

NCCN Guidelines® Update: Locoregional Treatment Approaches for Hepatocellular Carcinoma

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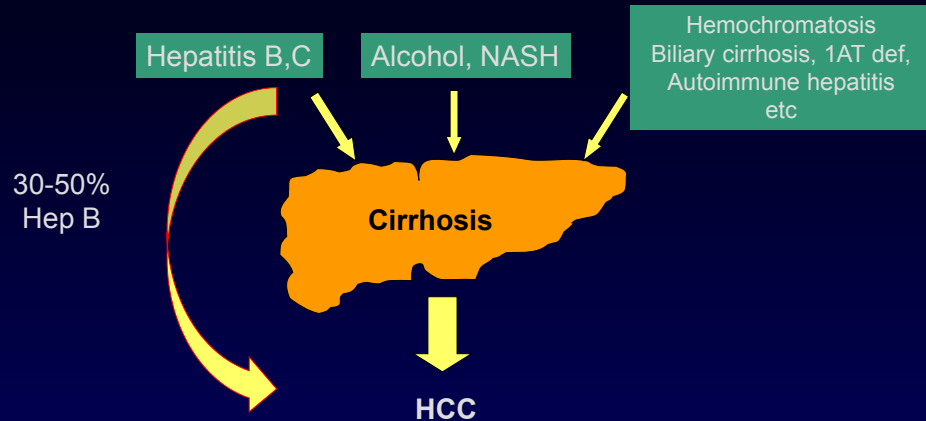


Locoregional Therapy in the Treatment of Hepatocellular Carcinoma

Anne M Covey, MD, FSIR

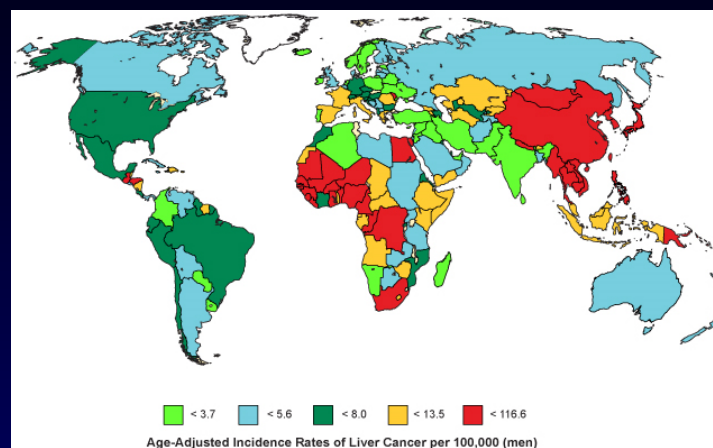
**Member, Memorial Sloan Kettering Cancer Center
Associate Professor of Radiology, Weill Cornell Medical Center**

Hepatocellular carcinoma most commonly occurs in the setting of underlying liver disease



The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Hepatobiliary Cancers (Version 1.2016). © 2016 National Comprehensive Cancer Network, Inc.

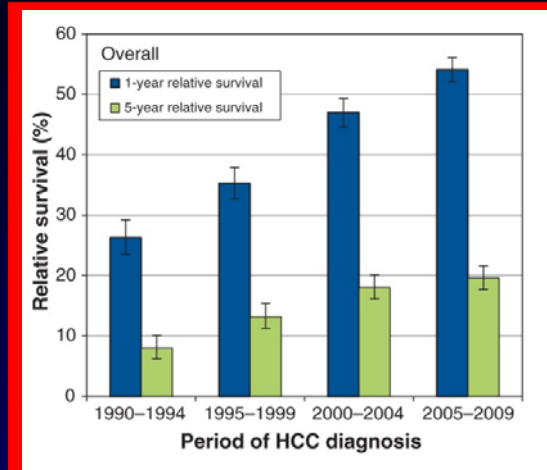
Hepatocellular carcinoma is a global problem; the 5th most common cause of cancer worldwide and the 3rd leading cause of cancer related death



Aucejo F. Hepatocellular Carcinoma. Cleveland Clinic Center for Continuing Education: Disease Management 2013. Available at: <http://bit.ly/1fw6xa>.

Thein H et al. CMAJ v3(2) Apr-Jun 2015 PMID 26389099

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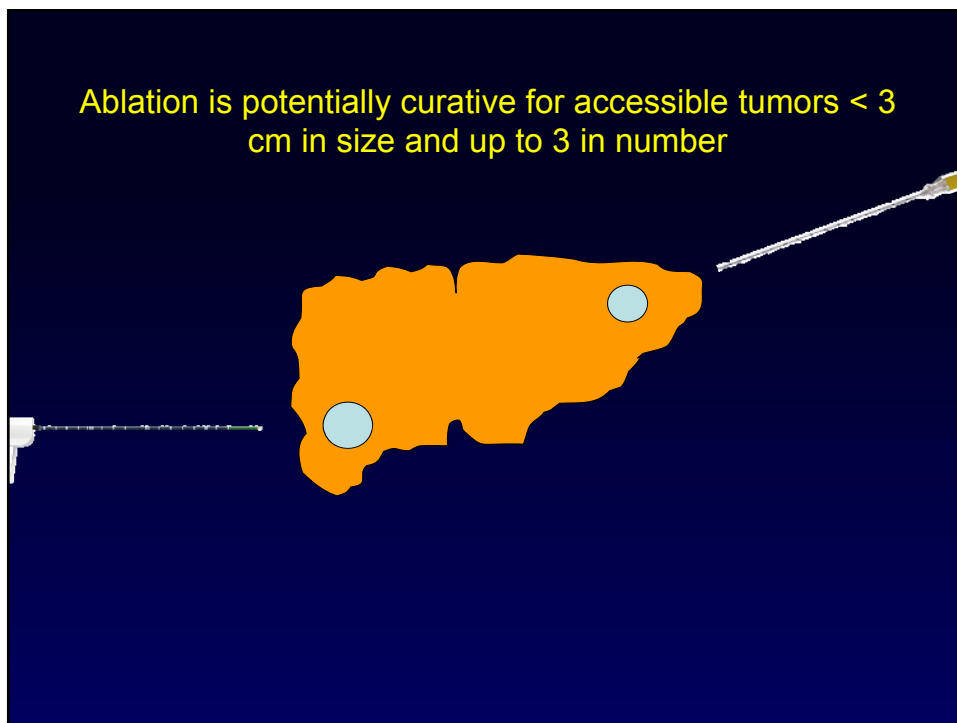
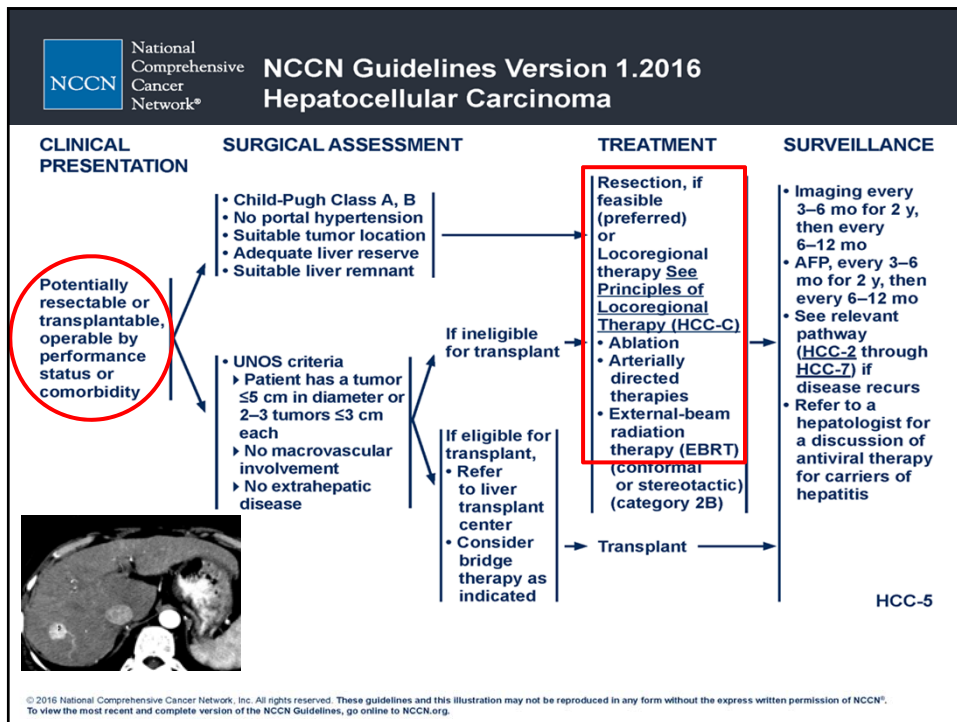
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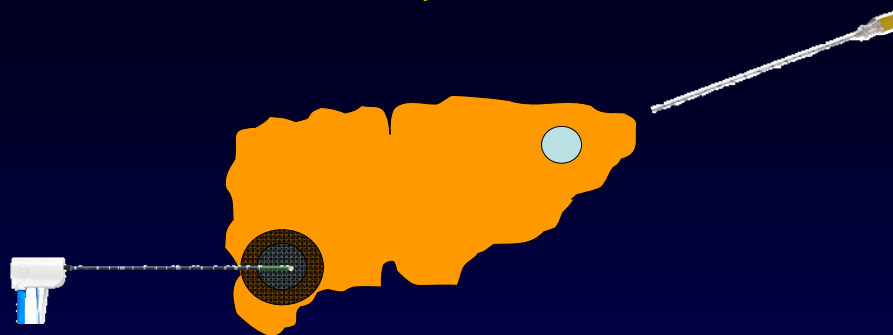
Treatment options depend on factors related to both tumor and underlying liver dysfunction



- 1-3 tumors < 3 cm → Resection
Transplantation
Ablation
- Multi-focal > 3 cm → Arterially directed therapy
+/- ablation
Chemotherapy
- Liver dominant
- Extrahepatic dz → Chemotherapy
Arterially directed therapy?
- Vascular invasion

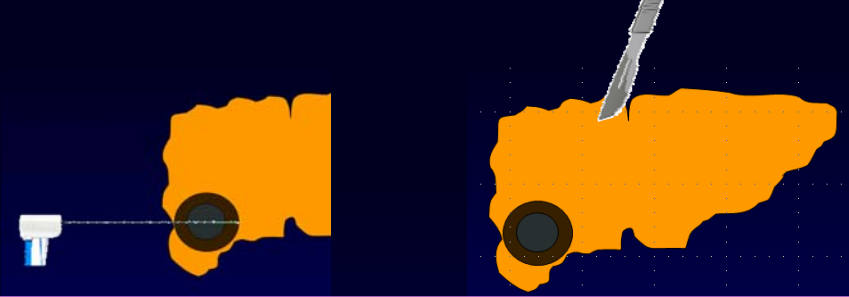


Ablation is potentially curative for accessible tumors < 3 cm in size and up to 3 in number



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There are 4 RCTs and several NRCTs comparing RFA and surgical resection in the treatment of small HCC

For lesions < 3 cm overall survival at 1, 3, 5 years is no different

+ Less transfusion	+ Lower rate of local recurrence
+ Shorter hospital stay	+ Better long-term disease-free
- <i>Limited by tumor location</i>	- <i>Increase risk of complications</i>

Feng K et al. J. Hepatol 2013 57:794-802
Chen MS et al. Ann Surg 2006 243:321-328

Huang JW et al. Ann Surg 2010 252:903-912
Lu et al. Zhonghua 2006 86(10):801-805



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Randomized controlled trials comparing RFA to resection for HCC < 3 cm show no difference in 1, 3 & 4 year survival

Table 4. Summary of finding table for Solitary HCC with tumor size ≤3 cm and 3–5 cm in RCTs.

Indicators	Subgroup	Years	No. of Participants (studies)	Event, %		Effect estimate [#]	
				RFA	HR	OR, 95% CI	I ² (%)
Overall survival	Tumor size ≤3 cm	1-y	181 (2)	93.6	97.7	0.49 [0.03, 8.45]	56
		3-y	181 (2)	74.5	81.6	0.65 [0.32, 1.33] [§]	49
		4-y	181 (2)	74.5	78.2	0.80 [0.20, 3.22]	73
	Tumor size 3–5 cm	1-y	153 (2)	91.8	96.7	0.38 [0.03, 4.85]	54
		3-y	153 (2)	62.3	83.7	0.26 [0.05, 1.36]	69
		4-y	153 (2)	57.4	72.8	0.51 [0.25, 1.03] [§]	3

PLoS One, 2014 Jan 3;9(1):e84484. doi: 10.1371/journal.pone.0084484. eCollection 2014.

Radiofrequency ablation versus hepatic resection for small hepatocellular carcinomas: a meta-analysis of randomized and nonrandomized controlled trials.

Wang Y¹, Luo Q², Li Y³, Deng S⁴, Wei S⁴, Li X³.

Non-randomized controlled trials show significant benefit to resection probably due to patient selection bias

Table 6. Summary of finding table for HCC patients with tumor size ≤3cm in NRCTs.

Indicators	Subgroup	Years	No. of Participants (studies)	Event, %		Effect estimate [#]		P value
				RFA	HR	OR, 95% CI	I ² (%)	
	Single HCC	1-y	1516 (8)	94.7	95.7	0.67 [0.42, 1.09]	9	0.11
		3-y	1516 (8)	80.4	87.2	0.59 [0.32, 1.09] [§]	70	0.09
		5-y	1516 (8)	64.3	77.5	0.52 [0.31, 0.87] [§]	74	0.01*

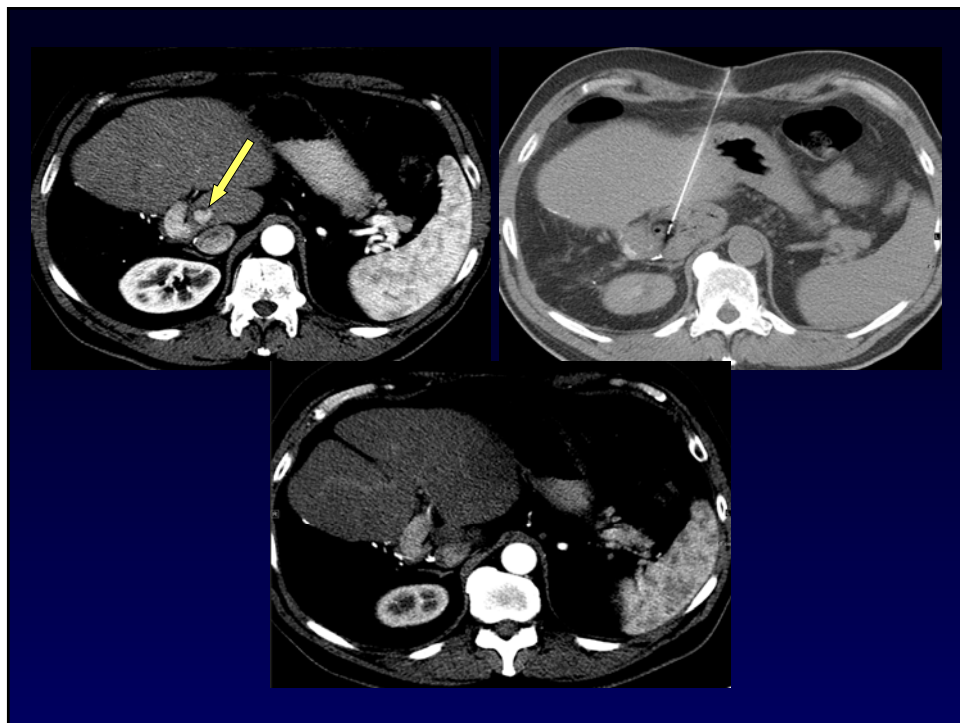
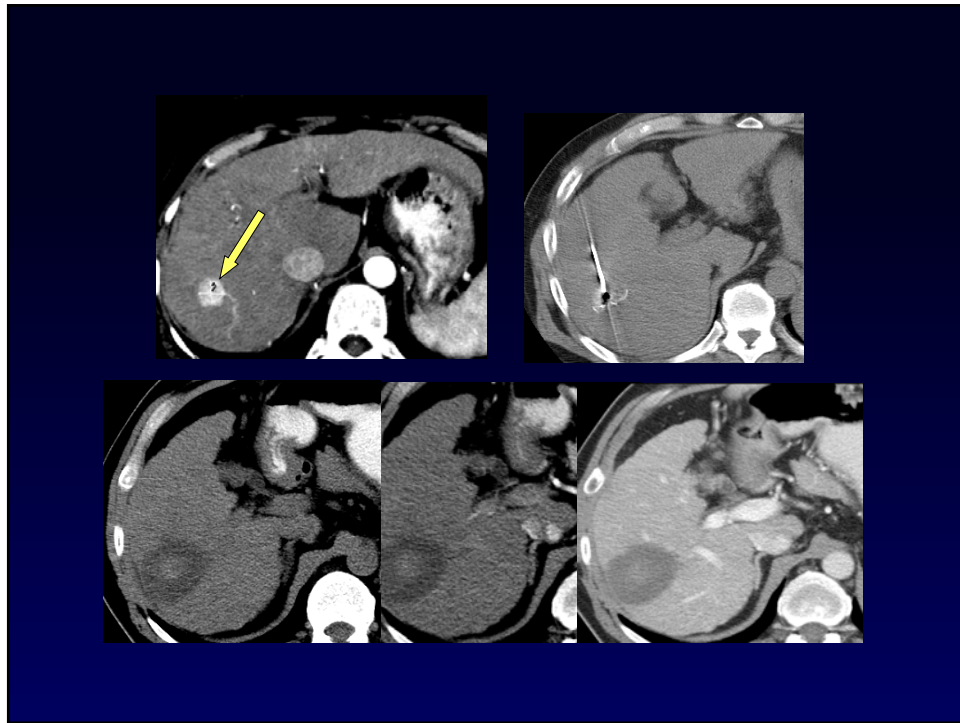
Table 5. Summary of finding table for HCC patients with tumor size between 3 and 5 cm in NRCTs.

Indicators	Years	No. of Participants (studies)	Event, %		Effect estimate [#]		P value
			RFA	HR	OR, 95% CI	I ² (%)	
Overall survival	1-y	243 (3)	95.4	92.9	1.62 [0.54, 4.84]	0	0.39
	3-y	243 (3)	56.2	61.9	0.80 [0.48, 1.34]	0	0.40
	5-y	243 (3)	26.2	45.1	0.43 [0.25, 0.73]	24	0.002*

PLoS One, 2014 Jan 3;9(1):e84484. doi: 10.1371/journal.pone.0084484. eCollection 2014.

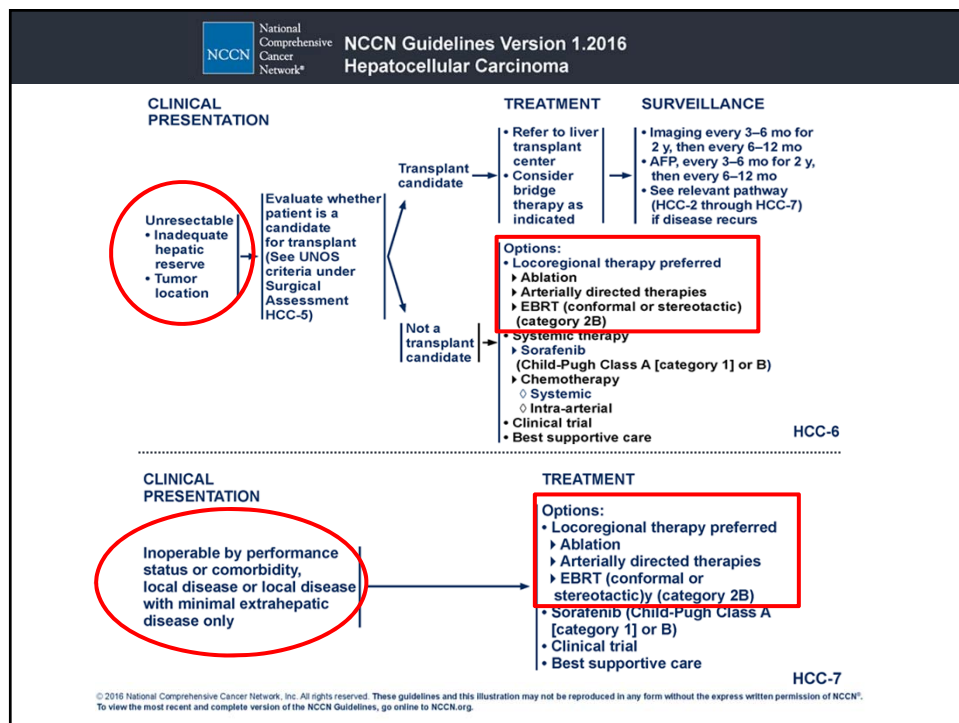
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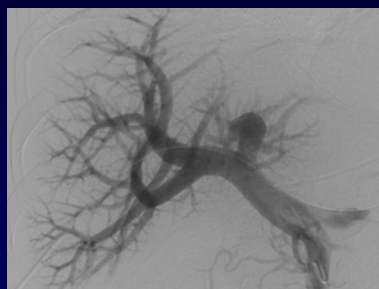
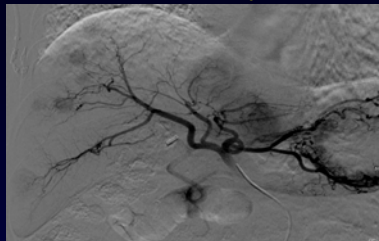
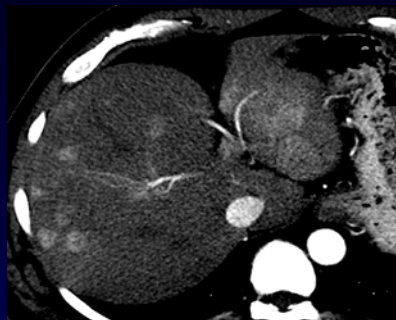


For resectable tumors, resection or transplant is preferred if feasible.

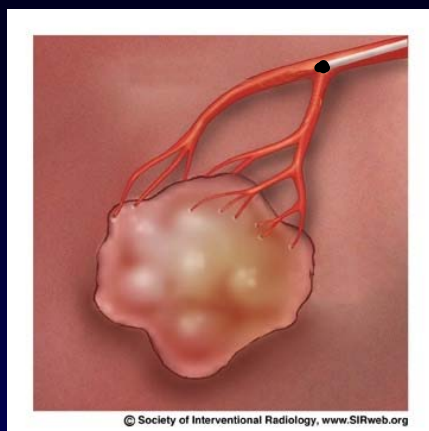
Ablation may also be curative for HCC < 3 cm.



Arterially directed therapies to the liver are possible due to the dual nature of hepatic blood supply



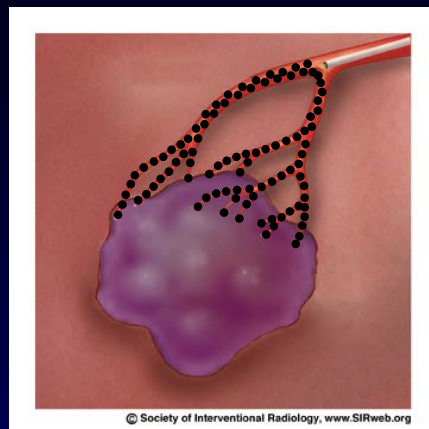
Bland embolization (TAE, HAE)



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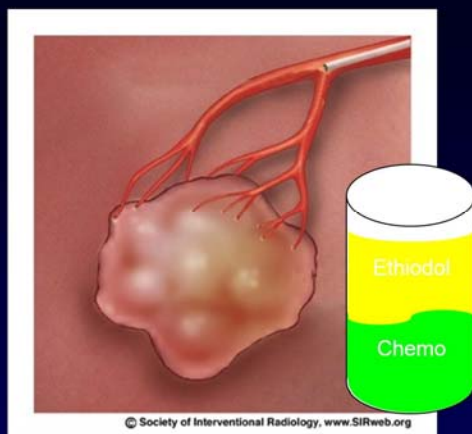
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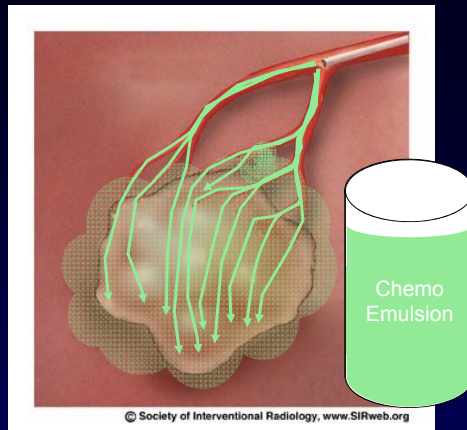
Bland embolization (TAE, HAE)



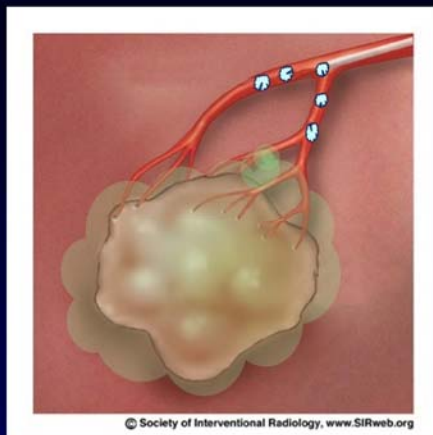
Transarterial chemoembolization (TACE)



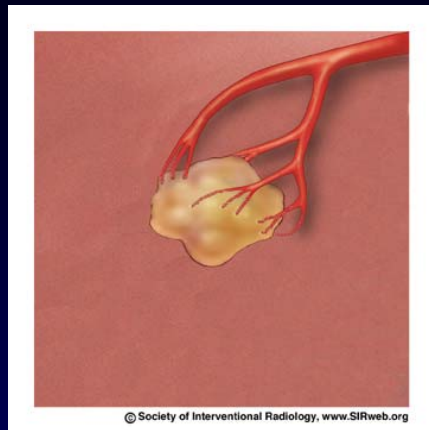
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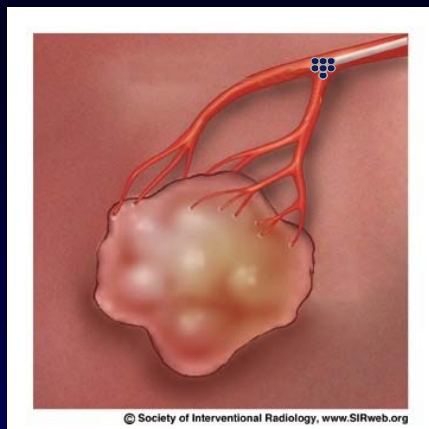
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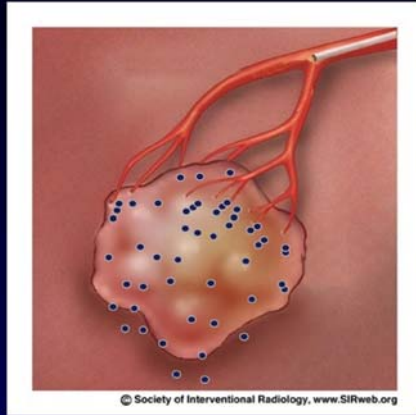
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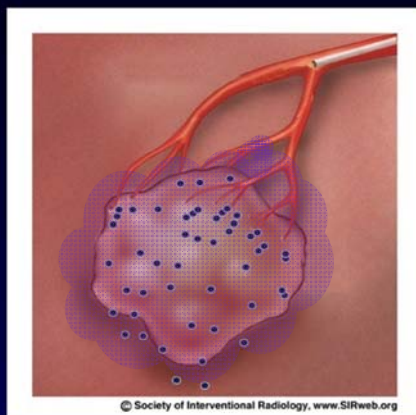
Embolization with drug eluting beads (DEB)



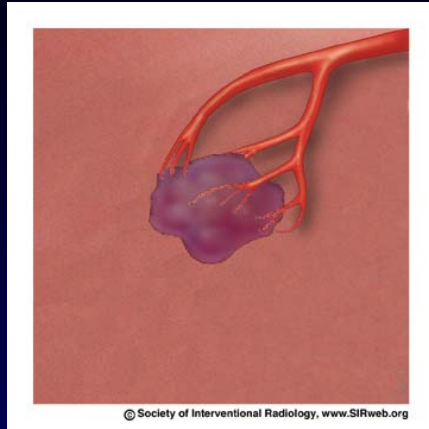
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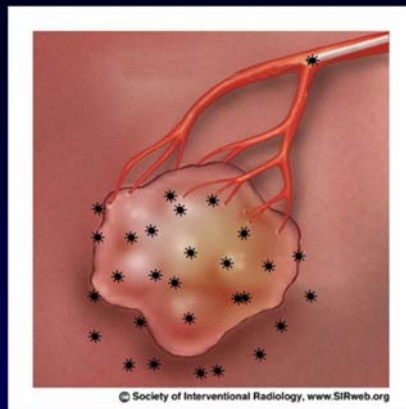


Embolization with drug eluting beads (DEB)



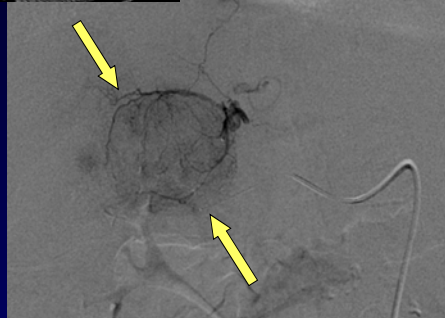
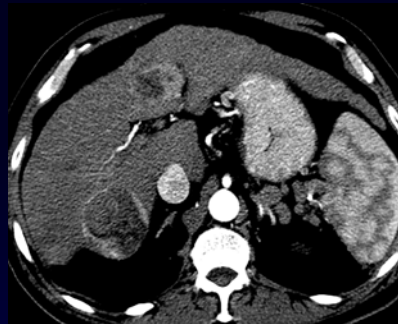
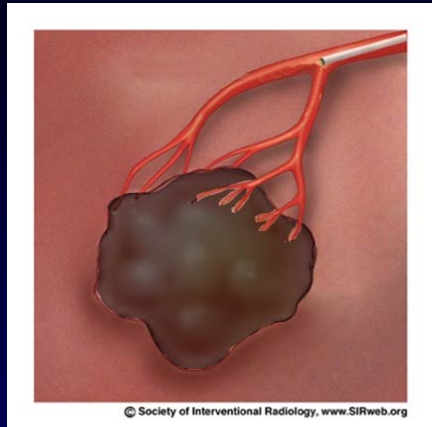
Radio “embolization” with Y90 (RAE)

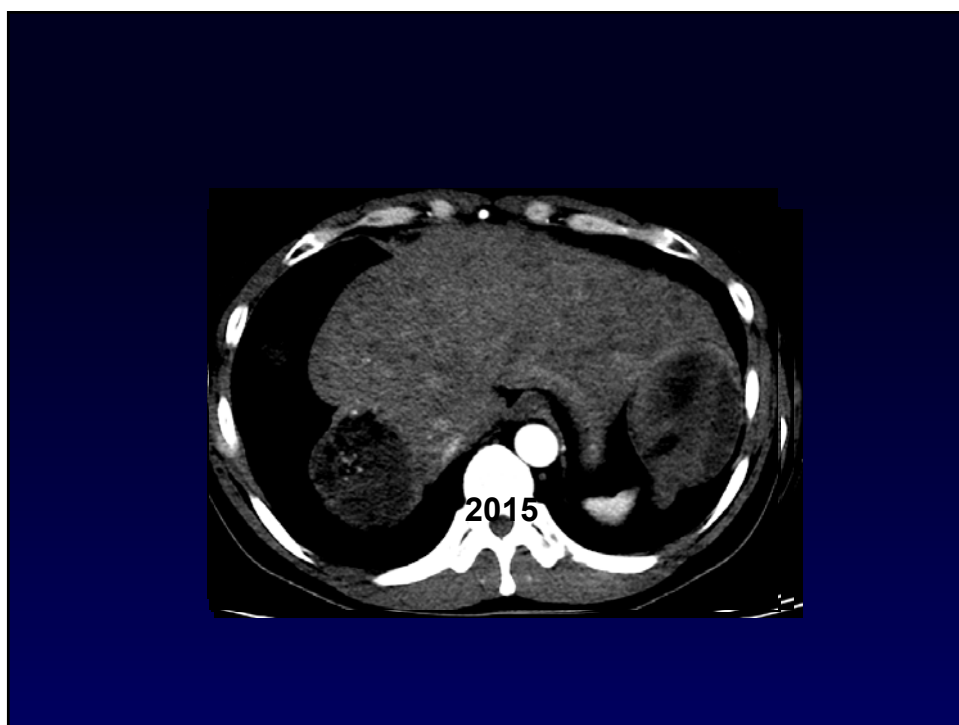
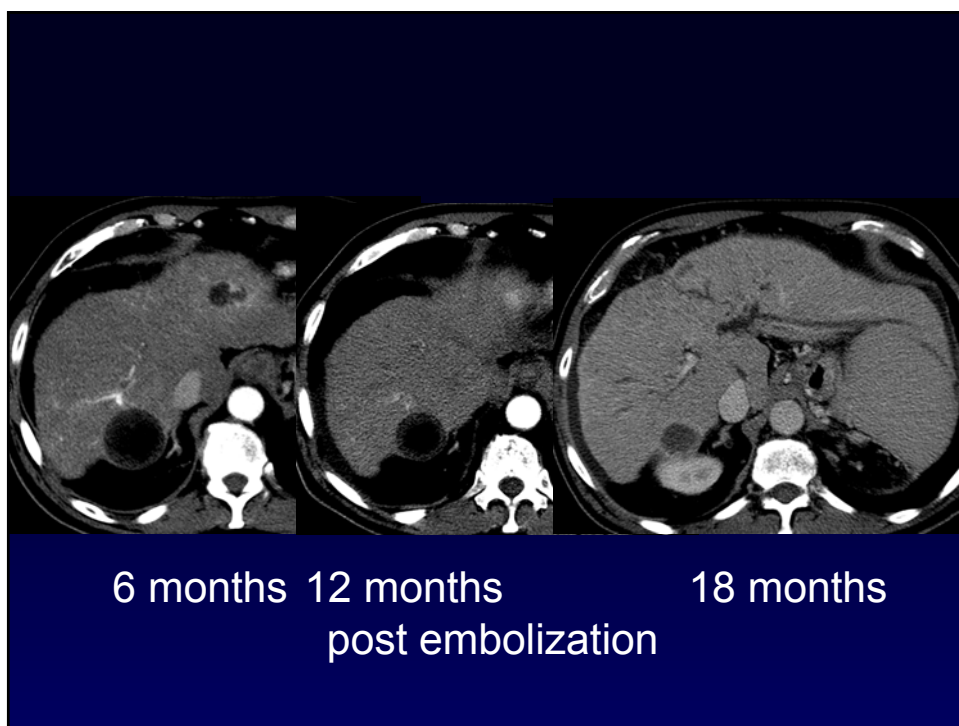
⁹⁰Y RAE

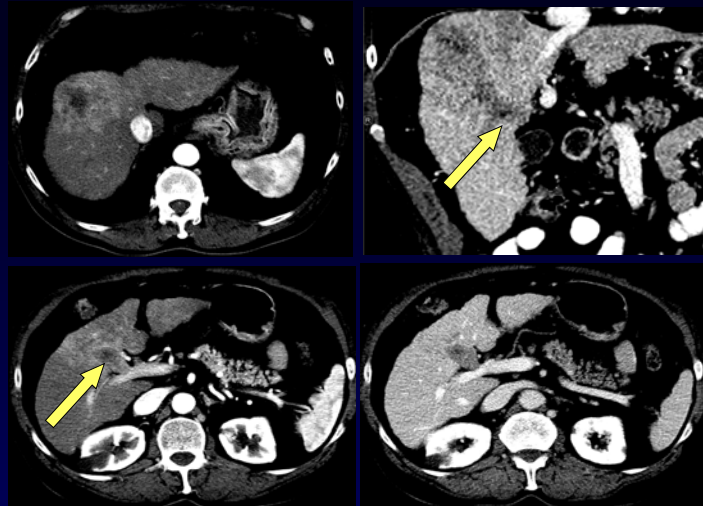


Radio “embolization” with Y90 (RAE)

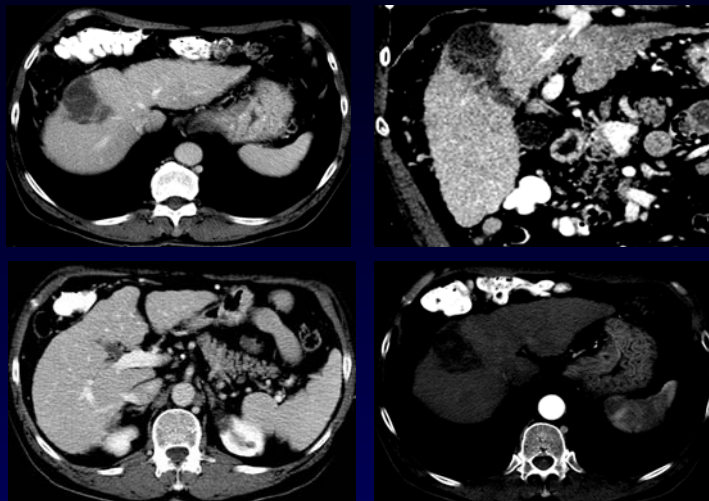
⁹⁰Y RAE





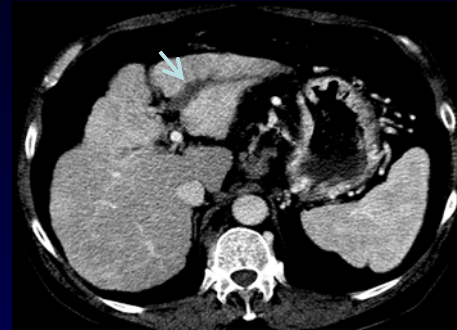
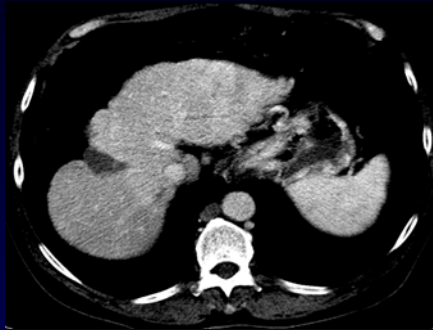


5/2012



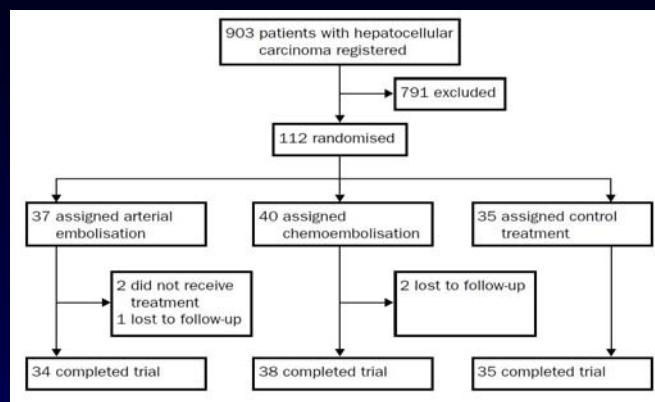
6/2012

No additional treatment 6/2012-1/2014



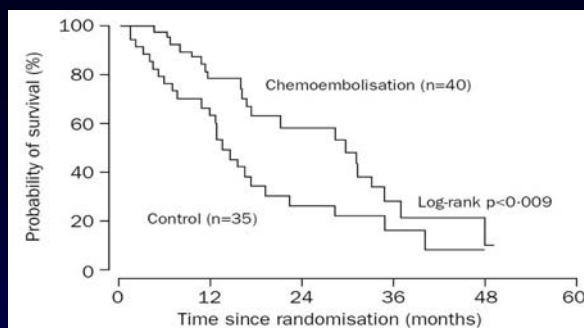
1/2014

Two randomized controlled trials showing embolization has a survival advantage compared to best supportive care.



Lancet. 2002 May 16;359(9319):1734-9.
Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial.
 Llovet JM¹, Real MJ, Montaña X, Planas R, Coll S, Aponte J, Avuso C, Sala M, Muchart J, Solà R, Rodés J, Bruix J; Barcelona Liver Cancer Group.

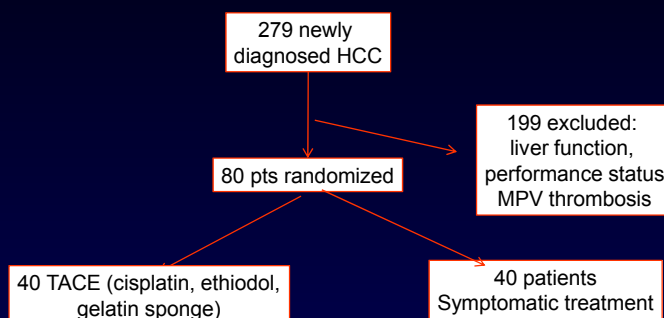
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OS at 3 years in TACE vs supportive care 29 vs 17%

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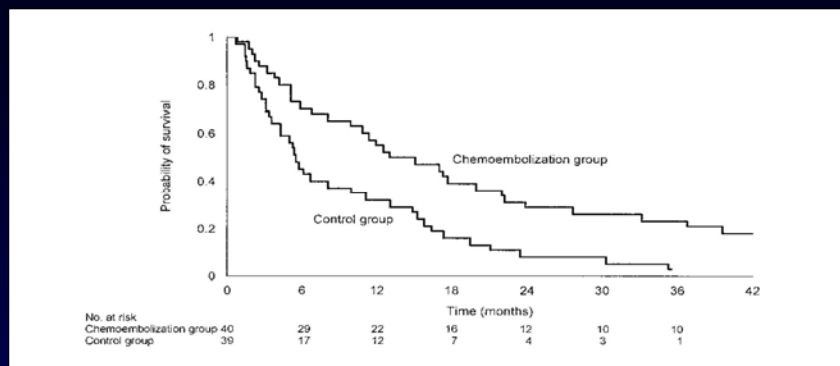
Two randomized controlled trials showing embolization has a survival advantage compared to best supportive care.



OS at 3 years in TACE vs supportive care 26 vs 3%

Hepatology, 2002 May;35(5):1164-71
Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma.
Lo CM¹, Ngan H, Tso WK, Liu CL, Lam CM, Poon RT, Fan ST, Wong J.

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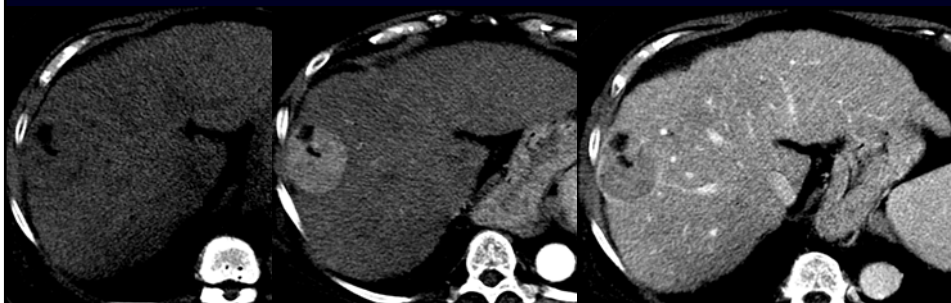
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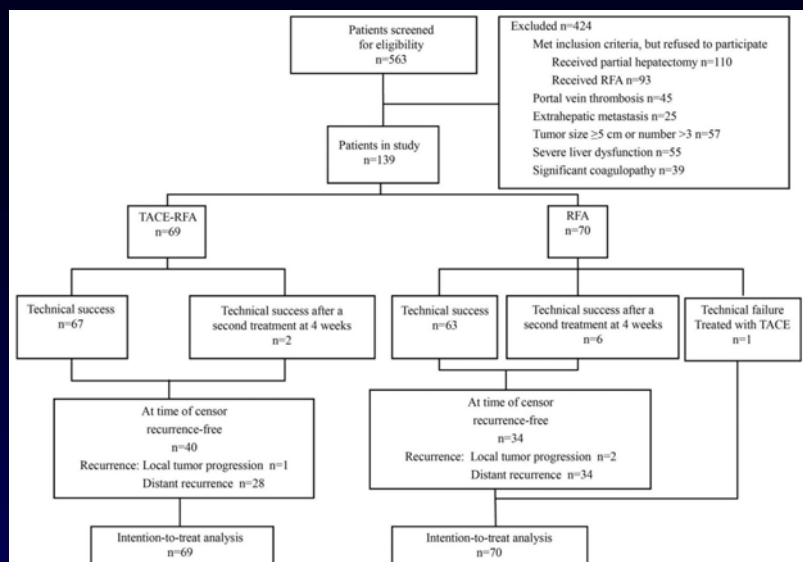
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Combination of arterially directed therapy and ablation is recommended when there are 1-3 tumors 3-5 cm





Radiology. 2012 Feb;262(2):689-700. doi: 10.1148/radiol.11110637. Epub 2011 Dec 12.

Recurrent hepatocellular carcinoma treated with sequential transcatheter arterial chemoembolization and RF ablation versus RF ablation alone: a prospective randomized trial.

Peng ZW¹, Zhang YJ, Liang HH, Lin XJ, Guo BP, Chen MS.

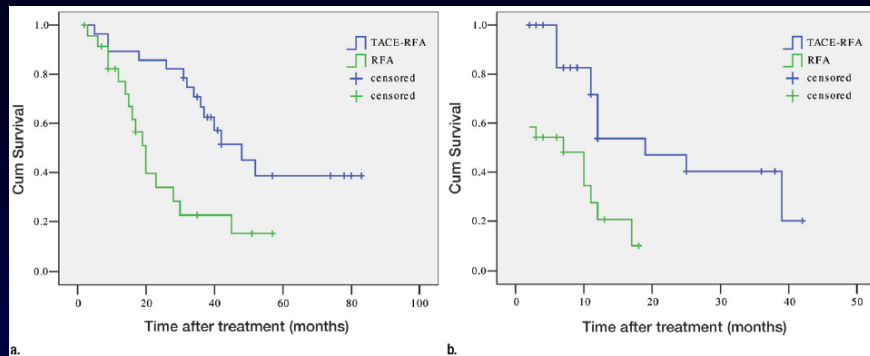
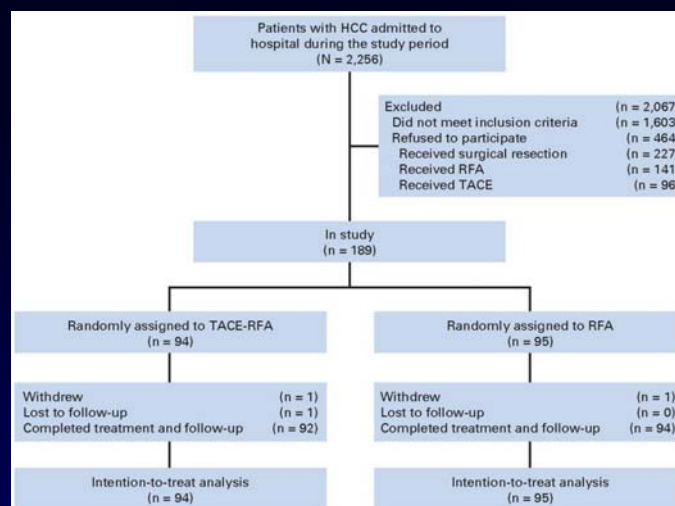


Figure 3: Cumulative (Cum) survival curves for subgroup analysis of patients with tumors measuring 3.1–5.0 cm. Curves show (a) overall and (b) recurrence-free survival for patients treated with sequential TACE-RF ablation and RF ablation alone.

Radiology. 2012 Feb;262(2):689-700. doi: 10.1148/radiol.11110637. Epub 2011 Dec 12.

Recurrent hepatocellular carcinoma treated with sequential transcatheter arterial chemoembolization and RF ablation versus RF ablation alone: a prospective randomized trial.

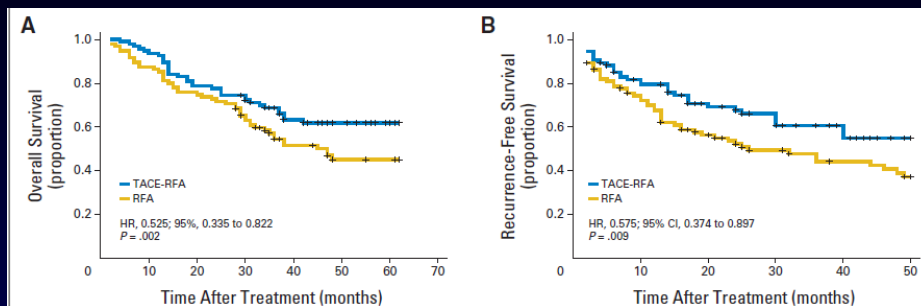
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J Clin Oncol. 2013 Feb 1;31(4):426-32. doi: 10.1200/JCO.2012.42.9936. Epub 2012 Dec 26.

Radiofrequency ablation with or without transcatheter arterial chemoembolization in the treatment of hepatocellular carcinoma: a prospective randomized trial.

Peng ZW¹, Zhang YJ, Chen MS, Xu L, Liang HH, Lin XJ, Guo RP, Zhang YQ, Lau WY.



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Radiofrequency ablation with or without transcatheter arterial chemoembolization in the treatment of hepatocellular carcinoma: a prospective randomized trial.

Peng ZW^a, Zhang YJ, Chen MS, Xu L, Liang HH, Lin XJ, Guo RP, Zhang YQ, Lau WY.

For unresectable tumors > 3 cm in patients with preserved liver function, treatment with arterially directed therapy is recommended.

The choice of which arterially directed therapy is based on local expertise.

Combination arterially directed therapy and ablation may be used to treat tumors 3-5 cm.

Phase II Trial of Sorafenib Combined With Concurrent Transarterial Chemoembolization With Drug-Eluting Beads for Hepatocellular Carcinoma

Timothy M. Pawlik, Diane K. Reyes, David Cogrove, Ihab R. Kamel, Nikhil Bhagat, and Jean-Francois H. Geschwind

Phase III study of sorafenib after transarterial chemoembolisation in Japanese and Korean patients with unresectable hepatocellular carcinoma ☆

Masatoshi Kudo ^{a,*}, Kazuho Imanaka ^b, Nobuyuki Chida ^c, Kohei Nakachi ^d, Won-Young Tak ^e, Tadatoshi Takayama ^f, Jung-Hwan Yoon ^g, Takeshi Hori ^h, Hiromitsu Kumada ⁱ, Norio Hayashi ^j, Shuichi Kaneko ^k, Hirohito Tsubouchi ^l, Dong Jin Suh ^m, Junji Furuse ⁿ, Takuji Okusaka ^o, Katsuaki Tanaka ^p, Osamu Matsui ^k, Michihiko Wada ^q, Iku Yamaguchi ^q, Toshio Ohya ^q, Gerold Meinhardt ^r, Kiwamu Okita ^q

Sorafenib or placebo plus TACE with doxorubicin-eluting beads for intermediate stage HCC: The SPACE trial

Riccardo Lencioni ^{1,2,*}, Josep M. Llovet ^{3,4,5,†}, Guohong Han ⁶, Won Young Tak ⁷, Jiamei Yang ⁸, Alfredo Guglielmi ⁹, Seung Woon Paik ¹⁰, Maria Reig ³, Do Young Kim ¹¹, Gar-Yang Chau ¹², Angelo Luca ¹³, Luis Ruiz del Arbol ¹⁴, Marie-Aude Leberre ¹⁵, Woody Niu ¹⁶, Kate Nicholson ¹⁷, Gerold Meinhardt ¹⁸, Jordi Bruix ^{3,†}

Adjuvant sorafenib for hepatocellular carcinoma after resection or ablation (STORM): a phase 3, randomised, double-blind, placebo-controlled trial

Jordi Bruix*, Tadatoshi Takayama, Vincenzo Mazzeferro, Gar-Yang Chau, Jiamei Yang, Masatoshi Kudo, Jianqiang Cai, Ronnie T Poon, Kwang-Hyub Han, Won Young Tak, Han Chu Lee, Tianqiang Song, Sasan Roayaie, Luigi Bolondi, Kwan Sik Lee, Masatoshi Makuuchi, Fabricio Souza, Marie-Aude Le Berre, Gerold Meinhardt, Josep M Llovet*, on behalf of the STORM investigators

Locoregional therapy for HCC

- Ablation alone may be curative for small HCC < 3 cm
- Arterially directed therapies are recommended for unresectable lesions > 3 cm
 - TAE/HAE, TACE, DEB, RAE
 - Specific treatment usually dictated by local expertise
- Combination arterially directed therapy and ablation is recommended for patients with 1-3 tumors 3-5 cm
- Sorafenib is reserved for residual/recurrent tumor not amenable to additional local therapy



PRINCIPLES OF LOCOREGIONAL THERAPY

All patients with HCC should be evaluated for potential curative therapies (resection, transplantation, and for small lesions, ablative strategies). Locoregional therapy should be considered in patients who are not candidates for surgical curative treatments, or as a part of a strategy to bridge patients for other curative therapies. These are broadly categorized into ablation and arterially directed therapies.

Ablation (radiofrequency, cryoablation, percutaneous alcohol injection, microwave):

- All tumors should be amenable to ablation such that the tumor and, in the case of thermal ablation, a margin of normal tissue is treated. A margin is not expected following percutaneous ethanol injection.
- Tumors should be in a location accessible for percutaneous/laparoscopic/open approaches for ablation.
- Caution should be exercised when ablating lesions near major vessels, major bile ducts, diaphragm, and other intra-abdominal organs.
- Ablation alone may be curative in treating tumors ≤ 3 cm. In well-selected patients with small properly located tumors, ablation should be considered as definitive treatment in the context of a multidisciplinary review. Lesions 3 to 5 cm may be treated to prolong survival using arterially directed therapies, or with combination of an arterially directed therapy and ablation as long as tumor location is accessible for ablation.
- Unresectable/inoperable lesions >5 cm should be considered for treatment using arterially directed or systemic therapy.
- Sorafenib should not be used as adjuvant therapy post-ablation.

HCC-C / 1 OF 3

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PRINCIPLES OF LOCOREGIONAL THERAPY

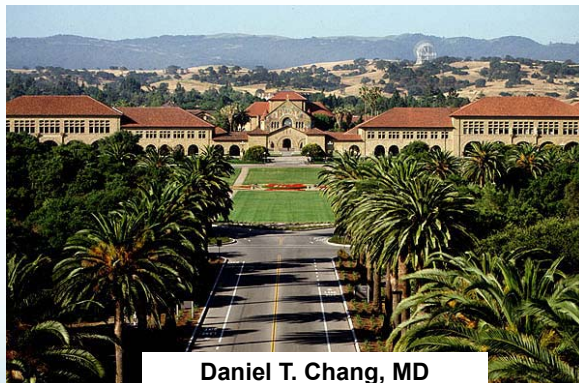
Arterially Directed Therapies:

- All tumors irrespective of location may be amenable to arterially directed therapies provided that the arterial blood supply to the tumor may be isolated without excessive non-target treatment.
- Arterially directed therapies include transarterial bland embolization (TAE), chemoembolization (transarterial chemoembolization [TACE]⁹ and TACE with drug-eluting beads [DEB-TACE]), and radioembolization (RE) with yttrium-90 microspheres.
- All arterially directed therapies are relatively contraindicated in patients with bilirubin >3 mg/dL unless segmental injections can be performed. RE with yttrium-90 microspheres has an increased risk of radiation-induced liver disease in patients with bilirubin over 2 mg/dL.
- Arterially directed therapies are relatively contraindicated in patients with main portal vein thrombosis and Child-Pugh Class C.
- The angiographic endpoint of embolization may be chosen by the treating physician.
- Sorafenib may be appropriate following arterially directed therapies in patients with adequate liver function once bilirubin returns to baseline if there is evidence of residual/recurrent tumor not amenable to additional local therapies. The safety and efficacy of the use of sorafenib concomitantly with arterially directed therapies has not been associated with significant benefit in two randomized trials; other randomized phase III trials are ongoing to further investigate combination approaches.

HCC-C / 1 OF 3

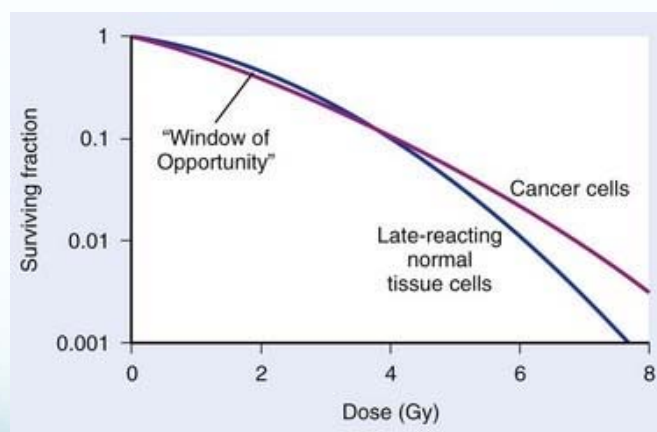
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Updates on Local-Regional Therapy for Hepatocellular Carcinoma: External Beam Radiation

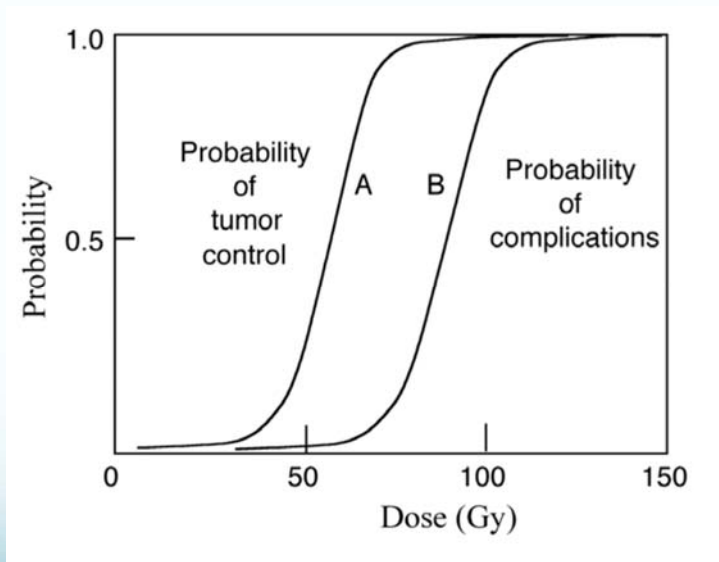


Daniel T. Chang, MD
Radiation Oncology
Associate Professor
Stanford University

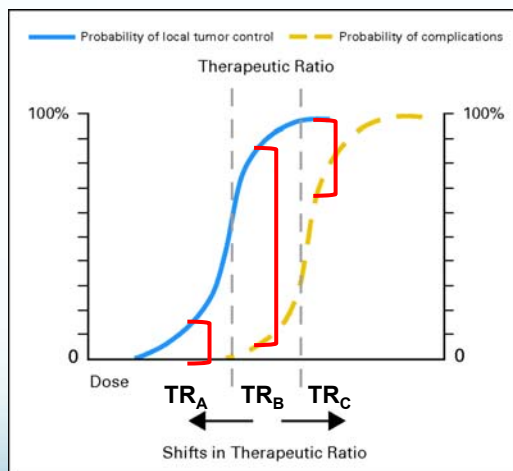
Basics of Radiobiology



Nag, S., et al. "High Dose Rate Brachytherapy", 2015.



Podgorsak, Review of Radiation Oncology Physics: A Handbook for Teachers and Students. IAEA 2005



Therapeutic Ratio

$$TR = \frac{\text{prob tumor control}}{\text{prob toxicity}}$$

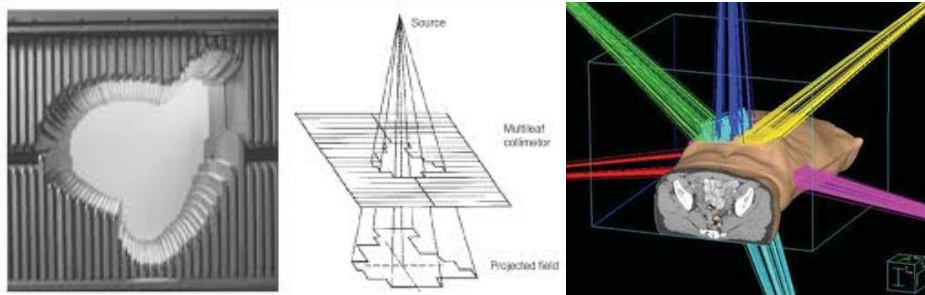
Optimize Ther Ratio

$$TR_B \gg TR_A \text{ and } TR_C$$

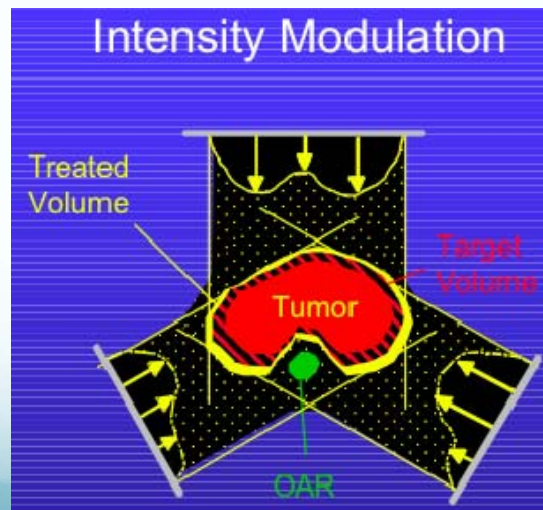
Brizel, D Pharmacologic Approaches to Radiation Protection JCO 2007

Terms and Definitions

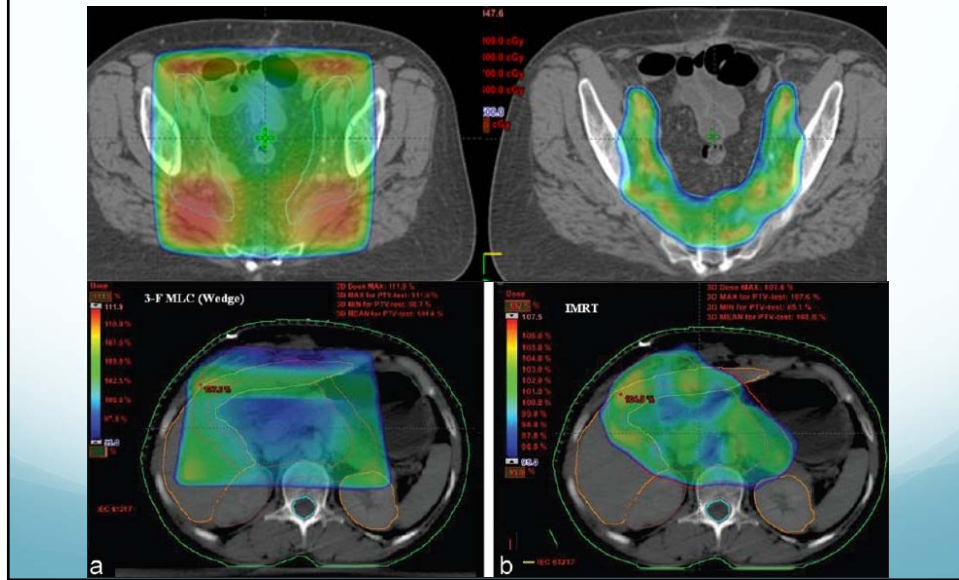
- EBRT – external beam radiotherapy
 - Radiation that comes from a machine into the patient
 - Photons or electrons, protons, heavy ions
- 3D CRT – 3D conformal RT
 - CT-based planning using uniform beams to treat a target



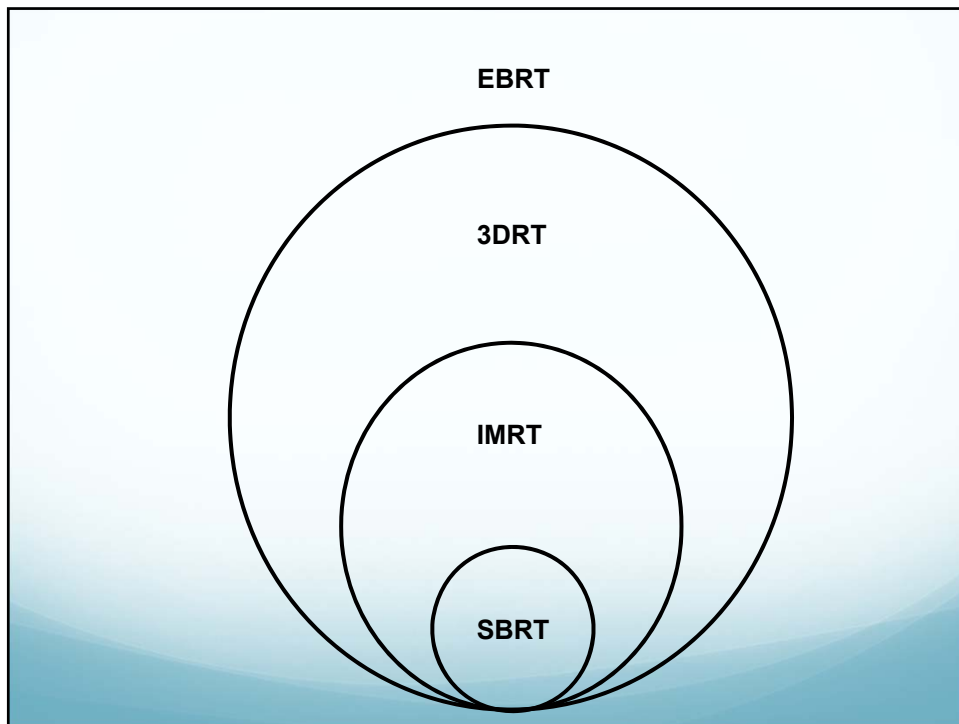
- IMRT – intensity modulated radiotherapy
 - Advanced conformal radiation using non-uniform beam intensities to shape the dose around critical structures



3D RT vs IMRT



- SBRT – stereotactic body radiotherapy
 - SABR – stereotactic ablative radiotherapy
 - High doses of radiation (8-25 Gy/day), usually with IMRT, delivered in ≤ 5 fractions
 - Ablative compared with conventional fractionation (2 Gy/day)
- IGRT – image guided radiotherapy
 - Any of the above using kV imaging to ensure target alignment



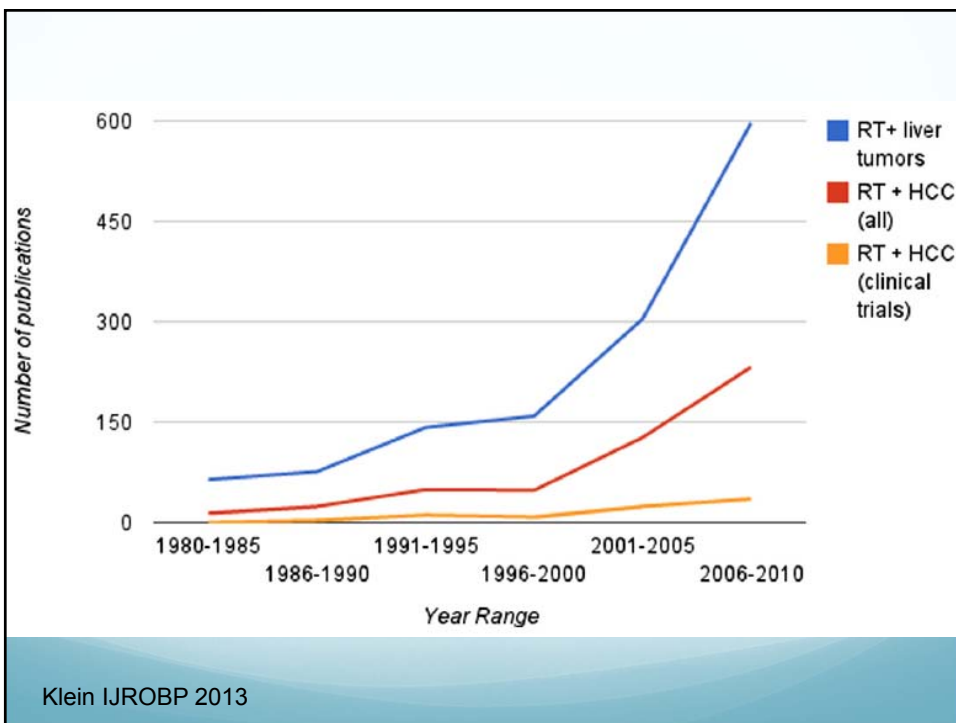
What's in a name?



Liver Radiotherapy

- Historically not used due to concerns of toxicity of liver radiation
 - 1965 paper from Stanford first described radiation hepatitis
- RT primarily reserved for palliation
- Development of 3-D radiation and recognition that partial liver volumes could tolerate higher doses of radiation (>30 Gy) lead to expanded use of liver radiotherapy

Ingold JA, Reed GB, Kaplan HS, et al: Radiation hepatitis. Am J Roentgenol Radium Ther Nucl Med 93:200-208, 1965
Reed GB Jr, Cox AJ Jr: The human liver after radiation injury. A form of veno-occlusive disease. Am J Pathol 48:597-611, 1966





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NCCN Guidelines Version 1.2016 Hepatocellular Carcinoma

CLINICAL PRESENTATION

Inoperable by performance
status or comorbidity,
local disease or local disease
with minimal extrahepatic
disease only

Metastatic
disease
or
Extensive
liver
tumor burden



Consider biopsy
to confirm
metastatic
disease

TREATMENT

Options:

- Locoregional therapy preferred
 - Ablation
 - Arterially directed therapies
 - EBRT (conformal or stereotactic) (category 2B)
- Sorafenib (Child-Pugh Class A [category 1] or B)
- Clinical trial
- Best supportive care

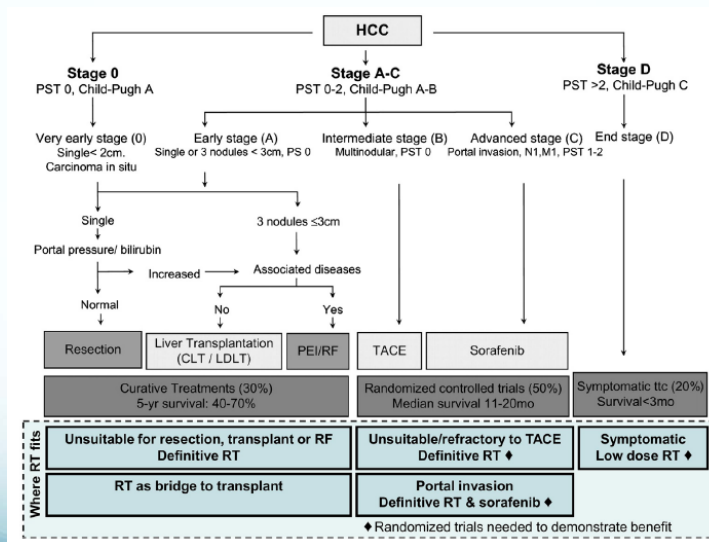
Options:

- Sorafenib (Child-Pugh Class A [category 1] or B)
- Clinical trial
- Best supportive care

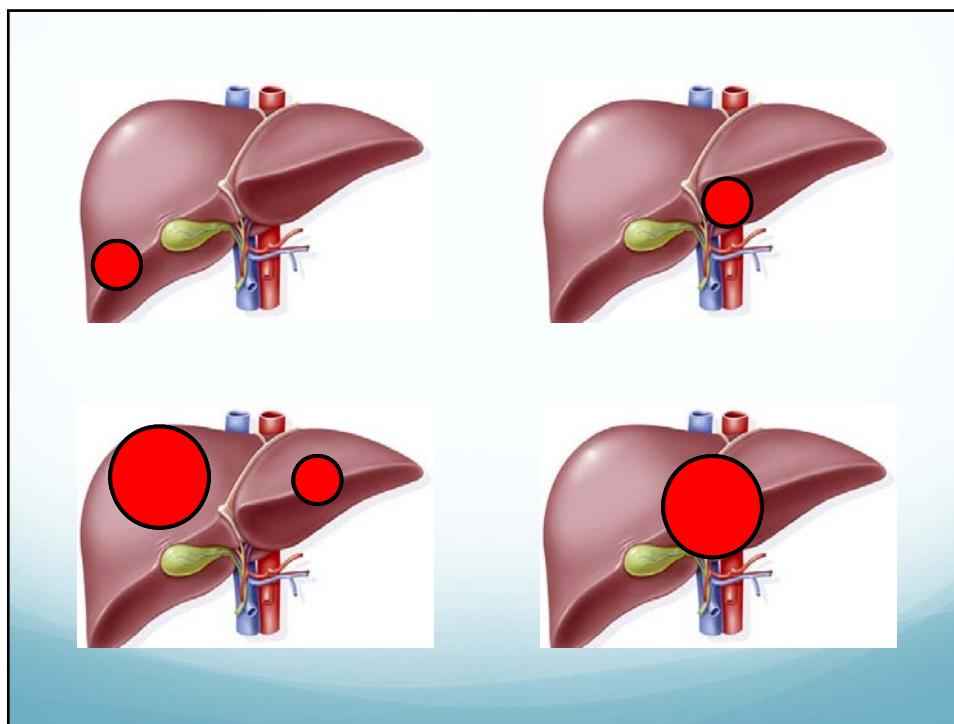
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Where does RT fit?



Klein IJROBP 2013

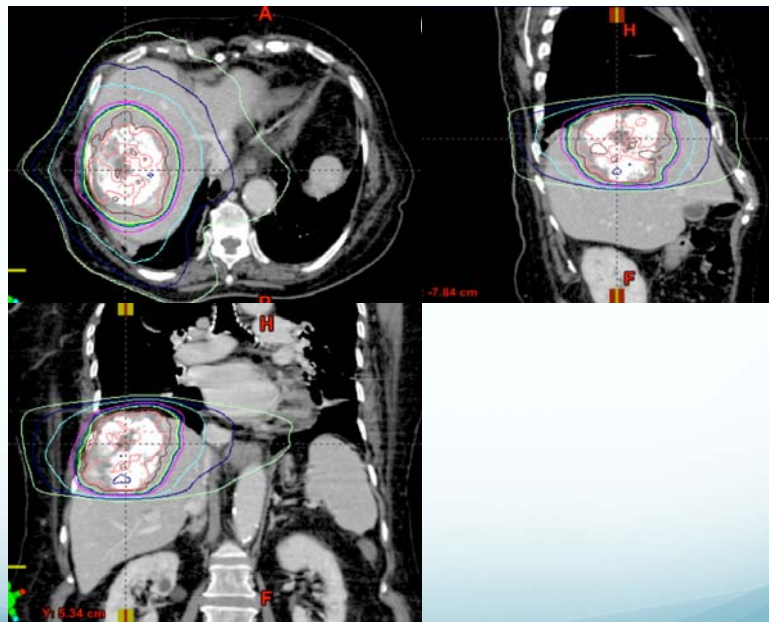


Take home points about radiation

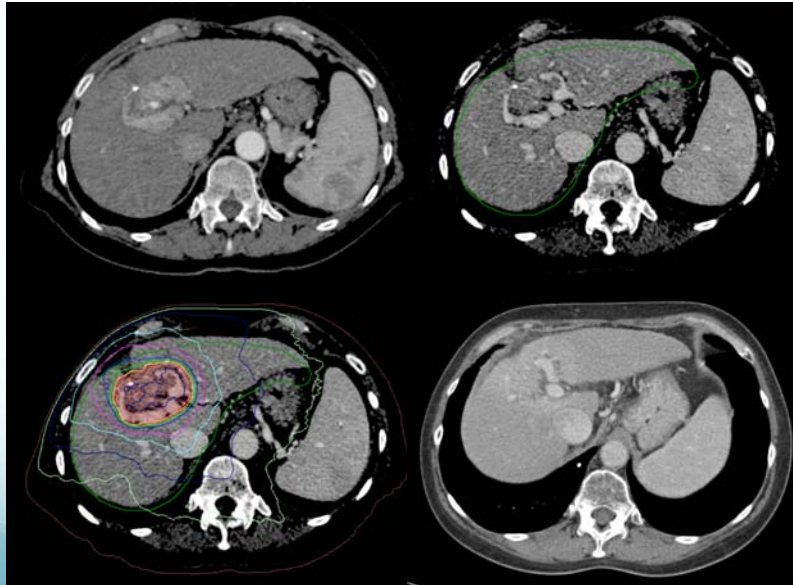
- Radiation is non-invasive
- No such thing as “too big,” though smaller is easier than bigger
- Can treat multiple tumors
- Dose can be adjusted based on size and location of critical structures
- Tumor thrombus is not a contraindication for treatment
- Caution about combining radiation with radioembolization

Combination of EBRT and Transarterial Chemoembolization (TACE)

- TACE with EBRT for salvage
- TACE combined with EBRT to treat the whole tumor
- TACE combined with EBRT to treat portal vein tumor thrombus

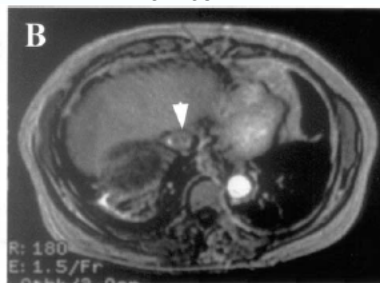
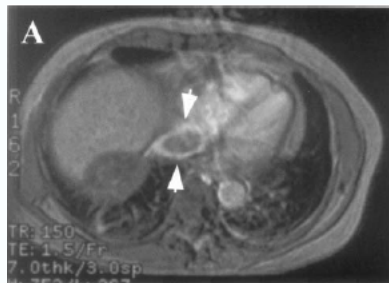


PVTT



Baseline

3 mos



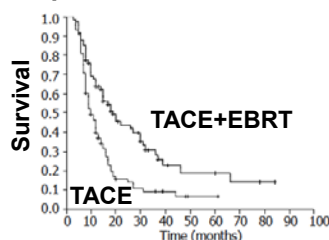
12 mos



Comparison between chemoembolization combined with radiotherapy and chemoembolization alone for large hepatocellular carcinoma

Guo World J Gastroenterol 2003

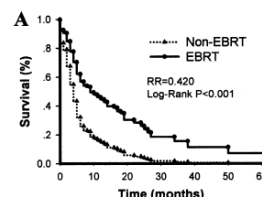
- HCC ≥ 5 cm, 22% with PVTT
- 76 pts – EBRT and TACE
- 89 pts – TACE alone
- ORR – 47% vs 28%, $p < 0.05$



A comparison of treatment combinations with and without radiotherapy for hepatocellular carcinoma with portal vein and/or inferior vena cava tumor thrombus

Zeng IJROBP 2005

- PVTT or IVC thrombus
- 44 pts – EBRT and TACE
- 73 pts – TACE alone
- 18 pts – Surgery alone
- 23 pts – No therapy
- 34% CR of PVTT or IVCT with EBRT



Studies using EBRT

Series	Pts	CP Class A (%)	Tumor Size (Diameter or Volume)	PVT (%)	Total Dose, Dose per Fraction	1-Year LC (%)	1-Year OS (%)
Ben-Josef et al ¹⁶	35	100	0.15-1,100 mL	0	40-90 Gy in 1.5 Gy twice daily	81	57
Mormex et al ¹⁸	27	59	1-5 cm	NA	36-66 Gy in 2-Gy fx	78	NA
Liu et al ²²	44	86	<5 cm in 36, 5-10 cm in 36, >10 cm in 27	32	40-60 Gy	61	61
Liang, et al ²¹	128	84		29	38-68 Gy in mostly 4- to 6-Gy fx	69 at 3 mo	65
Kim et al ⁴⁰	70	88	Median 7.5 cm (2-17 cm)	59	44-54 Gy in 2- to 3-Gy fx	54 CR+PR	43
Oh et al ⁵⁰	40	90	1.5-23 cm	10		63 CR+PR	72
Seong et al ²⁰	398	77	1-23.8 cm	27	25-60 Gy in mostly 1.8- to 5-Gy fx	NA	45
Seo et al ³⁰	65	66	Median 9.9 cm	69	61 Gy in 1.8-Gy fx in 85% of patients	Median TTP 4 mo	35

Studies using EBRT with TACE

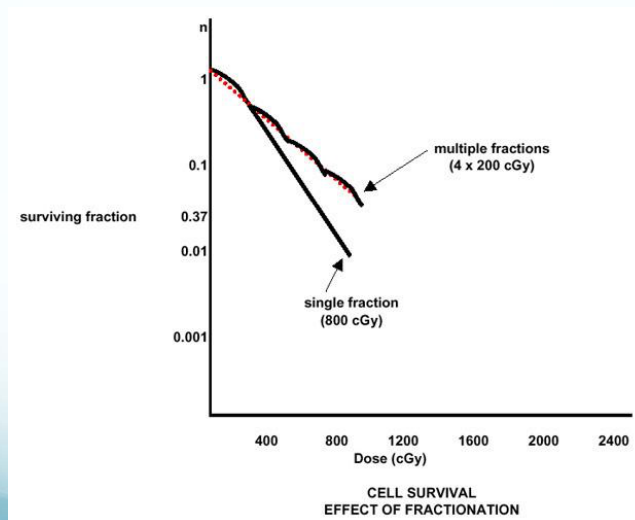
Study	Mean Tumor Size (range)	PVT (%)	No. of Patients	Treatment	Response			Median Survival (months)
					CR (%)	PR (%)	SD (%)	
Li et al ²⁰	8.5 cm (4-13)	15 (33)	45	TACE + 50.4 Gy	6 (13)	35 (78)	4 (9)	23
Zeng et al ¹⁹		0 (0)	54	TACE + 36-60 Gy	3 (6)	38 (70)	13 (24)	20
Seong et al ¹⁸	9.0 cm (6-12)	80 (51)	158	TACE + 48.2 \pm 7.9 Gy	1 (1)	105 (67)	41 (26)	10
Guo et al ²¹	10.2 cm (5-18)	23 (21)	107	TACE + 25-55 Gy	6 (6)	46 (43)	42 (39)	18

Feng and Ben-Josef Sem Radiat Oncol 2011

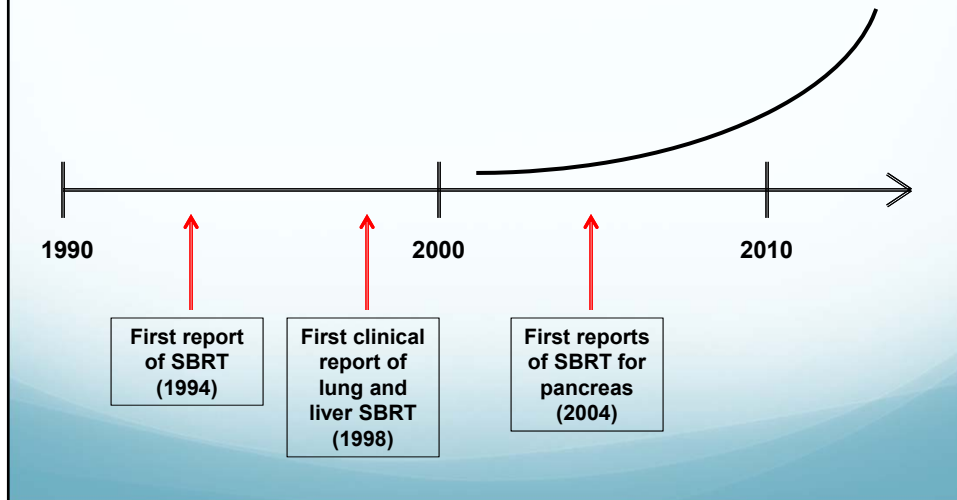
Potential Advantages of SABR/SBRT

- Improvement in local control
- Shorter course of treatment
 - Allows integration with more intensive systemic chemotherapy
 - Patient convenience
- Cost effective
- QOL

Model for Radiation Cell Killing



Stereotactic Body Radiotherapy (SBRT) Stereotactic Ablative Radiotherapy (SABR)



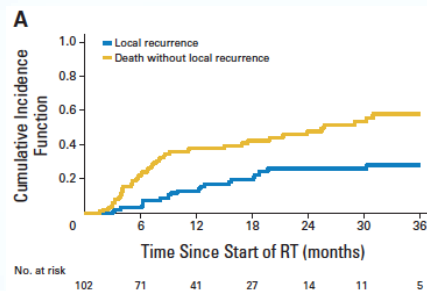
HCC SBRT Reports

	Patients	Lesions	SBRT	PTV	% Childs A/B	Local Control
Ibarra (2012)	32 21-HCC 11 - IHC	43	30-37.5 Gy/3 22 Gy/1 47 Gy/10	GTV + 3-5mm or 7-10(sup-inf)	CS 6-8	83% - 6 months 64% - 12 months
Andolino (2011)	60	71	30-48 Gy/3 – CPA 40 Gy/5 - CPB	GTV + 5axial, 10sup-inf	60/40	90% - 2 years
PMH	41	31 HCC 10 IHC	Variable, NTCP-based Median 6 Gy x 6	GTV+8mm+margin PTVprimary = GTV+5+mm	100/0	65% - 12 months
Choi (2008)	31	32	30-39 Gy/3	GTV + 5 mm	84/16	90% - crude
Seo (2010)	38	47	30-57 Gy/3	ITV + 2 mm axial, 4 mm sup-inf	89/8	78% - 12 months 66% - 2 years
Japan (Takeda)	16	16	20-50 Gy in 5-8 fractions	ITV + 5-10 mm	88/12	94% - crude

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

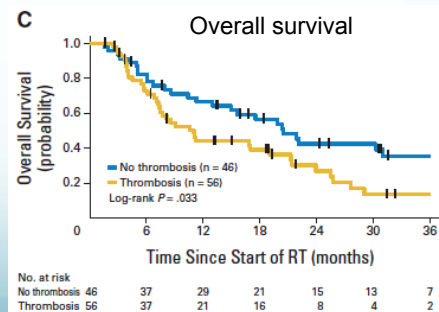
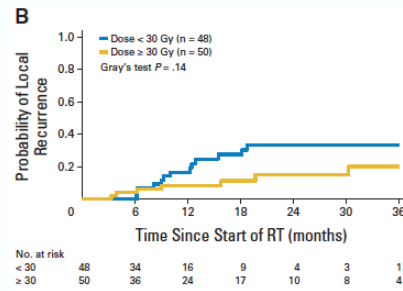
- 102 patients from 2 prospective trials
- All with Child Pugh A
- 38% with HBV, 38% with HCV, 25% with EtOH
- Median GTV 117 cc
- 54% with vascular tumor thrombus
- Dose – 36 Gy (24-54) in 6 fractions

Bujold JCO 2013



1-year Local control 87%

Tumor volume not significant for LC



Bujold JCO 2013

Outcomes After Stereotactic Body Radiotherapy or Radiofrequency Ablation for Hepatocellular Carcinoma

Daniel R. Wahl, Matthew H. Stenmark, Yebin Tao, Erqi L. Pollom, Elaine M. Caoili, Theodore S. Lawrence, Matthew J. Schipper, and Mary Feng

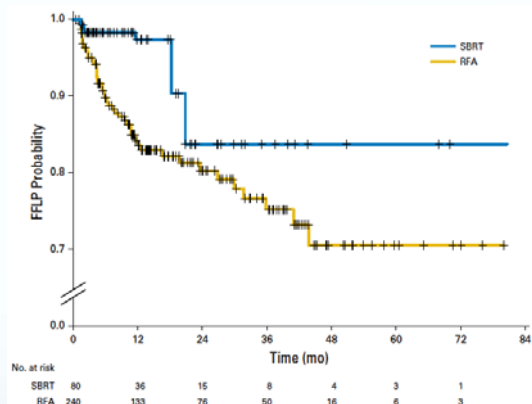
- 224 patients with inoperable HCC treated with:
 - RFA – 161 patients 249 tumors
 - SBRT – 63 patients 83 tumors
- SBRT dose range 27-60 Gy
 - 3 fractions – median 30 Gy
 - 5 fractions – median 50 Gy
- Freedom from local progression
 - Absence of disease progression within or at PTV margin or ablation zone
 - Tumors requiring multiple RFAs for residual disease not counted as failure until after all tumor successfully treated

Wahl JCO 2015

Freedom from local progression

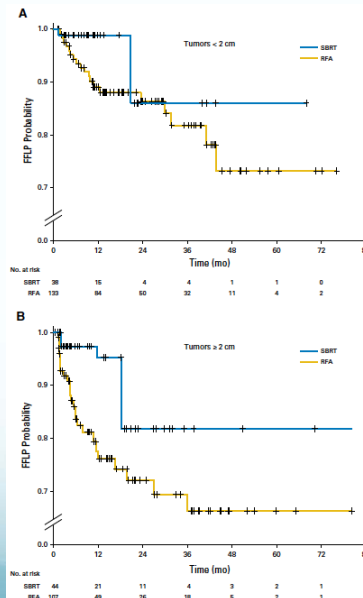
1-year FFLP
RFA – 84%
SBRT – 97%

2-year FFLP
RFA – 80%
SBRT – 84%

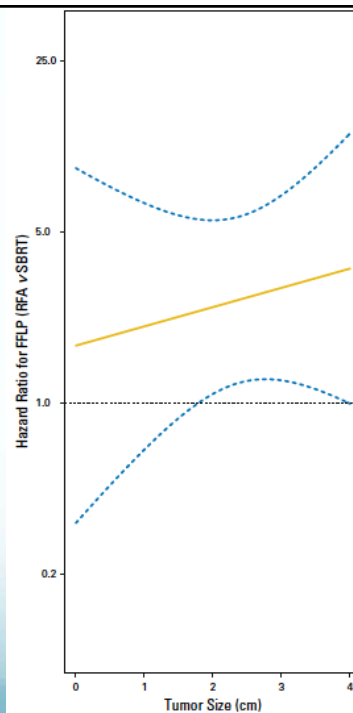


Wahl JCO 2015

FFLP by size



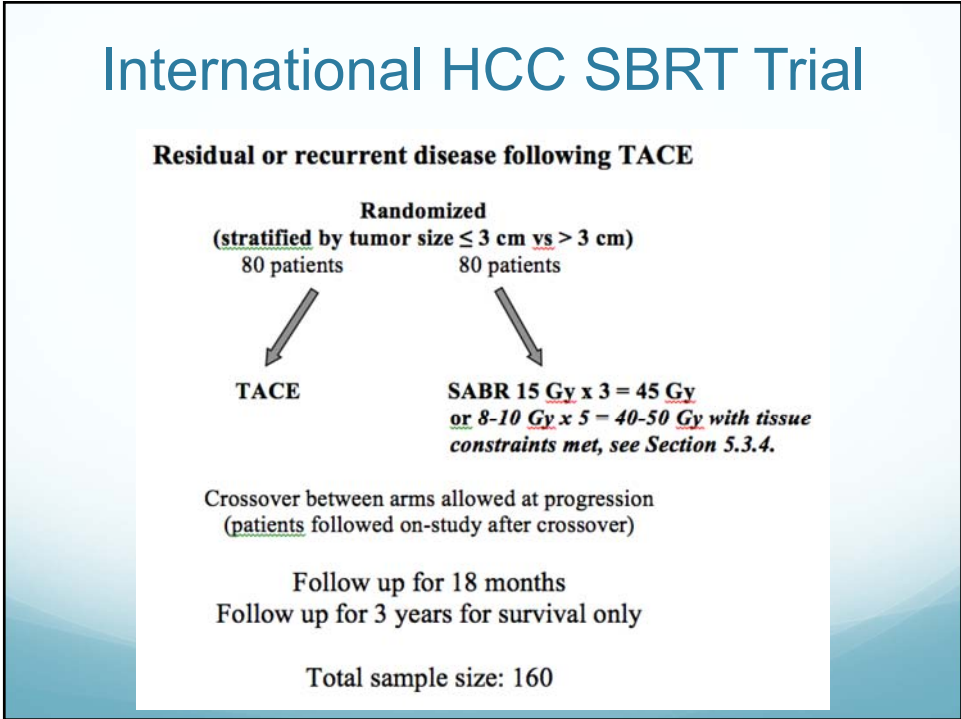
Wahl JCO 2015



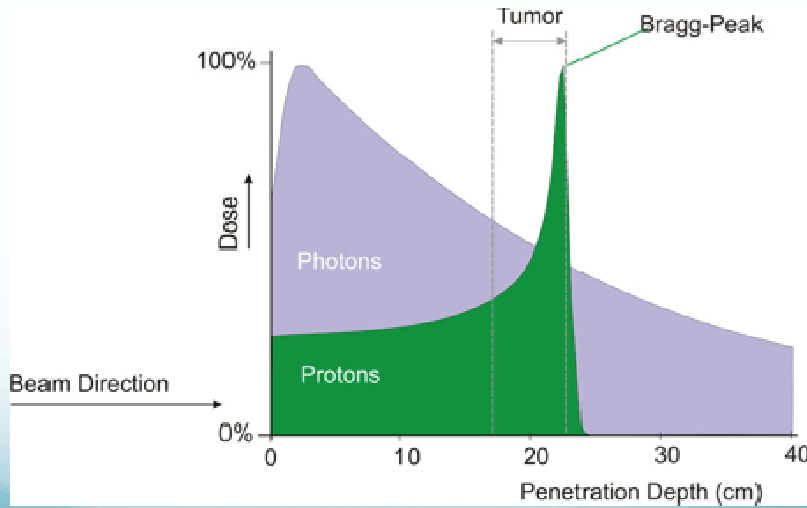
Wahl JCO 2015

RADIATION THERAPY ONCOLOGY GROUP			
RTOG 1112			
Randomized Phase III Study of Sorafenib versus Stereotactic Body Radiation Therapy followed by Sorafenib in Hepatocellular Carcinoma			
SCHEMA			
R E G I S T R A T I O N	S T R A T I F Y	R A N D O M I Z E	<u>Arm 1</u> Daily sorafenib
			<u>Arm 2</u> SBRT alone (27.5 Gy – 50 Gy in 5 fractions) Followed by Sorafenib alone daily
	Vascular involvement (IVC, main portal vein/right or left main branch portal vein vs. other vascular involvement vs. none)		
	Hepatitis B vs. C vs. other		
	North American site vs. Non-North American site		
	HCC volume/liver volume (<10% vs. 10-40 vs. >40%)		

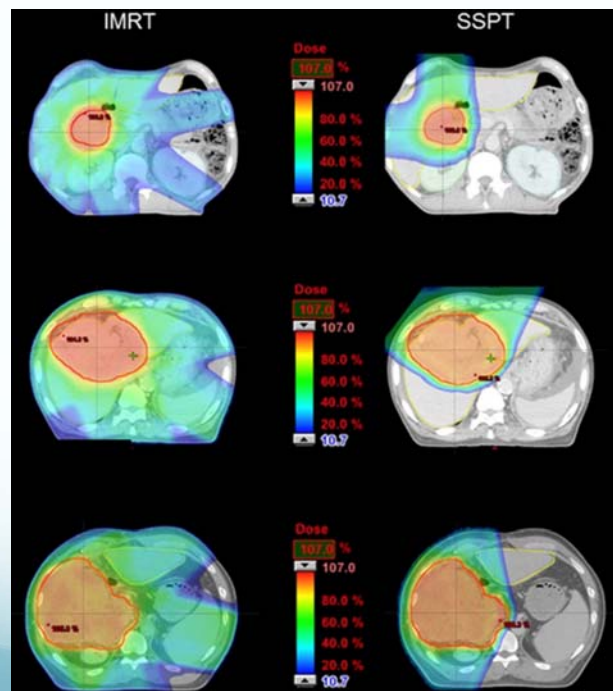
<https://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?action=openFile&FileID=13150>



Proton vs photon



Clinics. Proton Therapy Solutions. Available at: <http://bit.ly/1Ppotod>.



Charged Particle Therapy

Author, year	Particle	Dose (GyE)	No. fractions	Survival (1 y)	Survival (5 y)	Toxicity grade ≥ 3
Bush, 2011	P	63	15	18.4 mo (med)	NA	0%
Komatsu, 2011	P	52-84	4-38	90%*	38%	3%
	C	52.8-76	4-20	87%*	37%	4%
Mizumoto, 2011	P	66-77	10-35	87%	NA	3%
Nakayama, 2011	P	72.6-77	22-35	70%	NA	2%
Sugahara, 2010	P	47.3-89	10-35	64%	NA	0%
Imada, 2010	C	52.8	4	NA	56% (3 y)	39% (all grade 3)
Nakayama, 2009	P	55-77	10-35	90%	NA	2%
Fukumitsu, 2009	P	66	10	90%*	39%	2%
Sugahara, 2009	P	55-77	10-35	45% (2 y)	NA	8%
Mizumoto, 2008	P	72.6	22	57% (2 y)	NA	0%
Hata, 2007	P	60-70	10-35	84%	NA	10%
Hata, 2006	P	63-84	13-27	62% (2 y)	NA	0%
Hata, 2006	P	50-84	10-24	53%	NA	0%
Kawashima, 2005	P	76	20	78%*	62% (3 y)	40% (mostly biochemical [†])
Hata, 2005	P	50-72	10-22	88% (2 yr)	NA	0%
Chiba, 2005	P	50-88	10-24	75%	NA	3.1% (grade ≥ 2)
Kato, 2004	C	49.5-79.5	15	37 mo (med)	NA	26% (1 skin, 10 hematologic)

Klein and Dawson IJROBP 2013

Toxicities

- Classic radiation induced liver disease (RILD)
 - Typically occurs 6 weeks (4-12 weeks) after radiation
 - Clinical – anicteric ascites, hepatomegaly, and 2 X increase in alk phos
 - Pathologic – veno-occlusive disease due to fibrin and collagen deposition within sinusoidal vessels and central veins → vascular congestion → hypoxia/death of centrilobular hepatocytes → hepatic atrophy and dysfunction

Nonclassic RILD

- Non-classic RILD - ≥ 5 X increase in transaminases – suggesting direct damage to hepatocytes
 - 10/12 patients in Taiwan series had non-classic RILD
 - All patients were carriers of HCV or HBV

Cheng Radiat Oncol 2002

Liver Tolerance

- Child Pugh A cirrhosis appear to have good tolerance to radiation
- Child Pugh B cirrhosis appear to have reduced tolerance to radiation
 - Reduced dose and strict adherence to dose constraints required
- Child Pugh C cirrhosis – little to no data on liver tolerance
 - In general RT should be avoided

Worse tolerance of Child B than Child A

Phase I feasibility trial of stereotactic body radiation therapy for primary hepatocellular carcinoma

- Showed that Child A livers could be safely treated up to 48 Gy at 16 Gy/fraction
- 2/6 patients with Child B developed dose limiting toxicity
- Dose de-escalated to 40 Gy at 8 Gy/fraction

Cardenes et al, Clin Tranl Oncol 2010

Treatment variables related to liver toxicity in patients with hepatocellular carcinoma, Child-Pugh class A and B enrolled in a phase 1-2 trial of stereotactic body radiation therapy

No association of liver dosimetry with toxicity in Child A patients

Higher liver dosimetry seen in patients with toxicity in Child B patients

Table 3 Dosimetry data by hepatic toxicity in Child-Pugh class B patients

Maximal dose to normal volume in CPC-B patients	Normal volume receiving dose without hepatic toxicity	Normal volume receiving dose with grade III/IV hepatic toxicity	P value
<15 Gy	1053.1 mL	1515.9 mL	.0396
<12.5 Gy	946.1 mL	1432.0 mL	.0254
<10 Gy	797.8 mL	1293.0 mL	.0132
<7.5 Gy	625.9 mL	1149.7 mL	.0041
<5 Gy	480.8 mL	1024.1 mL	.0015
<2.5 Gy	304.9 mL	810.8 mL	.0011

CPC-B, Child-Pugh class B.

Lasley PRO 2015

Caution: *HBV reactivation*

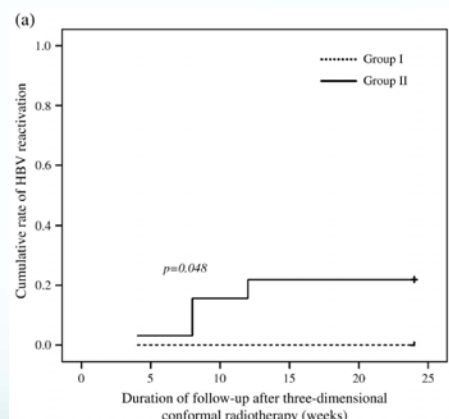
- Reported after conventional RT for HCC

- Consider in differential diagnosis of radiation-induced liver disease in high risk pt

- Antiviral therapy likely reduces risk

- Figure at right:

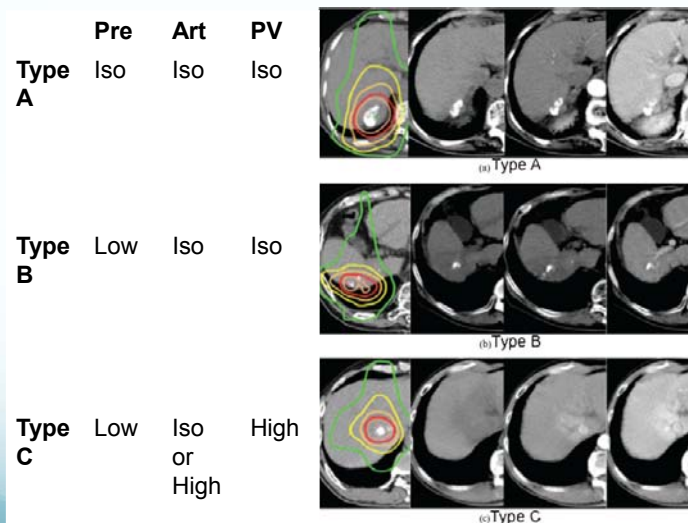
- Group I antiviral therapy
 - Group II none



Kim et al. IJROBP 69(3): 813–819, 2007
Center for Liver Cancer, South Korea

Courtesy of B. Kavanagh

Don't confuse post-radiation change with recurrence



Sanuki-Fujimoto Br J Rad 2010



PRINCIPLES OF LOCOREGIONAL THERAPY

External-beam Radiation Therapy (EBRT)

- All tumors irrespective of the location may be amenable to EBRT (stereotactic body radiation therapy [SBRT], intensity-modulated radiation therapy [IMRT], or 3D-conformal radiation therapy).
- SBRT is an advanced technique of EBRT that delivers large ablative doses of radiation.
- There is growing evidence for the usefulness of SBRT in the management of patients with HCC. SBRT can be considered as an alternative to the ablation/embolization techniques mentioned above or when these therapies have failed or are contraindicated.
- SBRT is often used for patients with 1 to 3 tumors. SBRT could be considered for larger lesions or more extensive disease, if there is sufficient uninvolved liver and liver radiation tolerance can be respected. There should be no extrahepatic disease or it should be minimal and addressed in a comprehensive management plan. The majority of data on radiation for HCC liver tumors arises from patients with Child-Pugh A liver disease; safety data are limited for patients with Child-Pugh B or poorer liver function. Those with Child-Pugh B cirrhosis can be safely treated, but they may require dose modifications and strict dose constraint adherence. The safety of liver radiation for HCC in patients with Child-Pugh C cirrhosis has not been established, as there are not likely to be clinical trials available for Child-Pugh C patients.
- Proton beam therapy (PBT) may be appropriate in specific situations.
- Palliative EBRT is appropriate for symptom control and/or prevention of complications from metastatic HCC lesions, such as bone or brain.

HCC-C / 2 OF 3

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Conclusions

- EBRT is an important and effective treatment option for HCC
- Improvements in technology have allowed safe delivery of ablative doses of radiation with excellent control rates
- Further studies and ideally randomized trials with other liver-directed therapies are needed in the overall treatment algorithm for HCC
- Need better understanding of liver tolerance to optimize dose fractionation

