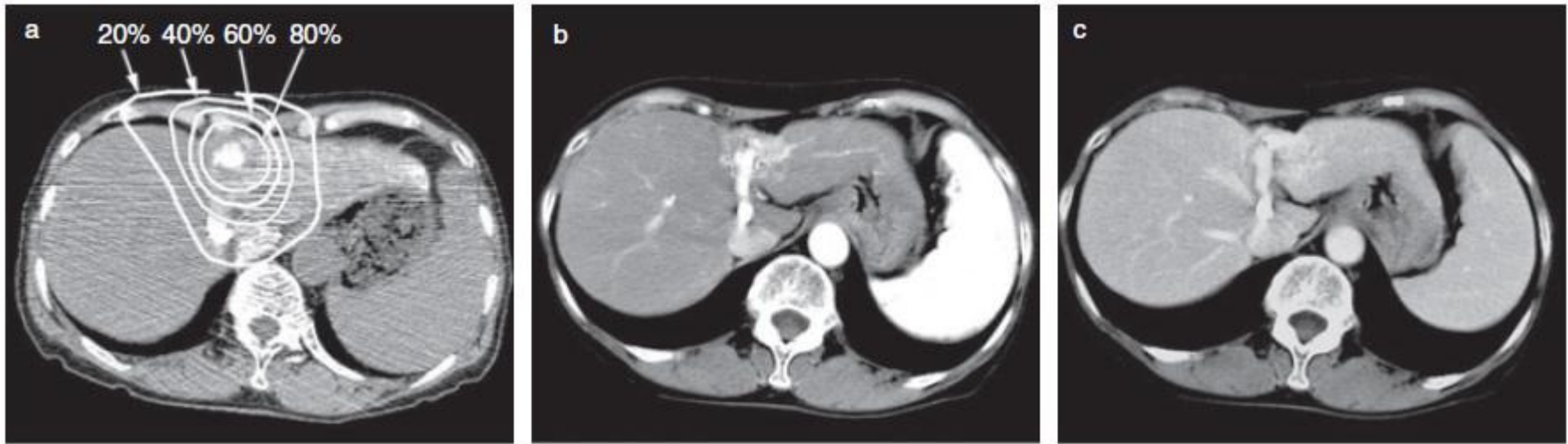
**SBRT
±
TACE**

Hypofractionated stereotactic radiotherapy with and without transarterial chemoembolization for small hepatocellular carcinoma not eligible for other ablation therapies: Preliminary results for efficacy and toxicity

Atsuya Takeda,^{1,2} Masahiko Takahashi,^{3*} Etsuo Kunieda,^{2,4} Toshiaki Takeda,² Naoko Sanuki,¹ Yuji Koike,^{3†} Kazuhiro Atsukawa,⁵ Toshio Ohashi,⁴ Hidetsugu Saito,⁶ Naoyuki Shigematsu⁴ and Atsushi Kubo⁴

- **Sixteen patients** who presented with solitary HCC, including two patients with a **tumor thrombus of the portal veins**, were treated with **SBRT with or without TACE**. The criteria for SBRT were existence of technical difficulties for other ablation therapies, inoperable disease or refusal to undergo surgery, tumor staged as Grade A or B according to the Child–Pugh classification, and solitary tumor distant from the gastrointestinal tract and kidney with a tumor volume <100 cm³. In 14 of 16 patients, a **total dose of 35–50 Gy was delivered in 5–7 fractions over 5–9 days**.
- **Eight** of 16 patients had **complete responses** and **seven** others were judged as **stable** with lipiodol accumulation. In **one** patient, **local recurrence** developed after 489 days.

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(a) Lipiodol pooled in the primary lesion before irradiation. The isodose curves for 20%, 40%, 60%, and 80% of the maximum dose are indicated. (b) **Arterial phase CT 74 weeks after irradiation.** Lipiodol remains pooled and contrast enhancement is observed in the high-dose area surrounding the primary lesion. (c) **Portal phase CT 74 weeks after irradiation.** Residual contrast enhancement is observed in the area surrounding the tumor. These enhancements are post-irradiation changes.

Stereotactic radiotherapy for HCC with or without TACE is feasible therapy and provides good local control with a short treatment period. Stereotactic radiotherapy may be of **clinical benefit in patients who are inoperable** or for whom there are difficulties in other ablation therapies.

Clinical Studies

Local radiotherapy as a complement to incomplete transcatheter arterial chemoembolization in locally advanced hepatocellular carcinoma

Shim SJ, Seong J, Han KH, Chon CY, Suh CO, Lee JT. Local radiotherapy as a complement to incomplete transcatheter arterial chemoembolization in locally advanced hepatocellular carcinoma.

Su Jung Shim¹, Jinsil Seong¹, Kwang Hyub Han², Chae Yoon Chon², Chang Ok Suh¹ and Jong Tae Lee³

Materials and methods:

One hundred and five patients with an unresectable HCC were treated with TACE from January 1992 to December 2002. In 73 of these patients, the TACE was incomplete. Among them, TACE was repeatedly performed in 35 patients (TACE group), and the remaining 38 patients were also treated with local RT (TACERT group).

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	TACE	TACE + RT	Tumor size
2 years OS	42%	63%	5-7 cm
	0%	50%	8-10 cm
	0%	17%	>10 cm

Conclusion:

There was a **significantly improved survival rate in the TACE-RT group** of unresectable HCC patients than in the TACE group, particularly in case of tumors 8 cm in diameter.

Therefore, **RT in addition to TACE is strongly recommended** for patients with an unresectable HCC.

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STAGE D

BCLC stage*	Okuda stage	Definition	Liver function/PST	Applications of radiation	Median survival
Terminal stage (D)	3	Disseminated	Child C/ >2	Palliative RT	2-5.1 ⁸⁰⁻⁸²



Radioresponse of Hepatocellular Carcinoma-Treatment of Lymph Node Metastasis

Sang Min Yoon, M.D.¹, Jong Hoon Kim, M.D., Ph.D.¹, Eun Kyung Choi, M.D., Ph.D.¹, Seung Do Ahn, M.D., Ph.D.¹, Sang-wook Lee, M.D.¹, Byong Yong Yi, Ph.D.¹, Young Wha Chung, M.D., Ph.D.², Young Sang Lee, M.D., Ph.D.² and Dong Jin Seo, M.D., Ph.D.²

Clinical Studies

Radiotherapy for painful bone metastases from hepatocellular carcinoma

Seong J, Koom WS, Park HC. Radiotherapy for painful bone metastases from hepatocellular carcinoma.

CLINICAL STUDY - PATIENT STUDY

Brain metastases from hepatocellular carcinoma: prognostic factors and outcome

Brain metastasis from HCC

Hye Jin Choi · Byung Chul Cho · Joo Hyuk Sohn · Sang Jun Shin · Se Hyun Kim · Joo Hang Kim · Nae Choon Yoo

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A Summary of the Definition of BCLC Stages and the Results of Radiotherapy

BCLC stage*	Okuda stage	Definition	Liver function/PST	Applications of radiation	Median survival
Very early stage (0)	0	Single <2 cm Carcinoma <i>in situ</i>	Child A/0	SBRT alone or TACE+SBRT	44.4 ⁵⁶
Early stage (A)	1-2	Single to 3 nodules, <3 cm	Child A-B/0	TACE+RT	16-20 ^{39,65}
Intermediate stage (B)	1-2	Multinodular	Child A-B/0	TACE+RT	
Advanced stage (C)	1-2	Portal invasion, N1, M1	Child A-B/1-2	CCRT→iA CTx	15.2-16.7 ^{69,76}
Terminal stage (D)	3	Disseminated	Child C/>2	Palliative RT	2-5.1 ⁸⁰⁻⁸²

CONCLUSIONS



A **variety of new RT machines** are currently available, which could make it difficult for physicians when determining their choice of treatment. Although 3D-CRT has been the standard mode, it is **highly recommended to use a precision RT technology** involving intensity modulation , SBRT and IGRT.

In particular, **IGRT is an essential component** of the advanced RT process.

However, the **superiority of these sophisticated technologies has not been proven in terms of survival benefits yet.** Further clinical study in the radiation treatment of HCC is necessary to confirm its role in **multidisciplinary management of HCC.**

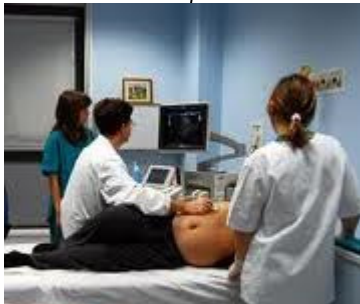
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MEDICAL ONCOLOGIST



RADIOLOGIST



HEPATOLOGIST



SURGEON



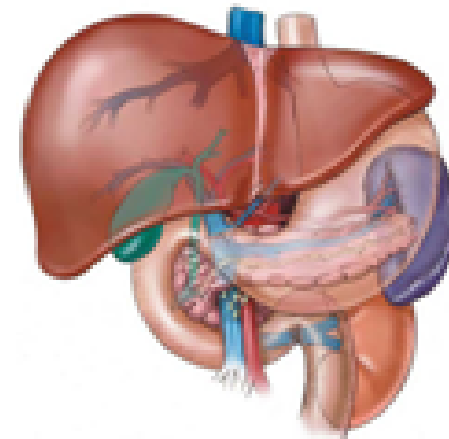
RADIATION ONCOLOGIST

MULTIDISCIPLINARY APPROACH

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SBRT CONSTRAINTS

ORGAN	Dose-Volume Limits	Other Conditions
Healthy liver (defined as total liver volume minus cumulative GTV)	> 700 cc at < 15 Gy in 3 F	The volume of healthy liver > 1000 cc
Spinal cord	< 18 Gy in 3 F	
Kidneys (R+L)	V15 Gy < 35%	
Stomach, duodenum, small intestine	< 21 Gy in 3 F (also for minimum volumes)	Patients with GTV < 8 mm from the heart, stomach, duodenum and small intestine to be excluded
Heart	< 30 Gy in 3 F	
Rib	V30Gy < 2cc	



SBRT FOR TUMOR THROMBUS

CLINICAL INVESTIGATION

Liver

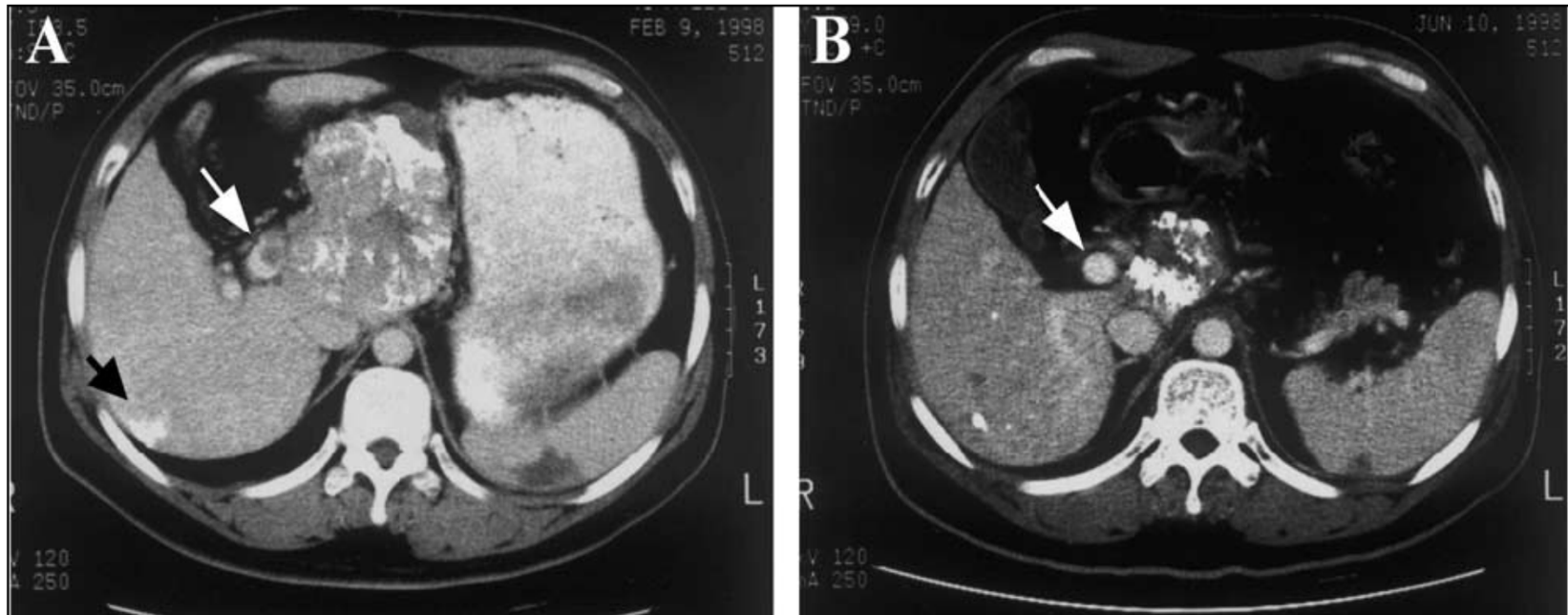


A COMPARISON OF TREATMENT COMBINATIONS WITH AND WITHOUT RADIOTHERAPY FOR HEPATOCELLULAR CARCINOMA WITH PORTAL VEIN AND/OR INFERIOR VENA CAVA TUMOR THROMBUS

ZHAO-CHONG ZENG, M.D.,* JIA FAN, M.D.,[†] ZHAO-YOU TANG, M.D.,[†] JIAN ZHOU, M.D.,[†]
LUN-XIU QIN, M.D.,[†] JIAN-HUA WANG, M.D.,[‡] HUI-CHUAN SUN, M.D.,[†] BIN-LIANG WANG, M.D.,*
JIAN-YING ZHANG, B.S.,* GUO-LIANG JIANG, M.D.,[§] AND YU-QI WANG, M.D.^{||}

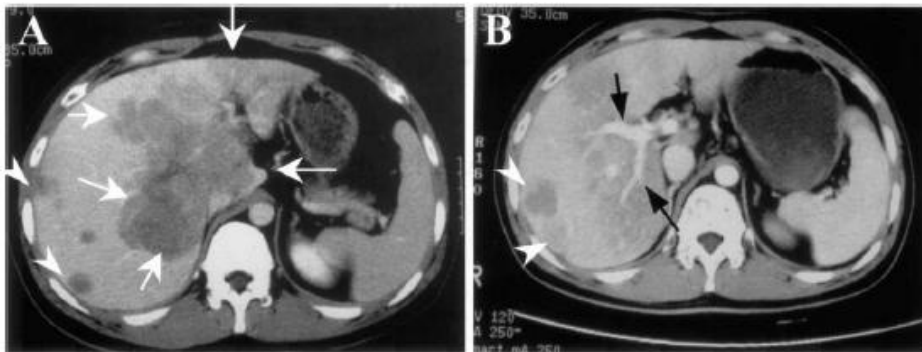
- **One hundred fifty-eight patients with HCC who had PV and/or IVC tumor thrombus were reviewed** and analyzed by Kaplan-Meier and Cox regression analysis.
- Forty-four patients with HCC who received local limited EBRT (in addition to other treatment modalities) were classified as the EBRT group.
- The total radiation **dose was 36–60 Gy** (median, 50 Gy) and was focused on the tumor thrombi.

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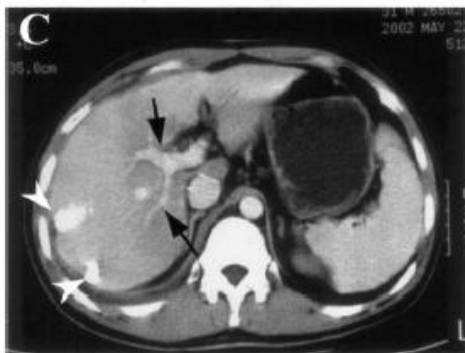


- Of the **44 patients who received EBRT**, 15 (34.1%) showed complete disappearance of tumor thrombi, 5 (11.4%) were in partial remission, 23 (52.3%) were stable in their tumor thrombi, and 1 (2.3%) showed disease progression at the end of the study period.
- Although **EBRT is palliative in intent**, it is preferred for prolonging survival in the **treatment of tumor thrombi**.

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Axial abdominal CT scan during PV phase in a 31-year-old man with hepatocellular carcinoma. (A) White arrows show a **large tumor surrounded by “satellite” lesions**.



(C) After EBRT combined with transarterial chemoembolization (TACE), iodized oil deposits were found in the “satellite” lesions, which could not be treated with EBRT. **This case indicates that EBRT can relieve PV occlusion by tumor thrombi; resultant TACE was used safely in this patient.**

Conclusion:

Although EBRT is palliative in intent, it is **preferred for prolonging survival** in the treatment of tumor thrombi.