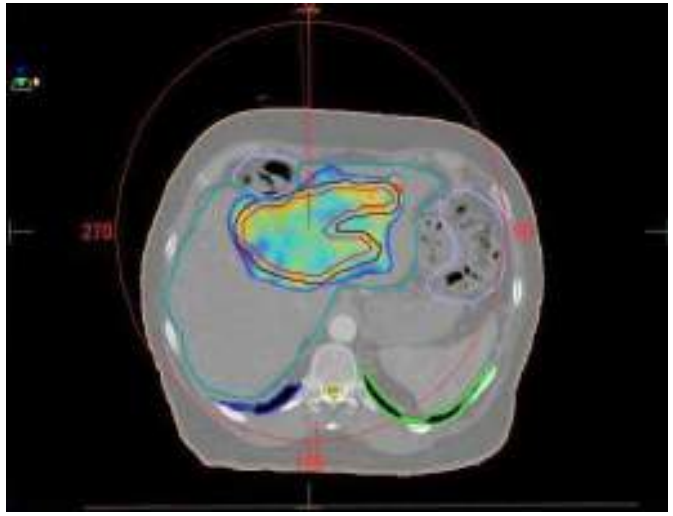
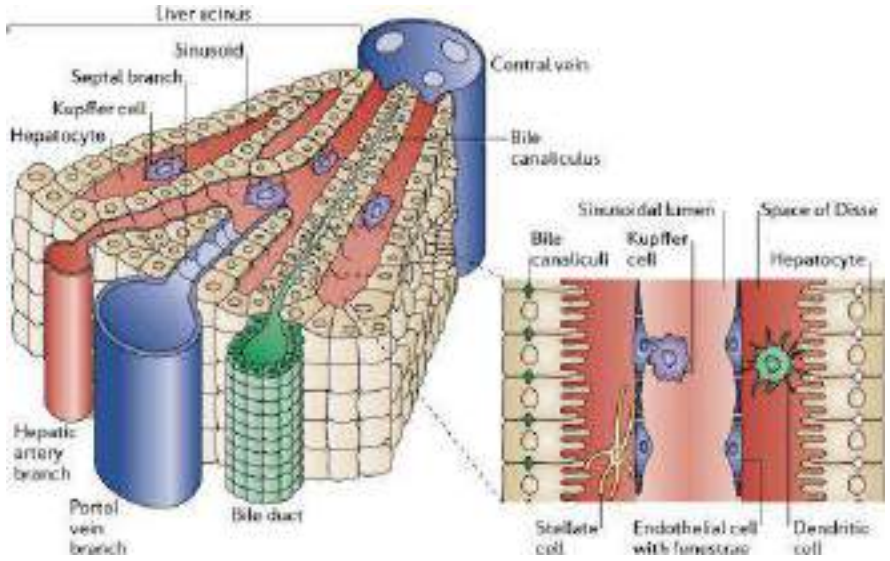
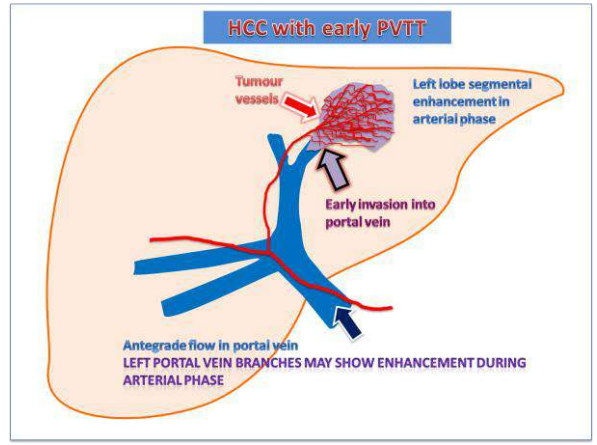


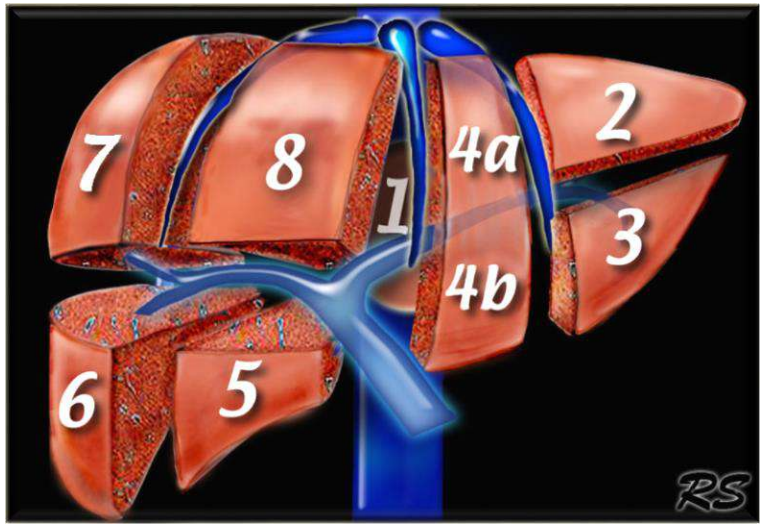
Emerging role of precision Radiotherapy SBRT in liver tumors

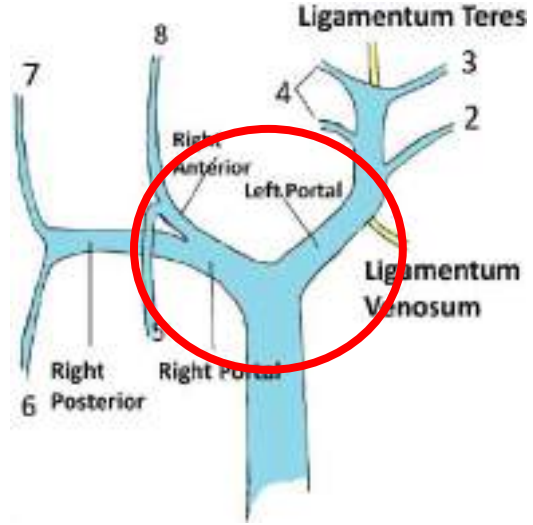
Dr Ashu Abhishek
Additional Director & Unit head
Fortis Memorial Research Institute, Gurgaon

Liver : Anatomy









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HCC: Treatment principle

HCC: 3rd M/c cancer

Surgery

Transplant

Popcorn effect: background of Cirrhosis

Gold standard
5 yr OS – 70%

MELD / Milan criteria

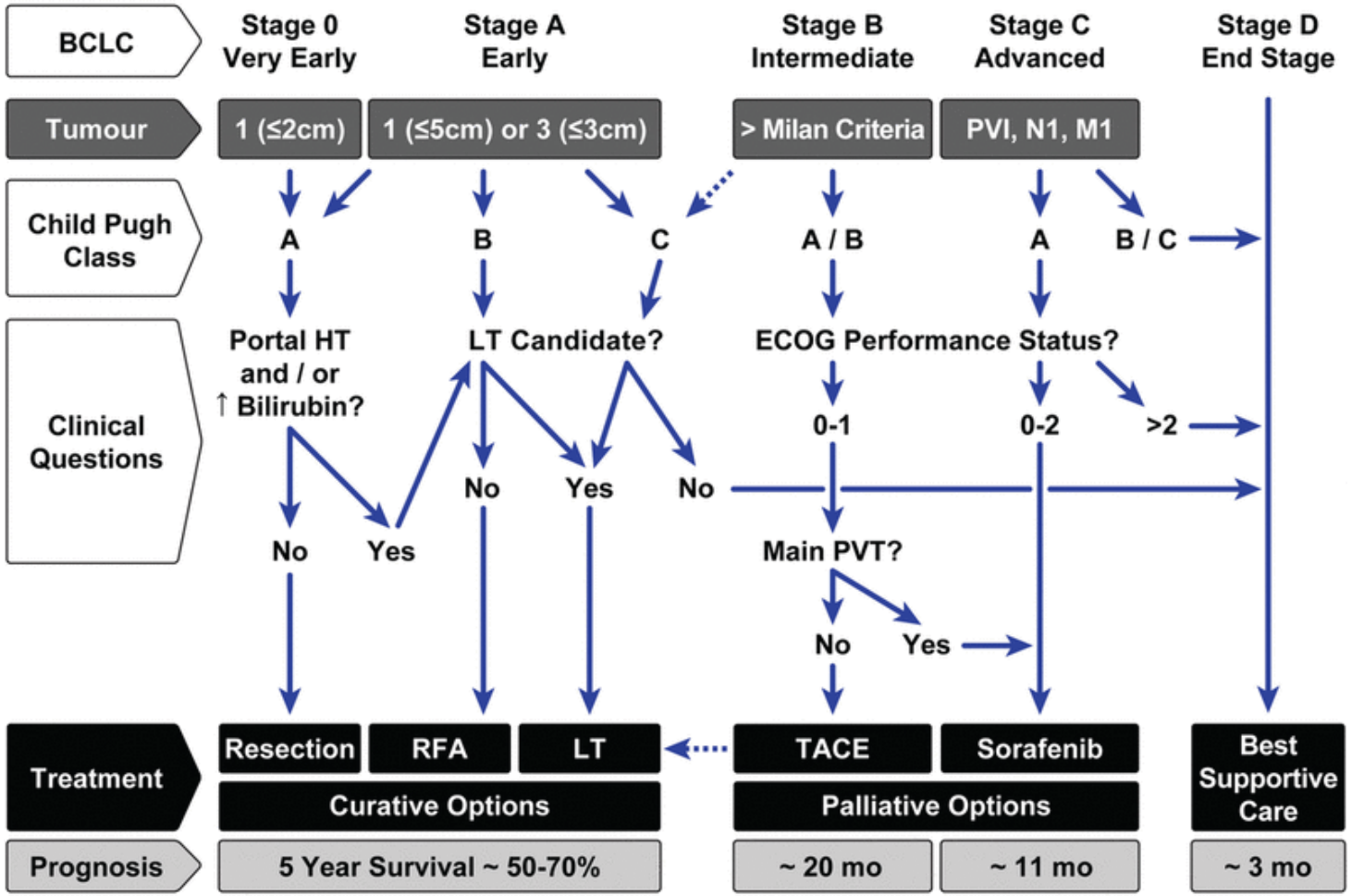
Only 20% fit for surgery

HCC: Treatment

- HCC: 3rd M/c cancer
- **Surgery**
- Resection: 85% recurrence
- **Limited availability of donor organs→ up to 20-40 % dropouts**
  - → Need for alternative non surgical management
  - → advanced HCC → progressive disease while on a waitlist
- Solution: local therapy as "bridge" → until a donor organ is available
- Traditionally : RFA and TACE → neoadjuvant/ downstaging
- However- RFA usable < 40% of cases –not for >5 cm/ close to vessels
- TACE better, although → only results in a 65% LC @ 1 yr

Operable	In-operable
Liver Transplant Gold standard 5 yr OS – 70% MELD / Milan criteria Only 20% fit for surgery	Radiofrequency Ablation
	Percutaneous Ethanol Ablation
	Transarterial Chemoembolization
Resection/ Partial Hepatectomy	Cryo-ablation
	Systemic Chemotherapy
	Radio-embolization
	Radiation Therapy

BCLC staging: Treatment decision



AASLD:

- In cirrhotics - Locoregional treatment better than no treatment
- No specific locoregional Rx preferred
- CP A or B < 3 cm / HCCs < 2 cm / BCLC 0 / A - Ablation may be 1st line
- TACE – 1st line for unresectable / large/multifocal no PVTT or extra hepatic disease (BCLC B)
- SIRT – alternative for unresectable HCC – safe / may not have OS benefit
- subgroup of patients benefitting from SIRT remains to be defined.

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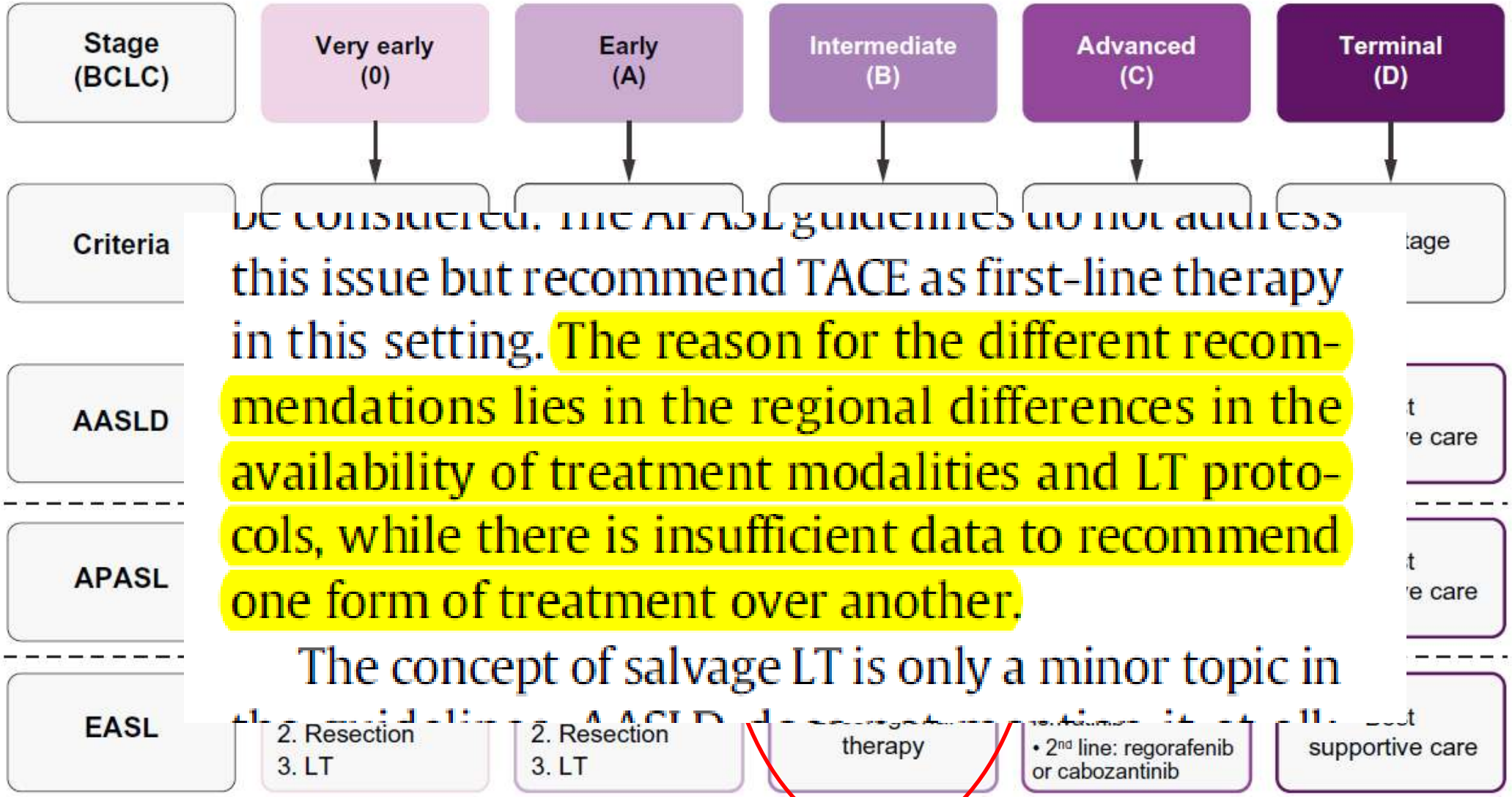
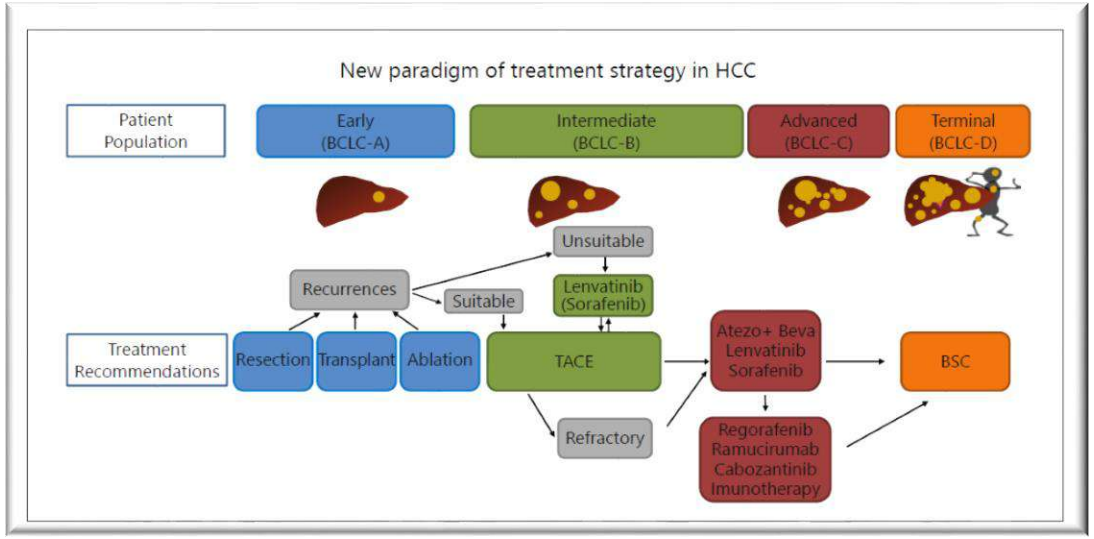


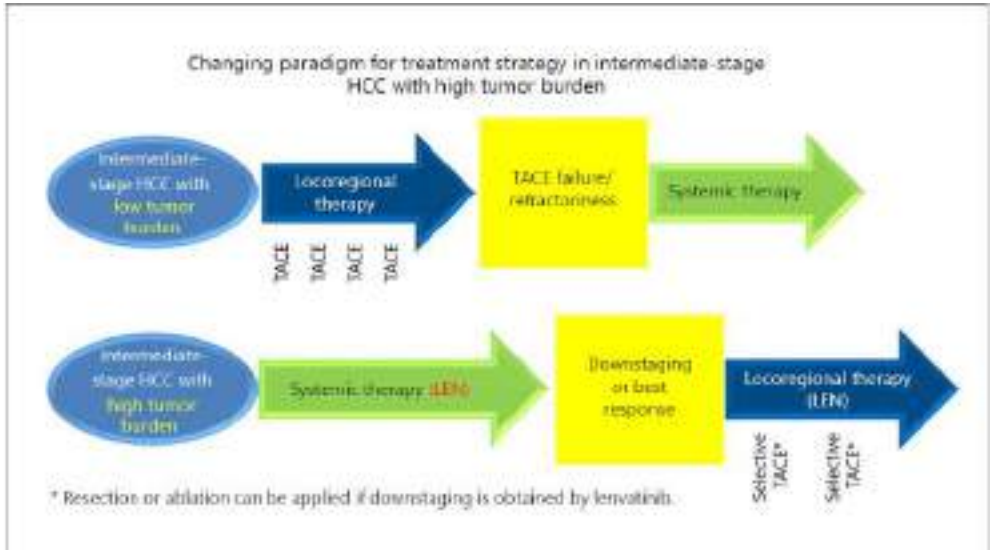
be considered. The APASL guidelines do not address this issue but recommend TACE as first-line therapy in this setting. The reason for the different recommendations lies in the regional differences in the availability of treatment modalities and LT protocols, while there is insufficient data to recommend one form of treatment over another.

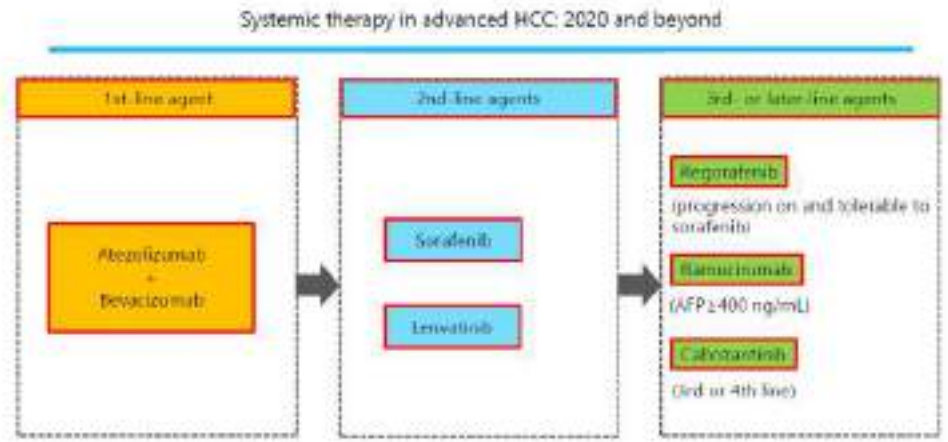
The concept of salvage LT is only a minor topic in the guidelines. AASLD does not mention it at all, best

Fig. 1. Summary of stage-dependent recommendations on the treatment of HCC by the international guidelines. AASLD, American Association for the Study of Liver Diseases; APASL, Asian Pacific Association for the Study of the Liver; BCLC, Barcelona Clinic Liver Cancer; BSC, best supportive care; CPA & B, Child-Pugh class A and B; EASL, European Association for the Study of the Liver; LRT, locoregional therapy; LT, liver transplantation; SIRT, selective internal radiation therapy; TACE, transarterial chemoembolisation.

HCC - proposed modern management – systemic approach







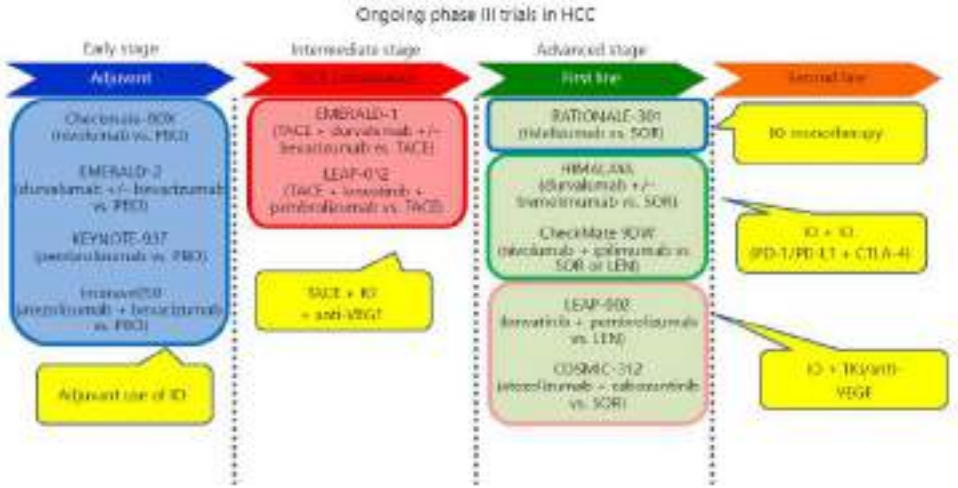


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Table 3. Differences in recommendations between the international HCC guidelines.

	AASLD	APASL	EASL
Surveillance	US every 6 months, AFP optional	US + AFP every 6 months	US every 6 months
CEUS	Not recommended	As sensitive as CT/MRI	Suitable for nodules ≥1 cm in cirrhosis
Biopsy	No routine use	For indeterminate nodules ≥1 cm	Required in non-cirrhotic HCC
Bridging	Recommended for T2	No recommendation	Recommended if feasible
LT after downstaging	Recommended	No recommendation	Possible
LRT	- Recommended in cirrhotic non-surgical patients (T2 or T3, no vascular involvement) - No preference regarding modality	- Ablation: For HCCs ≤2 cm in CP-A/B - TACE: For unresectable, large/multifocal HCCs - SIRT: Alternative to TACE	- Ablation: or unresectable BCLC 0 and A + selected surgical patients - TACE: For BCLC B - SIRT: Good safety profile, efficacy not yet proven
Radiotherapy	No recommendation	Option when other LRTs have failed	Insufficient evidence
Systemic therapy	- For patients with CP-A cirrhosis or well-selected patients with CP-B cirrhosis plus advanced HCC with macrovascular invasion and/or metastatic disease - No preference regarding drug	- Sorafenib for advanced HCC with CP-A liver function (possible with caution in CP-B)	- Sorafenib & lenvatinib: 1st line for BCLC-C - Treatment stage migration - Regorafenib: 2nd line - Cabozantinib: Benefit as 2nd line - Nivolumab: No recommendation yet

AASLD, American Association for the Study of Liver Diseases; AFP, alpha-fetoprotein; APASL, Asian Pacific Association for the Study of the Liver; BCLC, Barcelona Clinic Liver Cancer; CEUS, contrast-enhanced ultrasound; CP, Child-Pugh class; CT, computed tomography; EASL, European Association for the Study of the Liver; LRT, locoregional therapy; LT, liver transplantation; MRI, magnetic resonance imaging; SIRT, selective internal radiation therapy; TACE, transarterial chemoembolisation; US, ultrasound.

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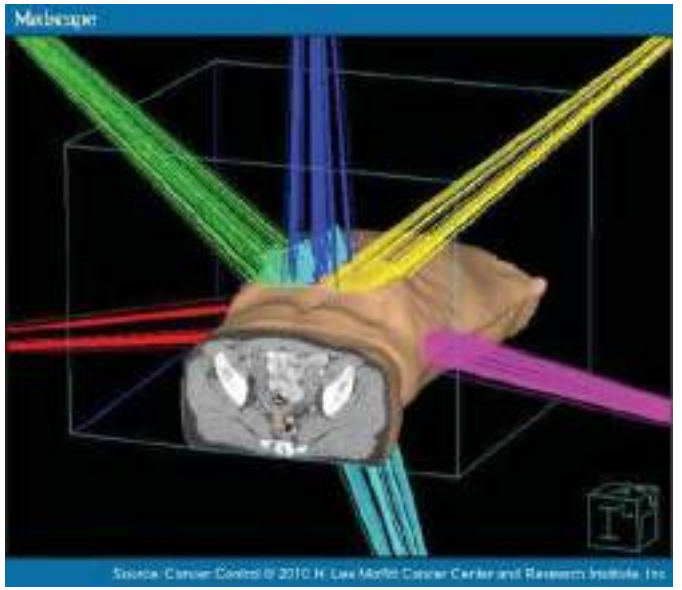
Liver – Radiotherapy - ? ineffective

- External Beam Radiation Therapy (EBRT):
  - palliative modality by 1980s - 1990s
  - Deemed ineffective for liver tumors in past



- Liver considered radio resistant
- Fear of RILD – Radiation induced liver disease
- Poor tolerance of whole liver radiation & Lack of knowledge of partial liver radiation
- Unavailability of modern radiation techniques for delivery
- No motion management techniques
- Lack of faith in effectiveness of radiation and No concept of multi disciplinary approach

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Initial Experience of Radiation therapy in liver

RT – Historical Perspective

Limited Role in past:

- Hepatocyte – well differentiated cell with low repair capacity (α/β = 1.5)
  - Whole liver tolerance @ conventional fractionation **25 Gy (5% RILD) & 35 Gy (50%)**
  - Non conventional # tolerances (whole liver) : **21-24 Gy @ 3 Gy/ fr; 24 Gy @ 2.5 and 30 Gy @ 1.5 Gy/ fr**

- Whole liver radiation
  - *Borgelt (IJROBP, 1983) –* palliation (Ascites, anorexia, pain,etc)
  - *Russell (IJROBP, 1993) -* Dose escalation 27Gy →30Gy →33Gy (toxicity beyond 33 Gy)
  - RTOG 8405 – dose escalation study with hyperfractionation
    - 1.5 Gy BD for 27, 30 and 33 Gy - **could not exceed 36 Gy**

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Initiating the liver SBRT program – RILD dilemma

RT contraindicated in past

RILD risk

? tumoricidal dose deliver

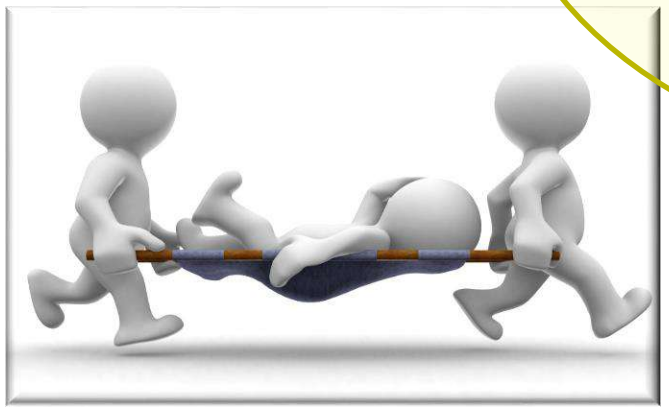
Radiation hepatitis of past

RILD

- transaminase or ALP > x 2.5-5 times
- Sr Bil - > x 1.5 -3 times
- non-malignant ascites in the absence of disease progression

Hallmark - Small venous obstruction - Central venous congestion and collagen deposition without inflammation

Rx: diuretics, paracentesis, and vitamin K



Literature support for Radiation safety

- The Indiana University - step-wise dose escalation safety
  - 36 Gy in 3 fractions in 2 Gy/fraction step increases
  - Child-Pugh (CP)-A cohort, → escalate to 48 Gy in 3 fractions without any dose limiting toxicity (DLT) - > grade 3 CTC toxicity
  - CP-B - developed DLT → instituted more protracted → 40 Gy in 5 #

  recommendations of differential dosing based on CP score (CP < B8)→ 700 cc of normal liver < 15 Gy → RILD unlikely

- The University of Toronto - Radiobiologically-guided partial volume dose escalation program
  - 24–54 Gy in 6 fractions daily
  - Normal liver > 700 cc spared
  - Few cases of transaminitis (similar episodes before RT also / minimal decline in CP scores)

Safety of partial liver RT safely studies in multiple centres – careful dose selection by CP score and normal liver sparing

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Modern Radiotherapy: Overcoming challenges of past

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HCC - RT

Pitfalls of past	Solutions
Radiation Induced Liver disease (RILD)	Data on partial liver tolerances
	Image Guided Radiotherapy (IGRT) and Stereotactic Body Radiotherapy (SBRT)
Target Delineation	Volumetric & Triple phase CECT, PET-CT, MRI
	Image fusion tools
Respiratory motion induced / Set-up uncertainties	ABC, Respiratory Gating (RPM), tracking (Cyberknife)
	Newer Immobilization devices/ 4D imaging
Uncertainties in dose distribution	Advanced Treatment machines/ Equipments
	Better planning software / dose engines

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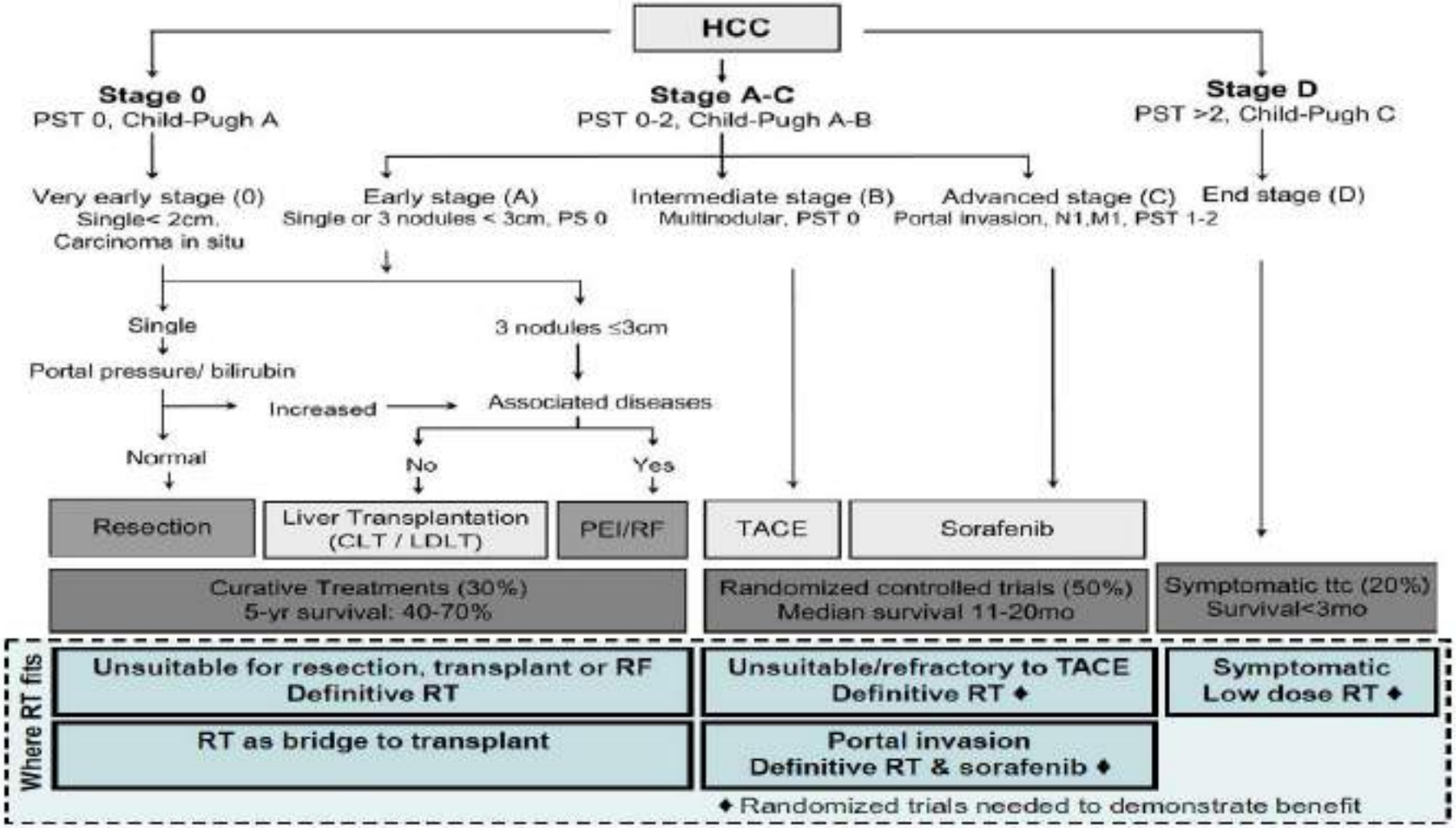
Exploring into depth of Liver RT : partial volume & functional liver

Redefined role of RT in HCC



Dawson L. Semin Radiat Oncol 2011;21:241-246

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Partial liver tolerance: effective & safe

- Austin – Seymour :
  - 1st quantitative anlysis of RILD as a function of dose – volume
  - Dose > 35 Gy limited to 30 % liver
- Emami et al
  - TD 5/5 – 50 Gy, 35 Gy, 30 Gy (1/3, 2/3 or whole)
  - TD 50/5 – 55, 45 or 40 Gy

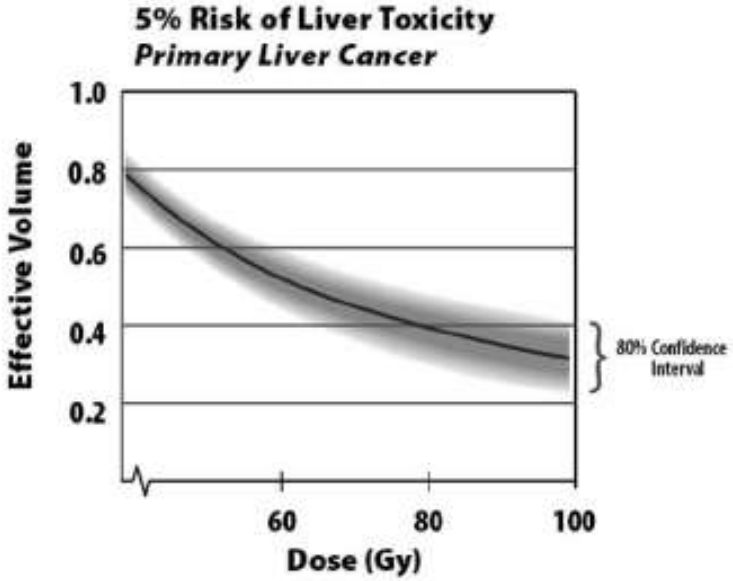

Figure 2 The Lyman-Kutcher-Burman NTCP model displaying 5% iso-NTCP curves, with 80% confidence limits, for patients with primary liver cancer. Effective volume (the organ volume that if irradiated to the prescribed dose uniformly would be associated with the same NTCP as the nonuniform dose distribution) versus normalized dose (prescribed dose normalized to 1.5 Gy bid).[11]

- U. of Michigan – Dawson, 2002
  - **Use of conformality for partial liver treatments**
    - Response rates 50-70%
    - No RILD (Radiation Induced Liver Disease) with mean liver dose <31 Gy
    - **RILD depends on volume of liver receiving radiation**

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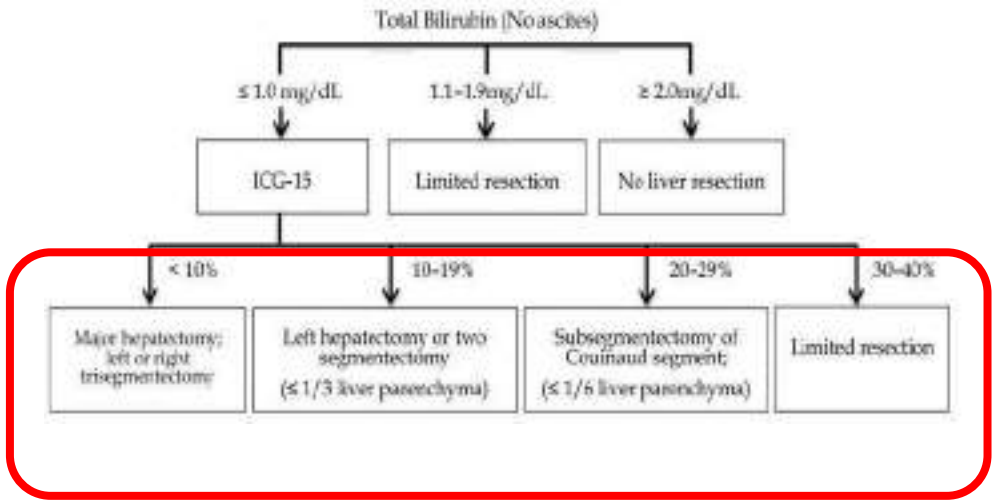
Indocyanine Green - ICG: assessing liver function for dose selection in RT-HCC



	ICG retention (dose- Gy)		
Nontumour part of liver	<10%	10.1%- 20%	20.1%- 30%
<1/3	40	No RT	No RT
1/3 – ½	50	40	No RT
>1/2	60	50	40

SBRT – local ablative therapies

Learning from surgical experience

- Rusthoven et al, JCO.[2009]

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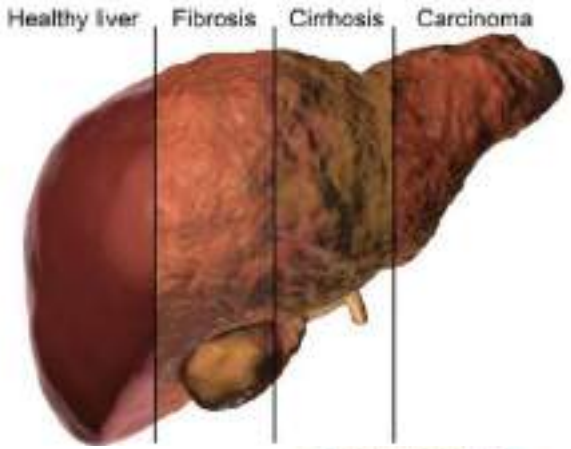
Functioning normal liver sparing



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Review

CT volumetry of the liver: Where does it stand in clinical practice?

M.C. Lim [a,*], C.H. Tan [b], J. Cai [b], J. Zheng [b], A.W.C. Kow [c]

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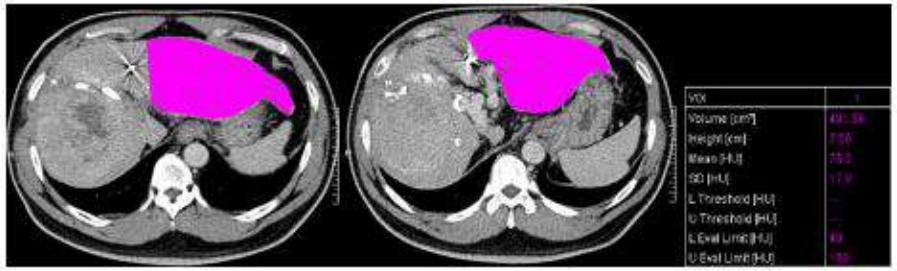
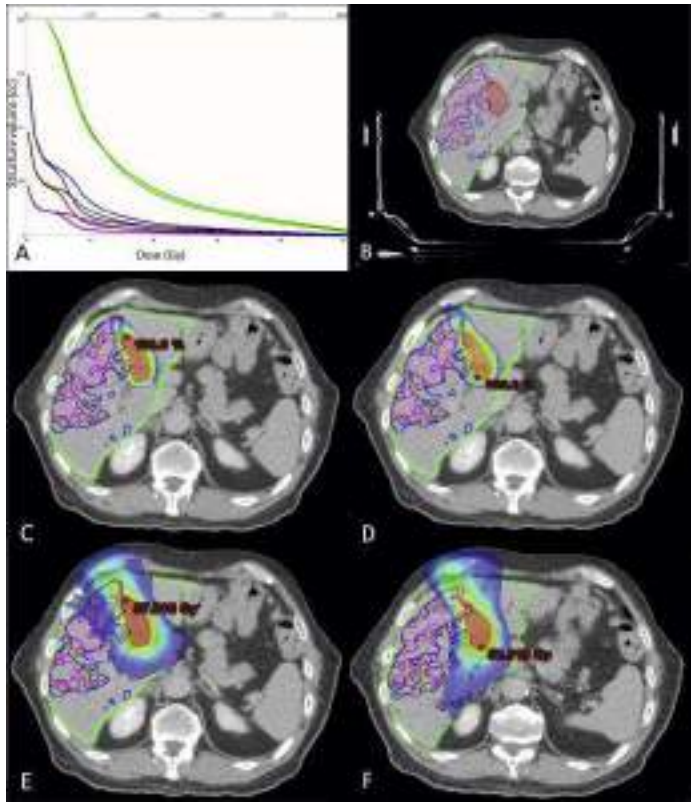
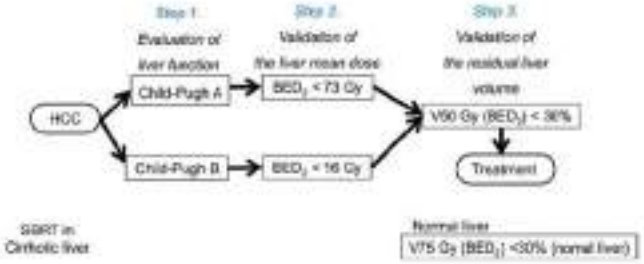
[b] School of Computer Engineering, Nanyang Technological University, Block N4 Nanyang Avenue #02a-32, Singapore 639798, Singapore
[c] University Surgical Cluster, National University Hospital, 5 Lower Kent Ridge Road, Singapore 119074, Singapore





FDG galactose based functional liver



Key to modern Liver RT success:

Adequate normal liver / minimize irradiated liver - RILD

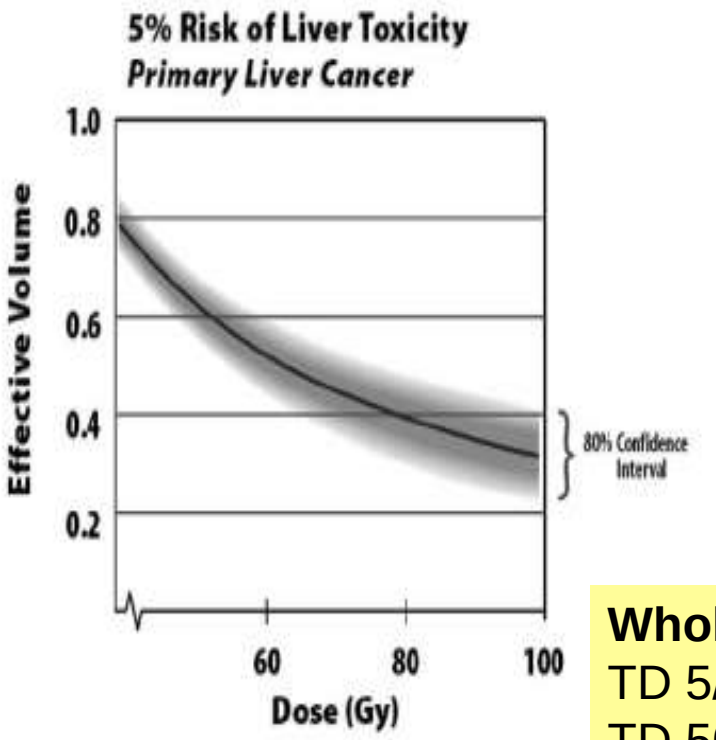


Figure 2 The Lyman-Kutcher-Burman NTCP model displ
iso-NTCP curves, with 80% confidence limits, for pati
primary liver cancer. Effective volume (the organ volu
irradiated to the prescribed dose uniformly would be
with the same NTCP as the nonuniform dose distributio
normalized dose (prescribed dose normalized to 1.5 Gy

Whole liver
TD 5/5: 30Gy/15 fx
TD 50/5: 42Gy/21 fx
2/3 Liver TD5/5: 50.4Gy/28fx
1/3 Liver TD5/5: 68.4Gy/38fx

IJROBP 2002

- Base line normal liver > 700 cc
  - **Liver volumetry from triple phase**
  - **Fibroscan – assess cirrhotic component**
  - FDG galactose scan (research)
  - ICG studies
- Case selection
  - safe anatomy / safe functions
- Technical improvement
  - **SBRT**
  - **Motion management**
  - Targeting – surrogate fiducials

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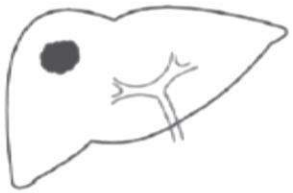
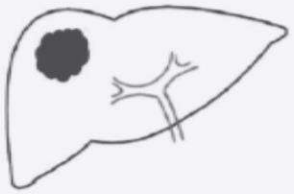
HCC Treatment in guidelines

Table 1. Comparison of Treatment Guidelines for Stereotactic Body Radiotherapy-Eligible Hepatocellular Carcinoma

		Guidelines			
		BCLC	NCCN	APPLE	KLSCG-NCC
Single, ≤2 cm, without VI 	Subgroup	Very early	Resectable or transplantable	Very early	mUICC Stage I
	Primary or preferred option	Resection (or LT/RFA/PEI, if portal pressure/bilirubin increased)	Resection or LT	Resection (or LT/RFA/PEI, if portal pressure/bilirubin increased)	Resection or RFA
	Alternative option	(-)	Locoregional treatment (Ablation, arterial directed therapies, EBRT)	EBRT	TACE, PEI, or EBRT
Single, >2 cm, without VI 	Subgroup	Early	Resectable or transplantable	Early	mUICC Stage II
	Primary or preferred option	LT or RFA/PEI	Resection or LT	LT or RFA/PEI	Resection or RFA
	Alternative option	(-)	Locoregional treatment (Ablation, arterial directed therapies, EBRT)	SABR, hypofractionated RT	TACE, LT, or EBRT

BCLC, Barcelona clinic liver cancer; NCCN, National Comprehensive Cancer Network; APPLE, Asia Pacific Primary Liver Cancer Expert Meeting; KLCSG-NCC, Korean Liver Cancer Study Group and the National Cancer Center; VI, vascular invasion; LT, liver transplantation; RFA, radiofrequency ablation; PEI, percutaneous ethanol injection; EBRT, external-beam radiotherapy; mUICC, modified Union for International Cancer Control; TACE, transarterial chemoembolization; RT, radiotherapy; SABR, stereotactic ablative radiotherapy.

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Difference in Guidelines for VI : West Vs East

DISCUSSION

Controversy exists among experts from the West and the East on the treatment of patients with HCC and PVTT. Western guidelines, which are based on the BCLC classification, consider HCC with PVTT to be at the advanced BCLC stage C, and sorafenib is the only recommended therapy.[2,22] In China/Southeast Asia, where the common etiology of HCC is hepatitis B virus, patients usually have better liver function reserves and long-term survival outcomes after hepatectomy compared with patients in Europe, North America, and Japan, where HCV-related HCC is predominant.[23,24] Furthermore, hepatitis B virus–related HCC usually progresses faster with worse survival outcomes from sorafenib treatment compared with HCV-related HCC.[23] As a consequence, surgery is more frequently adopted for treatment of selected patients with HCC and PVTT in China and Southeast Asia.[25-27]

West: Europe & Americas Vs East

- ✓ follow BCLC
- ✓ Hep C more common
- ✓ BCLC C → sorafenib alone

East → Hep B common

- ✓ Better liver functions
- ✓ Surgery feasible and better
- ✓ Hep B progress faster / worse outcome on sorafenib

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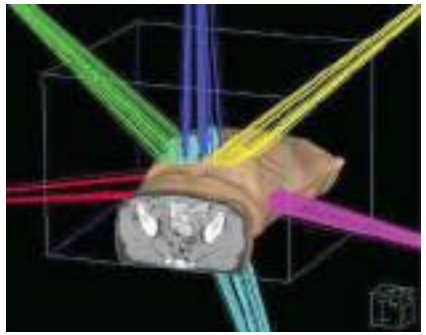
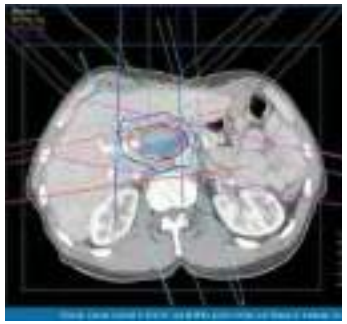
Liver SBRT: Re-defining the role of RT

- **SBRT Liver : highly precise Image Guided therapy**
  - ✓ 4D target definition
  - ✓ Accurate patient positioning
  - ✓ Multiple beams

Allowing for

  - ✓ Steep dose gradients
  - ✓ Hypofractionation





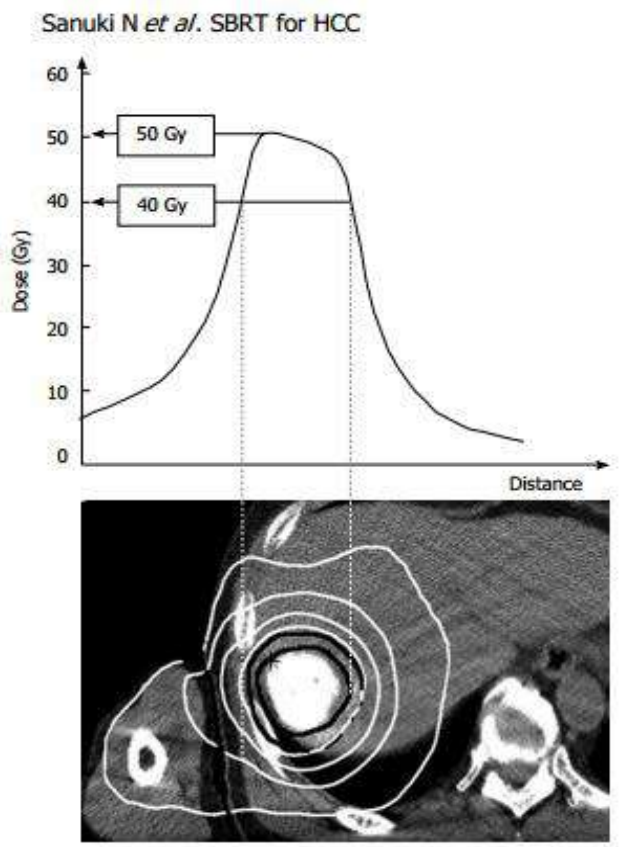


Figure 1 Dose distribution of stereotactic body radiation therapy for hepatocellular carcinoma at a dose of 40 Gy in 5 fractions, prescribed at the periphery of the target volume. The isodose lines (white solid lines) from inner to outer represent 40, 30, 20 and 10 Gy, respectively. The center of the tumor receives as high as 125% of the prescribed dose.

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SBRT in HCC

Advantages
• High possibility of local control
• Minimally invasive treatment modality, no requirements for anesthesia or injections
• High possibility to overcome anatomical limitations, including poorly defined tumors on ultrasound and tumors which are difficult to puncture
• No concern regarding the location close to major vessels, including the portal vein, inferior vein cava, and bile duct
• Possible to treat complicated forms of tumors, particularly using IMRT
• Short treatment term (usually within 2 weeks), possibility of benefit to the patient's quality of life and reduced medical cost
• Possibility to enhance the immune reaction to tumors
Current issues
• Poor outcomes and high possibility of toxicity with large tumors
• Challenges involved in the treatment of tumors close to critical organs, such as the gastrointestinal tract
• Effects of re-irradiation are unclear
• Inaccuracy due to respiration and the presence of ascites
Abbreviations: SBRT = stereotactic body radiation therapy; IMRT = intensity modulated radiation therapy.

Table 1. Features of SBRT for liver tumors.

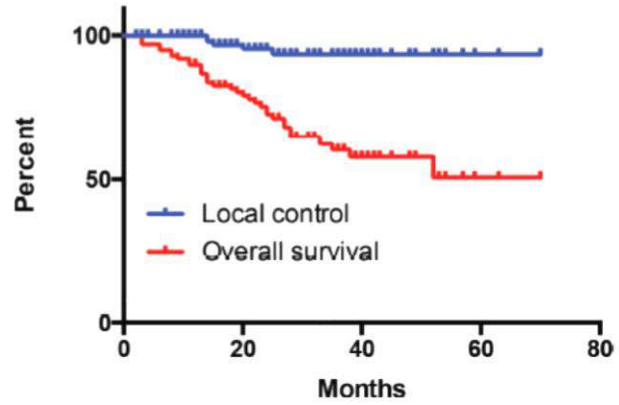

Figure 1. Local control and overall survival of HCC after SBRT. Local control (LC) and overall survival (OS) were described using the Kaplan Meier method in 100 patients with 116 HCCs underwent SBRT of BED_{10} ≥75 Gy in ≤10 fractions, between July 2007 and August 2016 at Miyakojima IGRT Clinic (Osaka, Japan, approval no. 9). The 1-, 2- and 3-year LC rate was 100.0, 95.4 and 93.5%, respectively. The 1-, 2- and 3-year OS rate was 83.7, 72.6 and 60.5%, respectively. Abbreviations: HCC, hepatocellular carcinoma; SBRT, stereotactic body radiation therapy.

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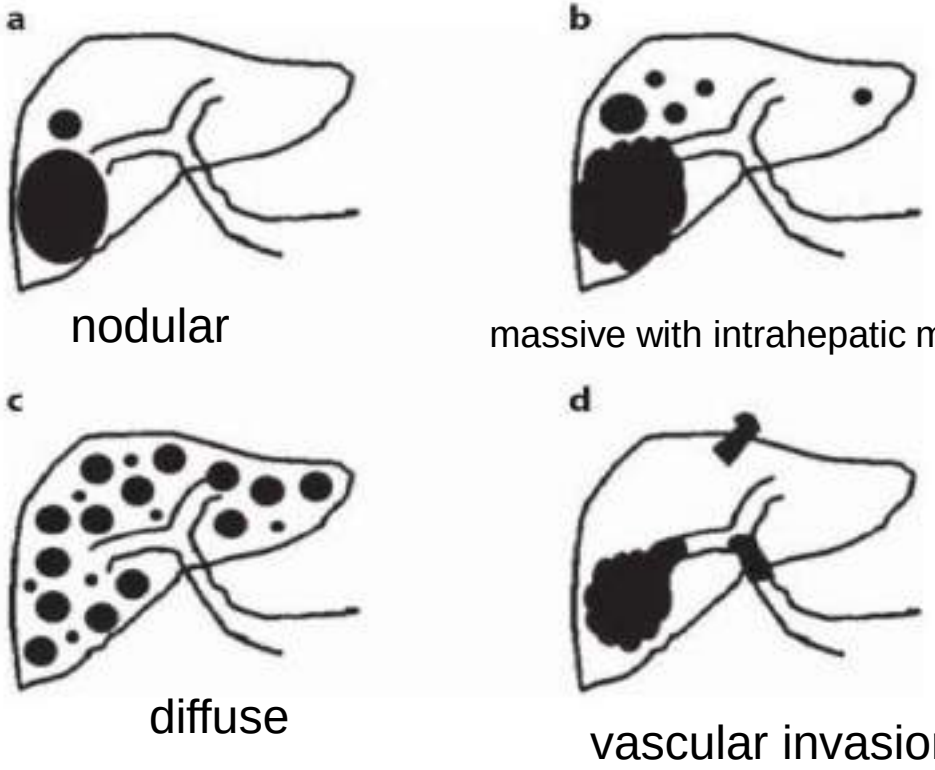
Sub-classification of Locally advanced HCC



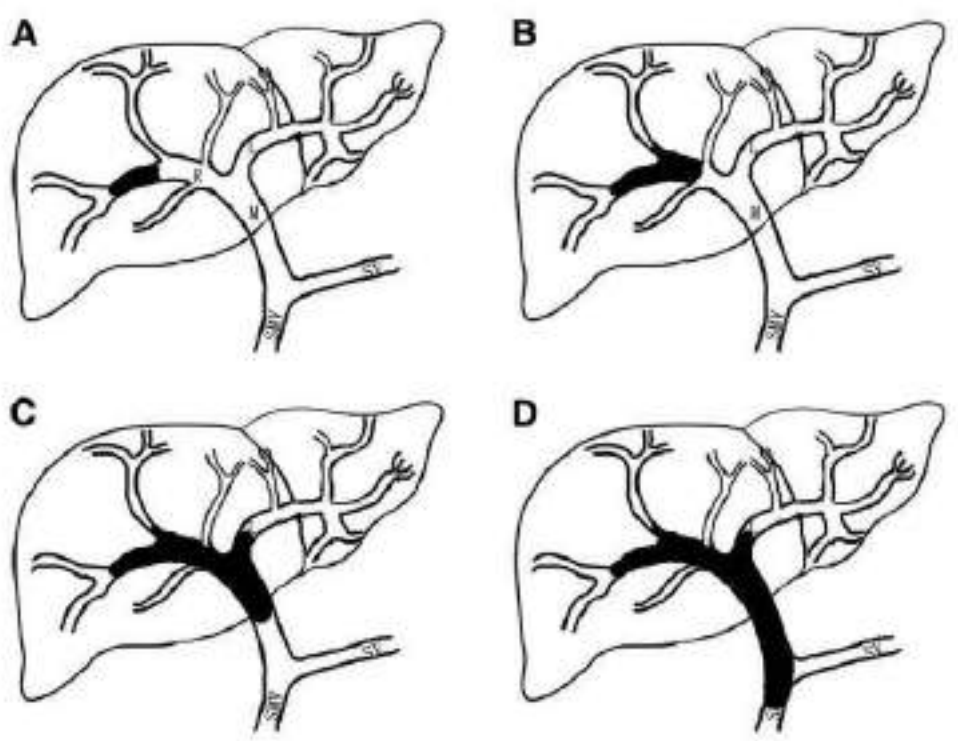
nodular

massive with intrahepatic metastasis

diffuse

vascular invasion

HCC



PVTT

Park et al. Oncology 2011

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Eligibility Criteria for Different Radiation Techniques

	CRT	SBRT	Proton	Brachy	Yttrium-90
<3 cm	++++	++++	++++	++++	+++
3-6 cm	+++	++++	++++	++++	++
6-10 cm	+++	+++	+++	++	+
>10 cm	++	++	+++	+	+
Diffuse	0	0	0	0	++
High bleeding risk	++	++	++	0	0
Child-Pugh B	++	+	+++	+	+
Vascular invasion	+++	+++	+++	+	+
Caudate lobe	+++	++	+++	+	++
Target <1 cm from GI tissues #	++	+	+++	++	++

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RT for HCC - possible case profile / indications

Operable

- Bridge to transplant
- Down staging / Pre-op
- ? Post op

Borderline/ inoperable

- Medically inoperable or unfit for ablative Rx
- Down staging
- Unfit for RFA (exophytic/ capsular/ heat sink/ > 3-5 cm

Inoperable

- Alternative or combination (TACE/ Sorafenib)
- With PVTT – combination (TARE)

HCC-PVTT irradiation: A neo-adjuvant route to transplant

Salvage/ Palliative

- Post TACE/ TARE residual / recurrence
- Post surgery – limited recurrence
- Palliation of mets / pain relief

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SBRT selection : Suitable Vs more challenging

Suitable

1. Liver confined disease
2. Non diffuse focal lesions (< 3-5)
3. Small < 6- 8 cm diameter
4. GC / function adequate – CP A/B
5. No / Minimal underlying hepatitis/ cirrhosis
6. > 700 -1000 cc un-involved liver
7. Breathing motion < 5 -10 mm
8. Away from lumen - bowel/ stomach
9. Not suitable for other Rx

More challenging

1. Underlying hepatitis/ cirrhosis (CP B +/ C)
2. Post viral hepatitis/ deranged liver f/n
3. ≤ 700 cc uninvolved liver
4. > 1 lesions – same lobe/ segment
5. > 8 cm lesion
6. 5-30 mm breathing motion
7. Proximity to OARs
8. PVTT – scheduling combinations

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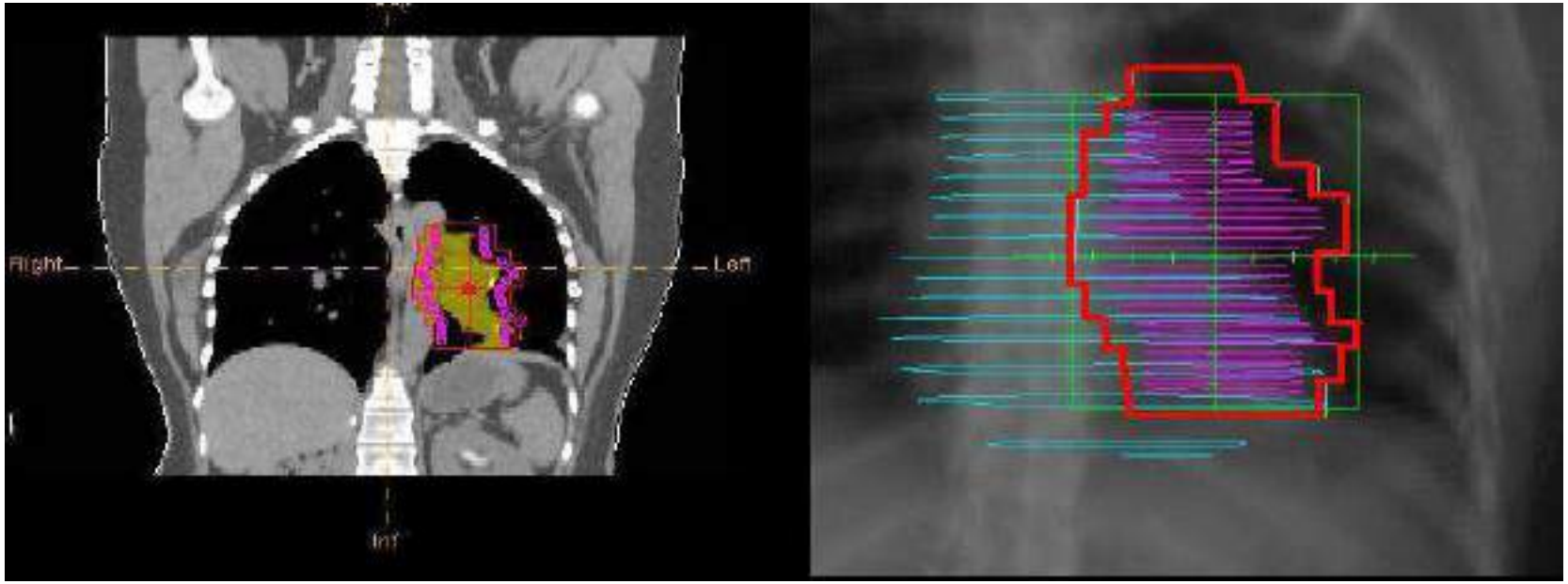
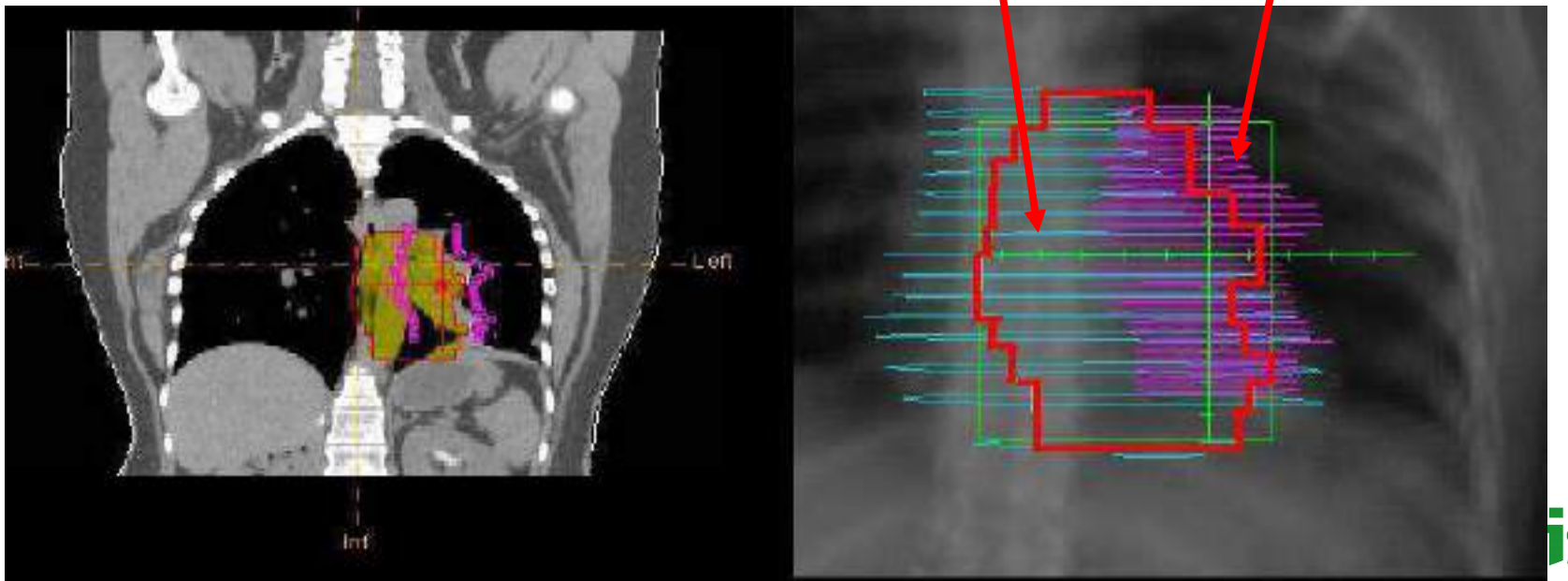
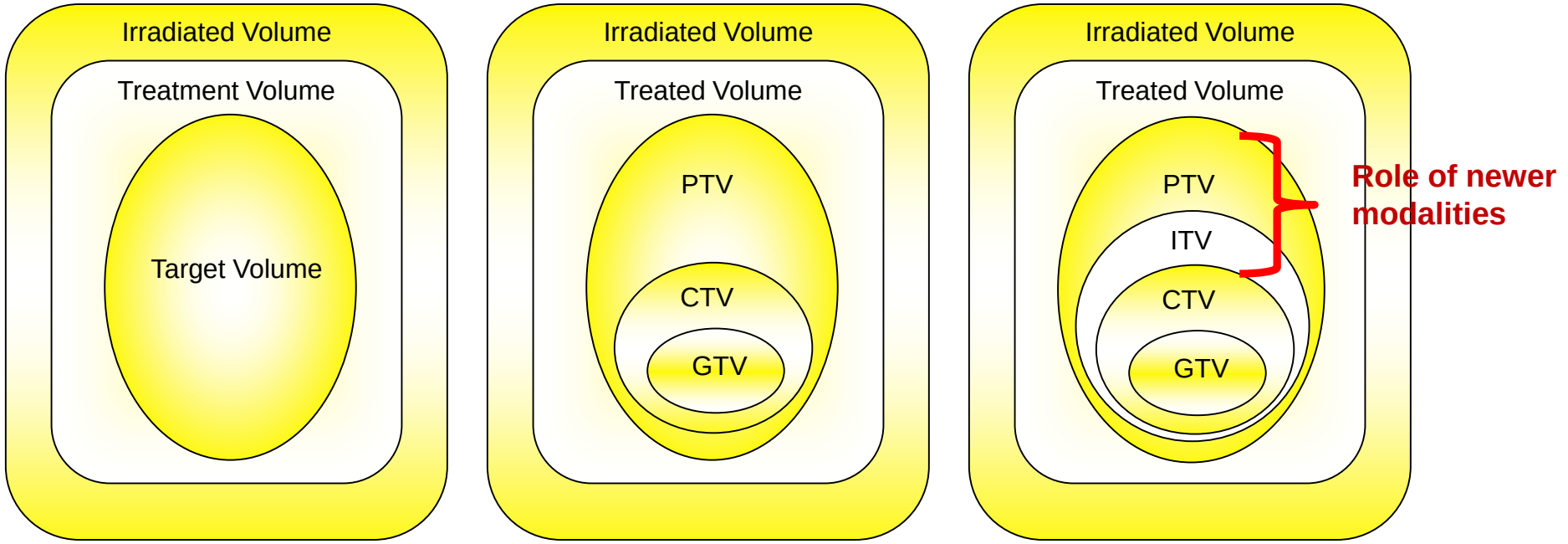


Problems with respiratory movement: Organ Hit & Tumor miss



Modern age Radiotherapy

Paradigm shift from conventional to conformal Radiotherapy



(a) ICRU 29 (b) ICRU 50 (c) ICRU 62

Motion management

➢ **Five main strategies** are currently used :

❖ integration of motion: (geometrical or dosimetric)

4DCT- acquisition of anatomical data specific to a respiratory phase

Motion dampening:

❖ forced shallow breathing with abdominal compression : Karolinska hospital → good for motion > 5 mm

❖ breath-hold techniques (active or voluntary) : ABC (active breathing control, Elekta, proposed by MSKCC)

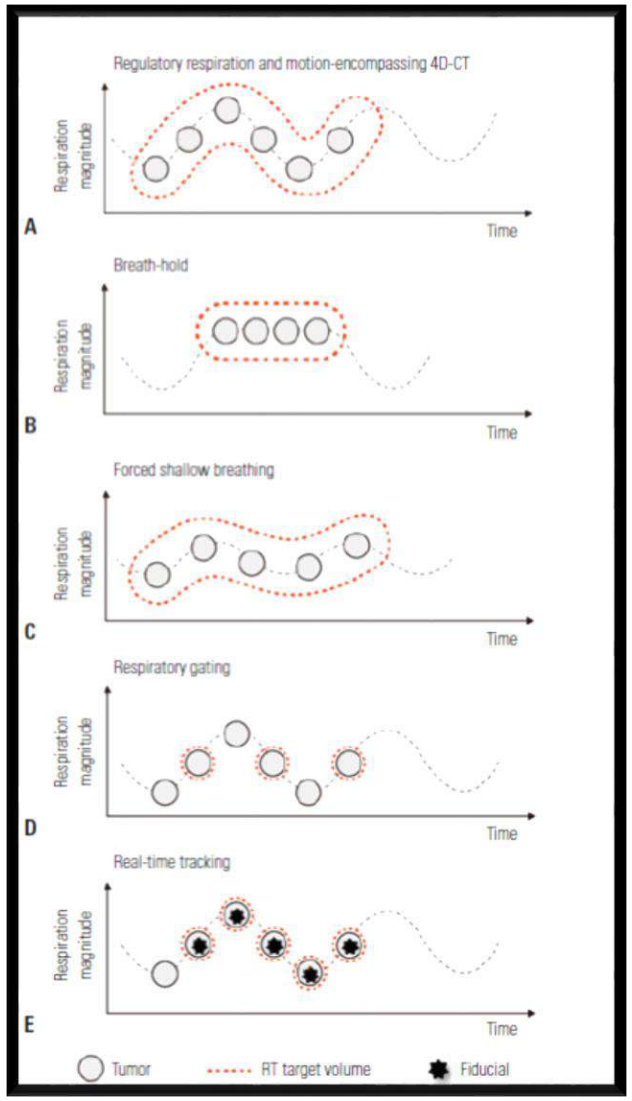
Motion tracking:

❖ respiratory gating techniques : RPM [real time position management, Varian, 2000]

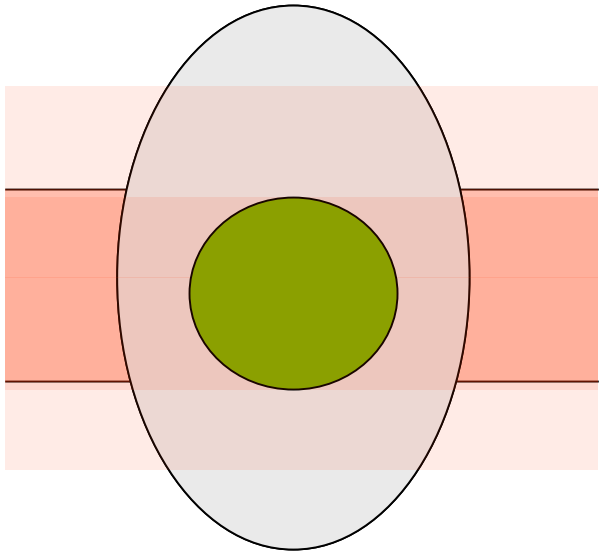
❖ tracking techniques : involves real time localization + beam adaptation

Fortis

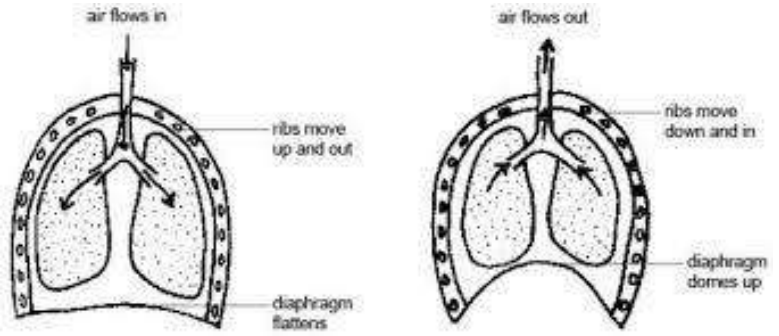
Respiratory motion management: Breath dampening/ Holding



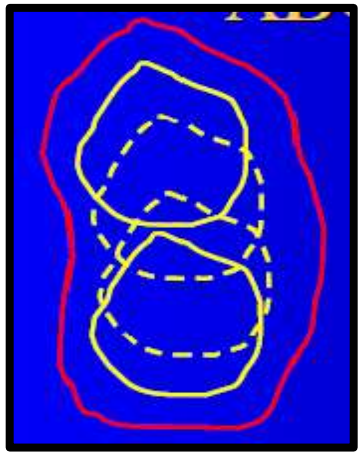
Change breathing pattern and not hold breathing



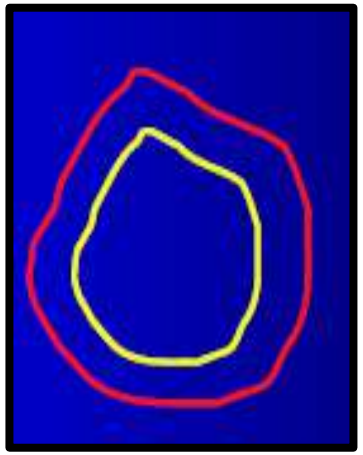
Respiratory motion management: Breath Holding

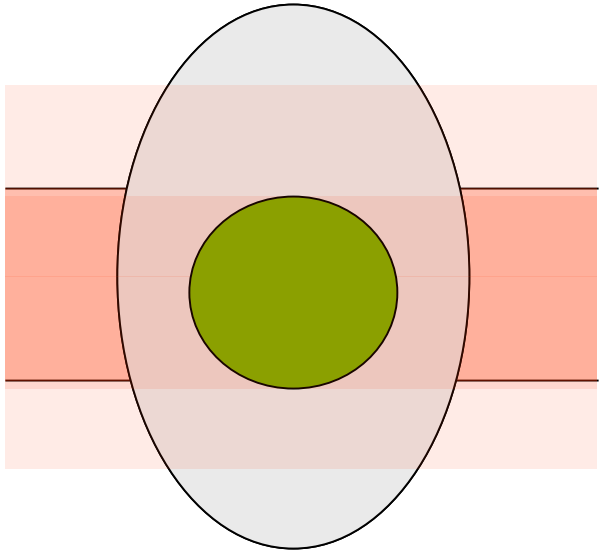


Free Breathing

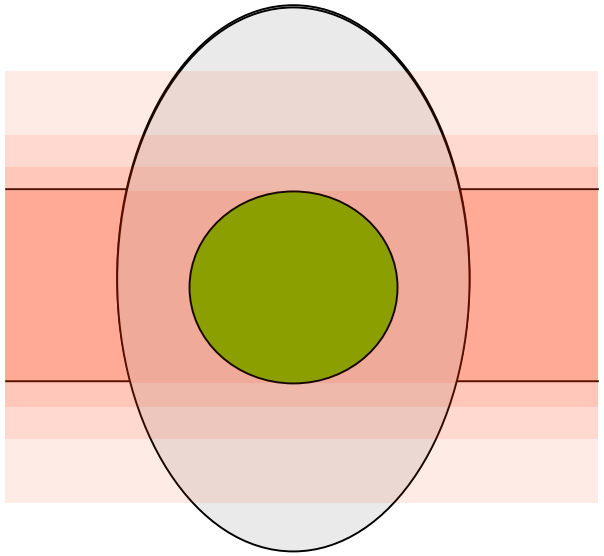


Breath-Hold

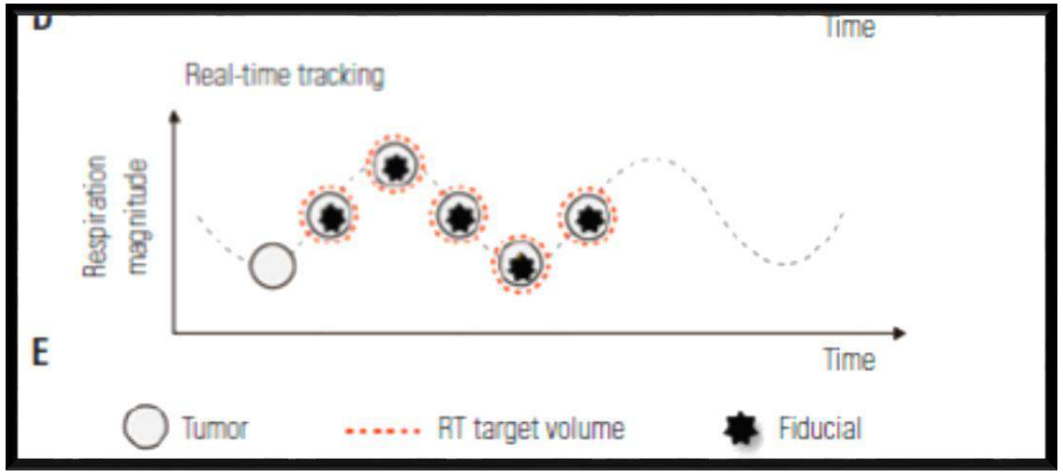




Respiratory motion management: Gating



Synchrony® Respiratory Tracking System



Literature review: RT in HCC / PVTT – growing evidence

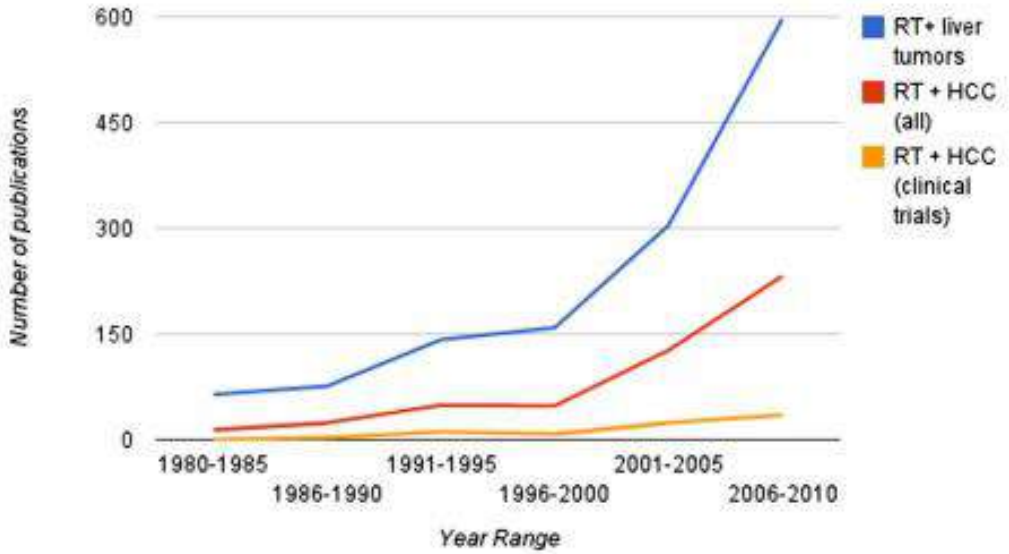


Fig. 2. Graph of number of liver cancer RT publications over time. Citation count based on a search of the MEDLINE database limited to each 5-year period. Blue line: search for "radiation therapy" and "liver neoplasms." Red line: search for "radiation therapy" and "hepatocellular carcinoma." Orange line: search for "radiation therapy" and "hepatocellular carcinoma," with results limited to clinical trials only. HCC = hepatocellular carcinoma; RT = radiation therapy.

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World J Gastroenterol 2014 March 28; 20(12): 3100-3111
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

TOPIC HIGHLIGHT

WJG 20th Anniversary Special Issues (1): Hepatocellular carcinoma

Role of stereotactic body radiation therapy for hepatocellular carcinoma

Naoko Sanuki, Atsuya Takeda, Etsuo Kunieda

[2014]

[Prospective studies]

Table 1 Eligibility criteria for different treatment modalities

	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
the	High	Low	Low-moderate	Low-moderate

tactic body radiation therapy; TACE: Transarterial chemoem-

Table 2 Prospective studies of stereotactic body radiation therapy for hepatocellular carcinoma and other liver tumors

Ref.	Country	Patient number	Median volume, mL	Median size, cm	Median dose (range)/ fraction, Gy	Median follow-up (range), mo	Local control	Overall survival
Cárdenes *et al*[29]	United States (Indiana)	17	34 (8-95)	-	Variable CP-A: 36-48 Gy/3 fr CP-B: 40 Gy/5 fr	24 (10-42)	100%	75% (1 yr) 60% (2 yr)
Andolino *et al*[37]	United States (Indiana)	60	29 (2-112)	3.2 (1-6.5)	Fixed CP-A: 44 Gy/3 fr CP-B: 40 Gy/5 fr	27 (2-52)	90% (2 yr)	67% (2 yr)
Bujold *et al*[30]	Canada	102	117 (1-1913)	7.2 (1.4-23.1)	Variable 36 (24-54) Gy/6 fr	31 (2-36)	87% (1 yr)	Median 17 mo
Kang *et al*[31]	South Korea (Korea Inst. of Radiological and Medical Sciences)	47	15 (2-213)	2.9 (1.3-7.8)	57 (42-60) Gy/3 fr	17 (6-38)	95% (2 yr)	69% (2 yr)

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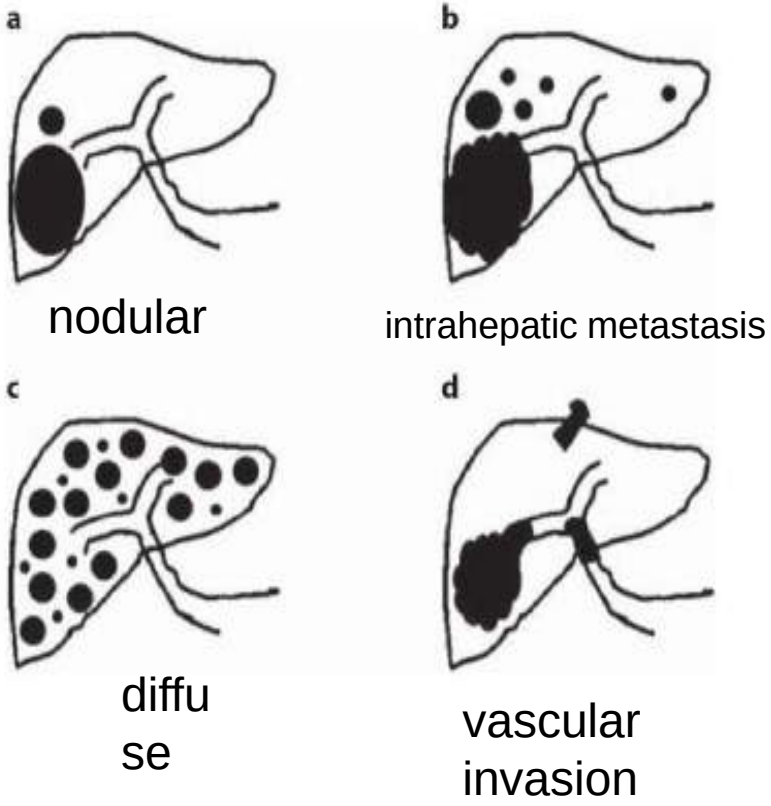
SBRT in HCC



nodular

intrahepatic metastasis

diffu
se

vascular
invasion

HCC SBRT

- Operable & awaiting Bridge
- Inoperable- Definitive
- Upfront inoperable/ borderline
- Downstaging

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Liver SBRT Role

2011

Int. J. Radiation Oncology Biol. Phys., Vol. 81, No. 4, pp. e447–e453, 2011

0360-3016/$ - see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2011.04.011

CLINICAL INVESTIGATION **Liver**

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.,*

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. © 2011 Elsevier Inc.

diana University Simon Cancer Center: 36 Child-Turcotte-Pugh (CTP) Class A and 2 (7%) CTP Class B. The median num-
ber of fractions, dose per fraction, and total dose, was 3, 14 G
cirrhosis and 5, 8 Gy, and 40 Gy, respectively, for those with C
and in nearly all cases was prescribed to the 80% isodose line. T
response was scored according to Response Evaluation Criteria
the Common Terminology Criteria for Adverse Events v4.0. Lo
free survival (PFS), and overall survival (OS) were calculated
Results: The median follow-up time was 27 months, and the
PFS, and OS were 90%, 48%, and 67%, respectively, with n
underwent transplant, with a median time to transplant of
toxicities. Thirteen percent of patients experienced an incre
1 grade, and 20% experienced progression in CTP class wi
Conclusions: SBRT is a safe, effective, noninvasive option for p
sidered when bridging to transplant or as definitive therapy fo

Table 2

Tumor response, RECIST.

	Tumor size						
	≤4 cm (N=52)		>4–<10 cm (N=55)		≥10 cm (N=34)		
Parameters	**No**	**%**	**No**	**%**	**No**	**%**	***P***
Complete response	40	76.92	25	45.45	5	14.71	
Partial response	10	19.23	25	45.45	21	61.76	
Stable	1	1.92	3	5.45	8	23.53	
Tumor progression	1	1.92	2	3.64	0	0	<.0001

RECIST = response evaluation and criteria in solid tumors.
*Log-rank test.

SBRT - Cyberknife

Stereotactic Body Radiation Therapy for Hepatocellular Carcinoma: Prognostic Factors of Local Control, Overall Survival, and Toxicity

2013

Jean-Emmanuel Bibault[1], Sylvain Dewas[1], Claire Vautravers-Dewas[1], Antoine Hollebecque[2], Hajer Jarraya[3], Thomas Lacornerie[1], Eric Lartigau[1], Xavier Mirabel[1]*

1 Academic Radiation Oncology Department & University Lille II, CLCC Oscar Lambret, Lille, France, 2 Department of Medicine, Institut Gustave Roussy, University Paris , Villejuif, France, 3 Department of Radiology, CLCC Oscar Lambret, Lille, France

Abstract

Purpose: Stereotactic bo... several recent studies. Th... purpose of this study wa... treatment.

Patients and Methods: ... Comprehensive Cancer C... track the lesion's moveme... survival were calculated u... prognostic factors was per...

Results: There were 67 ... Treatment was administer... median follow-up was 10 ... survival was 78.5% and 5... events. Higher alpha-feto... [1.000, 1.002]; p=0.0063). ... p=0.0441). A Child-Pugh score higher than 5 was associated with worse overall survival (HR= 3.413; 95% CI [1.235, 9.435]; p=0.018).

Conclusion: SBRT affords good local tumor control and higher overall survival rates than other historical controls (best supportive care or sorafenib). High aFP levels were associated with lesser local control, but a higher treatment dose improved local control.

Results: There were 67 patients with Child-Turcotte-Pugh (CTP) Class A and eight patients with CTP Class B. Treatment was administered in three sessions. A total dose of 40–45 Gy to the 80% isodose line was delivered. The median follow-up was 10 months (range, 3–49 months). The local control rate was 89.8% at 1 and 2 years. Overall survival was 78.5% and 50.4% at 1 and 2 years, respectively. Toxicity mainly consisted of grade 1 and grade 2 events. Higher alpha-fetoprotein (aFP) levels were associated with less favorable local control (HR=1.001; 95% CI [1.000, 1.002]; p=0.0063). A higher dose was associated with better local control (HR=0.866; 95% CI [0.753, 0.996]; p=0.0441). A Child-Pugh score higher than 5 was associated with worse overall survival (HR= 3.413; 95% CI [1.235, 9.435]; p=0.018).

Conclusion: SBRT affords good local tumor control and higher overall survival rates than other historical controls (best supportive care or sorafenib). High aFP levels were associated with lesser local control, but a higher treatment dose improved local control.

Citation: Bibault J-E, Dewas S, Vautravers-Dewas C, Hollebecque A, Jarraya H, et al. (2013) Stereotactic Body Radiation Therapy for Hepatocellular Carcinoma: Prognostic Factors of Local Control, Overall Survival, and Toxicity. PLoS ONE 8(10): e77472. doi:10.1371/journal.pone.0077472

Editor: Erica Villa, University of Modena & Reggio Emilia, Italy

Received June 14, 2013; **Accepted** September 2, 2013; **Published** October 11, 2013

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Bridge: available literature

- Scarce data in past → thought to induce local fibrosis/ vascular damages → (i) theoretical dissection difficulties (ii) anastomosis-related complications (iii) increased perioperative morbidity
- **PMH series**: ***Sandroussi C, Dawson LA, et al 2010***
  - 10 patients - refractory to or ineligible for other therapies → 3D-CRT as a bridge to OLT
  - Median dose- 33 Gy (range:8.5–54 Gy)/ 1–6 fractions→ 100% local control & 10%-50% volume regression
  - 5 OLT → treatment effect with 40%–90% necrosis and fibrosis / All without recurrence @ 14 months
- **Mount Sinai University** : ***Facciuto ME et at 2012***
  - 27 patients → treated with SBRT (26–36 Gy in 2–4 fr)→ CR in 14%, PR in 23%, and SD in 63%
- **Baylor Medical Center**: ***O'Connor et al. 2012*** → 27% pathologic CR
- **3D-CRT and SBRT: safe and effective to bridge selected patients with advanced HCC**

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SBRT as bridge –Pittsburgh group

- 27 HCC with cirrhosis → SBRT with intent for OLT [since 2010 @ Allegheny Health Network
- 19 - within Milan →bridge to transplantation & 8 - **outside of Milan → downsized to Milan criteria and listed for liver transplant**
- Child's B cirrhosis - 18, while Child's A – 9. No Child's C : No serious complications post SBRT / no hepatic decompensation
- Bridge-to-transplant:
  - 18/19 (95%) pts - successfully controlled with SBRT
  - 1 - HCC progression in the non-treated portion of liver at 9 months
  - 13/19 (68%) underwent liver transplant at 1-23 mth post SBRT
  - 5 are still listed – without evidence of recurrence
  - No recurrence post-transplant in 13 pts @ 3 mth - 4.5 yrs
  - Pathology: 13/13 reduction of tumor & 7/13 with no residual
- Down-sized group:
  - 8/8 were successfully down-sized to within Milan Criteria
  - 3 - HCC recurrence outside of treatment area
  - 3- liver transplantation / 2 awaiting

SBRT(Stereotactic Body Radiotherapy) to Bridge or Down-Size HCC for Liver Transplantation

N. Thai,[1] K. Tom,[1] M. Szramowski,[1] P. Abrams,[1] J. Oliva,[3] D. Monga,[4] M. Raj,[4] D. Parda,[2] A. Kirichenko.[2]

[1]Transplant Surgery, Allegheny Health Network, Pittsburgh, PA
[2]Radiation Oncology, Allegheny Health Network, Pittsburgh, PA
[3]Hepatology, Allegheny Health Network, Pittsburgh, PA
[4]Medical Oncology, Allegheny Health Network, Pittsburgh, PA.

Meeting: 2015 American Transplant Congress

Abstract number: D179

Keywords: Hepatocellular carcinoma, Liver transplantation

Overall success in bridge-to-transplant was 95% and down-sizing was 63%.

Tumor response to SBRT was 100% and local tumor control was 100%

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SHORT:
SBRT bridge to transplant

50 Gy in 10 fr

International Journal of Radiation Oncology biology • physics

www.redjournal.org

2011

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.‡

*Departments of *Radiation Oncology, †Solid Organ Transplant, and ‡Medicine, Division of Hematology and Oncology, University of Rochester Medical Center, Rochester, New York; and ¶Anatomic Pathology, William Beaumont Hospital, Royal Oak, Michigan*

Received Apr 21, 2011, and in revised form Aug 1, 2011. Accepted for publication Aug 11, 2011

Summary

Patients with hepatocellular carcinoma awaiting liver transplantation need effective treatment to retard their tumors. This study evaluated stereotactic hypofractionated radiation therapy (SHORT) in this bridging role. No patients developed grade 3 or higher gastrointestinal or liver toxicity. 100% necrosis was seen in most of the lesions of those who underwent surgery. Most of the operated patients were alive with no recurrence at last follow-up. SHORT appears to be a safe and effective bridging therapy for HCC patients awaiting liver

Purpose: We sought to determine efficacy, safety, and outcome of stereotactic hypofractionated radiation therapy (SHORT) as a suitable bridging therapy for patients awaiting liver transplantation (LT) for hepatocellular carcinoma (HCC). We also examined histological response to radiation in the resected or explanted livers.

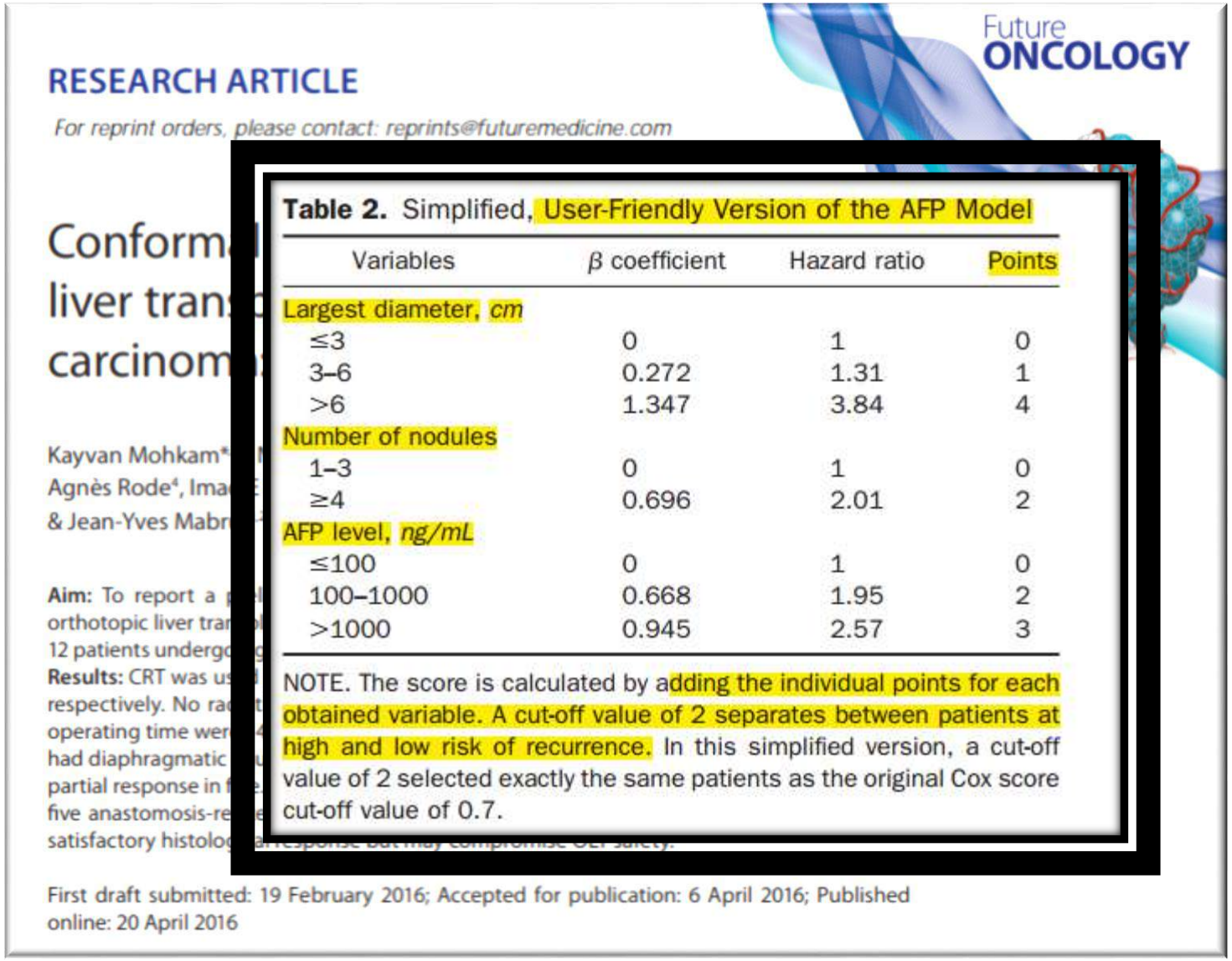
Methods and Materials: Between August 2007 and January 2009, 18 patients with 21 lesions received SHORT. A median total dose of 50 Gy was delivered in 10 fractions. Three patients underwent either chemoembolization ($n = 1$) or radiofrequency ablation ($n = 2$) prior to SHORT. Radiographic response was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

Results: Six of 18 patients were delisted because of progression ($n = 3$) or other causes ($n = 3$). Twelve patients successfully underwent major hepatic resection ($n = 1$) or LT ($n = 11$) at a median follow-up of 6.3 months (range, 0.6–11.6 months) after completion of SHORT. No patient developed gastrointestinal toxicity Grade ≥3 or radiation-induced liver disease. Ten patients with 11 lesions were evaluable for pathological response. Two lesions had 100% necrosis, three lesions had ≥50% necrosis, four lesions had ≤50% necrosis, and two lesions had no necrosis. All patients were alive after LT and/or major hepatic resection at a median follow-up of 19.6 months.

Conclusions: SHORT is an effective bridging therapy for patients awaiting LT for HCC. It provides excellent in-field control with minimal side effects, helps to downsize or stabilize tumors prior to LT, and achieves good pathological response. © 2012 Elsevier Inc.

Keywords: Hepatocellular carcinoma, Stereotactic hypofractionated radiation therapy, Transplant

RT as Bridge: safety & selection



RESEARCH ARTICLE

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Future ONCOLOGY

Conforma
liver trans
carcinom

Kayvan Mohkam*
Agnès Rode[4], Ima
& Jean-Yves Mabr

Aim: To report a
orthotopic liver tra
12 patients undergo
Results: CRT was us
respectively. No ra
operating time wer
had diaphragmatic
partial response in
five anastomosis-re
satisfactory histolo

Table 2. Simplified, User-Friendly Version of the AFP Model

Variables	β coefficient	Hazard ratio	Points
Largest diameter, *cm*			
≤3	0	1	0
3–6	0.272	1.31	1
>6	1.347	3.84	4
Number of nodules			
1–3	0	1	0
≥4	0.696	2.01	2
AFP level, *ng/mL*			
≤100	0	1	0
100–1000	0.668	1.95	2
>1000	0.945	2.57	3

NOTE. The score is calculated by adding the individual points for each obtained variable. A cut-off value of 2 separates between patients at high and low risk of recurrence. In this simplified version, a cut-off value of 2 selected exactly the same patients as the original Cox score cut-off value of 0.7.

First draft submitted: 19 February 2016; Accepted for publication: 6 April 2016; Published online: 20 April 2016

OLT eligibility:
AFP score ≤2 – low risk of recurrence

Bridging therapies →
- AFP score ≤2 [maximize chance to stay on the waiting list]
- >2 with potentially controllable disease → reassessed for eligibility according to treatment response

3DCRT as bridge →
- large HCC (>4 cm)
- HCC located close to great vessels or main bile ducts, which were deemed unsuitable for RFA or TACE alone

Fortis

SBRT Vs TACE or RFA : 2017

J Hepatol. 2017 Jul;67(1):92-99. doi: 10.1016/j.jhep.2017.02.022. Epub 2017 Feb 28.

Stereotactic body radiotherapy vs. TACE or RFA as a bridge to transplant in patients with hepatocellular carcinoma. An intention-to-treat analysis.

Sapisochin G[1], Barry A[2], Doherty M[3], Fischer S[4], Goldaracena N[5], Rosales R[6], Russo M[2], Beecroft R[7], Ghanekar A[5], Bhat M[6], Brierley J[2], Greig PD[5], Knox JJ[3], Dawson LA[2], Grant DR[5].

Author information

Abstract

BACKGROUND & AIMS: There is limited information on the use of stereotactic body radiotherapy (SBRT) as a bridge to liver transplantation for hepatocellular carcinoma and no study comparing its efficacy to transarterial chemoembolization (TACE) and radiofrequency ablation (RFA). We aimed to ascertain the safety and efficacy of SBRT on an intention-to-treat basis compared with TACE and RFA as a bridge to liver transplantation in a large cohort of patients with hepatocellular carcinoma.

METHODS: Outcomes between groups were compared from the time of listing and from the time of transplant. Between July 2004 and December 2014, 379 patients were treated with either SBRT (n=36, SBRT group), TACE (n=99, TACE group) or RFA (n=244, RFA group).

RESULTS: The drop-out rate was similar between groups (16.7% SBRT group vs. 20.2% TACE group and 16.8% RFA group, p=0.7); 30 patients were transplanted in the SBRT group, 79 in the TACE group and 203 in the RFA group. Postoperative complications were similar between groups. Patients in the RFA group had more tumor necrosis in the explant. The 1-, 3- and 5-year actuarial patient survival from the time of listing was 83%, 61% and 61% in the SBRT group vs. 86%, 61% and 56% in the TACE group, and 86%, 72% and 61% in the RFA group, p=0.4. The 1-, 3- and 5-year survival from the time of transplant was 83%, 75% and 75% in the SBRT group vs. 96%, 75% and 69% in the TACE group, and 95%, 81% and 73% in the RFA group, p=0.7.

LAY SUMMARY: Patients with liver cancer included in the waiting list for liver transplantation are at risk of tumor progression and death. Stereotactic body radiotherapy may be a good alternative to conventional therapies to reduce this risk.

between groups. Patients in the RFA group had more tumor necrosis in the explant. The 1-, 3- and 5-year actuarial patient survival from the time of listing was 83%, 61% and 61% in the SBRT group vs. 86%, 61% and 56% in the TACE group, and 86%, 72% and 61% in the RFA group, p=0.4. The 1-, 3- and 5-year survival from the time of transplant was 83%, 75% and 75% in the SBRT group vs. 96%, 75% and 69% in the TACE group, and 95%, 81% and 73% in the RFA group, p=0.7.

Fortis

Review

Stereotactic Body Radiation Therapy for Hepatocellular Carcinoma: Current Trends and Controversies

Stephanie K. Schaub, MD[1], Pehr E. Hartsgrove, MD[1], Michael I. Lock, MD, CCFP, FRCPC, FCFP[2], Morten Høyer, MD, PhD[3], Thomas B. Brunner, MD[4], Higinia R. Cardenes, MD, PhD[5], Laura A. Dawson, MD FRCPC, FASTRO[6], Edward Y. Kim, MD[1], Nina A. Mayr, MD, FASTRO, FAAAS[1], Simon S. Lo, MB, ChB, FACR, and Smith Apisarnthanarax, MD[1]

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Comparison: SBRT vs others

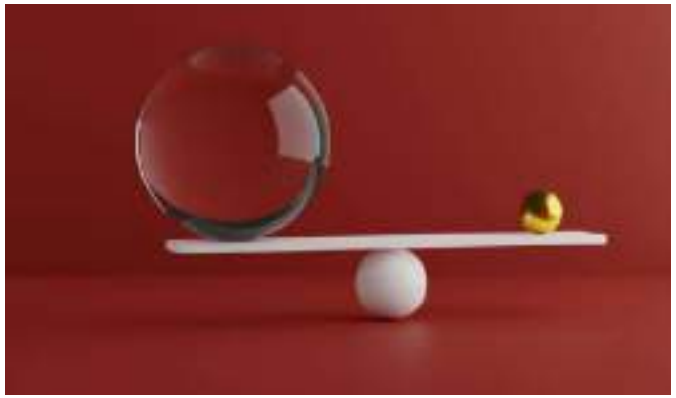

Table 5. Summary of Key Clinical Data of SBRT Compared to Other Liver-Directed Therapies.

Study, Year	Study Type	n	Modalities Compared	Inclusion Criteria	SBRT Details	Tumor Control	OS	Comments
Wahl, 2016[73]	Single-center retrospective	224	SBRT vs RFA	Inoperable, nonmetastatic	30 Gy/3 or 50 Gy/5	Freedom from local progression 1-year 97 vs 84% 2-year 84 vs 80%	1-year 74 vs 70% 2-year 46 vs 53%	SBRT associated with better local control for tumors ≥ 2 cm
Rajyaguru, 2018[74]	NCDB	3980	SBRT vs RFA	T1-2N0M0	≤50 Gy/3-5	NR	5-year 19 vs 30%[a]	Significant patient differences remained after propensity matching
Sapir, 2018[75]	Single-center retrospective	209	SBRT vs TACE	1-2 tumors, non-metastatic	30 Gy/3 or 50 Gy/5	Absence of progressive disease by RECIST 1-year 97 vs 47%[a] 2-year 91 vs 23%[a]	No significant difference	SBRT patients were older, but tended to have better performance status
Su, 2016[76]	Single-center retrospective	77	TAE/TACE+SBRT vs SBRT	Tumor > 5 cm; CP-A/B; N0 M0; WHO PS 0-1	30-50 Gy/3-5	Local relapse-free survival No significant difference	1-year 76 vs 62%[a] 3-year 51 vs 33%[a] 5-year 47 vs 33%[a]	$BED_{10} \geq 100$ Gy and EQD2 ≥ 74 Gy significantly associated with improved OS, PFS, LRFS, and DMFS
Su, 2017[77]	Single-center retrospective	117	SBRT vs Resection	1-2 tumors ≤ 5 cm; No prior LDT; CP-A; N0 M0; WHO PS 0-2; No PVT	42-48 Gy/3-5	Intrahepatic progression free survival 1-year 84 vs 69% 3-year 59 vs 62% 5-year 44 vs 36%	1-year 100 vs 98% 3-year 92 vs 89% 5-year 74 vs 62%	SBRT recommended for patients with comorbidities who could not tolerate surgery or were medically inoperable. No incidence of hepatic hemorrhage or pain in SBRT group, but more acute nausea and weight loss[a]
Yuan, 2013[78]	Single-center retrospective	48	SBRT vs resection	Stage I HCC; CP A-C; R0 surgical resection	39-54 Gy/3-8	Local control 1-year 93 2-year 90 3-year 68	1-year 73 vs 89% 2-year 67 vs 73% 3-year 57 vs 69%	Higher proportion of CP-B/C in SBRT vs surgery, 55% vs 12%[a] Higher proportion of systemic disease in SBRT vs surgery, 41% vs12%[a]
Jacob, 2015[79]	Single-center retrospective	161	TACE + SBRT vs TACE	Tumor ≥ 3 cm	45 Gy / 3	Crude local recurrence 11 vs 26%[a]	MST 33 vs 20 months[a]	SBRT started 2 wks post-TACE. Low rates of GI toxicity
Paik, 2016[80]	Single-center retrospective	154	iTACE + SBRT vs cTACE/iTACE + curative Tx vs iTACE+noncurative Tx	Initial TACE; 1 to 3 tumors ≤ 10 cm; CP-A/B; N0 M0	40-60 Gy/3-5	NR	iTACE + SBRT vs iTACE + noncurative Tx 2-year 73 vs 54%[a] 5-year 53 vs 28%[a]	No significant differences in OS between iTACE + SBRT and cTACE/iTACE + curative Tx

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Table 5. (continued)

Study, Year	Study Type	n	Modalities Compared	Inclusion Criteria	SBRT Details	Tumor Control	OS	Comments
Sapisochin, 2017[81]	Single-center retrospective	379	SBRT vs TACE or RFA	Received bridging therapy of SBRT, TACE, or RFA prior to transplant	36 Gy/6	Partial and complete necrosis in explanted livers No significant difference	No significant difference	No significant difference in risk of recurrence after liver transplant between SBRT, TACE, or RFA
Shiozawa, 2015[82]	Single-center pilot	73	SBRT vs RFA	Solitary tumor ≤ 3 cm (RFA) or ≤ SBRT; CP-A/B8; Who PS 0-2; N0 M0	60 Gy/3-5 (adapted based on size)	Local control	1-year 95 vs 100%	SBRT patients were deemed unable to receive RFA based on comorbidities, location, or size
Yoon, 2018[17]	Single-center phase 3	90	TACE-hypofractionated RT vs sorafenib	First line for CP-A patients with PVT	45 Gy in 2-3 Gy-fractions (3DCRT)	1-yr 97 vs 97% PFS 12-weeks 86.6 vs 34.3%[a] Radiologic response rate 24-weeks 33% vs 2.2%[a] Median time to progression 31 vs 11.7 weeks[a]	MST 55 vs 43 weeks[a]	In TACE-RT arm, no patient discontinued treatment due to hepatic decompensation. 11.1% in the TACE-RT arm were able to undergo curative surgical resection due to downstaging

Abbreviations: BED, biological equivalent dose; CP, Child-Pugh; cTACE, complete TACE; curative, includes surgery, RFA, and percutaneous ethanol injection; DMFS, distant metastasis free survival; EQD2, equivalent dose in 2 Gy fractions; GI, gastrointestinal; HCC, hepatocellular carcinoma; iTACE, incomplete TACE; LDT, liver-directed therapy; LRFS, local recurrence free survival; MST, median survival time; n, patient number; NCDB, National Cancer Database; non-curative, includes TACE, sorafenib, or chemotherapy; NR, not reported; OS, overall survival; PFS, progression-free survival; PVT, portal vein thrombosis; RFA, radiofrequency ablation; SBRT, stereotactic body radiation therapy; TACE, transarterial chemoembolization; TAE, transarterial embolization; Tx, treatment; WHO, World Health Organization.
[a]Statistically significant.

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

2021

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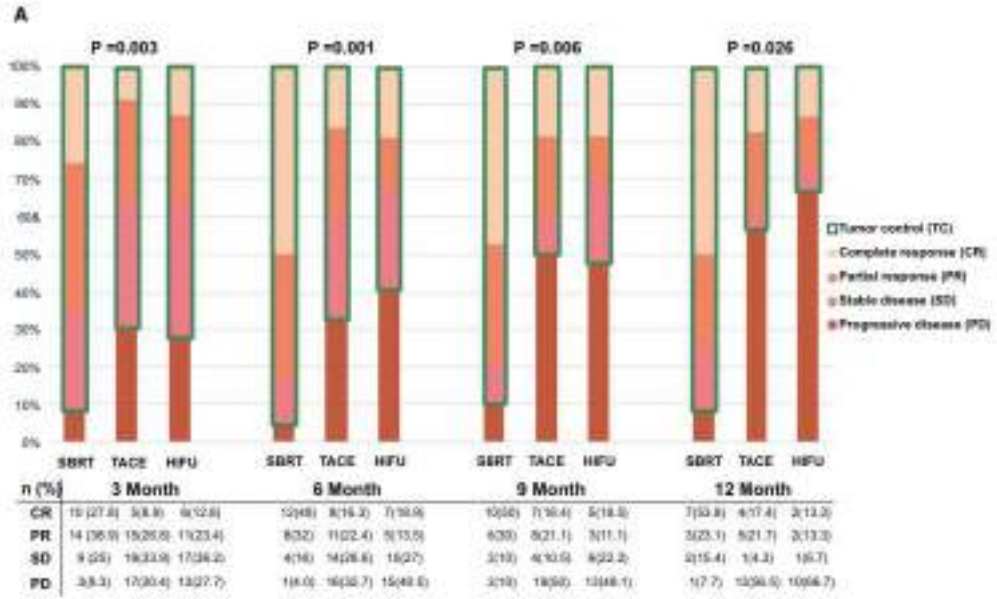
BACKGROUND AND AIMS: There are no prospective data on stereotactic body radiation therapy (SBRT) as a bridge to liver transplantation for HCC. This study aimed to evaluate the efficacy and safety of SBRT as bridging therapy, with comparison with transarterial chemoembolization (TACE) and high-intensity focused ultrasound (HIFU).

APPROACH AND RESULTS: Patients were prospectively enrolled for SBRT under a standardized protocol from July 2015 and compared with a retrospective cohort of patients who underwent TACE or HIFU from 2010. The primary endpoint was tumor control rate at 1 year after bridging therapy. Secondary endpoints included cumulative incidence of dropout, toxicity, and posttransplant survival.

During the study period, 150 patients were evaluated (SBRT, n = 40; TACE, n = 59; HIFU, n = 51). The tumor control rate at 1 year was significantly higher after SBRT compared with TACE and HIFU (92.3%, 43.5%, and 33.3%, respectively; P = 0.02). With competing risk analysis, the cumulative incidence of dropout at 1 and 3 years after listing was lower after SBRT (15.1% and 23.3%) compared with TACE (28.9% and 45.8%; P = 0.034) and HIFU (33.3% and 45.1%; P = 0.032). Time-to-progression at 1 and 3 years was also superior after SBRT (10.8%, 18.5% in SBRT, 45%, 54.9% in TACE, and 47.6%, 62.8% in HIFU; P < 0.001). The periprocedural toxicity was similar, without any difference in perioperative complications and patient and recurrence-free survival rates after transplant. Pathological complete response was more frequent after SBRT compared with TACE and HIFU (48.1% vs. 25% vs. 17.9%, respectively; P = 0.037). In multivariable analysis, tumor size <3 cm, listing alpha-fetoprotein <200 ng/mL, Child A, and SBRT significantly reduced the risk of dropout.

CONCLUSIONS: SBRT was safe, with a significantly higher tumor control rate, reduced the risk of waitlist dropout, and should be used as an alternative to conventional bridging therapies. (HEPATOLOGY 2021;74:2580-2594).

Liver transplantation (LT) is the best treatment option for selected patients with early HCC.[1,2] The implementation of the Model for End-Stage Liver Disease (MELD) exception points for patients with HCC aimed to alleviate the



SBRT scores :

- ✓LC @ 1 yr
- ✓Dropouts @ 1 & 3 yrs
- ✓Pathological response

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2020

ORIGINAL RESEARCH

Stereotactic Body Radiation Therapy vs. Transarterial Chemoembolization in Inoperable Barcelona Clinic Liver Cancer Stage a Hepatocellular Carcinoma: A Retrospective, Propensity-Matched Analysis

OPEN ACCESS

Conclusions: SBRT was an alternative to TACE for inoperable BCLC-A stage HCC with better local and intrahepatic control. Controlled clinical trials are recommended to evaluate the actual effects of this novel regimen adequately.

Results: There was a smaller median tumor size in the SBRT group than in the TACE group (3.4 cm vs. 7.2 cm, $P < 0.001$). After propensity score matching in the selection of 95 patient pairs, SBRT had better LC, IC, and PFS than TACE but showed comparable OS. The accumulative 1-, 3-, and 5-year OS rates were 85.7, 65.1, and 62.8% in the SBRT group and 83.6, 61.0, and 50.4% in the TACE group, respectively ($P = 0.29$). The accumulative 1-, 3-, and 5-year PFS were 63.4, 35.9, and 27.5% in the SBRT group and 53.5, 27.4, and 14.2% in the TACE group, respectively ($P = 0.049$). The accumulative 1-, 3-, and 5-year LC were 86.8, 62.5, and 56.9% in the SBRT group and 69.3, 53.3, and 36.6% in the TACE group, respectively ($P = 0.0047$). The accumulative 1-, 3-, and 5-year IC were 77.3, 45.9, and 42.4% in the SBRT group and 57.3, 34.1, and 17.7% in the TACE group, respectively ($P = 0.003$). On multivariate analysis, treatment (SBRT vs. TACE) was a significant covariate associated with local and intrahepatic control (HR = 1.59; 95% CI: 1.03–2.47; $P = 0.04$; HR = 1.61; 95% CI: 1.13–2.29; $P = 0.009$).

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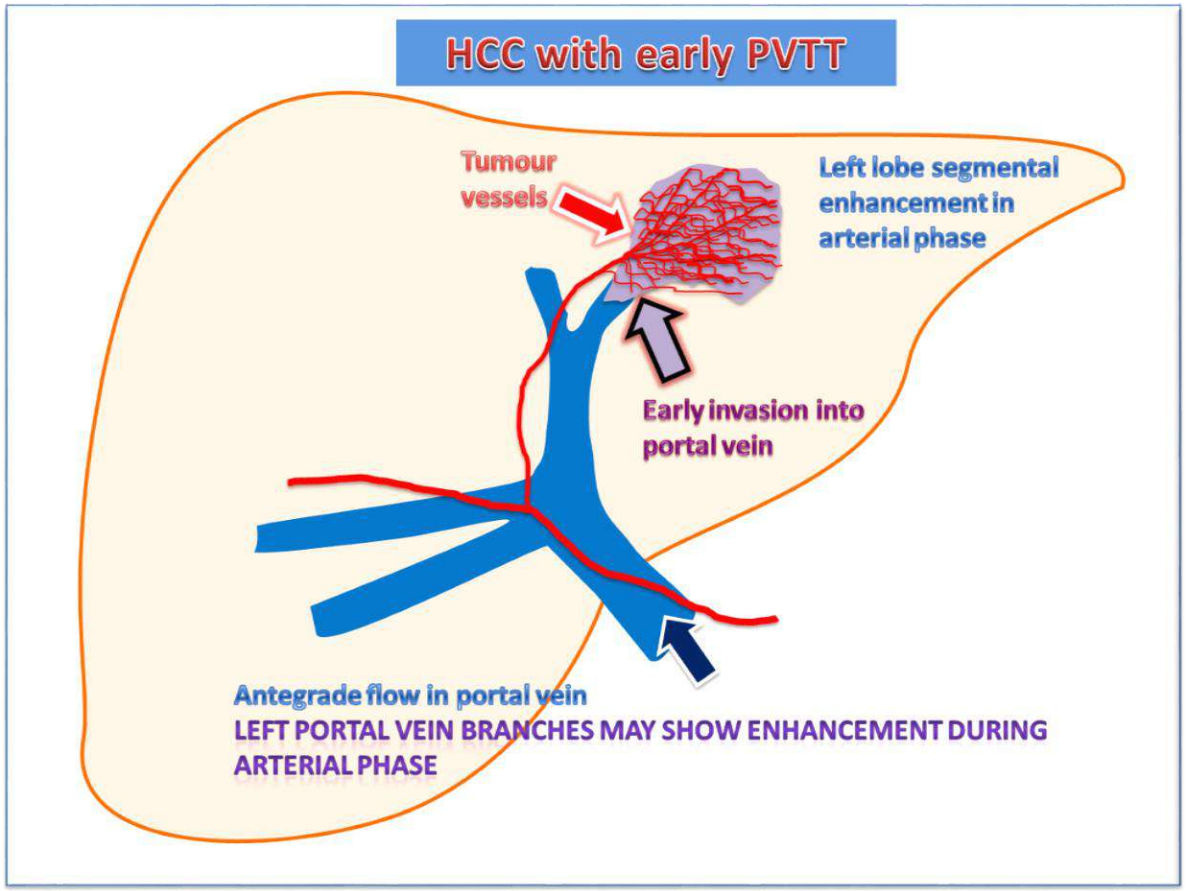
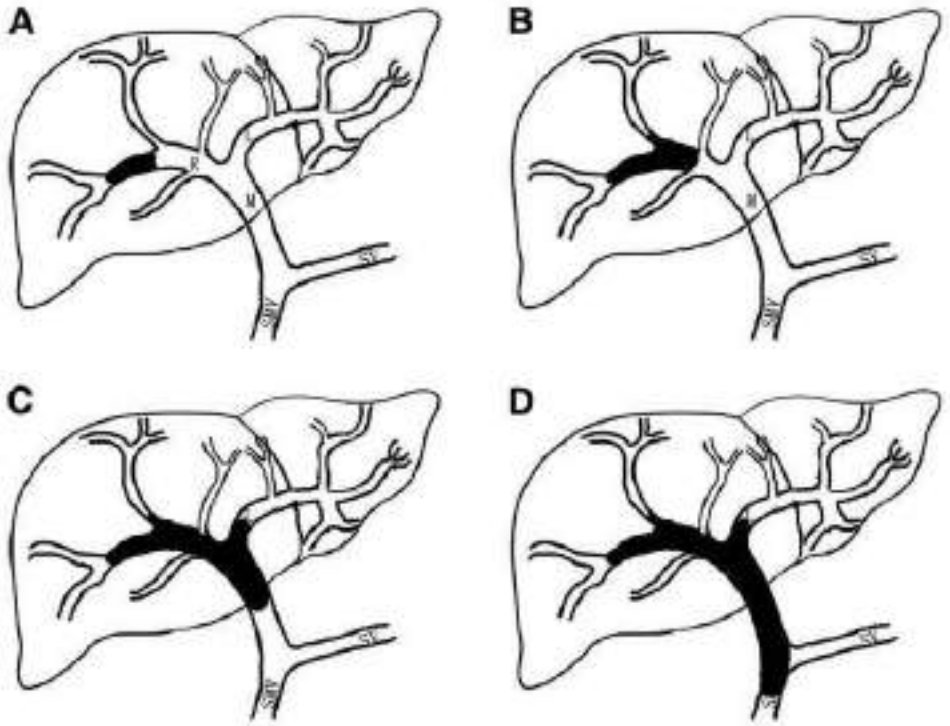
HCC with PVTT





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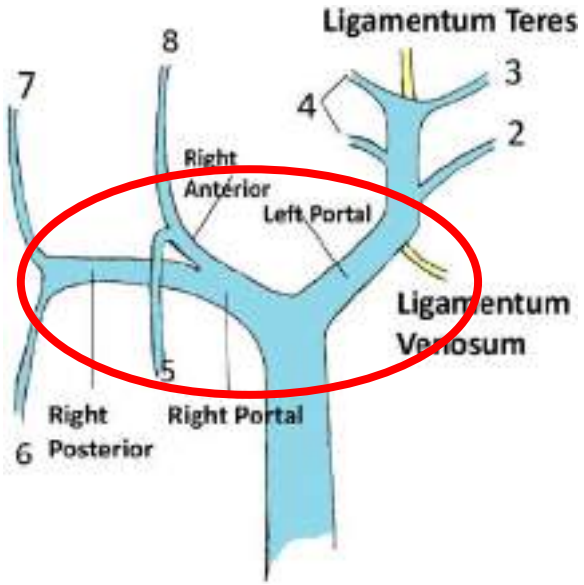
HCC & PVTT

- Untreated→ Poor prognosis : median survival – 6-9 mths (early)/ 1-3 mths advanced)
- PVTT – 10-40% (at diagnosis) – further complicate



Presence of PVTT:

- outside MILAN- BCLC C- No transplant
- Standard therapies (TACE) – challenging
- Increased risk of : complications
- Poor prognosis
- Median survival: 2.7 months (PVTT+) Vs 10-24 months [No PVTT]

Cheung TK, Lai CL, Wong BC, Fung J, Yuen MF. Clinical features, biochemical parameters, and virological profiles of patients with hepatocellular carcinoma in Hong Kong. Aliment Pharmacol Ther2006; 24: 573-583

Minagawa M, Makuuchi M. Treatment of hepatocellular carcinoma accompanied by portal vein tumor thrombus. World J Gastroenterol2006; 12: 7561-7567

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Bland Vs Malignant Thrombus

- Bland thrombus - in patients with/ or without malignant disease - 4.5%–26% of CLD & 42% of HCC.
  - Both can be coexistent : detection is crucial
  - Reference standard: histopathologic examination → However in clinical practice radiology is relied upon

- Shah et al : criteria for Malignant (any criteria met) Vs Bland (none are met)
  - Expansion of the involved vessel
    - vessel diameter ≥1.8 cm (MPV); ≥1.6 cm (RPV'; ≥1.8 cm (LPV)
    - disproportionate enlargement as compared to non-affected same-order portal vein branches in the same lobe
  - Enhancement on dynamic contrast enhanced CT and MR
    - arterial phase - enhancement on the contrast-enhanced images when compared with baseline images (≥20 HU on CT and ≥15% on MR images)

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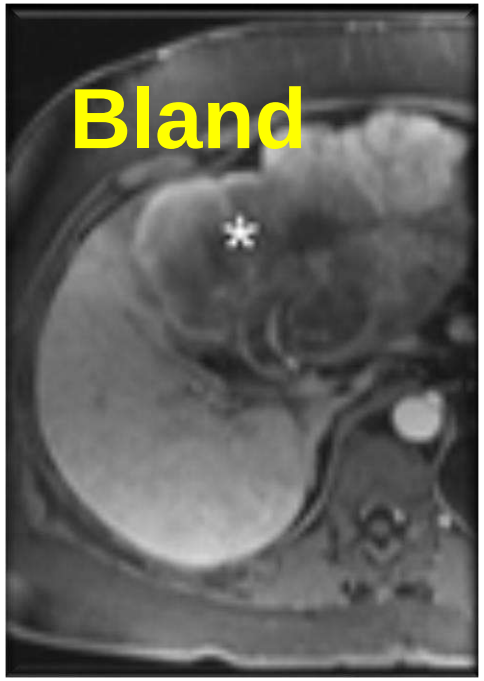
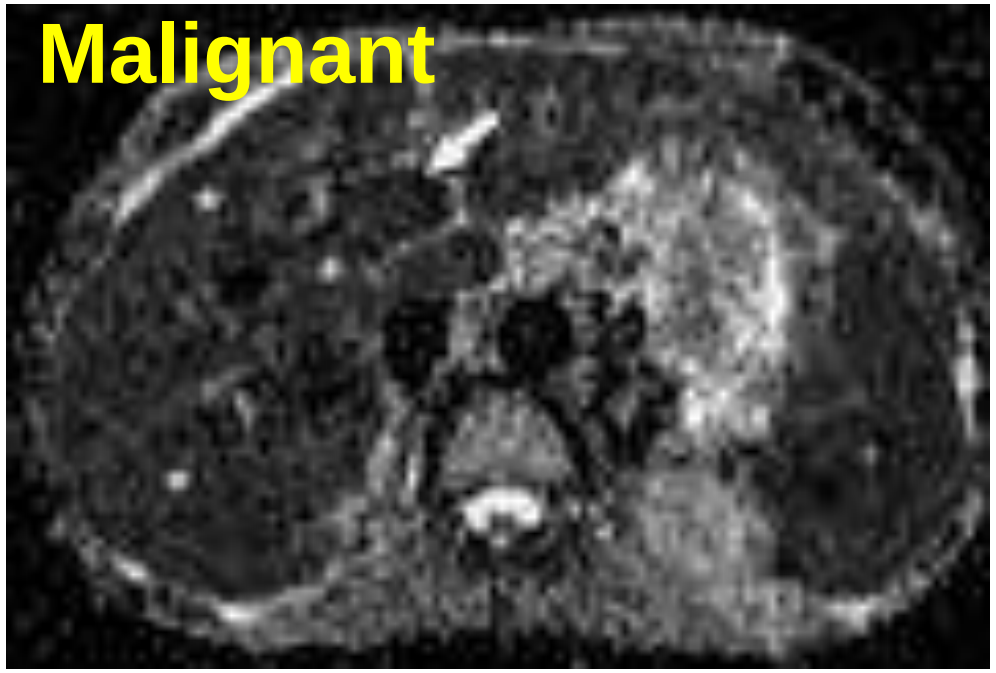
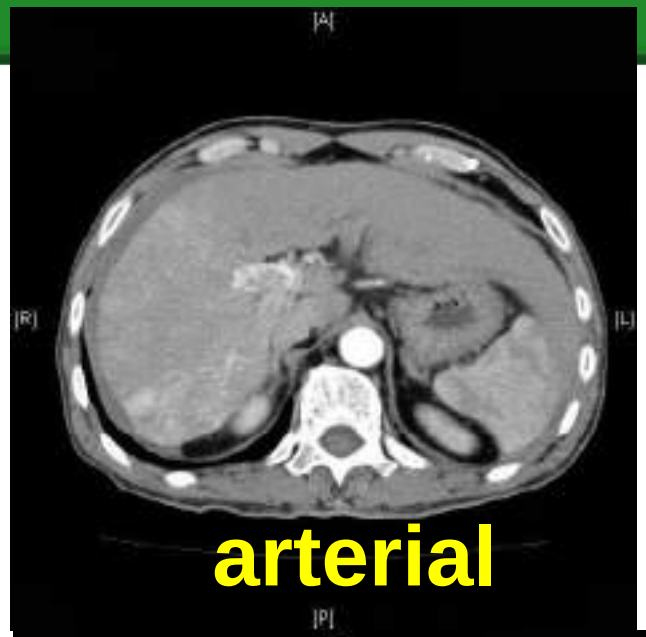
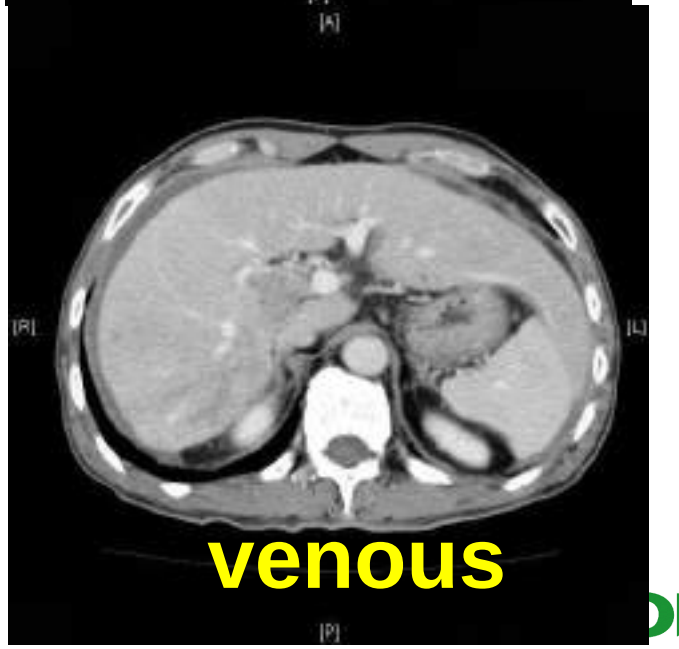
PVTT - radiology

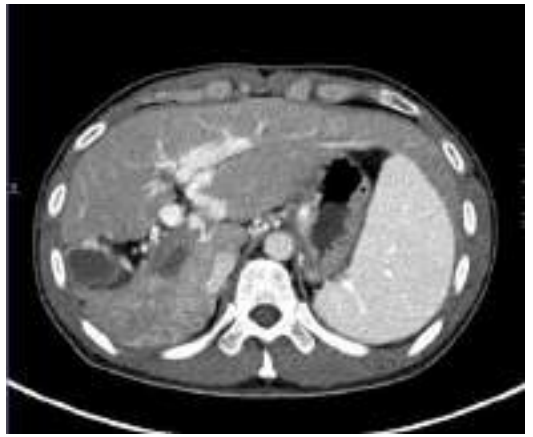








PVTT: Diagnosis



- Liver Imaging Reporting and Data System (LiRADs v14)
  - Enhancement similar to primary HCC
  - Not diagnostic but features to alert:
    - occluded vein with **expanded lumen, or ill-defined walls**, or restricted diffusion on diffusion-weighted MRI sequences, or contiguous with typical HCC lesion
    - obscured, **partially visualized vein**
    - heterogeneous enhancement of vein
  - **Non-tumoral thrombus does not enhance or expand the lumen**
  - If standard imaging is controversial → Contrast-enhanced Ultrasound or PET-CT contrast or Biopsy

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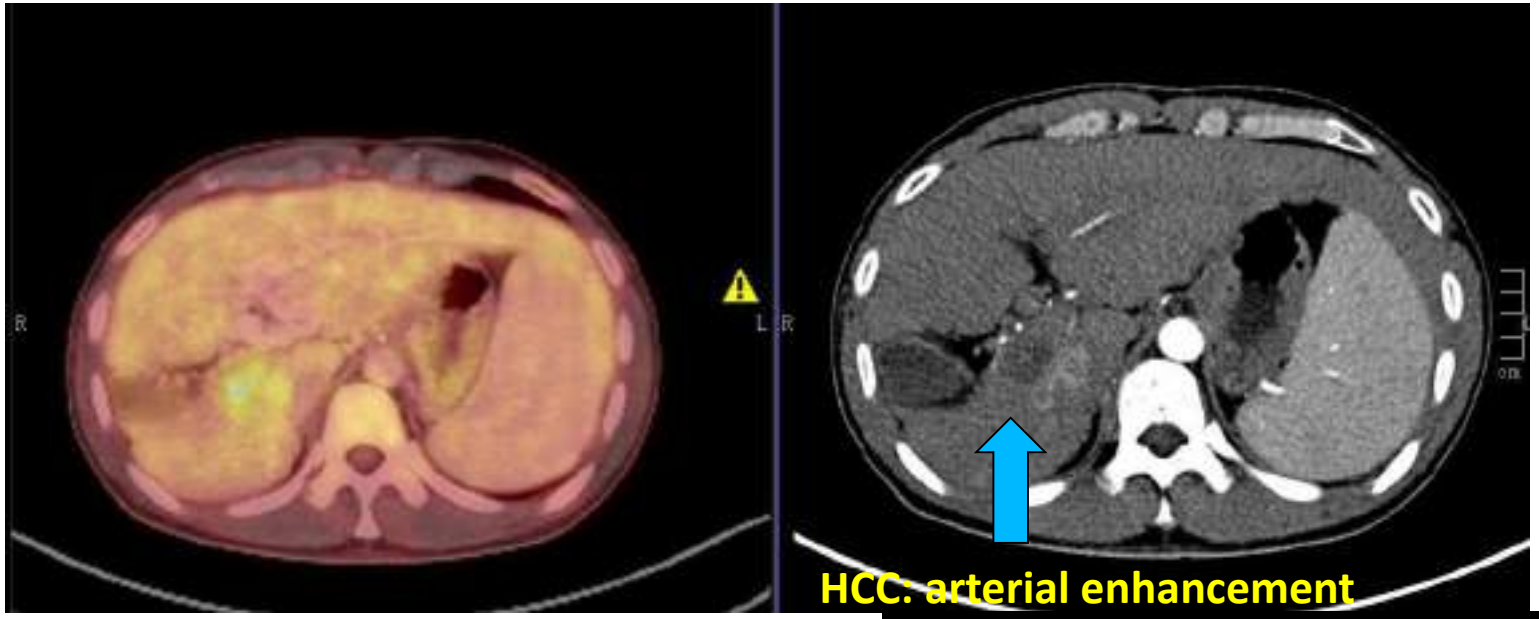
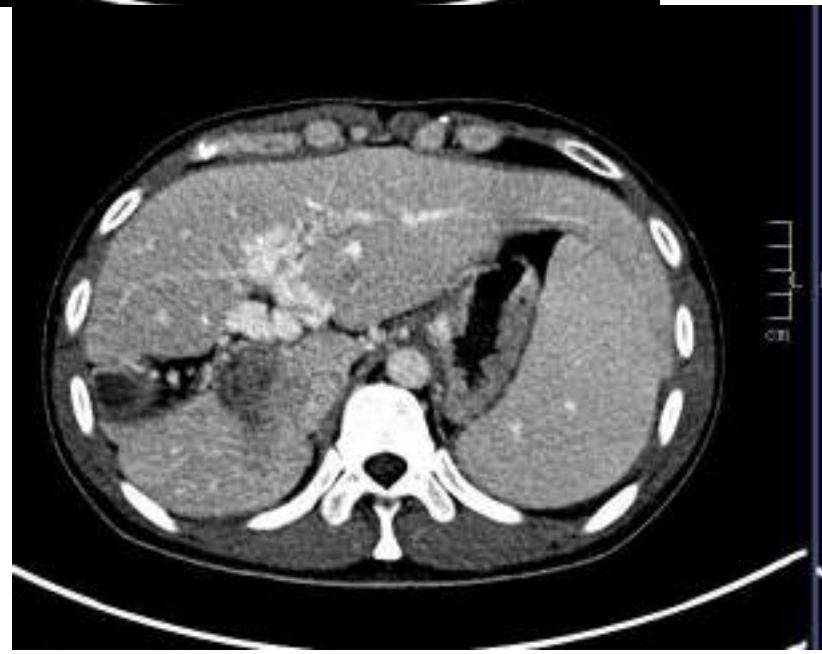
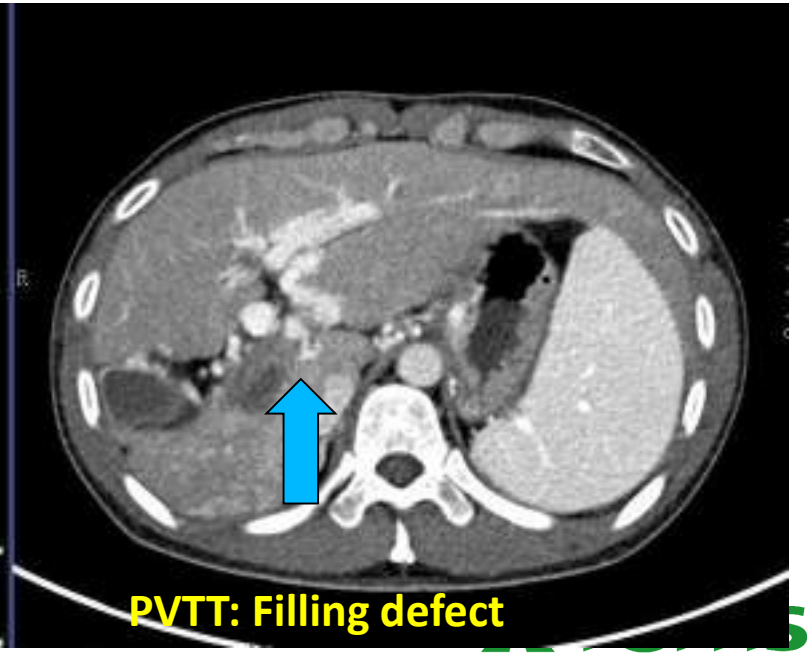
PET + CT



HCC: arterial enhancement

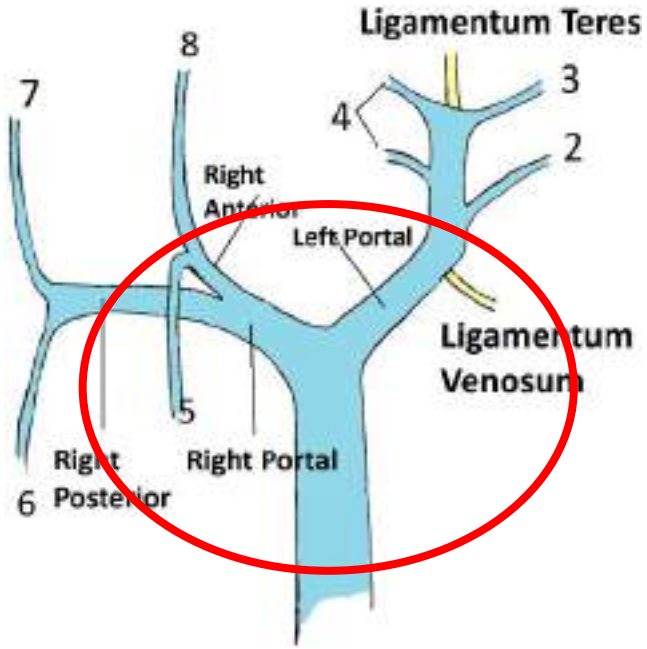




PVTT: Filling defect

PVTT:

- PVTT mechanism:
  - Majority around primary HCC – **aPVTT direct invasion, hepatic AV fistula & PV countercurrent**



  - Many potential biomarkers studied to predict micro PVTT
    - AFP
    - MiRNAs
    - DCP (de-gamma-corboxy prothrombin)]
      - **> 101 mAu/ ml DCP, > 3.6 cm dia HCC, SUVmax > 4.2 –** 100% sensitive and 90.9% specific [Shirabe K et al, 2014]

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Is All PVTT the same?

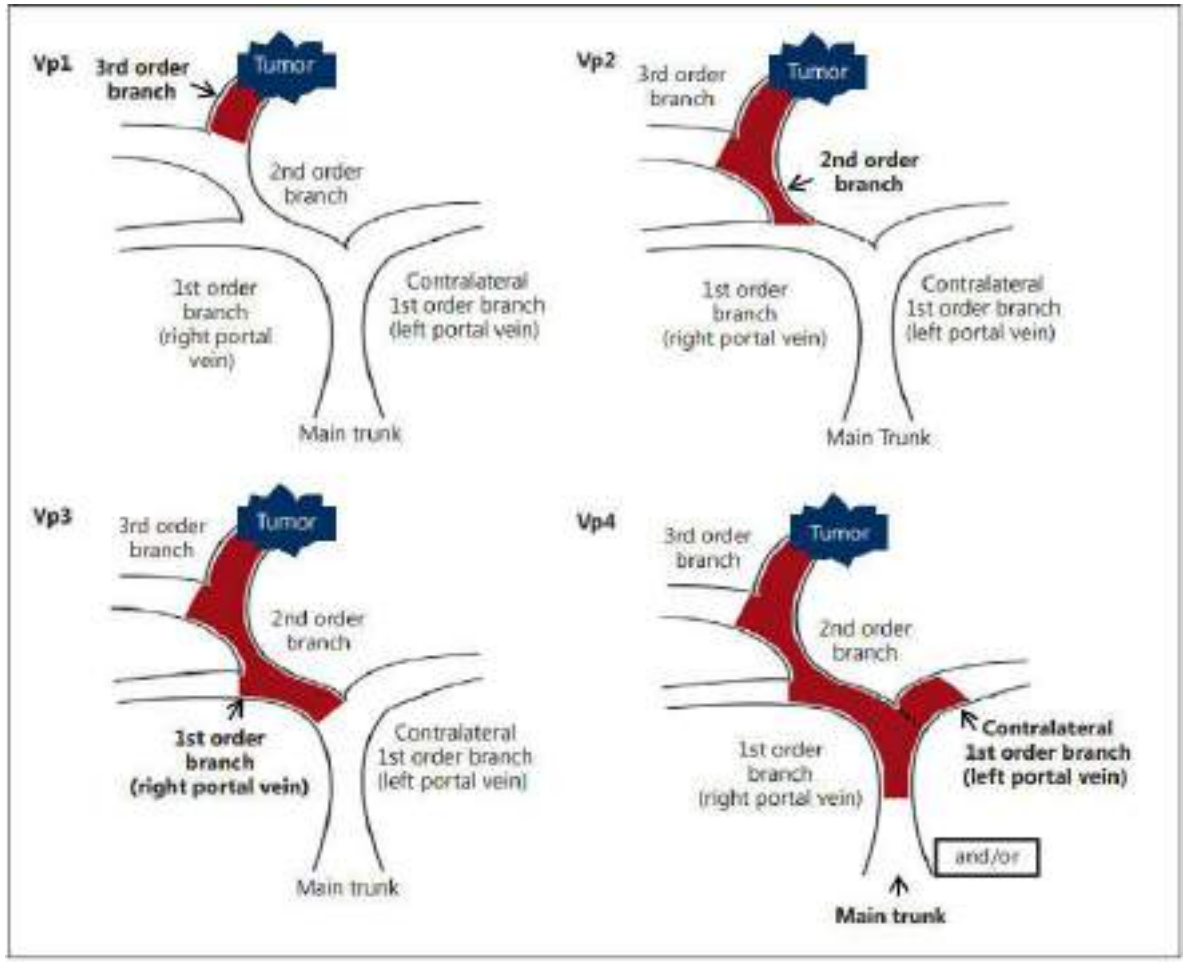

Fig. 1. Classification for hepatocellular carcinoma with portal vein tumor thrombosis according to the Liver Cancer Study Group of Japan classification.

- Liver Cancer Study Group of Japan:
  - PVTT into 4 classes
    - **Vp1 i**s defined by the presence of a PVTT distal to, but not in, the second-order branches of the portal vein
    - **Vp2** is defined by the presence of a PVTT in the second-order branches of the portal vein
    - **Vp3** is defined by the presence of a PVTT in the first-order branches of the portal vein
    - **Vp4** is defined by the presence of a PVTT in the main trunk of the portal vein or a contralateral portal vein branch or both
  - HVTT in 3 categories:
    - tumor thrombosis in a **peripheral** hepatic vein (pHVTT or Vv1)
    - in a **major** hepatic vein (mHVTT or Vv2
    - in the **inferior vena cava** (IVCTT or Vv3)

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Guidelines for HCC-PVTT

- BCLC – Stage C :
  - Recommends - Sorafenib

    Forner A, Reig ME, de Lope CR, Bruix J. Current strategy for staging and treatment: the BCLC update and future prospects. Semin Liver Dis 2010; 30: 61-74
- AASLD and EASL:
  - TARE – recognized as effective by AASLD but not specifically recommended
  - EASL – discourage TACE and state safety of TARE – but not recommended

    Bruix J, Sherman M. Management of hepatocellular carcinoma: an update. Hepatology2011; 53: 1020-1022 European Association For The Study Of The Liver; European

    Organisation For Research And Treatment Of Cancer. EASLEORTC clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol 2012; 56: 908-943
- NCCN – 2015:
  - Sorafenib / locoregional therapies – indicated
  - Arterially directed therapies – relatively contraindicated

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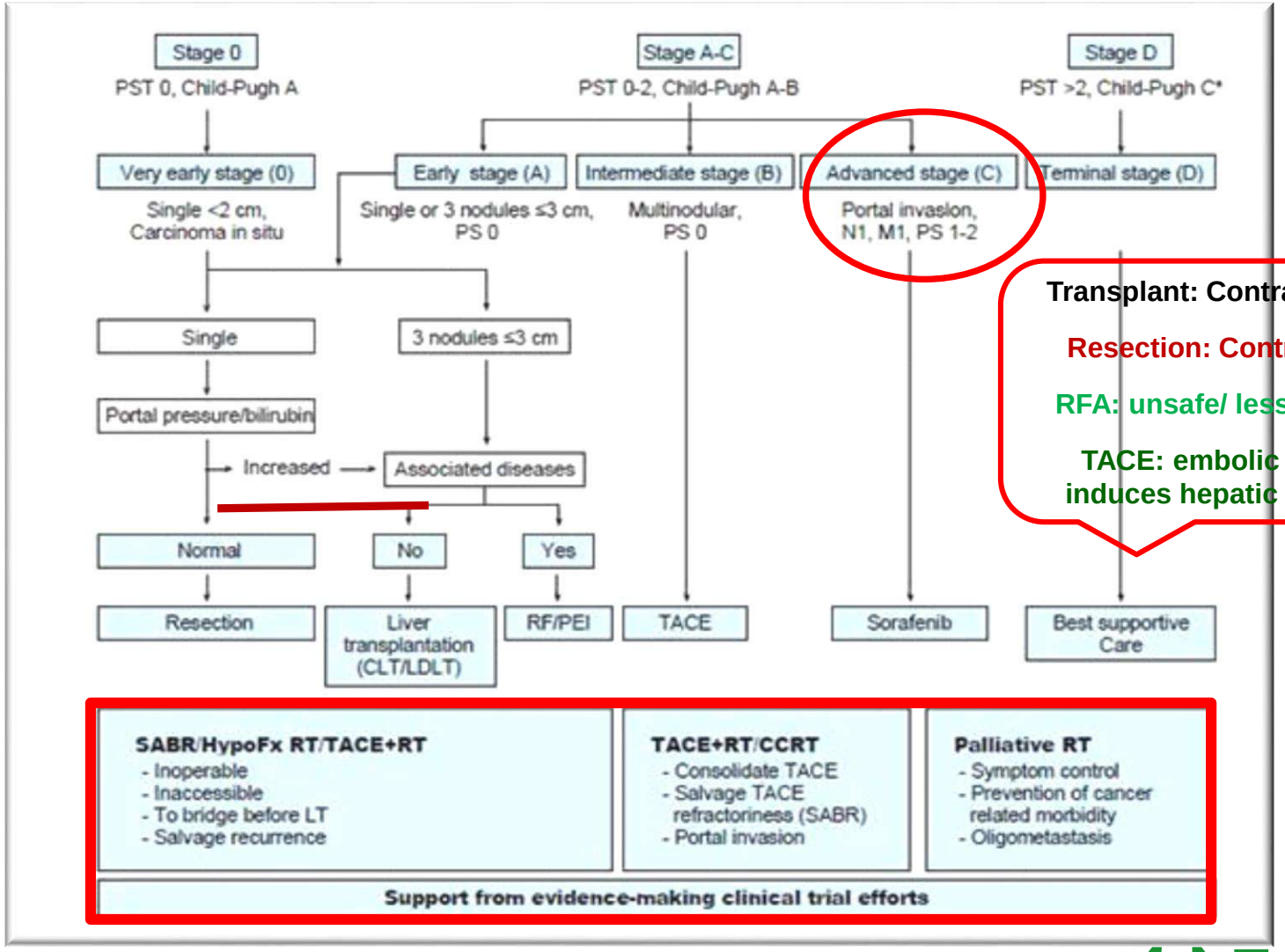
PVTT : significance

- Ineligible for many standard Rx (Sx/ PEI/ RFA (specially hilar/ major PV)
- Poor prognosis: Untreated → MST - only 2–4 months
- Limited treatment option: exploration of liver directed RT +/- TACE
  - Transplant – C/I – outside Milan
  - TACE: ? Limited efficacy→ never demonstrated in RCT

    : limitation - treatment related ischemic injury/ risk of liver failure



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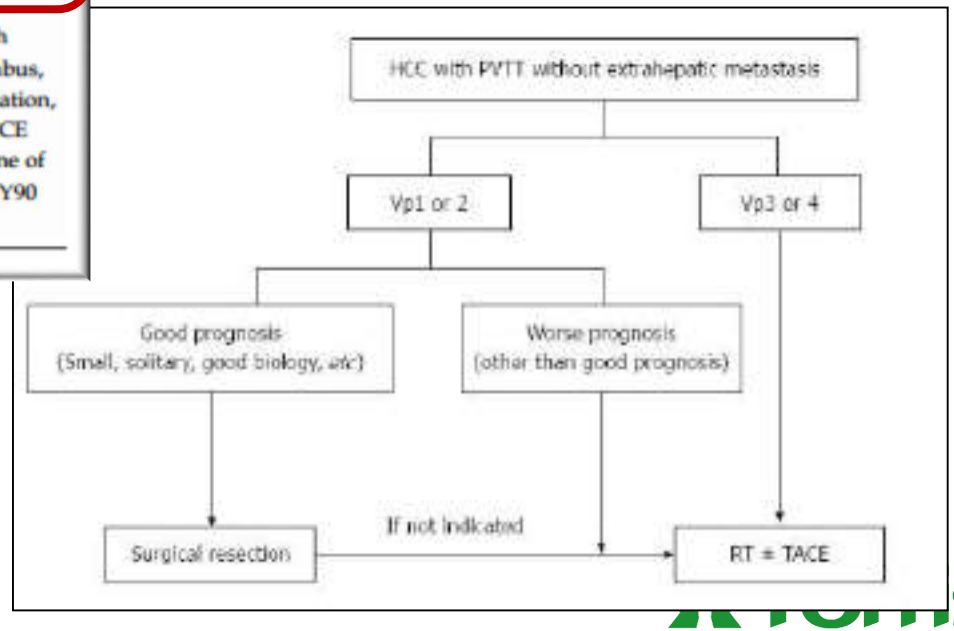
HCC – PVTT: Limited treatment options

Quirk M *et al*. Management of HCC with PVT

Table 1 Up-to-date summary of management options for hepatocellular carcinoma with portal vein thrombosis

	Survival data (mo)					Adverse effects	Key references	Additional comments
	Overall survival	Main PVTT	Branch PVTT	CP-A	CP-B			
Supportive care	2-4						Schoniger *et al*[12], Minagawa *et al*[9], Llovet *et al*[10]	
Surgical resection	9-33	9-10				0%-6% operative mortality	Lau *et al*[13], Shi *et al*[17], Chen *et al*[18], Lin *et al*[21]	Employed in select centers
Sorafenib	6-8			8.1		skin reaction, diarrhea, fatigue	Llovet *et al*[27], Cheng *et al*[29]	Recommended by AASLD and EASL guidelines; Dose reduction in 25%, interruption in 44% Investigational
XRT	9.6					radiation induced liver disease	Toya *et al*[53]	
TACE	7-10	5.3	10.2	7.4	2.8	liver failure, postembolization syndrome	Pinter *et al*[40], Chung *et al*[41], Luo *et al*[43], Xue *et al*[44]	Lowest risk with nonocclusive thrombus, cavernous transformation, superselective TACE
Y-90 SIRT	5-17	9	17	10.4	5.6	fatigue, hyperbilirubinemia, GI ulceration	Salem *et al*[59], Hilgard *et al*[60], Sangro *et al*[61]	Currently, PVT is one of the indications for Y90



Management of PVTT as per location

- Although considered inoperable/ attempted R0 & R1 resection – moderate outcomes
- **However in Vp3-4 outcomes have not improved over time → most important scope for non operative modalities – WHERE SBRT CAN SCORE**

Table 1. Summary of management for hepatocellular carcinoma with portal vein thrombosis

	Survival data (months)			Adverse events
	Overall survival	Main PVTT	Branch PVTT	
Supportive care[5]	2-4			
Surgical resection[6]	9-33	9-10		Operative mortality; 0-6%
TACE[23]	7-10			Liver failure, postembolization syndrome
External radiation therapy[26]	9.2			Radiation induced liver disease
HAIC[42,43]	6-7			
Radioembolization[33-35]	10	4.5	16	Fatigue, hyperbilirubinemia, GI ulceration
Sorafenib[44,46]	6-8			Skin reaction, diarrhea, fatigue

HAIC, hepatic artery infusion chemotherapy; PVTT, portal vein tumor thrombosis; TACE, transarterial chemoembolization; GI, gastrointestinal.

Hyun Young Woo, Clinical and Molecular Hepatology 2015;21:115-121

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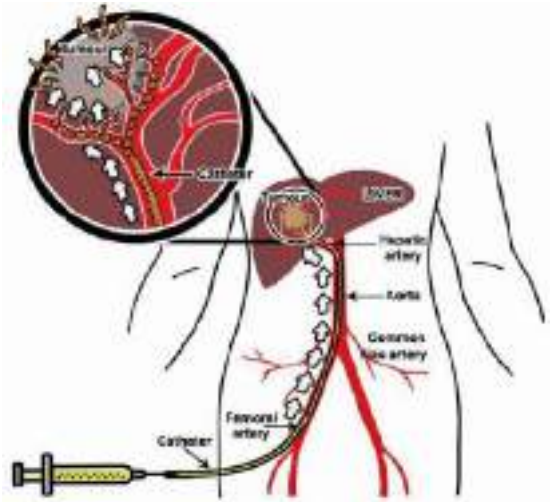
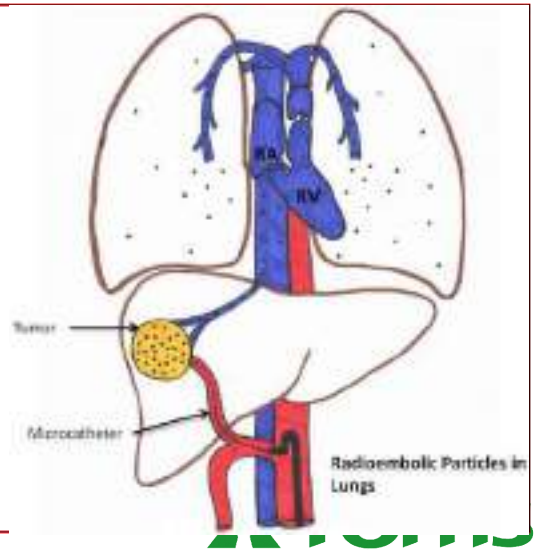
TACE & TARE

- TACE : M/C - unresectable HCC
- Usually contraindicated in Vp4 or Vp3 : fear of hepatic ischemia by embolizing compromised liver vasculature/ acute failure
- **1997- Lee et al**: super selective TACE – owing to collateral circulation
- Overall – viable option for selected:
  - Non occlusive thrombus
  - With normal preserved liver function
  - Lesser tumor burden - <70% of the entire liver
  - MPV not completely blocked, or it is completely blocked but collaterals have formed

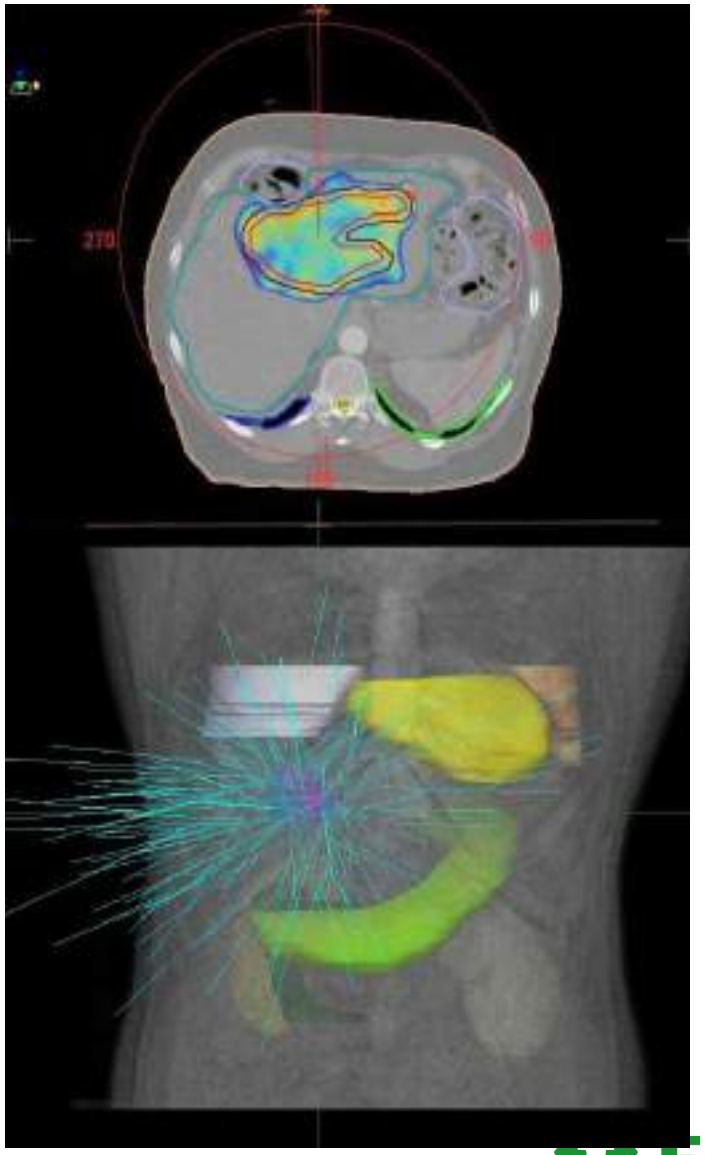


- TARE: New therapeutic modality
- Effective dose may vary from 100 Gy to 3000 Gy
- weaker embolic effect → use in PVTT
- Alternative or superior to TACE in unresectable – diffuse/ multifocal
- **Need prior mapping – rule out lung shunt/ mesenteric anomalous branching**

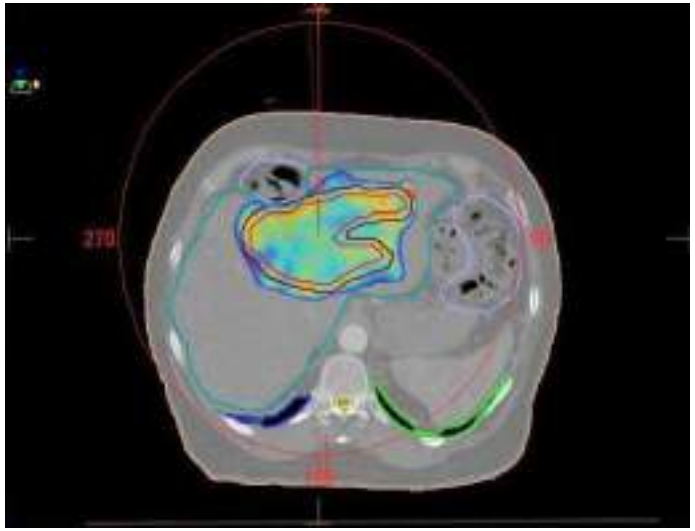


HCC with PVTT

- Benefits of controlling PVT by SBRT in HCC:
  - **Reduction in intrahepatic metastasis** through portal vein
  - **Decrease in portal pressure & related complications**
  - **Possibility of re-canalization** with feasibility of transplant/ TACE



Radiation in HCC – PVTT:
Literature review



PVTT-RT : evidence

- Takagi et al. 1989/ 1994: **1st use of PVTT –RT** [2/7 cases: histologic & angiographic response]
- Lin CS et al, 2006: Taiwan → **71% rate of partial venous recanalization** after FSRT / 3D-CRT in 16 cases
- University of Tsukuba, Japan: **MST - 22 mth & local PFS 21 mths**
- Xi et al, 2013 : SBRT – median 36 Gy (range: 30-48) in 6 fr→ CR,PR,SD,PD of 36%, 39%,17%, and 7%
- Bujold et al, 2013: largest SBRT series (56 cases) – median dose of 36 Gy (range: 24–54 Gy) in six fr → 1-year OS - 44% and MST - 10.6 months

Table 2. Liver-directed radiation outcomes for hepatocellular carcinoma with tumor vascular thrombosis

Study	Institution	Year	Study design	No. of patients	Tumor size (range)	Treatment	Dose (Gy), median (range)	Fx	1-year OS	MS (months)	Grade ≥3 toxicity (%)
Bujold et al. [51]	Princess Margaret Hospital, Canada	2013	Prospective	56	1.8–23.1 cm	SBRT	36 (24–54)	6	44%	10.6	36[a]
Xi et al. [76]	Guangzhou, China	2013	Retrospective	41	NR	SBRT	36 (30–48)	6	50%	13	2.40
Sugahara et al. [77]	University of Tsukuba, Japan	2009	Retrospective	35	2.5–13 cm	Proton	72.6 (55–77) GyE	2.2–5.5 GyE/Fx	48% at 2 years	22	8.60
Choi et al. [78]	Catholic University, Korea	2008	Retrospective	9	3.9–47.7 mL	SBRT	36 (30–39)	3	43.20%	8	16[a]
Yoon et al. [79]	Asan Medical Center, Korea	2012	Retrospective	412	2–21 cm	3D-CRT plus TACE	40 (21–60)	2–5 Gy/Fx	43%	10.6	10
Rim et al. [80]	Korea University Medical Center, Korea	2012	Retrospective	45	1.5–17.3 cm	3D-CRT	61.2 (38–65)	1.8–2.5 Gy/Fx	52%	13.9	2
Chuma et al. [81]	Hokkaido University, Japan	2011	Retrospective	20	6–14.5 cm	3D-CRT plus intra-arterial 5-FU and subcutaneous IFN	30–48	6–20	NR	10.6	15
Huang et al. [82]	Kaohsiung Medical Center, Taiwan	2009	Retrospective	326	≥10 cm in 39%	3D-CRT	60	20–30	17%	3.8	0
Lin et al. [75]	Taipei, Taiwan	2006	Prospective	9	6.5 cm (median)	Fractionated SBRT	45	15		6	
				7	13.8 cm (median)	3D-CRT	45	25		6.7	

[a]Grade 3+ toxicity reported for all patients with and without tumor vascular thrombosis.
Abbreviations: 3D-CRT, three-dimensional conformal radiation therapy; 5-FU, 5-fluorouracil; Fx, fractions; GyE, Gray equivalent; IFN, interferon; IMRT, intensity-modulated radiation therapy; LC, local control; NR, not reported; OS, overall survival; SBRT, stereotactic body radiation therapy; TACE, transarterial chemoembolization.

Fortis

Radiotherapy: HCC-PVTT

- As early as 1994: Chen at al

- Later major reports only after 2000

2005 - 2009

Table 3 Radiotherapy and ablation therapy in patients with HCC and major PVTT

First author	year	No.	Classification of PVTT	Treatment	Survival rate	Median survival time
Hata [37]	2005	12	Vp 3–4	Proton beam therapy (50–72 Gv)	24 % (5-year)	11 mo (CR + PR)
Nakagawa [38]	2005	52	Vp 2–4	3D-CRT (39–60 Gy)	5.1 % (5-year)	NA
Zeng [39]	2005	44	Vp l–4, Vv3	External beam radiation (36–60 Gy)	34.8 % (1-year)	8.0 mo
Kim [40]	2005	59	Vp 3–4	3D-CRT (39–70.2 Gy)	20.7 % (2-year)	10.7 mo (CR + P)
Lin [41] [RCT]	2006	43	Vp 3–4	Stereotactic radiotherapy (22)	NA	6.0 mo
				3D-CRT (21)	NA	6.7 mo
Zhang [42]	2008	10	Vp 3	125-iodine seed implantation for PVTT	NA	NA
Shirai [42]	2009	26	Vp 3–4	3D-CRT using SPECT	30 % (2-year)	10.3 mo
Giorgio [44]	2009	13	Vp 4	Percutaneous RFA	77 % (3-year)	NA
Zheng [45]	2009	108	Vp 3–4	Percutaneous laser ablation	22.38 % (3-year)	NA

Table 1. Stereotactic body radiotherapy outcomes for hepatocellular carcinoma **2006 - 2013**

SE ASIAN data – very promising

Study	Institution	Year	Design	No. of patients	CP class	Tumor size (range)	TVT	Dose (Gy), median (range)	Fx	1-year OS	1-year LC	Grade ≥3 toxicity
Bujold et al. [51]	Princess Margaret Hospital, Canada	2013	Phase I/II	102	A	1.4–23.1 cm	55%	36 (24–54)	6	55%	87%	36%
Méndez Romero et al. [52]	Erasmus MC, Netherlands	2006	Phase I/II	8	A, B	0.5–7.2 cm	25%	25–37.5	3–5	75%	75%	12.50%
Kang et al. [53]	KIRMS, Korea	2012	Phase II	47	A, B	1.3–8 cm	11%	57 (42–60)	3	69% at 2 years	95% at 2 years	26%
Cárdenes et al. [54]	Indiana University, USA	2010	Phase I	17	A, B	≤6 cm (cumulative)	18%	36–48	3–4	75%	100%	18%
Tse et al. [46]	Princess Margaret Hospital, Canada	2008	Phase I	31	A	9–1,913 mL	42%	36 (24–54)	6	48%	65%[a]	26%
Ibarra et al. [55]	Multi-institutional	2012	Pooled analysis	21	A, B	9.5–1,493.8 mL	NR	30 (18–50)	1–10	87%	64%	8% RILD only
Sanuki et al. [56]	Tokai University, Japan	2013	Retrospective	185	A, B	0.8–5 cm	NR	30–40	5	95%	99%	13%
Jang et al. [58]	KIRMS, Korea	2013	Retrospective	108	A, B	1–7 cm	NR	51 (33–60)	3	63% at 2 years	87% at 2 years	10%[b]
Yoon et al. [59]	Asan Medical Center, Korea	2013	Retrospective	93	A, B	1–6 cm	0%	30–60	3–4	86%	95%	6.5% RILD only
Bibault et al. [60]	Lille, France	2013	Retrospective	75	A, B	3–4.4 cm	NR	45 (24–45)	3	79%	90%	16%[b]
Honda et al. [61]	Hiroshima, Japan	2013	Retrospective	30	A, B	1–3 cm	0%	48–60	4–8	100%	100%	7%
Yuan et al. [62]	Tianjin Medical University, China	2013	Retrospective	22	A, B, C	1.6–9.5 cm	NR	45 (39–54)	3–8	73%	93%	4.5% grade ≥2
Huang et al. [63]	Taipei, Taiwan	2012	Retrospective	36	A, B, C	1.1–12.3 cm	NR	37 (25–48)	4–5	64% at 2 years	98%	3%
Andolino et al. [64]	Indiana University, USA	2011	Retrospective	60	A, B	1–6.5 cm	NR	44 (24–48)	3–5	67% at 2 years	90% at 2 years	37%
Son	Gyeongsang	2010	Retrospective	47	A, B, C	3.0–81.3 mL	NR	30–39	3	NR	NR	33%

Table 3. Clinical results after RT to both the PVTT and primary liver tumor

Authors [reference]	No. of patients	Treatment	Total RT dose (range)/ fractional dose (in Gy)	Response rate (CR+PR,%)	Median survival (months)
Ishikura et al. [10]	20	EBRT+TACE	50 (N/A)/2	50 (CR 0)	5.3
Kim et al. [21]	59	3D-CRT	N/A (30–54)/2–3	45.8 (CR 6.8)	Responders 10.7, non-responders 5.3
Kim et al. [36]	41	3D-CRT	54 (44–54)/2–3	39 (CR 9.7)	Responders 20.1, non-responders 7.2
You et al. [48]	49	3D-CRT+TACE	N/A (40–45)/1.8–2	48 (CR 0)	
Toya et al. [46]	38	3D-CRT	40 (17.5–50.4)/1.8–4	44.7 (CR 15.8	
Yu et al. [37]	281	3D-CRT+TACE	N/A (30–54)/1.8–4.5	53.8 (CR 3.6)	
Yoon et al. [11]	412	3D-CRT+TACE	40 (21–60)/2–5	27.9 (CR 3.6)	

RT PVTT alone

RT- HCC + PVTT

Table 2. Clinical results after radiation therapy to PVTT only

Authors [reference]	No. of patients	Treatment	Total RT dose (range)/ fractional dose (in Gy)	Response rate (CR+PR,%)	Median survival (months)
Tazawa et al. [41]	24	EBRT+TACE	50 (N/A)/2	50 (CR 16.7)	CR/PR (9.7), NR/PD (3.8)
Yamada et al. [42]	19	3D-CRT+(TACE for liver tumor)	Mean 57 (46–60)/2	57.9 (CR 0)	7
Nakazawa et al. [24]	52	3D-CRT	57 (39–60)	50 (CR 15.4)	3-year survival 15.2%
Zeng et al. [43]	44	RT+TACE	50 (36–60)/2	45.5 (CR 34.1)	RT 8, non-RT 4
Katamura et al. [39]	32	iA 5-FU/IFN+3D-CRT/ iA 5-FU/IFN	39 (30–45)/3	RT 75, non-RT 25	RT 7.5, non-RT 7.9
Zhang et al. [44]	45	PV stenting+TACE +3D-CRT/PV stenting+TACE	40 (30–60)/2	35.6 (CR 0)	RT 16.5, non-RT 4.8

RT = radiation therapy; NR = no response; PD = progressive disease; iA = intra-arterial; IFN = interferon.

RT in PVTT as neo-adjuvant: possible candidates for Sx

Benefits:

- Compensatory enlargement of non irradiated liver – increases reserve
- Neoadjuvant role / or as part of multi modality therapy: compensatory hypertrophy and reducing venous occlusion → Sx or TACE feasible

- **Yeh et al 2015** → downsized tumor/ hypertrophied C/L lobe [Yeh et al, 2015]
  - Child Pugh A / Unilobar
  - Unilateral PVTT MPV or C/L PVTT < 2 cm of confluence
  - Remnant liver > 40% liver or 1% body weight
  - ICG retention @ 15 min < 15%
  - P/c- > 100,000/ mcl

Fortis

PVTT downstaging → Transplant feasible

Original Clinical Science—Liver

JCO 2019

Experience With LDLT in Patients With Hepatocellular Carcinoma and Portal Vein Tumor Thrombosis Postdownstaging

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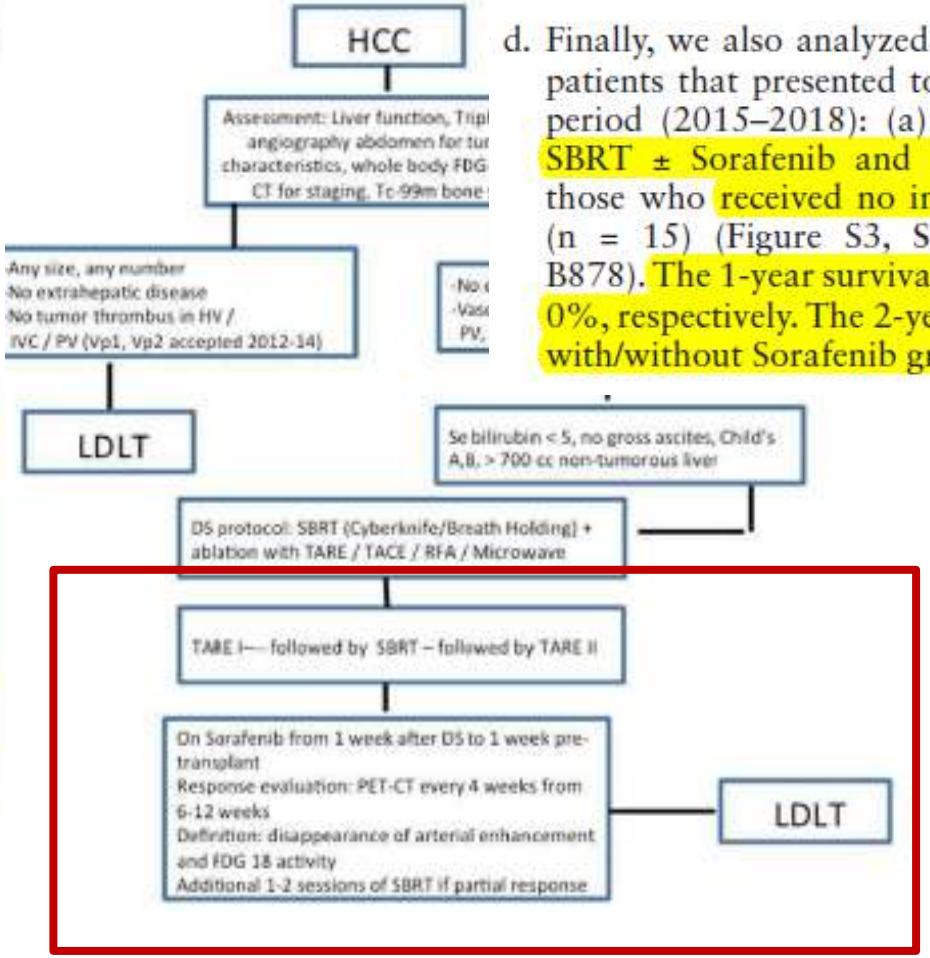
Background. Median survival in patients with hepatocellular carcinoma (HCC) and portal vein tumor thrombosis (PVTT) is 2–6 months; conventionally liver transplantation is contraindicated. **Methods.** We studied outcomes following living donor liver transplantation (LDLT) post-PVTT downstaging (DS) with stereotactic body radiotherapy (SBRT), and tumor ablation (with transarterial chemo- or radio-embolization). **Results.** Of 2348 consecutive LDLTs, 451 were for HCC, including 25 with PVTT (mainly Vp1-3) after successful DS and 20 with Vp1/2 PVTT without previous treatment. DS was attempted in 43, was successful in 27 (63%), and 25 underwent LDLT. Median alpha fetoprotein (AFP) at diagnosis and pre-LDLT were 78.1 ng/mL (3–58 200) and 55 ng/mL (2–7320), respectively. Mean DS to LDLT time was 10.2 weeks (5–16). Excluding 2 postoperative deaths, 1- and 5-year overall survival (OS) and recurrence-free survival (RFS) were 92%, 57%, and 77%, 51%, respectively, comparable to survival in 382 HCC patients without PVTT undergoing upfront LDLT (5-y OS 60%, $P = 0.06$; RFS 66%, $P = 0.33$, respectively). There was a trend toward better OS in DS+LDLT versus non-DS LDLT group (5-y OS/RFS—49%/40%). OS was significantly better than in HCC-PVTT patients receiving no intervention or palliative Sorafenib alone (1-y OS of 0%) or Sorafenib with TARE/SBRT (2-y OS of 17%) at our center during the study period. Initial AFP <400 ng/mL and AFP fall (initial minus pre-LDLT) >2000 ng/mL predicted better RFS; Grade III/IV predicted worse OS in DS patients. **Conclusions.** HCC patients with PVTT can achieve acceptable survival with LDLT after successful DS. Low initial AFP level, a significant drop in AFP with DS and low tumor grade, favorably influence survival in these patients.

(Transplantation 2020;104:2334–2344).



d. Finally, we also analyzed the OS of 2 other cohorts of patients that presented to the facility during the study period (2015–2018): (a) those with palliative TARE/SBRT ± Sorafenib and no LDLT (n = 29), and (b) those who received no intervention, or Sorafenib only (n = 15) (Figure S3, SDC, http://links.lww.com/TP/B878). The 1-year survival in these groups was 42% and 0%, respectively. The 2-year survival in the TARE/SBRT with/without Sorafenib group was 17%.

a. After a mean follow-up of 33 months (range: 2–86 mo), the 1-, 3-, and 5-year OS in all DS patients (n = 25) was 75%, 53%, and 53%, respectively. The RFS was 78%, 78%, and 52%, respectively(Figure 3A and B).

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PVTT: Multi modality treatment

Table 1 Summary of combination treatments for hepatocellular carcinoma patients with portal vein tumor thrombosis

	Overall survival (mo)	Extent of PVTT (mo)		Ref.
		Main PVTT	Branch PVTT	
BSC	2-4			Llovet *et al*[3], Schöniger-Hekele *et al*[3]
Sorafenib	6.5-8.1			Llovet *et al*[8], Cheng *et al*[11]
TACE	7-10	5.3	10	Chung *et al*[21], Luo *et al*[22]
HAIC	6.5-14			Park *et al*[26], Ando *et al*[27], Eun *et al*[28]
RT	9.6-10.9			Toya *et al*[34], Nakazawa *et al*[44]
TARE	6-16.9	7.7	16.9	Salem *et al*[47], Kulik *et al*[48], Sangro *et al*[58], Memon *et al*[59]
TACE plus sorafenib	11-13	3	13-15	Pan *et al*[38], Zhu *et al*[39]
Sorafenib plus RT	8.6-10.6			Chen *et al*[53], Chow *et al*[61]
TACE plus RT	10.6-12	12		Yoon *et al*[64], Chung *et al*[72], Kim *et al*[73]
HAIC plus RT	12.1			Fujino *et al*[74]

BSC: Best supportive care; TACE: Transarterial chemoembolization; HAIC: Hepatic arterial infusion chemotherapy; RT: Radiation therapy; TARE: Transarterial radioembolization; PVTT: Portal vein thrombosis.

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Combination therapy

- **TACE alone** when used in advanced HCC, has **limited effects on PVTT**.
- **Local radiotherapy + TACE more beneficial**: RT for PVTT & TACE/ TARE for liver

- Large HCCs: with TACE alone → rarely achieve complete remission.
  - combination of systemic chemotherapy and TACE :
    - more beneficial than conservative treatment alone
    - **median survival, 8.7 months vs. 3.5 months, respectively**

Fortis

Comparison of intra-arterial chemoembolization with and without radiotherapy for advanced hepatocellular carcinoma with portal vein tumor thrombosis: a meta-analysis

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Purpose: Numerous studies have tried to combine transarterial chemoembo or hepatic arterial infusion chemotherapy (HAIC) with radiotherapy (RT) for hepatocellular carcinoma (HCC) patients with portal vein tumor thrombus (P the efficacy of TACE or HAIC combined with RT versus TACE or HAIC alone versial. Thus, we performed a meta-analysis to compare the efficacy and safet chemoembolization combined with RT versus intra-arterial chemoembolizat treatment of HCC patients with PVTT.

Methods: PubMed, Embase, and Cochrane Library databases were systematic eligible studies. Two authors independently reviewed the abstracts, extracted relevant data and rated the quality of studies. The major end points were objective response rate (ORR), overall survival (OS), and adverse events.

Results: Eight studies with a total of 1,760 patients were included in this meta-analysis. The pooled results showed that intra-arterial chemoembolization combined with RT significantly improved ORR of PVTT (OR, 4.22; 95% CI, 3.07–5.80; $P<0.001$) and OS (HR, 0.69; 95% CI, 0.57–0.83; $P=0.001$), but did not affect ORR of primary liver tumor (OR, 1.37; 95% CI, 0.67–2.79; $P=0.390$). The incidence of grade 3 or 4 leukopenia (OR, 5.80; 95% CI, 2.478–13.56; $P<0.001$) and thrombocytopenia (OR, 3.77; 95% CI, 1.06–13.43; $P=0.041$) was higher in the intra-arterial chemoembolization plus RT group than in the intra-arterial chemoembolization group.

Conclusion: Combination therapy of intra-arterial chemoembolization and RT for HCC patients with PVTT could bring higher ORR of PVTT and better survival benefits. This combination therapy was also associated with a significantly increased risk of adverse events. However, they were mostly mild to moderate and successfully treated with conservative treatment.

Conclusion: Combination therapy of intra-arterial chemoembolization and RT for HCC patients with PVTT could bring higher ORR of PVTT and better survival benefits. This combination therapy was also associated with a significantly increased risk of adverse events. However, they were mostly mild to moderate and successfully treated with conservative treatment.

Fortis

Multi modality: TACE + RT

TACE plus radiotherapy improves survival for HCC, portal vein tumor thrombus

Li X-L, et al. *Hepatol Res*. 2106;doi:10.1111/hepr.12657.

2016

November 4, 2016

The use of transarterial chemoembolization with radiotherapy led to improved survival outcomes for patients with unresectable hepatocellular carcinoma and portal vein tumor thrombus, compared with patients who underwent transarterial chemoembolization alone, per published findings in *Hepatology Research*.

"In recent years, transarterial chemoembolization has become the most popular palliative treatment for patients with unresectable HCC, and it is no longer considered as a contraindication to HCC with [portal vein tumor thrombus (PVTT)]. However, the effect of TACE alone on PVTT is not satisfactory," **Xiao-Long Li**, of Eastern Hepatobiliary Surgery Hospital, The Second Military Medical University, Shanghai, China, and colleagues wrote.

Researchers evaluated 112 patients with HCC and PVTT undergoing TACE combined with radiotherapy and 735 patients undergoing TACE alone. Additional pairs of patients were selected from each treatment arm (n = 108) and matched with patients from the original cohort by using a propensity score matching analysis.

The researchers found that patients who underwent combined therapy with TACE and radiotherapy had a longer median survival rate compared with patients treated with TACE alone (11 months vs. 4.8 months; $P < .001$). This was even more apparent in patients with PVTT involving the right/left portal vein (12.5 months vs. 5.2 months; $P < .001$) and main portal vein trunk (8.9 months vs. 4.3 months; $P < .001$), per the research.

TACE + RT : strategies

- **Sequential:** RT (PVTT) + TACE (HCC)
  - TACE less effective for PVTT
- Planned consolidation - RT for TACE residual
  - Targets peripheral residual cells- due to collateral supply or recanalization
- **Salvage**: RT or TACE upfront – other as salvage for recurrence

Fortis

Treatment response

MOLECULAR AND CLINICAL ONCOLOGY 2: 43-50, 2014

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

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Received March 30, 2013; Accepted July 26, 2013

DOI: 10.3892/mco.2013.196

101 cases

Group A: SBRT f/b TACE
Group B: TACE f/b SBRT
Group C: SBRT alone

Table II. Tumor and portal vein tumor thrombus (PVTT) response rates.

Cases	CR	PR	SD	PD	RR (CR+PR)	P-value
Tumor response (n)						NS
Group A (34)	9	21	2	2	88.2 % (30/34)	
Group B (37)	11	22	2	2	89.2 % (33/37)	
Group C (30)	9	16	3	2	83.3% (25/30)	
Total (101)	29	59	7	6	87.1% (88/101)	
PVTT response (n)						NS
Group A (34)	7	18	4	5	73.5% (25/34)	
Group B (37)	6	20	6	5	70.3% (26/37)	
Group C (30)	5	15	5	5	66.7% (20/30)	
Total (101)	18	53	15	15	70.3% (71/101)	

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; RR, response rate; NS, non-significant.

Table IV. Improvement of life quality following radiotherapy.

	Relief of abdominal discomfort and distension	Jaundice resolution	Ascites release
Group A	72.2% (13/18)	66.6% (6/9)	62.5% (5/8)
Group B	71.4% (15/21)	60.0% (6/10)	55.6% (5/9)
Group C	62.5% (10/16)	50% (3/6)	62.5% (5/8)

SBRT and TACE

2013

MOLECULAR AND CLINICAL ONCOLOGY 2: 43-50, 2014

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

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Received March 30, 2013; Accepted July 26, 2013

combination of γ-SBRT and TACE was shown to be a relatively effective local treatment for primary HCC patients with PVTT. Compared to γ-SBRT followed by TACE and γ-SBRT alone, TACE followed by γ-SBRT may exert a negative effect on liver function. These results suggested that the combination of TACE and γ-SBRT may be considered a relatively effective, safe and feasible treatment method for primary HCC patients with PVTT, although TACE followed by γ-SBRT may negatively affect liver function.

Fortis

RT and Sorafenib

Surg Oncol Clin N Am. 2014 Apr;23(2):353-368. doi: 10.1016/j.soc.2013.10.007. Epub 2013 Dec 7.

An Emerging Role for Radiation Therapy in the Treatment of Hepatocellular Carcinoma and Intrahepatic Cholangiocarcinoma.

Wo JY[1], Dawson LA[2], Zhu AX[3], Hong TS[4].

COMBINATION THERAPY

Sorafenib and Radiation Therapy

Despite high rates of local control after SBRT, distant liver failure remains the predominant site of failure for patients with HCC. Sorafenib (Nexavar) is a small-molecule multikinase inhibitor that targets tumor-cell proliferation and tumor angiogenesis by inhibiting the Raf/MAPK/ERK signaling pathway and the receptor tyrosine kinase of vascular endothelial growth factor receptors 1, 2, and 3 and platelet-derived growth factor receptor β. The SHARP trial established sorafenib as an active systemic agent in the treatment of advanced HCC, conferring an improvement in median survival of 2.8 months compared with placebo.[3] Recent in vitro and in vivo studies suggest that low-dose sorafenib may act as a radiosensitizer in HCC cells via downregulation of STAT3 phosphorylation.[41] One retrospective review studied 23 patients with advanced HCC treated in Taiwan with radiation therapy and sunitinib (a tyrosine kinase inhibitor with a similar mechanism to sorafenib), given at least 1 week before and 2 weeks after radiation therapy. With a median radiation dose of 52.5 Gy in 15 fractions, the objective response rate was 74%. The 1-year survival rate was 70%, with maintenance sunitinib being the most significant prognostic factor for survival. Based on these results, the investigators concluded that conformal hypofractionated RT and sunitinib could be delivered safely in patients with HCC.[42] However, data from an early phase 1 study from the University of Toronto combining a 6-fraction SBRT with escalating doses of sorafenib before, during, and after RT suggested that higher doses of sorafenib (400 mg daily) when combined with radiation delivered to a higher effective liver volume (Veff 30%–60%), may yield significant grade 3+ toxicity. RTOG 1112 is an ongoing phase 3 study of sorafenib versus SBRT followed by sorafenib in HCC. In this study, sorafenib will be delivered after completion of radiation, rather than concurrently with radiation, to reduce the risk of treatment toxicity.

Fortis

Multimodality treatment: The way to go

1993 - 2006

TABLE 1. *Clinical outcomes after photon RT for hepatocellular carcinoma*

Study	n	RT	Added therapy	Objective response rate	Grade ≥3 toxicity rate	In situ recurrence rate	Multifocal recurrence rate	Median survival (mo)	Survival rate
Robertson et al., 1993[8]	11	48–72 Gy	HAI FUDR	100%	16%	–	–	–	–
Yasuda et al., 1999[50]	44	36–70 Gy	TAE/PEI	–	–	–			81% (3 y)
Dawson et al., 2000[73]	27	30–90 Gy	HAI FUDR	45%	10%	–	–	11	–
Park et al., 2002[74]; Seong et al., 2003[75]	158	40–60 Gy	TACE (107)	67%	–	7%	34%	10	42% (1 y) 20% (2 y)
Chia-Hsien Cheng et al., 2001[52]	26	41–53 Gy	TACE (17)	–	–	11%, 12%	33%, 59%	–	57% (2 y)
Guo et al., 2003[76]	76	30–50 Gy	TACE	48%	–	13%	–	19	64% (1 y) 19% (5 y)
Li et al., 2003[77]	45	50.4 Gy	TACE	91%	27%	27%	–	24	69% (1 y) 23% (3 y)
Cheng et al., 2004[14]	89	36–66 Gy	TACE (74)	–	–	–	–	–	–
Liu et al., 2004[78]	44	40–60 Gy	-	61%	0%	0%	43%	15	61% (1 y) 40% (2 y)
Zeng et al., 2004[79]	54	40–60 Gy*	TACE	76%	–	0%	65%	20	72% (1 y) 6% (5 y)
Wu et al., 2004[80]	94	48–60 Gy	TACE	91%	–	3%	–	25	94% (1 y) 26% (3 y)
Ben-Josef et al., 2005[9]	35	40–90 Gy	HAI FUDR	56%	30%	0%	64%	15	
Park et al., 2005[81]	59	30–55 Gy		66%	0%	24%	–	10	27% (2 y)
Zhou et al., 2006[82]	50	30–54 Gy*	TACE	18%	6%	62%	60%	17	60% (1 y) 28% (3 y)
Mornex et al., 2006[33]	27	66 Gy	–	92 %	41%	22%	41%	–	–

RT, radiotherapy; HAI, hepatic arterial infusion; FUDR, floxuridine; TAE, transarterial embolization; PEI, percutaneous ethanol injection; TACE, transarterial chemoembolization.

* Hypofractionated regimens used.

SBRT Practice patterns

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ORIGINAL RESEARCH

WILEY Cancer Medicine

Stereotactic body radiation therapy for hepatocellular carcinoma: Practice patterns, dose selection and factors impacting survival

Jared R. Robbins[1,2] | Ryan K. Schmid[2] | Abdulrahman Y. Hammad[3] | Thomas Clark Gamblin[3] | Beth A. Erickson[2]

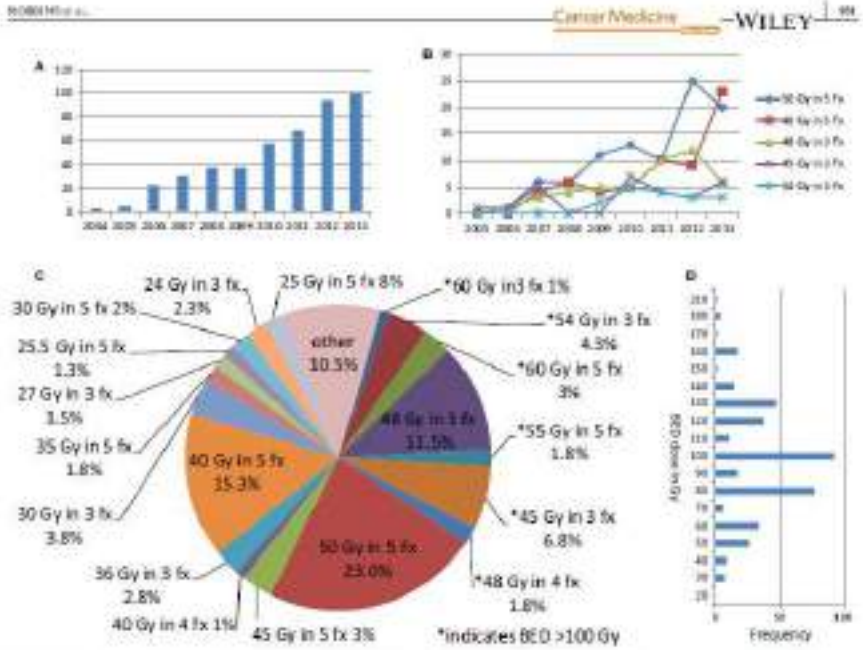

FIGURE 1 A, Incidence of SBRT use from 2004 to 2013; B, Use of common fractionation regimens over the study period; C, Distribution of SBRT dose regimens; D, Distribution of BED

TABLE 2 Comparisons between common fractionation schedules

Fractionation (BED in Gy)	n	BED (Gy)	Median age (y)	Stage 1/2/3	AFP elevated	Size median (cm)	Size groups ≤2/2-4/>4 (cm)	Facility volume Low/mod/high	Academic facility	Charlson 0/1/2	Received Chemo	Time to SBRT <2/2-4/>4 (m)	2 y OS
50 in 5 (100)	92	100	60.2	60/27/6	50%	2.8	26/56/18	26/10/64	89%	53/27/20	61%	13/39/48	43.4%
40 in 5 (72)	61	72	63.7	56/28/16	49%	3.1	22/38/40	27/25/48	87%	59/23/18	15%	41/38/21	44.8%
48 in 3 (125)	46	125	63.2	76/17/7	46%	2.4	37/59/13	15/2/83	94%	57/20/24	2%	50/30/20	79.0%
45 in 3 (113)	27	113	65.0	54/37/11	52%	3.5	24/44/32	59/15/26	63%	74/7/19	44%	26/44/30	52.4%
54 in 3 (151)	17	151	60.2	77/24/0	47%	2.1	50/38/12	47/0/53	77%	35/18/47	65%	24/47/29	70.1%
P-value		<0.001	0.411	0.116	0.309	0.006	0.014	<0.001	0.003	0.114	<0.001	<0.001	<0.001
3-fractions	158	114	62.3	58/28/14	53%	3.27	25/43/33	30/18/51	70%	65/14/22	26%	35/41/24	50.8%
5-fractions	220	98.9	62.9	54/32/14	51%	3.30	21/44/36	31/20/48	85%	57/24/19	37%	27/36/36	42.3%
P-value		<0.001	0.370	0.624	0.174	0.044	0.678	0.784	0.001	0.064	0.013	0.032	0.083

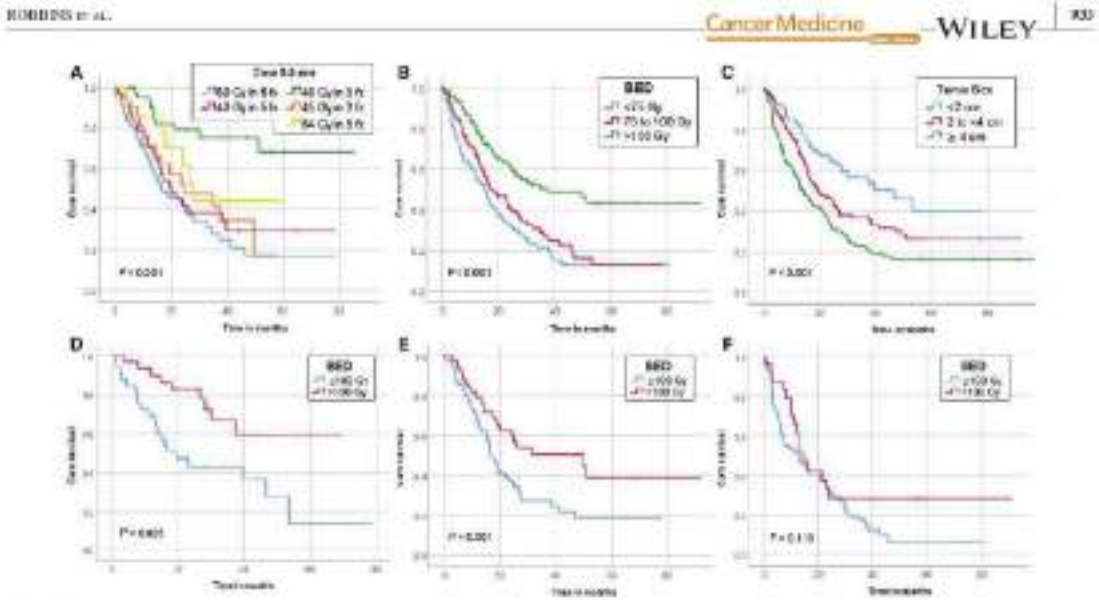

FIGURE 2 Kaplan Meier curves for overall survival: A, Commonly used regimens; B, BED; C, Size; D, Tumors <2 cm; E, Tumors 2 cm to <4 cm; F, Tumors ≥4 cm

Fortis

Response evaluation

REPORTS OF PRACTICAL ONCOLOGY AND RADIOTHERAPY 22 (2017) 170–175

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Original research article

Evaluation of response after SBRT for liver tumors

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Review Article

Page 1 of 8

Challenges in imaging assessment following liver stereotactic body radiotherapy: pitfalls to avoid in clinical practice

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Contributions: (I) Conception and design: C. Yip; (II) Administrative support: None; (III) Provision of study materials or patients: C. Yip; (IV) Collection and assembly of data: C. Yip; (V) Data analysis and interpretation: C. Yip; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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RECIST / EASL – diff in criterias
Liver Imaging Reporting and Data System (LI-RADS)

Focal normal liver reaction:

- volume reduction of 18% (13–33%) @ 2–6 months post SBRT
- Normal reaction - Unrelated to RILD
- Compensatory hypertrophy subsequently

- 7-10 HU decrease in CT density (irradiated Vs non irradiated)

Response - mRECIST

- RFA / chemoembolization → reshapes targets - leaving scars
- Not just size criteria
- Necrosis / changes in enhancement pattern
- Size of enhancing lesion vs total lesion
- Vascular re-canalization

- MRI – Diffusion and ADC – qualitative measures

- **PERCIST** – PET based changes in avidity/ necrosis response

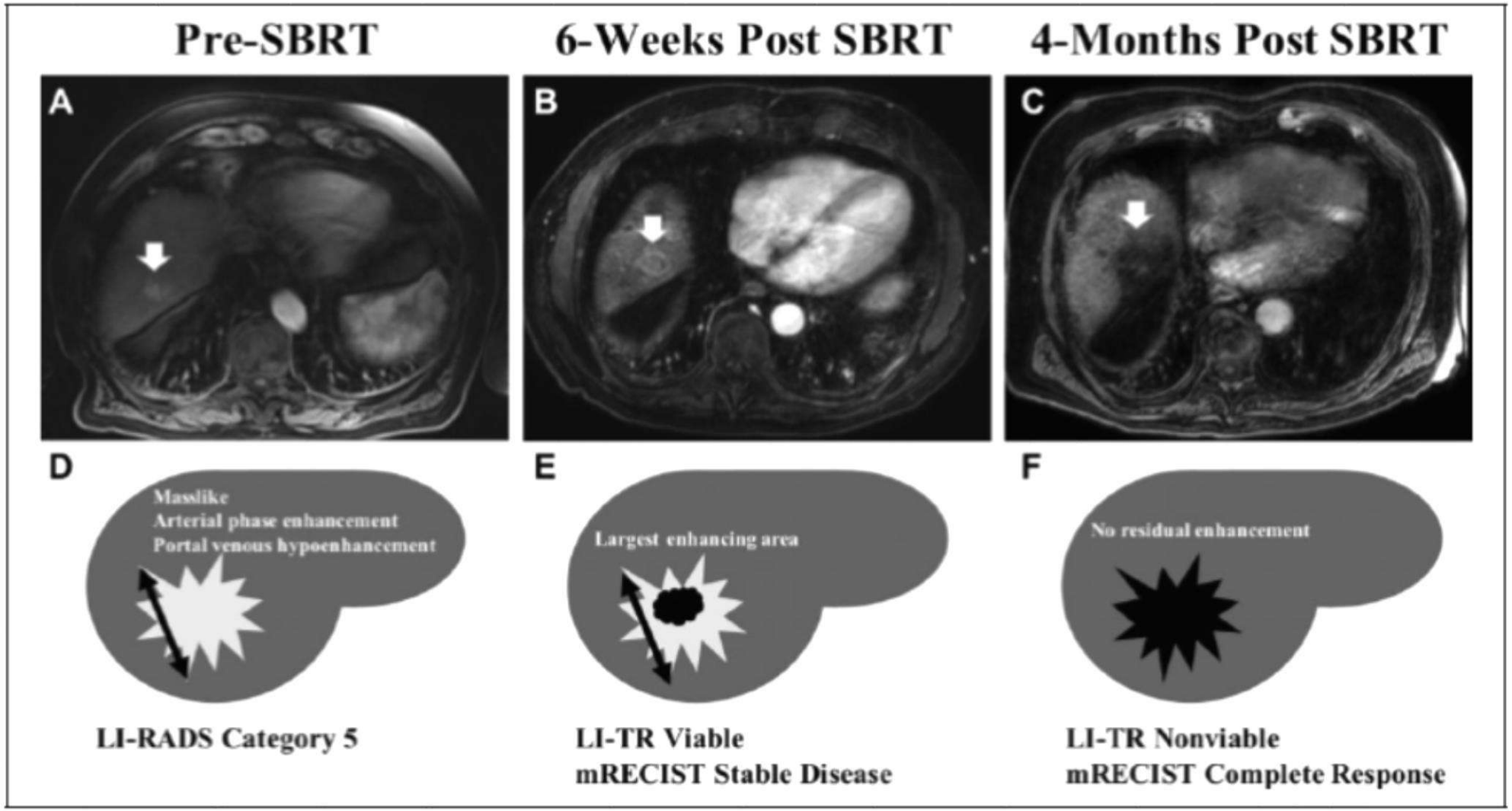


Figure 1. Characteristic arterial phase T1 MR imaging for a Child-Pugh A5 patient with HCC (arrow) treated with SBRT to 50 Gy in 5 fractions are shown: pre-SBRT (A), 6-weeks post-SBRT (B), and 4-months post-SBRT (C). Below each MR image is a correlative schematic to demonstrate either the corresponding LI-RADS diagnostic category (D), or treatment response assessment criteria of LI-RADS treatment response (LI-TR) and the modified RECIST criteria (mRECIST) (E-F). HCC denotes hepatocellular carcinoma; LI-RADS, Liver Imaging Reporting and Data System; LI-TR, Liver Imaging Treatment Response; RECIST, Response Evaluation Criteria in Solid Tumors; SBRT, stereotactic body radiation therapy.

Fortis

How to approach a HCC / PVTT case

Base line work up

History
Hepatitis
Previous Rx

Blood profile
CBC – p/c & INR
LFT
AFP

Examination
CP classification
Ascites +/-

Inclusion
Sr Bil ≤ 3
P/c- > 50,000
Normal Liver volume

Fortis

Selecting cases

April 2011 to June 2016

60 HCC+ PVTT cases referred for SBRT

Baseline/ Metastatic work-up

Normal liver > 700 cc / Sr Bilirubin < 3 mg/dl / No Extra hepatic disease

Yes

No

Curative Intent [42 cases]

≦ ECOG 2 / Child Pugh A or B

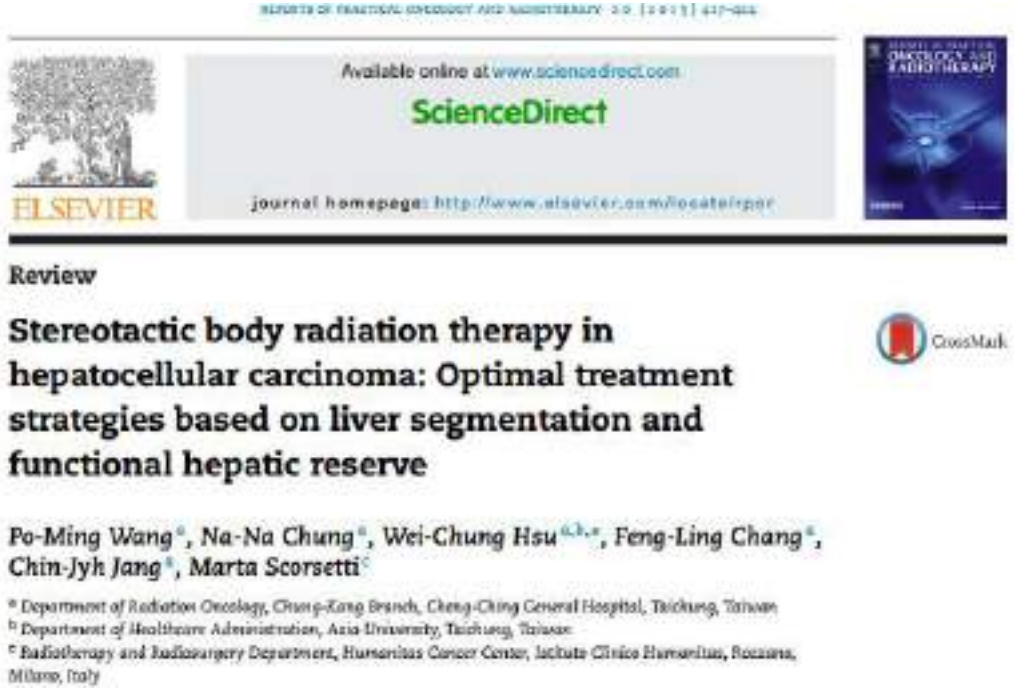
> 5 mm away from luminal structures (duodenum/ stomach/ bowel)

Palliative Intent [18 cases]

Multicentric / Bulky HCC unfit for surgery/ alternative therapies

What dose and how much toxicity is expected??

SBRT case selection: risk based on segment & function



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Review

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]

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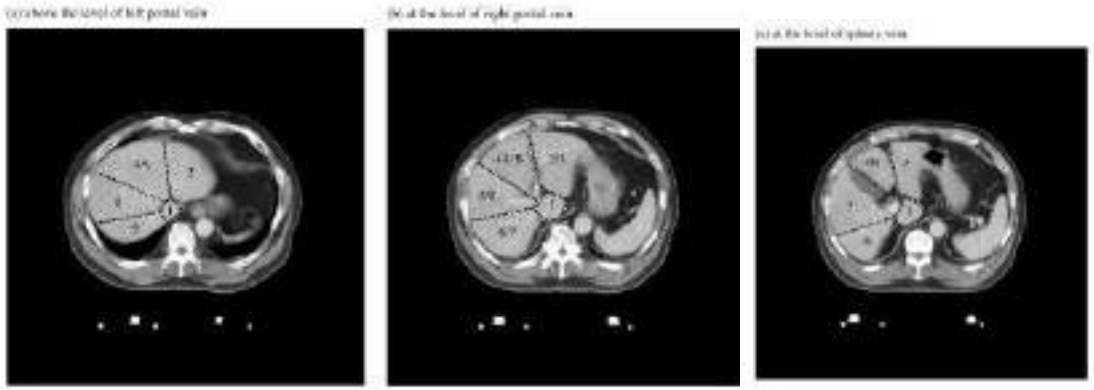
[c] Radiotherapy and Radiosurgery Department, Humanitas Cancer Center, Istituto Clinico Humanitas, Rozzano, Milano, Italy

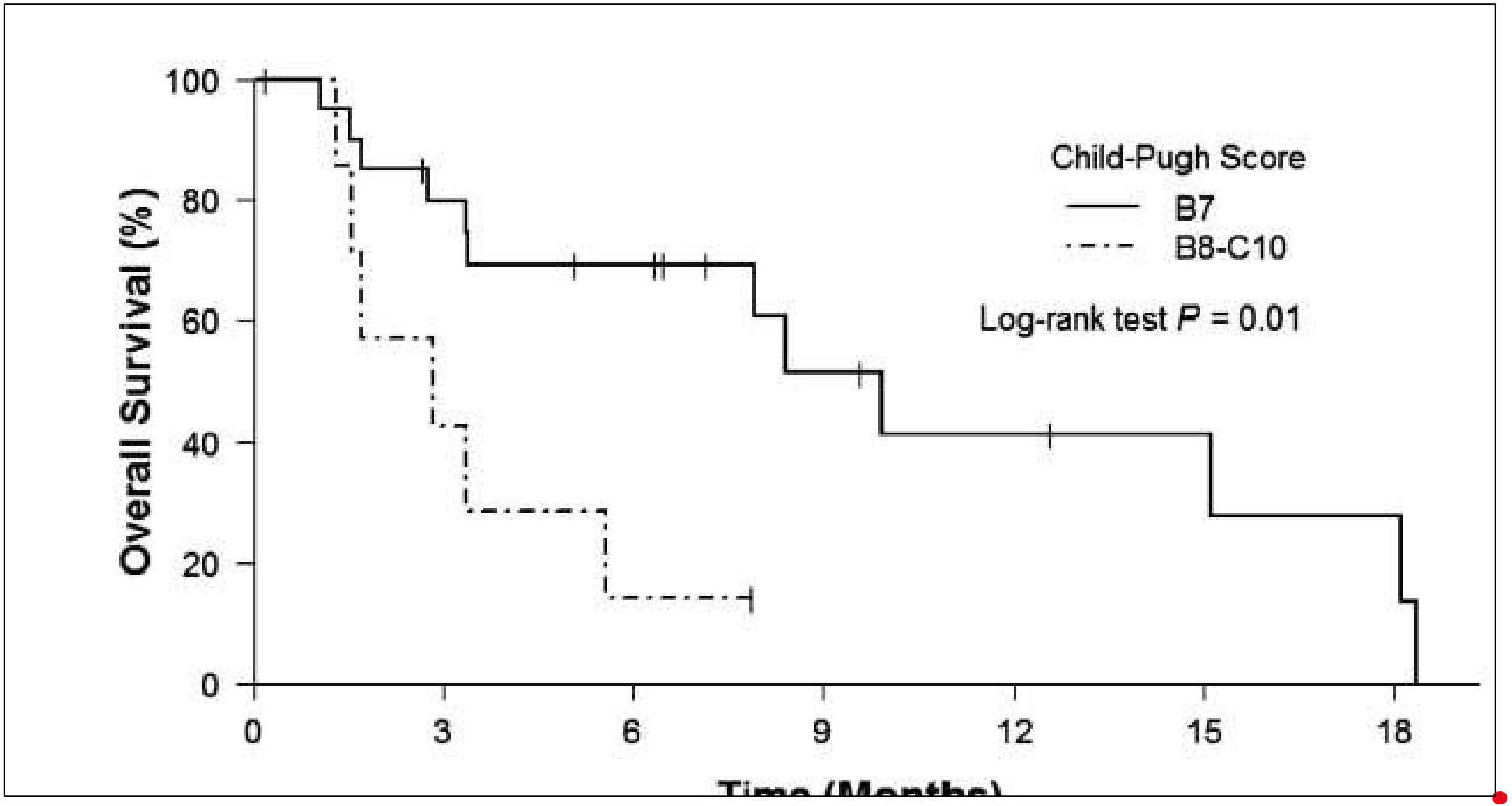
- **SEGMENT based**
  - Seg 1: **most dangerous** – OAR – duodenum – cone down SBRT
  - Seg 2: OAR- stomach –fasting before RT helps
  - Seg 3: OAR- stomach/ GIT – non coplanar beams help
  - Seg 4a: relatively safe – OAR – kidney, spine
  - Seg 4b: dangerous – OAR – duodenum, pylorus
  - Seg 5: relatively safe – OAR – colon
  - Seg 6: liver tip – OAR – bowel, right kidney, ribs
  - Seg 7: relatively safe – OAR – Rt kidney pole, spine
  - Seg 8: **safest**: even large upto 10 cm HCC can be safely treated



- **FUNCTION based**
  - CP [Child Pugh] score better than CP stage
  - CP score independent risk factor for solitary HCC [Kudo et al]
  - CP-A5 better OS than CP-A6
  - CP-A6 – more inflammation/ fibrogenecity than CP-A5

Fortis

Better functioning liver – better outcomes



Dose selection & outcomes

- Liver SBRT : HCC TD 50 – 53 Gy EQD2 Vs Mest 70 Gy EQD2
- **2012 study → M/C regimen 45 Gy/ 3 fr ; 45 Gy/15 fr ; 40-50 Gy/ 5 fr**
- La
- R
- A

Table 2 Landmark dose selection studies, equivalent doses and outcomes by EQD2

Study	Dose/fraction	EQD2 (assumes an alpha beta 10)	Outcome reported
Liver metastases studies			
Lee (28)	41.8 Gy median (27.7–60) Gy/6	59.1 Gy (33.7–100 Gy)	1 year LC 71%
Hoyer (29)	45 Gy/3	93.8 Gy	1 year LC 95%
Chang (30)	48–52 Gy/3	104–118.4 Gy	1 year LC 90%
Rule (27)	60 Gy/5	110 Gy	2 years LC 100%
Hepatocellular Carcinoma Studies			
Bujold (31)	36 Gy (24–54Gy)/6	48 Gy (28–85.5Gy)	2 years LC 74%
Sanuki (32)	40 Gy/5 for CP-A, 35 Gy/5 for CP-B	60 Gy, 49.6 Gy	2 years LC 93%
Cárdenes (17)	48 Gy/3 for CP-A, 40/5 for CP-B	104 Gy, 60 Gy	2 years LC 100%

- Cárdenes et al. → 48 Gy in 3 fractions at a maximum of two treatments per week
  - > CP-B7 - reduced dose of 40 Gy in 5 fractions → safer as no benefit from dose escalation in them

Initiating the liver SBRT program – Toxicity dilemma

- **RILD** – not a limiting factor for implementation of radiotherapy of the liver
- other non-RILD toxicities:
  - **gastroduodenal damage** –
    - only significant limiting factor / more concerning
    - median time to toixicity – 6 months (past h/o cholangio / ulcers- strong predictor)
    - Steep rise beyond 35 Gy (> 10% risk if Dmax > 38 Gy)
  - Chest wall and rib injury
  - Coagulopathies
  - Esophageal ulceration
  - Renal failure
  - Reactivation of viral hepatitis
  - Cardiac injury
  - Pneumonitis
  - Skin necrosis.

Table 1 Summary of dose constraints

Organ at risk	SBRT constraints (22,23)	Quantec (1.8–2 Gy per fraction) (24)	Toxicity
Liver excluding CTV	V10 <70%	Dmean <30 Gy	RILD
Esophagus	D0.5 mL <32 Gy	V35 <50%	Esophagitis
Stomach	D0.5 mL <30 Gy	D100 <35 Gy	Ulceration
Kidney	Dmean <10 Gy	Dmean <28 Gy (1.8–2 Gy per fraction)	Renal insufficiency
Ribs	D30<9.5 cc, D27.3<2 cc		Fracture
Bowel and duodenum	D0.5 ml <30 Gy, Dmax <35 Gy	D45 <195 cc	Enteritis/fistula, bleeding/perforation
Spinal cord	D0.5 mL <25 Gy	Dmax =45	Myelopathy
Chest wall	D30 <30 cc		Necrosis/pain
Heart	D30 mL <30 Gy	V25 <10%	Pericarditis

SBRT, stereotactic body radiotherapy; RILD, radiation induced liver disease; CTV, clinical target volume.

Dose p

ACTA ONCOLOGICA
2020, VOL. 59, NO. 5, 558–564
https://doi.org/10.1080/0284186X.2019.17012

ORIGINAL ARTICLE

Isotoxic dose prescrip price of dose uniform

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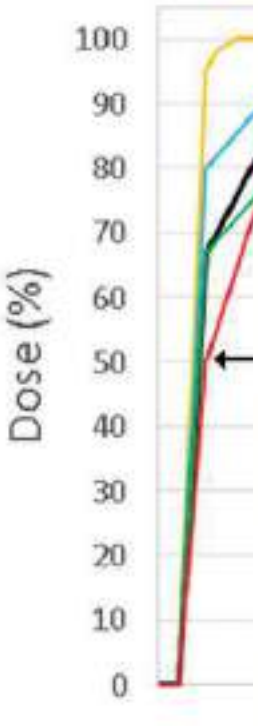
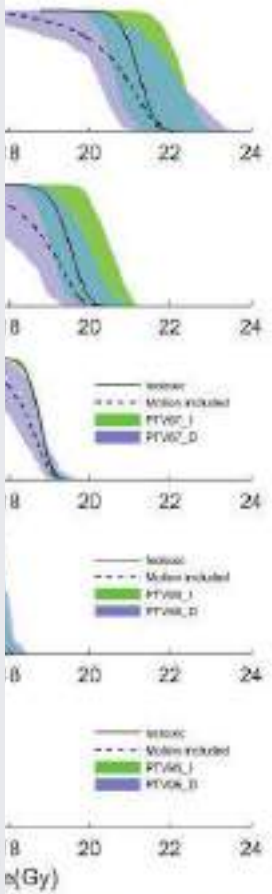


Table 1 – Prescription, local control and toxicity from selected series.

	Sample	Dose	Prescription	Local control	Toxicity > = grade 3
Blomgren et al. (1995)	14 pts with mets	7 Gy–45 Gy	ICRU point	50% response rate	1 hemorragic gastritis
Herfarth et al. (2004)	37 pts with mets	1x(14–26 Gy)	Isocenter 80%isodose surrounding PTV	71% 1 year 68% 2 years	None
Schefter et al. (2005) Rusthoven et al. (2005)	63 mets	3 × 12 Gy To 3 × 20 Gy	Isodose surrounding PTV (80%–90%)	92% at 2 years 100% for tumors < 3 cm	DLT not reached
Wulf et al. (2006)	39 pts with mets 5 with HCC	3 × 10 Gy 3 × 12.5 Gy 1 × 26 Gy	65% isodose	100% HCC last follow up 66% 2 years mets	None
Mendez-Romero et al. (2006)	34 pts with mets 11 with HCC	3 × 12.5 Gy At risk patients 5 × 5 Gy	65% isodose line	84% 2 years	1 classic RILD (liver failure and fatal infection, pt Child B initial) 1 portal hypertension with melena 2 elevation GGT Grade3
Hoyer et al. (2006)	44 pts with mets	3 × 15 Gy	Isocenter	79% 24 mths	One lethal hepatic failure 1 colic perforation (surgery) 2
McCammon et al. (2009)	81 pts Mets and primaries	3 × 10 Gy to 3 × 20 Gy	Isodose surrounding PTV (80%–90%)	100% (54–60 Gy) 89% (31.1–53.9 Gy)	None
Lee et al. (2009)	68 pts with mets	Median 41.8 Gy 6 fns 2 wks	Envelop isodose Max in PTV 140%	71% 1 year	Grade 5 SBO + grade 4 bleed (progression) SBO abdominal hernia Grade 3 gastritis/oesophagitis 2
Rusthoven et al. (2009)	47 pts with 63 mets	3 × 12–20 Gy	80 or 90% isodose	92% 2 years	1 grade 3 soft tissue toxicity
Goodman et al. (2010)	26 pts 40 lesions 19 mets 5 IHC and CHC	18 Gy to 30 Gy single dose Cyber Knife	Isodose surrounding PTV	77% 1 year	No limiting toxicity



(DVH) for the CTV for each prescrip- the isotoxic plans without (_), solid dosimetric effects of intrafraction to 90th percentile range.

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Centrifugal effect of SBRT on liver

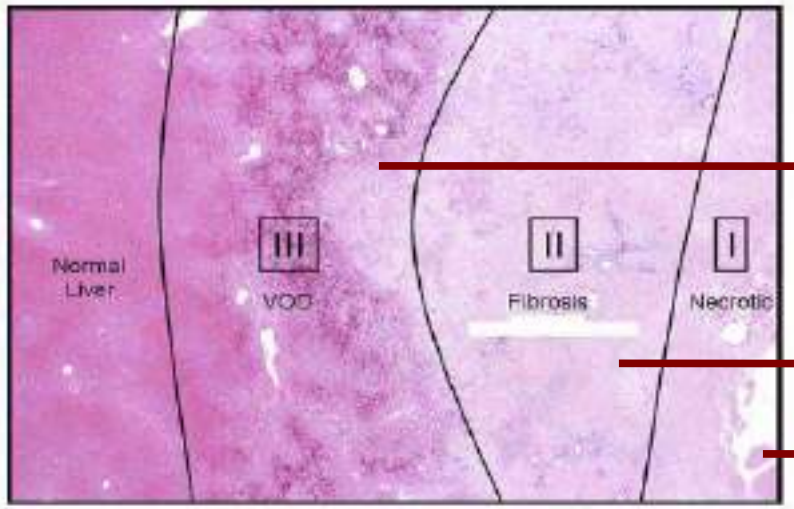
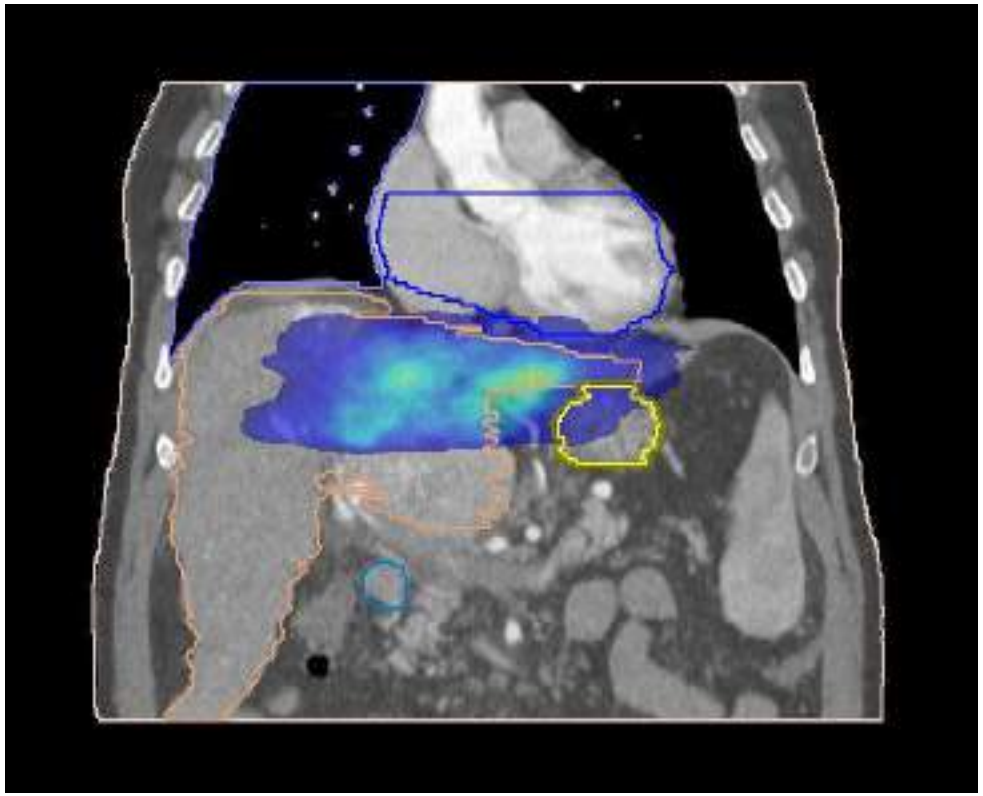


Fig. 6. Histopathologic zones of injury. See text for details. VOD = veno-occlusive disease; SBRT = stereotactic body radiotherapy.

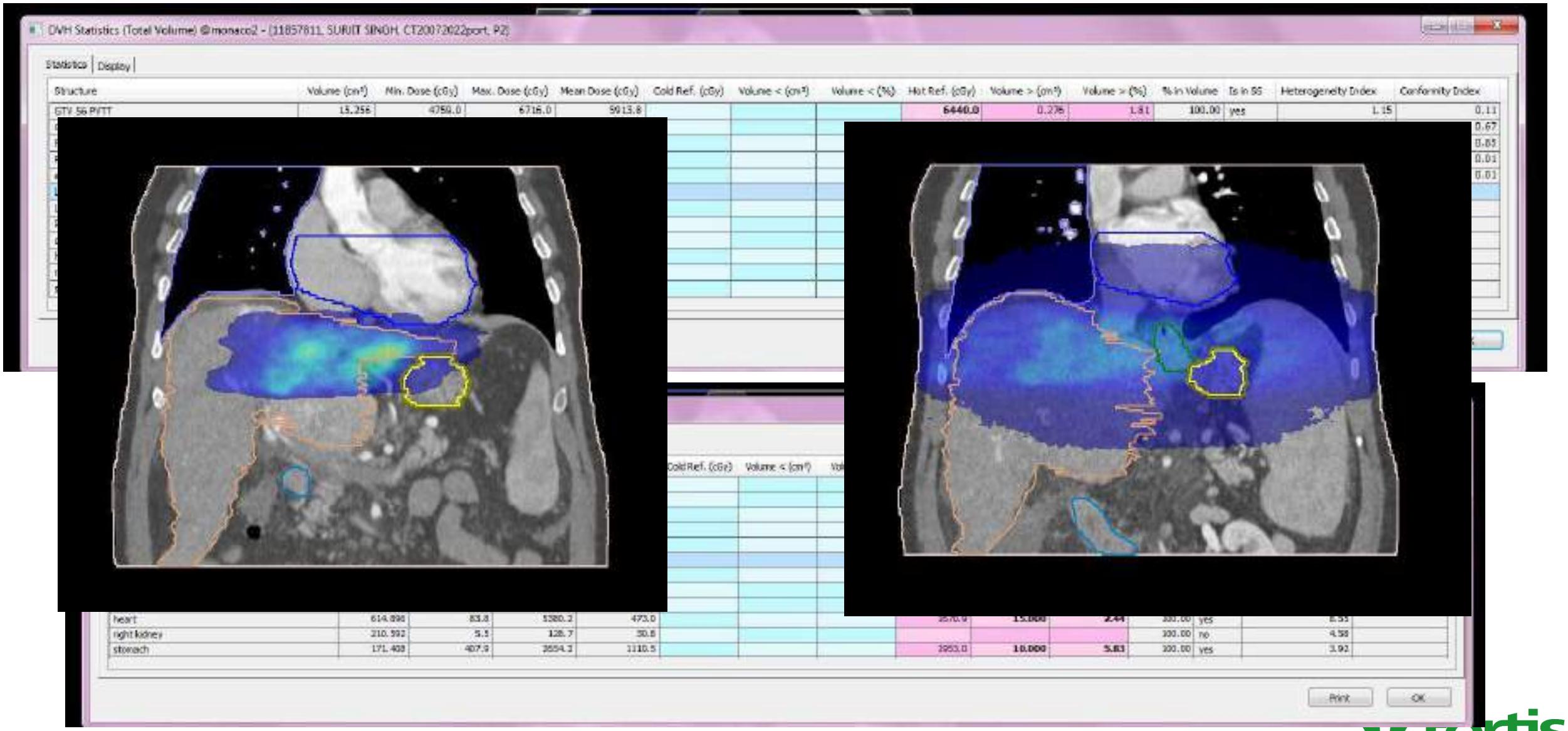
Occluded veins/ congestion

Area of repopulation

Necrosis/ fibrosis

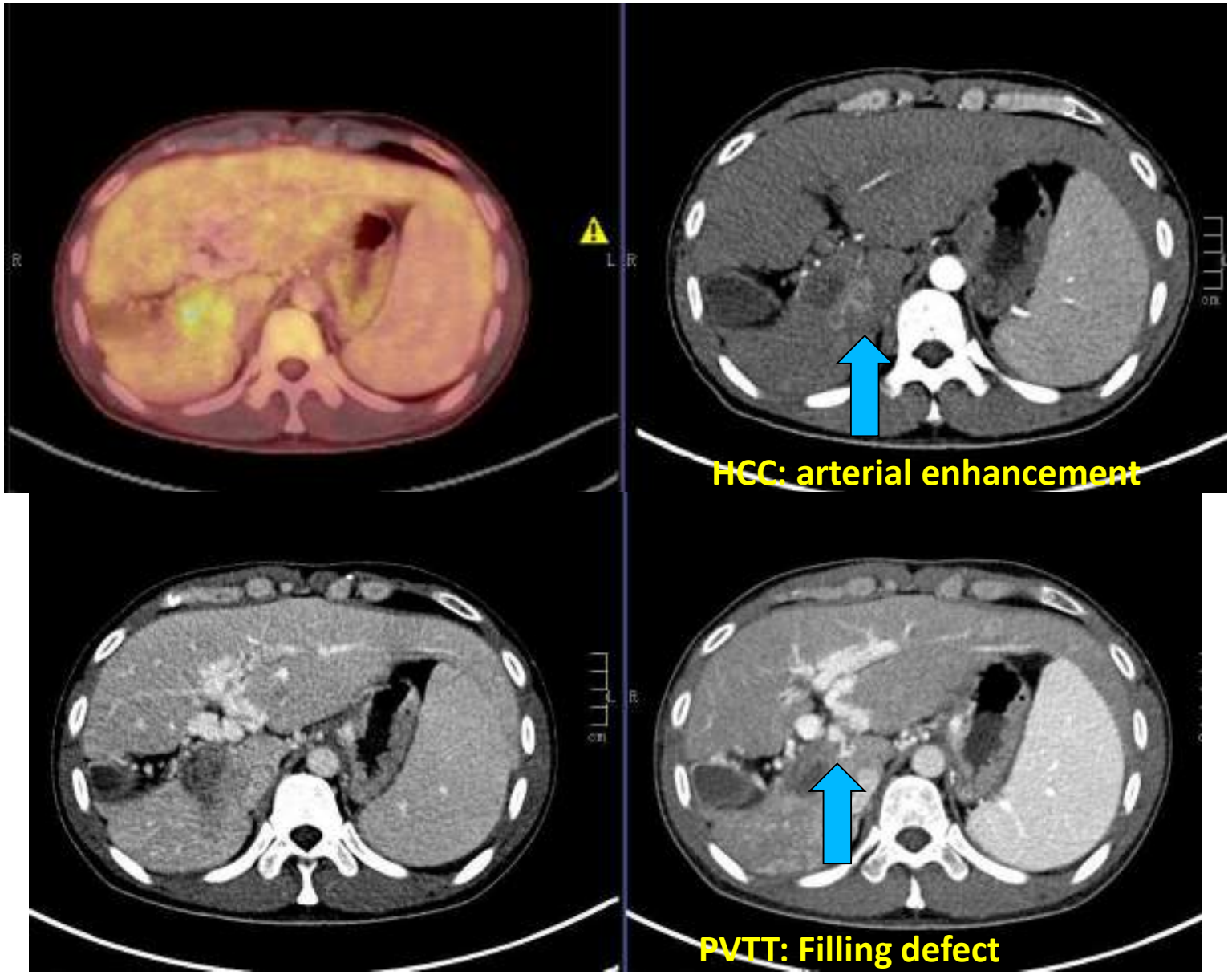


Tips to evaluate 700 cc normal liver

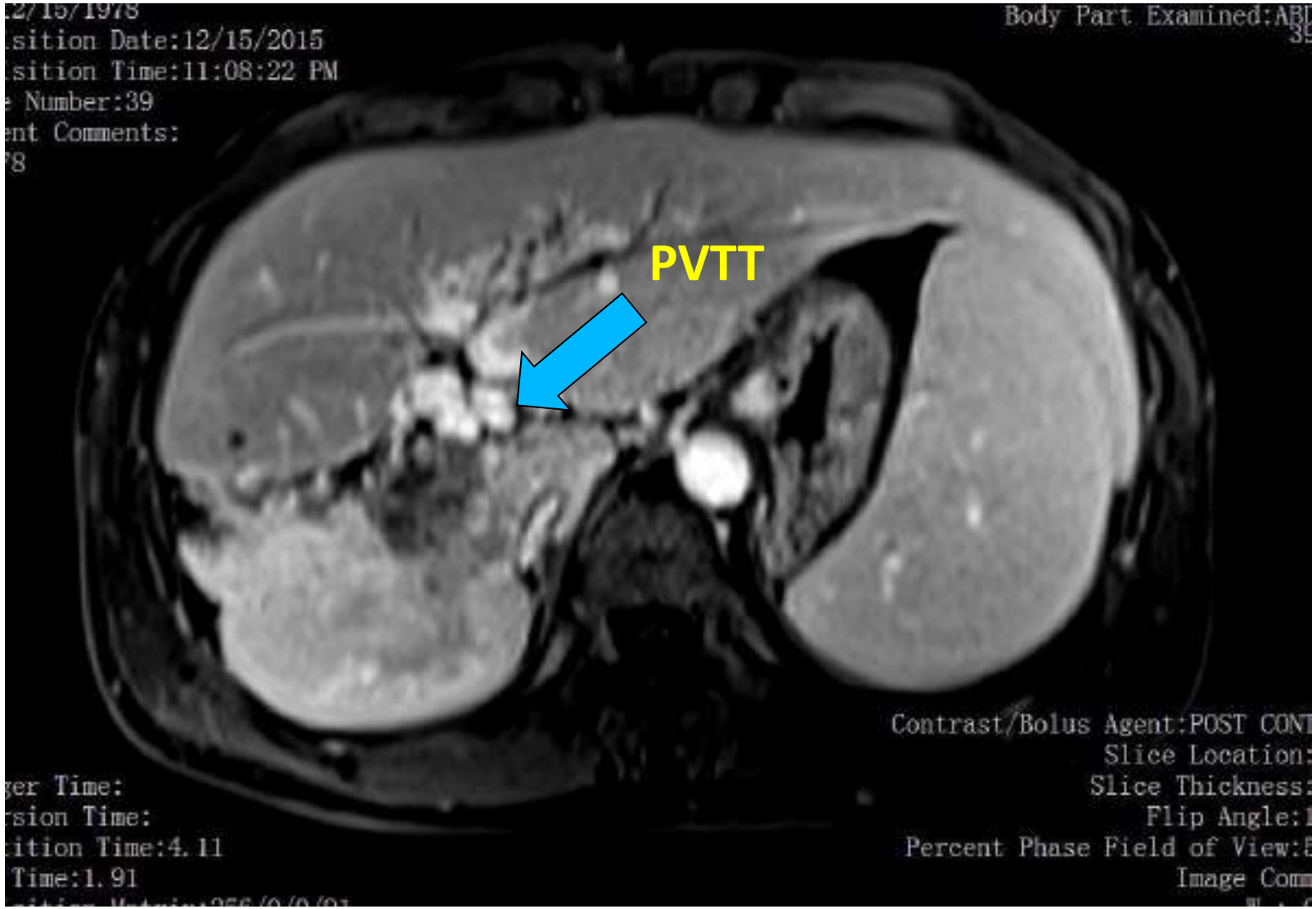


SBRT Liver – our Experience

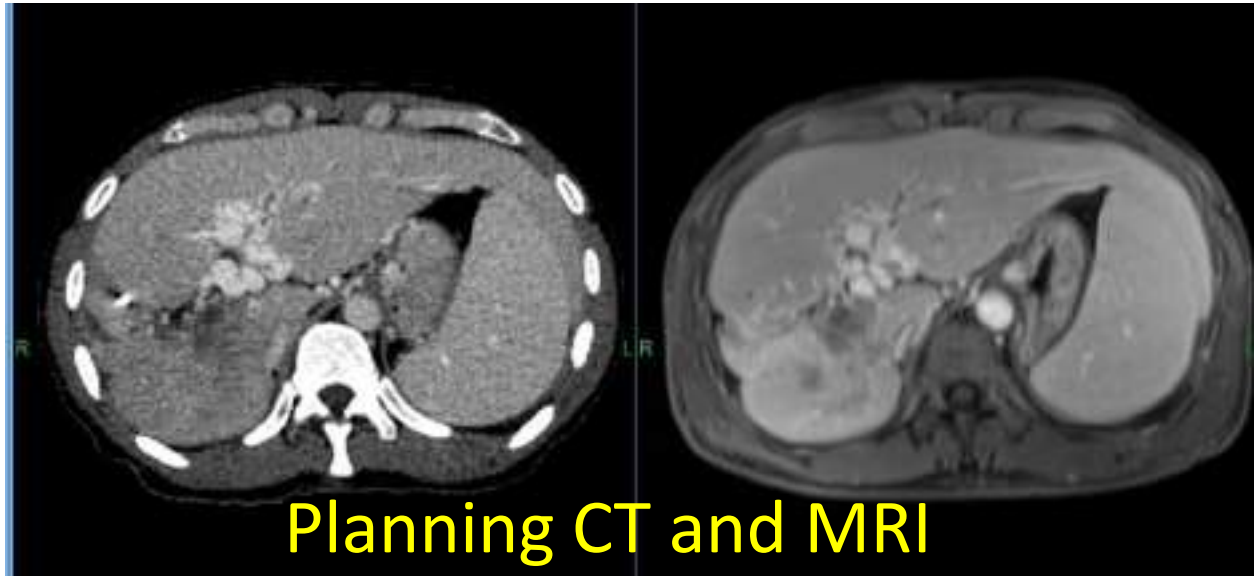
Planning a new case

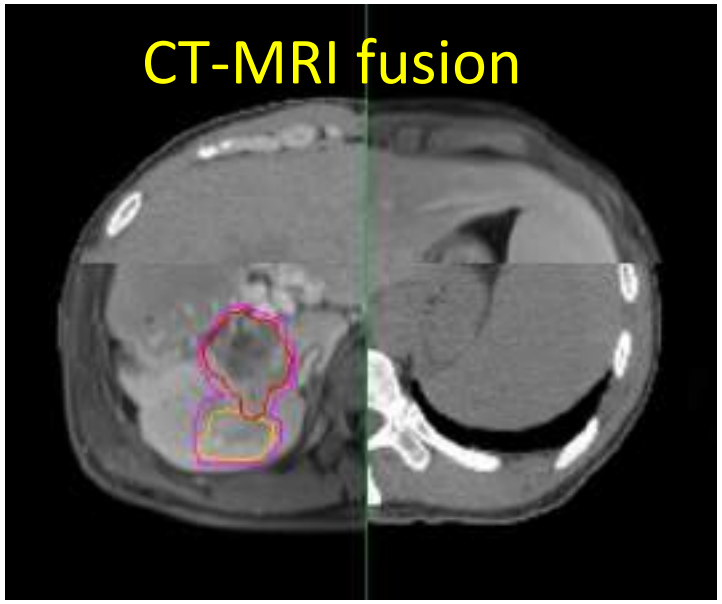


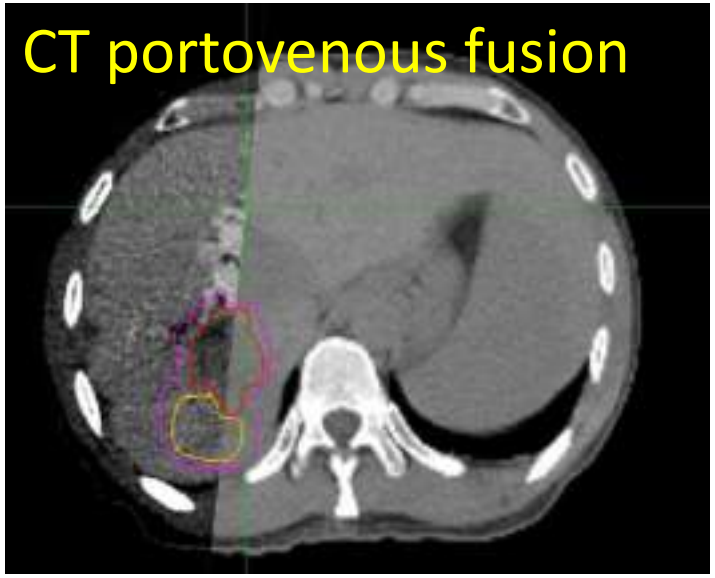
Planning triple phase MRI



ImageFusion







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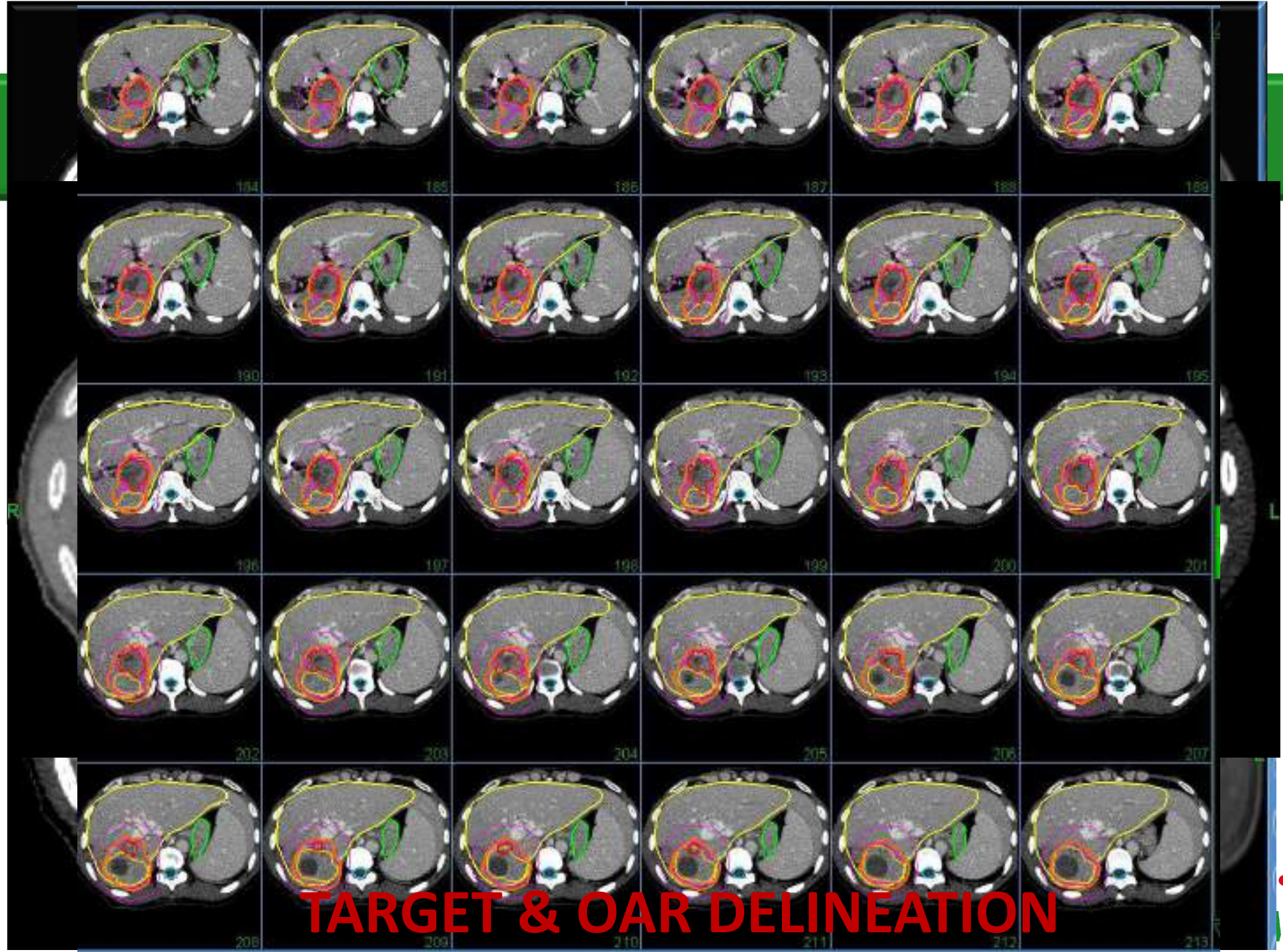

TARGET & OAR DELINEATION

Fortis

Dose prescription

- Depend on intent
- Normal liver volume available and mean dose
- Proximity to OARs

Table 3. Multivariate analysis of parameters associated with survival in hepatocellular carcinoma with portal vein thrombosis for radiation therapy

Parameter	Comparison	HR	95% CI	*p* Value
Radiation dose	<50 Gy vs. ≥50 Gy	2.175	1.546–3.059	<0.001
ECOG performance status	3 or 4 vs. 1 or 2	2.234	1.506–3.316	<0.001
Ascites	Severe vs. none or mild	1.432	1.020–2.010	0.038
AFP	≥1,500 ng/ml vs. <1,500 ng/ml	1.540	1.116–2.124	0.009
Albumin	<3.5 g/dl vs. ≥3.5g/dl	1.491	1.070–2.077	0.018
HBsAg	Positive vs. negative	1.453	1.037–2.035	0.030

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Dose volume recommendations: QUANTEC

- CP A
  - 6 #: mean liver dose (Liver- GTV) < 18 Gy
  - 3 #: mean liver dose (Liver- GTV) < 13 Gy
  - 3 #: > 800 ml of normal liver should receive < 18 Gy

- Spinal cord : Max 18 Gy
- Small intestine : Max 30 Gy
- Stomach/ Duodenum: Max : 30 Gy. Vol of stomach > 22.5 Gy should be < 5 ml
- Kidney: V 15 < 35% (b/l)

Rusthoven et al, JCO

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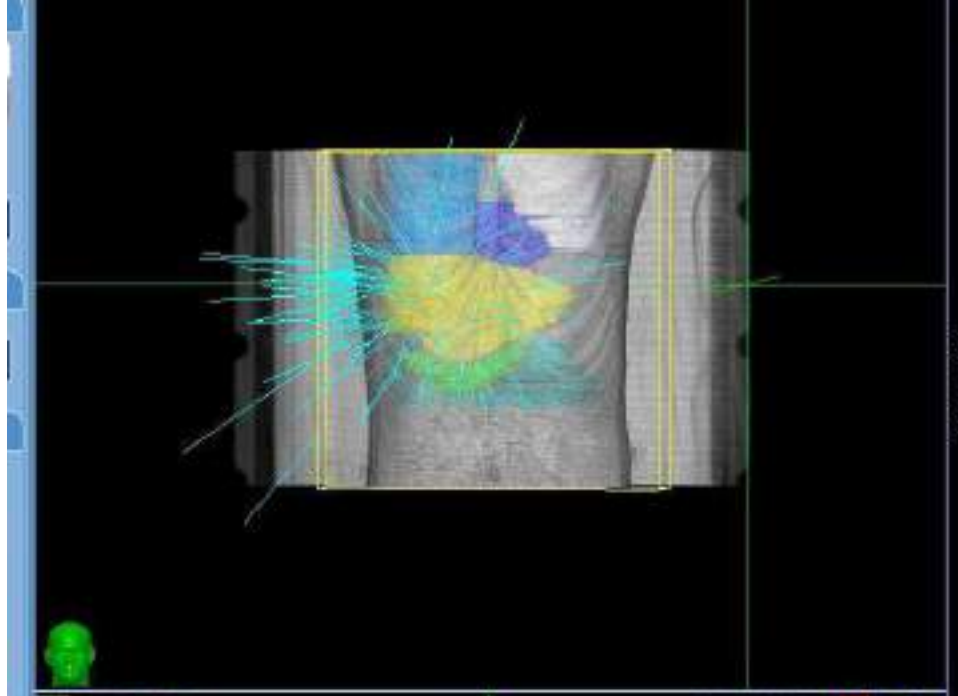
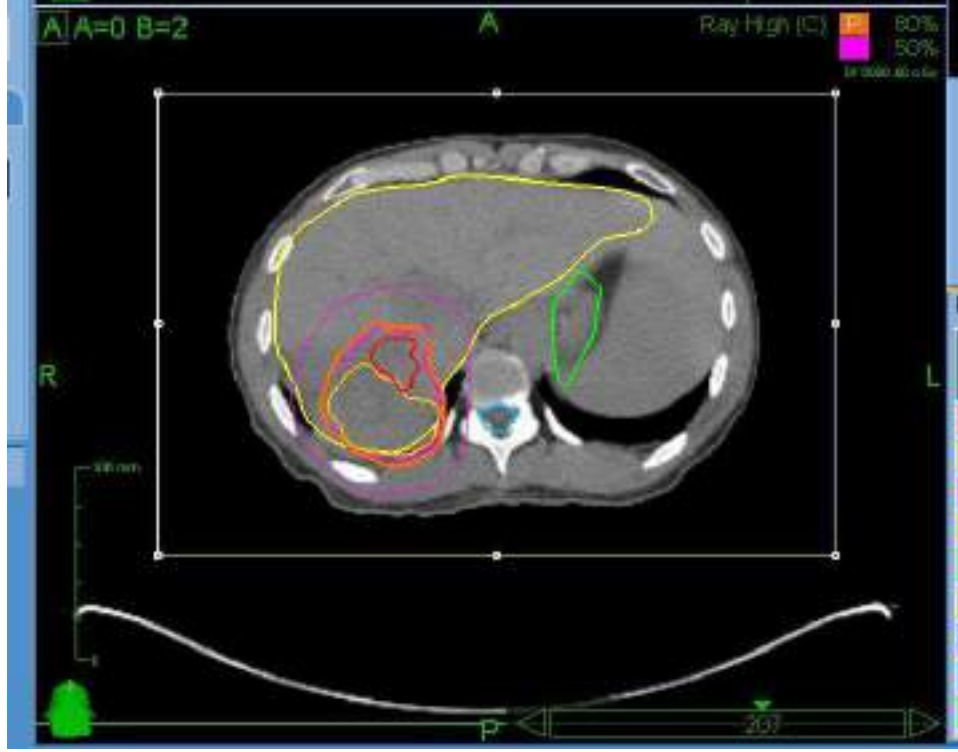
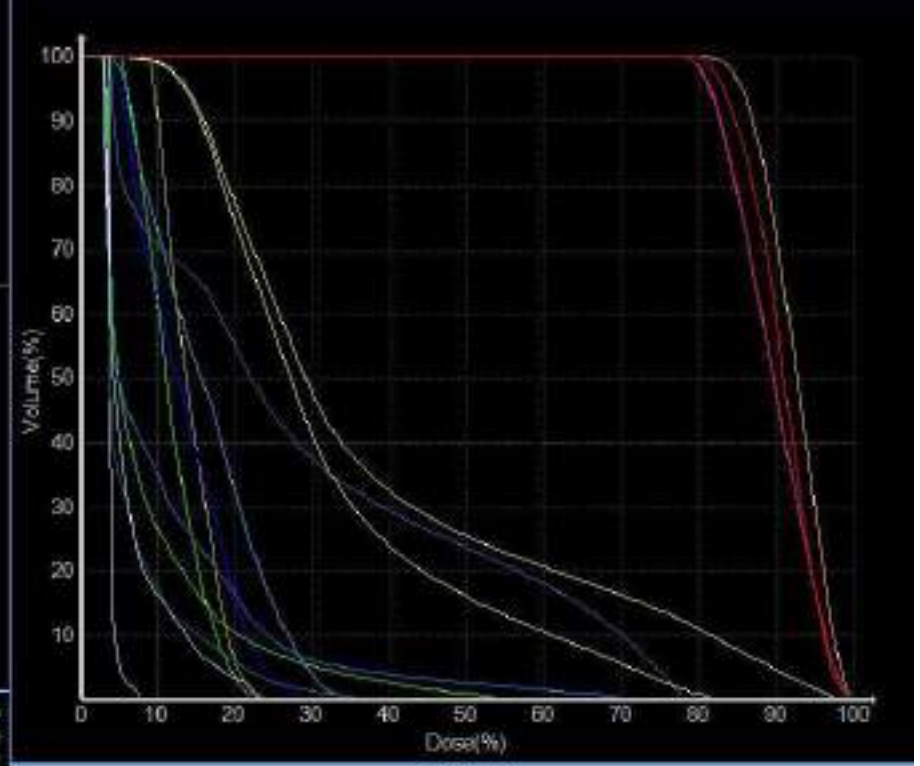






Nodes	72	Total MU	33571.14
Beams	193	Min MU	33.35
Max Dose (cGy)	6000.00	Max MU	347.85

Estimated Treatment Time Per Fraction (minutes) 69

Dose Statistics Table | Dx Vx Values | Plan Information

Name	Min (cGy)	Mean (cGy)	Max (cGy)	CI	nCI	HI	Coverage (%)
GTV PVTT	4763.29	5438.13	5978.48	5.67	5.68	1.25	99.88
GTV arterial	4771.34	5539.44	6000.00	2.86	2.86	1.25	99.97
PTV	4530.56	5367.43	6000.00	1.24	1.27	1.25	98.15
liver	231.82	2302.47	6000.00	n/a	n/a	n/a	n/a
stomach	230.72	700.76	1504.33	n/a	n/a	n/a	n/a
duodenum	495.31	850.35	1424.22	n/a	n/a	n/a	n/a
heart	222.38	789.41	1948.36	n/a	n/a	n/a	n/a
spinal cord	321.63	967.12	2225.59	n/a	n/a	n/a	n/a
rt kidney	194.92	549.11	3856.90	n/a	n/a	n/a	n/a

Fortis

Planned for
48 Gy in 3 fractions

BED: 124 Gy

Fortis

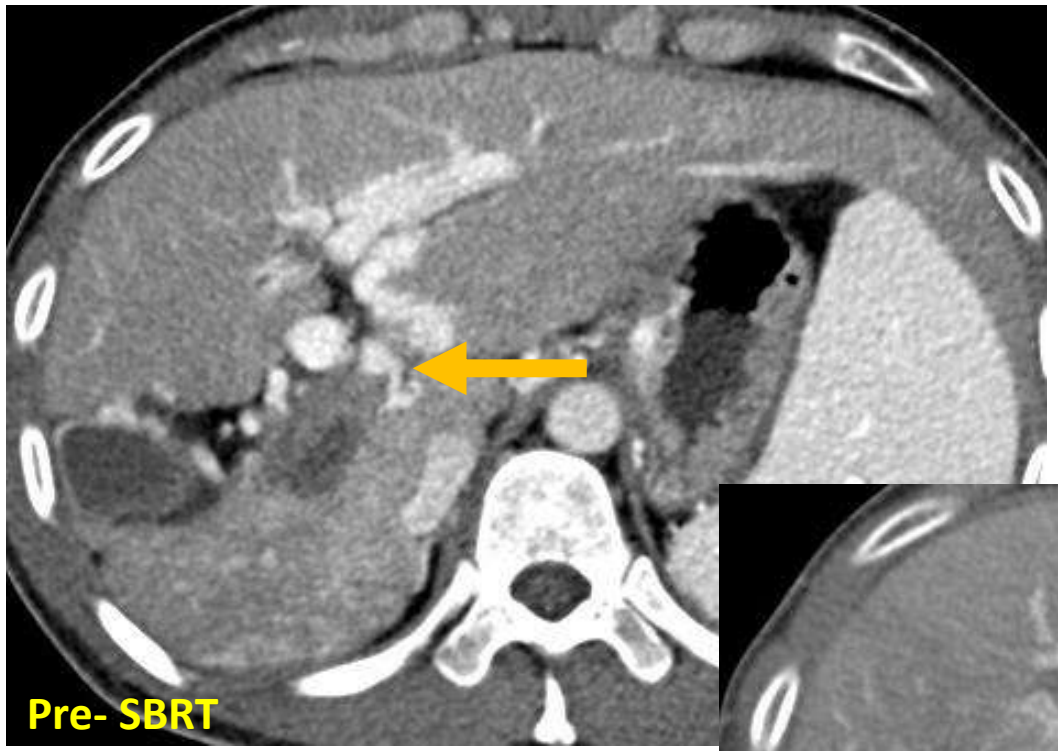
Assessment

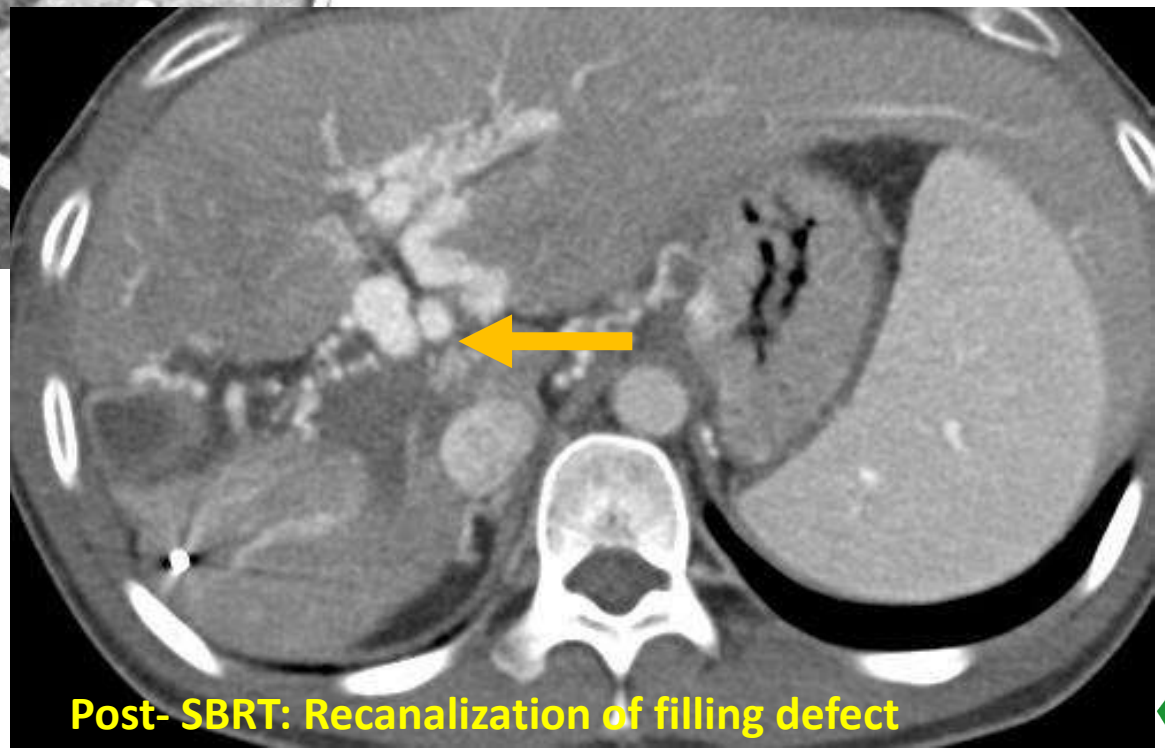
Post treatment:

- Cases follow up with Radiation oncology and Liver surgery
- Continue TARE/ Sorafenib as per plan for HCC
- Clinical & Radiological assessment @ 6 weeks then 3 monthly
- Liver surgery assessment for transplant

- PVTT response:
  - Radiological response: post SBRT → improvement in vascular flow/ re-canalization
  - Pathological response: post transplant→ Histopathology for necrosis

Post SBRT : response





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LDLT - Transplant

Underwent successful LDLT – on 24.2.16

1) VII / VII measuring 35x30x20 mm. Reaching upto capsule (1mm.)
80 mm away from hilum.
Cut surface shows grey white, with areas of haemorrhage and necrosis.
2) VI / VII measuring 20x10x15 mm. 1st 10 mm away.
Capsule : 25 mm.
Hilum : 20 mm.
No definite lesion identified in segment V.
However, suspicous area are submitted.
Gall Bladder : *Not identified.*

TISSUE SUBMITTED FOR MICROSCOPY:
A, B : Tumor with capsule
C to E : Tumor proper
F, G : 2nd lesion with ?portal V thrombus
H, I : Suspicous area in segment V
J : Right lobe periphery
K : Right lobe centre
L : Left lobe random
M : Caudate lobe
N : Hilum
More Sections Taken:
MS1 to MS4 : 1st lesion
MS5 to MS12 : 2nd lesion

MICROSCOPIC EXAMINATION:
Multiple section studied from 1st and 2nd lesion reveal large area of necrosis. No viable tumor seen. The adjoining areas show reactive changes.
The remaining grossly non tumorous hepatic parenchyma show evidence of mixed nodular cirrhosis.

IMPRESSION: *Explant hepatectomy :*

- *No viable tumor area.*
- *Only tumor necrosis (therapy related change).*
- *Background liver is cirrhotic.*

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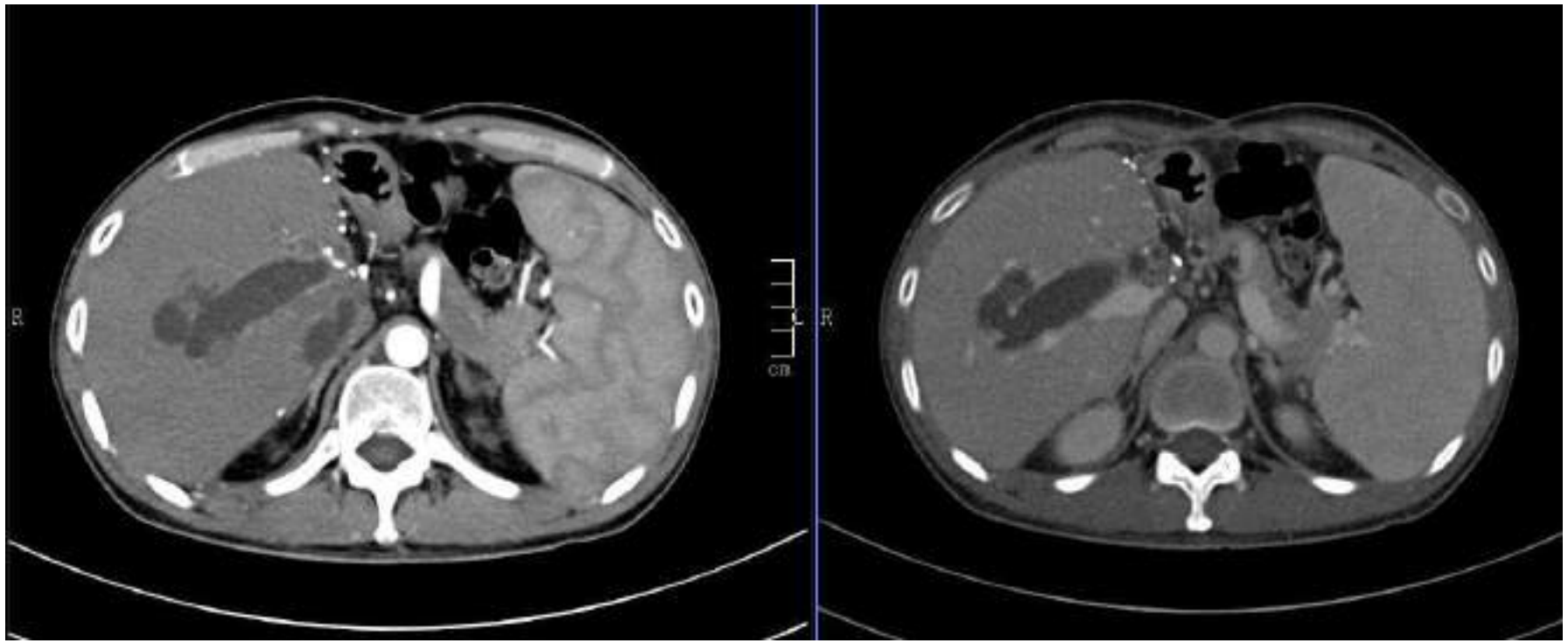
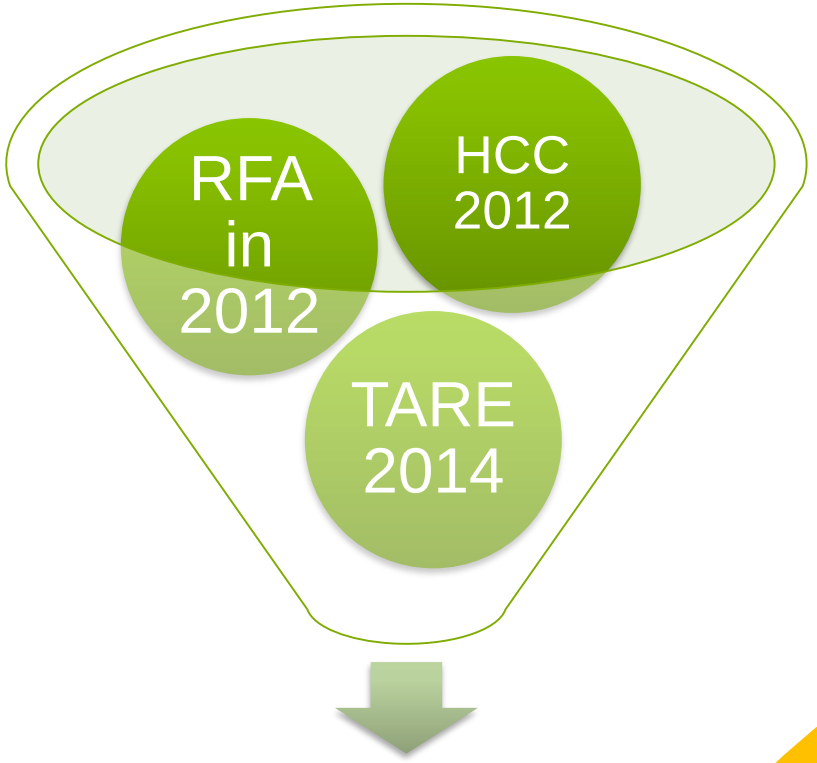
Post Transplant CECT



Present status: Summary



PVTT and recurrence in 2015

SBRT PVTT – Dec 2015

Transplant – LDLT- Feb 2016

Post transplant – 5 year – alive & healthy

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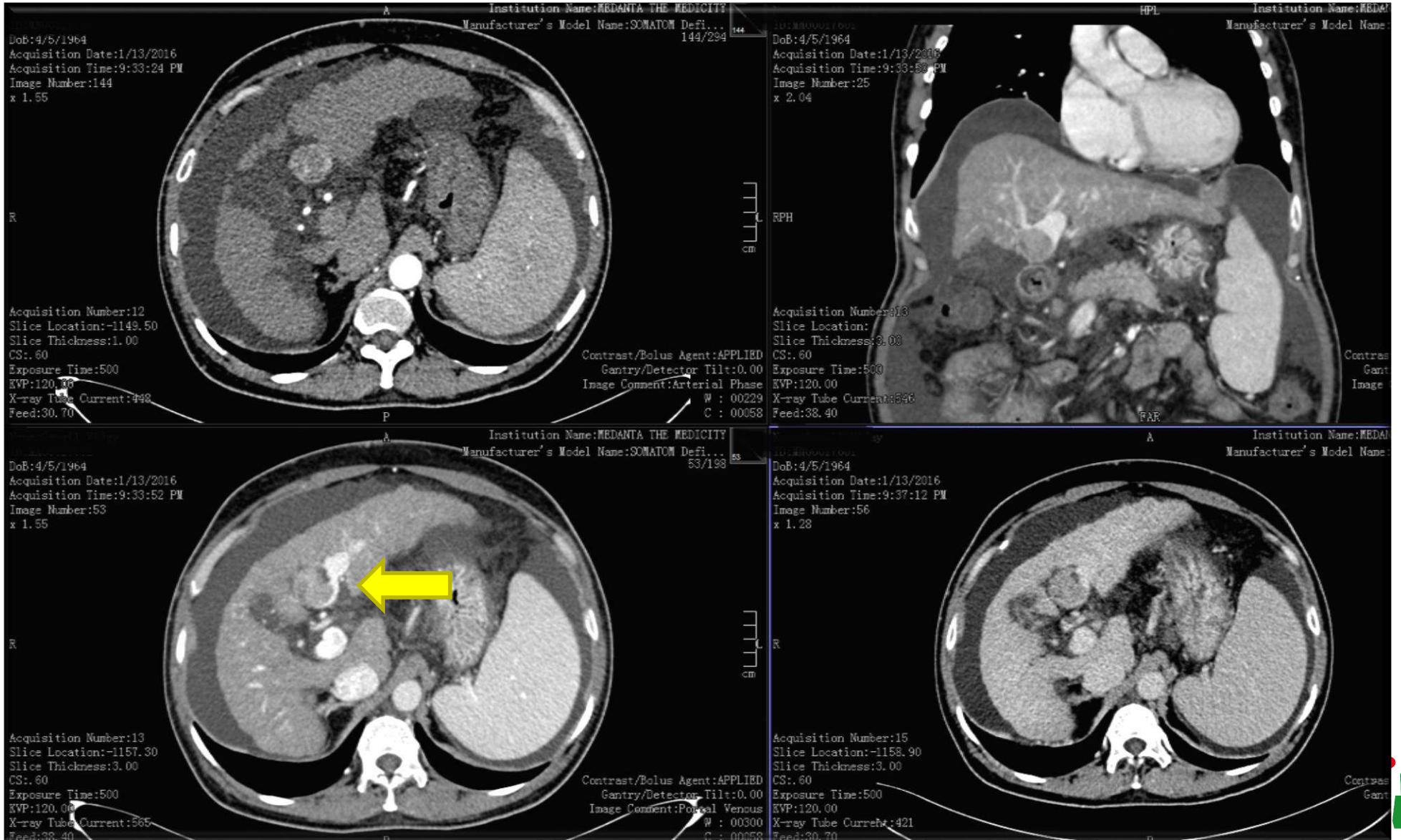
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DoB:4/5/1964
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Gantry/Detector Tilt:0.00
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C : 00058
HPL
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DoB:4/5/1964
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x 1.28
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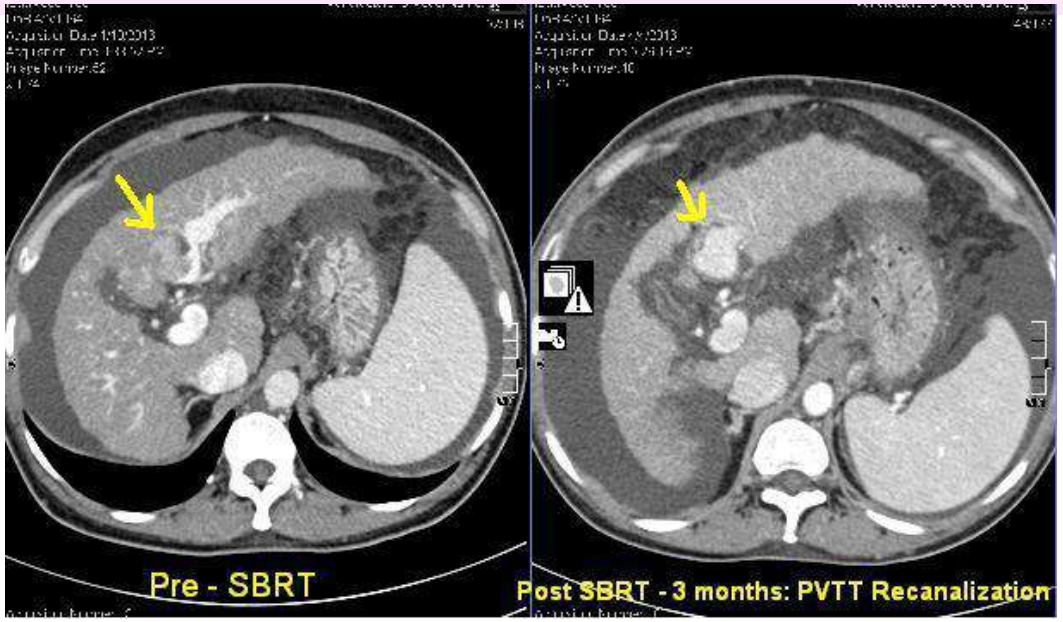
Exposure Time:500
KVP:120.00
X-ray Tube Current:421

- ***Diagnosis: HCC multifocal with PVTT***
- *Planned for SBRT to PVTT with breath hold – ABC followed by TARE*
- ***Dose planned 6000cGy/5 fractions***

IMPRESSION:

CT findings are suggestive of chronic liver disease with HCC in segment IVA showing post TARE changes in the form of mild reduction in size with near complete resolution arterial enhancement sparing its periphery which is becoming isodense on subsequent phases.
Interval reduction in the size of contiguous tumoral thrombus in segment IV branch of left portal vein with complete loss of arterialized component.
No new lesion evident.
Sequelae of portal hypertension in the form of splenomegaly, portosystemic collaterals with esophageal varices with small lienorenal shunt and moderate to gross ascites.
Large right inguinoscrotal hernia containing ascitic fluid.



Post op - HPE

Alive for 1 year 7 months post surgery – developed lung mets - expired

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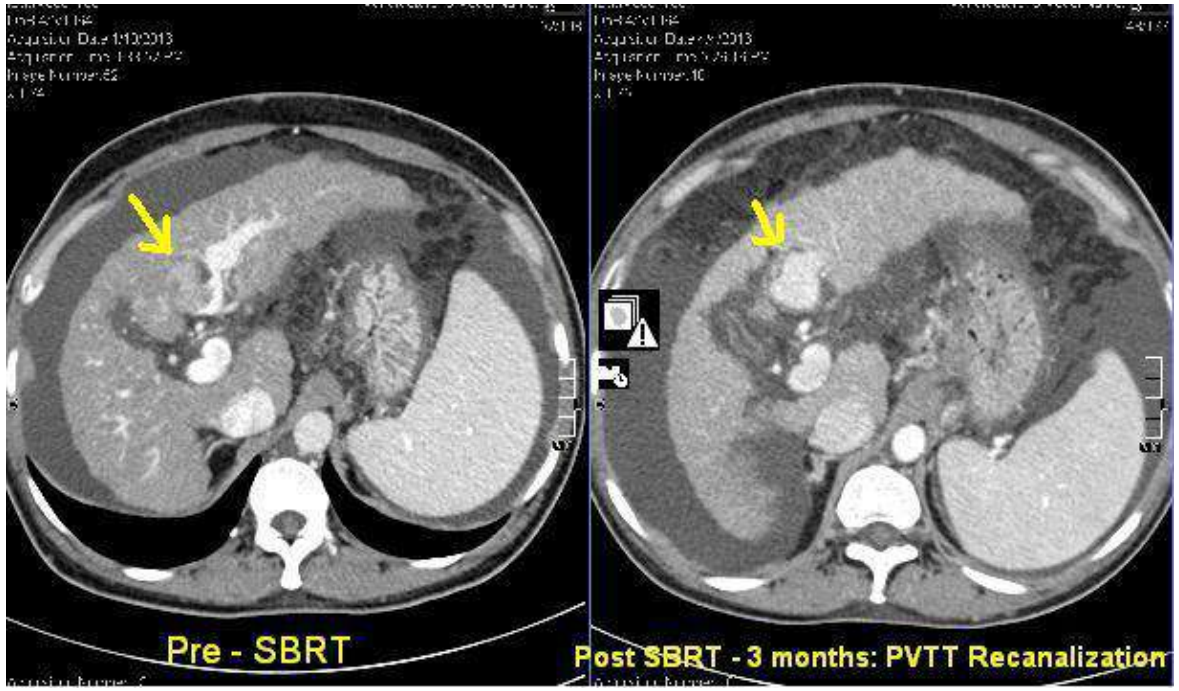
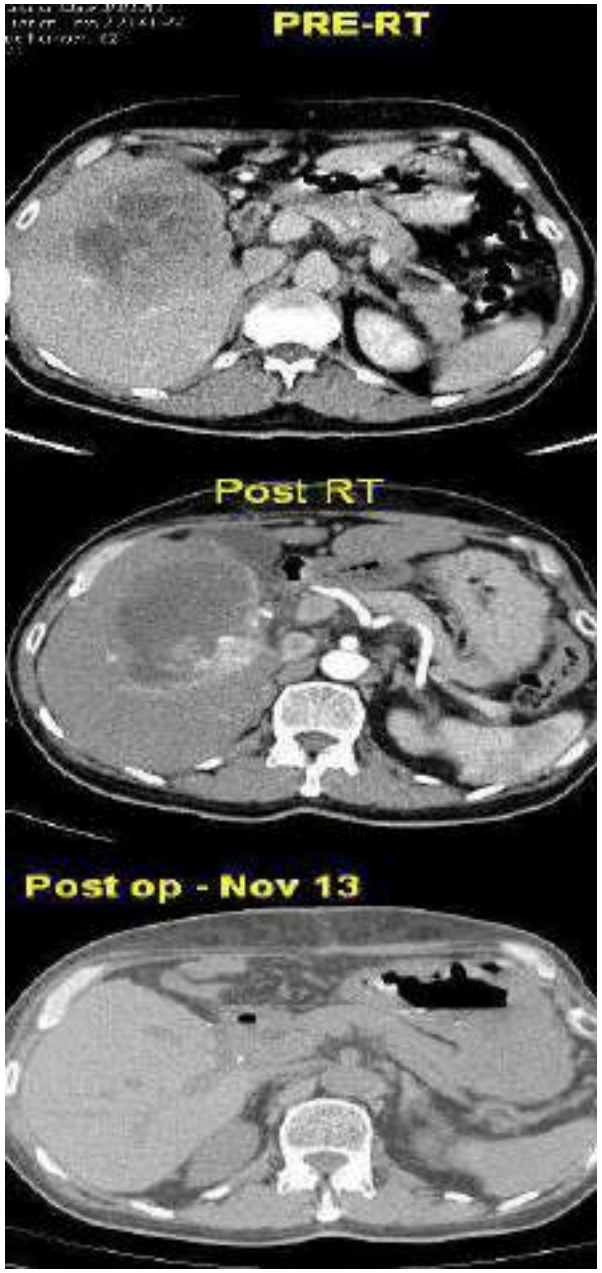
Survival (months) in specific groups		
	Post Diagnosis	Post RT
All Cases [n=60] (mean)	15 [1-55]	7 [0-42]
Curative cases [n=42] (mean)	15 [1-55]	8 [0-42]
❖ Transplant [n=13] mean	29 [5-55]	20 [6-42]
❖ Non Transplant [n=29] mean	9 [1-41]	3 [0-12]
Palliative [n=18] mean	13 [2-38]	4 [0-14]



PVTT recanalization



Post Transplant

Fortis

Role of SBRT in HCC – PVTT: Medanta Experience

JOURNAL OF CLINICAL AND EXPERIMENTAL HEPATOLOGY

PORTAL VEIN THROMBUS IRRADIATION—AN ALTERNATIVE IN INOPERABLE HEPATOCELLULAR CARCINOMA

A Abhishek, T Kataria, K Sharma, KP Karrthick, K Madan, T Piplani

Cancer Institute, Medanta—The Medicity, Gurgaon, India; Institute of Liver and Biliary Sciences (ILBS), New Delhi, India

Background: Portal vein tumor thrombosis (PVTT), in a case of hepatocellular carcinoma (HCC), is considered poor risk and has been reported to be associated with unfavorable outcomes to the established treatment regimens like surgical resection or TACE (transarterial chemoembolization). Radiotherapy (RT) has shown survival benefits and promises [illegible] therapy in such cases.

Aim: To review and establish the role of RT in advanced HCC with portal [illegible]

Materials and Method: Literature was reviewed for the role of radiotherapy in PVTT along with the case selection criteria, technique, expected benefits, and possible side effects of the treatment.

Discussion: Definitive treatment strategy is not established for PVTT in advanced HCC. With 34–84% incidence, PVT cannot be overlooked and demands alternative approaches. Results of surgery in such cases are dismal and palliative chemotherapy (TACE) may increase the risk of ischemic events. In such cases, radiotherapy has been widely reported to have an objective response rate of 37.5–57.9%, with a median survival time of 6.7–10.7 months. Post PVTT-RT, re-canalization may be achieved in 60–75% cases and re-considered for TACE/primary management with acceptable outcomes. Therefore, RT is a promising salvage alter-

2011

2014

2016

Portal vein tumor thrombus irradiation: A bridge to successful liver transplant

Ashu Abhishek

Associate Consultant Radiation Oncology - Medanta the Medicity, Gurgaon. E-mail: ashuabhishek@gmail.com

2014

Courtesy: Medanta –The Medicity

Introduction: Liver transplant remains the treatment of choice for Hepatocellular carcinoma (HCC). Presence of portal vein tumor thrombus (PVTT) is one of the commonest reasons for inoperability and is considered to be associated with poor survival. Such medically inoperable cases are offered alternative treatments like Radio frequency ablation (RFA), Trans arterial chemo-embolization (TACE) and conventional external beam radiotherapy (EBRT). Owing to documentation of poor liver tolerance to radiation from conventional techniques in past, the role of EBRT has not been explored adequately. Stereotactic body radiotherapy (SBRT) is an emerging modality of cancer treatment, promising better o[illegible]VTT since April 2011. SBRT planning with breathing motion management(either on linac with Automatic br[illegible]an details, imaging response, transplant status and survival as per last follow up in these cases were reviewed for analysis. **Results:** Out of 20 cases, 10 were treated till December 2013 (pre 2014 cases) and rest 16 were treated till July 2014 (2014 cases). Adequate follow up was available for pre 2014 cases while most cases of 2014 are still awaiting evaluation. Intent of treatment was curative in 5/10 and palliative in

Successful Transplant post neo-adjuvant PVTT-RT: limited available world literature

Brief Communication

Yonsei Med J 2016 Sep;57(5):1276-1281

http://dx.doi.org/10.3349/ymj.2016.57.5.1276

pISSN: 0513-5796 · eISSN: 1976-2437

Korea 2016

Living Donor Liver Transplantation for Advanced Hepatocellular Carcinoma with Portal Vein Tumor Thrombosis after Concurrent Chemoradiation Therapy

Dai Hoon Han[1,2], Dong Jin Joo[1,2,3], Myoung Soo Kim[1,4], Gi Hong Choi[1,2,3], Jin Sub Choi[1,2,3], Young Nyun Park[2,4], Jinsil Seong[2,5], Kwang-Hyub Han[2,6], and Soon Il Kim[1,3]

[1]Department of Surgery, [2]Liver Cancer Special Clinic, [3]Research Institute for Transplantation, Departments of [4]Pathology, [5]Radiological Oncology, and [6]Internal Medicine, Yonsei University College of Medicine, Seoul, Korea.

IJROBP

Abhishek et al 2016

< Previous Article | October 1, 2016 Volume 96, Issue 2, Supplement, Page E164 | Next Article >

Portal Vein Tumor Thrombus Irradiation: Paving the Way for Liver Transplant

A. Abhishek, T. Kataria, D. Gupta, T. Basu, S.S. Bisht, S. Goyal, K.P. Karrthick

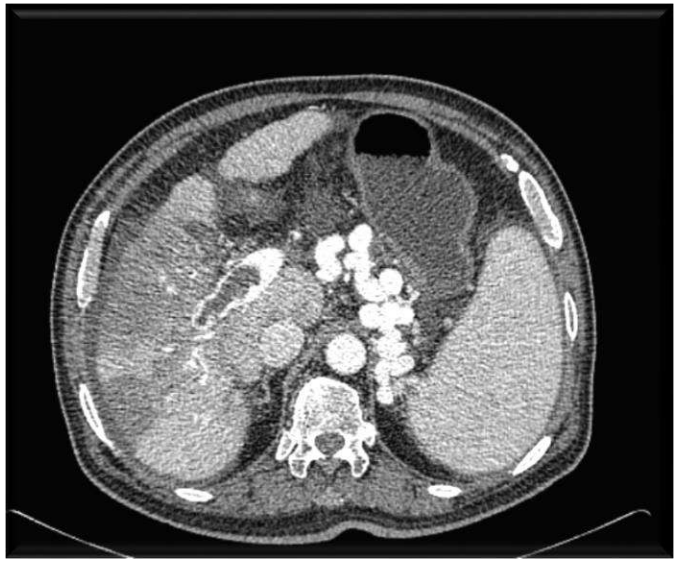
Medanta-The Medicity, Gurgaon, India

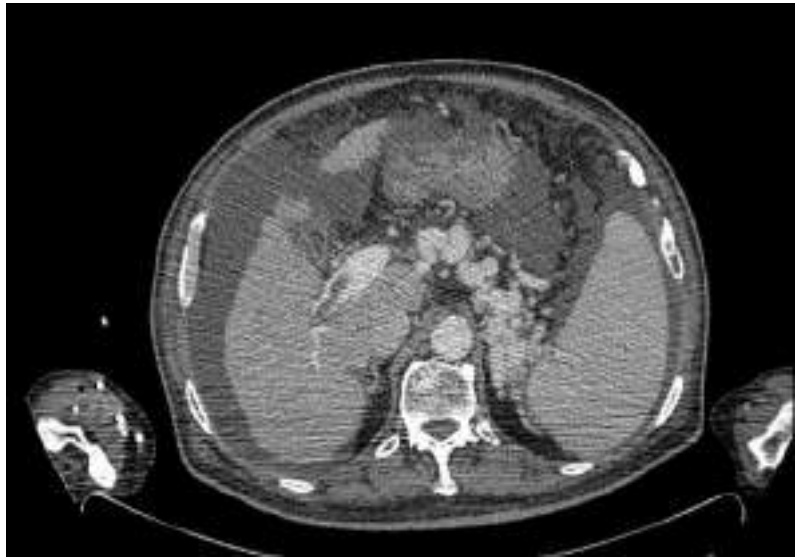
2401

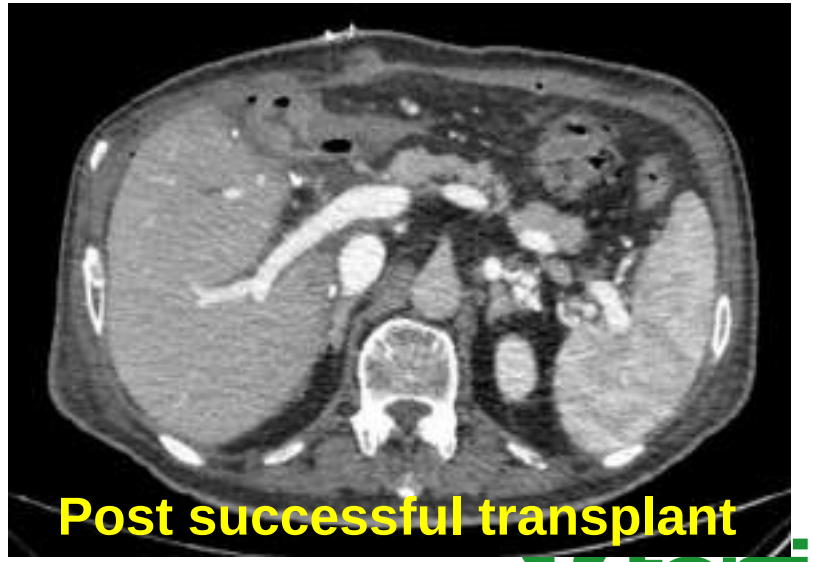
Courtesy: Medanta –The Medicity

	Korea	Abhishek et al
No of cases	8	40
No of transplant	8	17
Awaiting assessment	N/A	11
Responders	N/A	18 (CR or PR) - 43% 8 (stable) – 20%
Median survival (transplant cases)	33 months	29 mths (6-55 mths)
Tumor	3 @ median	

HCC –PVTT : SBRT + TARE → Transplant

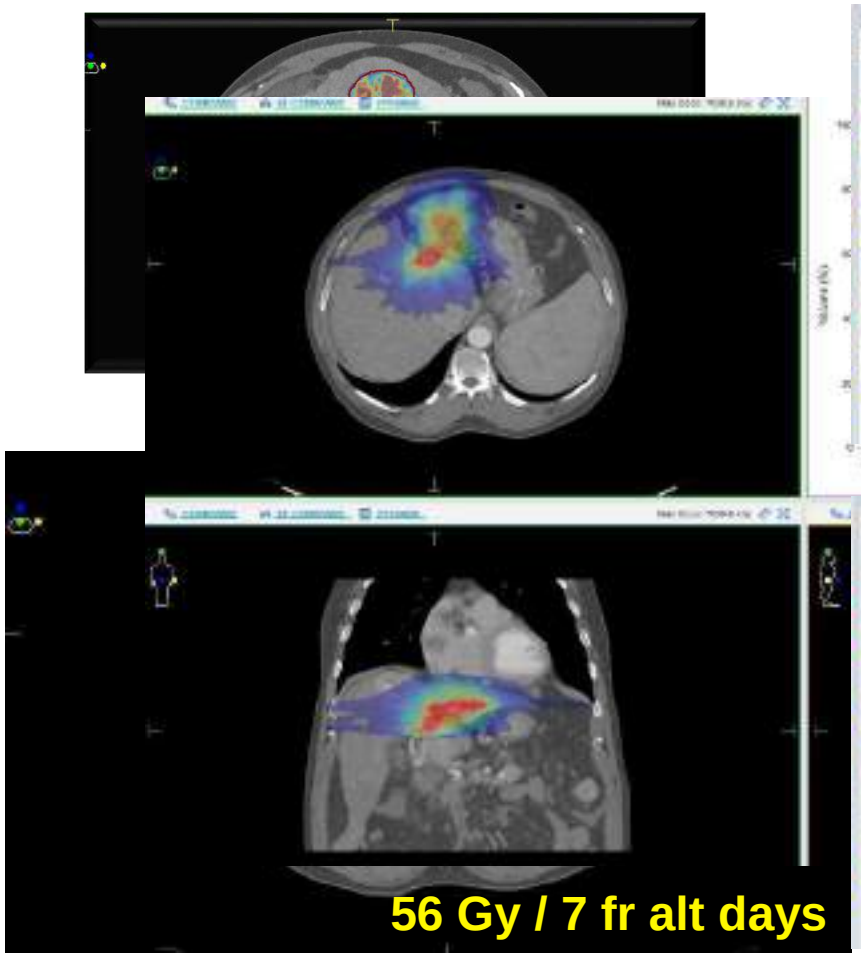


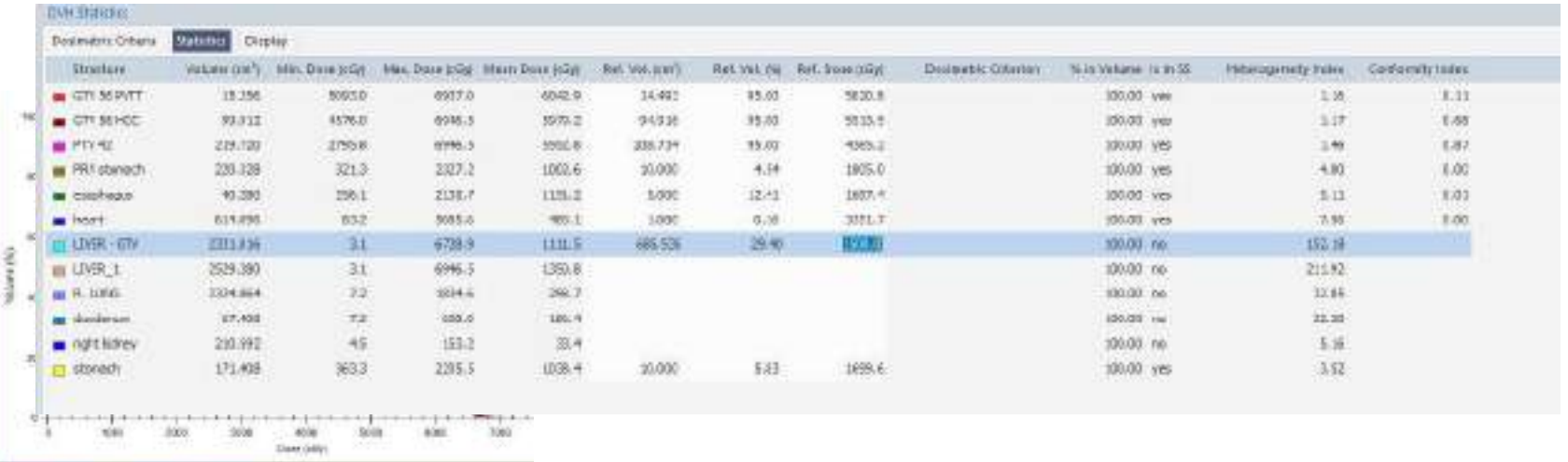




Post successful transplant

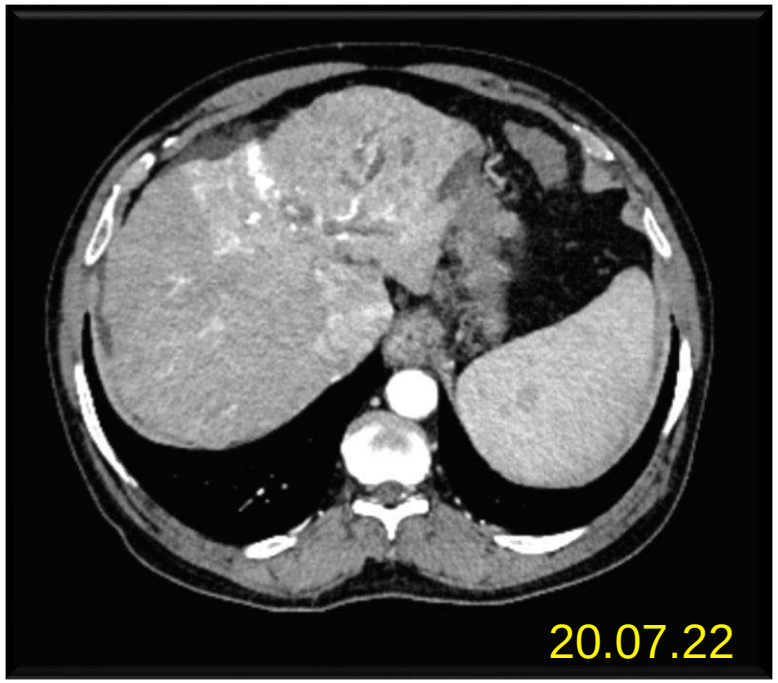
HCC – PVTT – unfit for TARE (multiple collaterals)

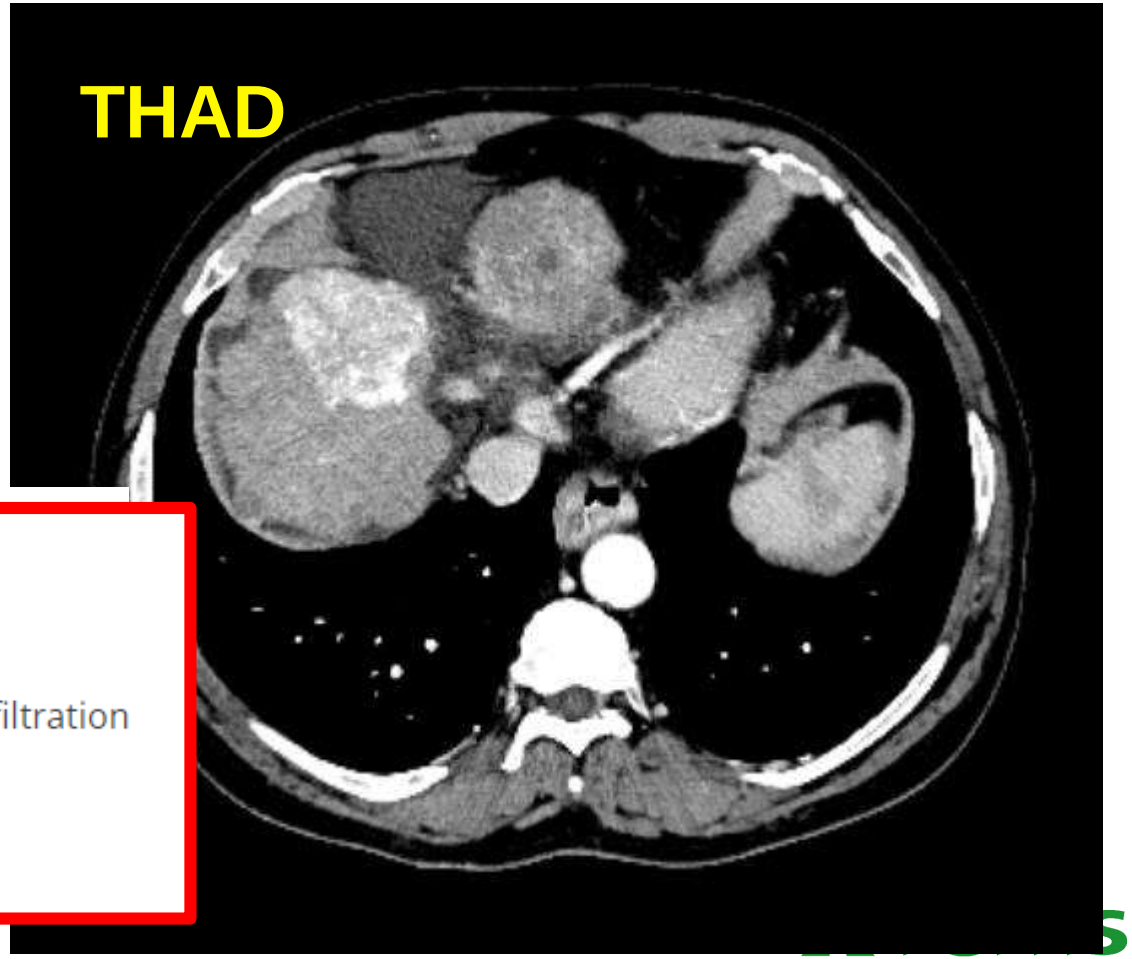




Structure	Volume (cm³)	Min. Dose (cGy)	Max. Dose (cGy)	Mean Dose (cGy)	Ref. Vol. (cm³)	Ref. Vol. (%)	Ref. Dose (cGy)	Dosimetric Criterion	% in Volume	is in SS	Heterogeneity Index	Conformity Index
GTV 56 PVTT	15.256	5093.0	6937.0	6042.9	14.491	95.00	5620.8		100.00	yes	1.16	0.11
GTV 56 HCC	99.912	4576.0	6946.5	5979.2	94.916	95.00	5513.5		100.00	yes	1.17	0.68
PTV 42	219.720	2795.8	6946.5	5552.8	208.734	95.00	4366.2		100.00	yes	1.46	0.87
PRV stomach	220.328	321.3	2327.2	1002.6	10.000	4.54	1805.0		100.00	yes	4.00	0.00
esophegus	40.280	256.1	2135.7	1151.2	5.000	12.41	1687.4		100.00	yes	5.11	0.01
heart	614.896	83.2	5065.6	488.1	1.000	0.16	3351.7		100.00	yes	7.56	0.00
LIVER - GTV	2351.836	3.1	6738.9	1111.5	1611.000	68.55	4930		100.00	no	152.18	
LIVER_1	2529.380	3.1	6946.5	1350.8					100.00	no	211.92	
R. LUNG	2324.864	7.2	6834.6	298.7					100.00	no	32.85	
duodenum	67.408	7.2	628.0	186.4					100.00	no	22.20	
right kidney	210.592	4.5	153.2	33.4					100.00	no	5.16	
stomach	171.408	363.3	2205.5	1038.4	10.000	5.83	1698.6		100.00	yes	3.52	

HCC – PVTT – unfit for TARE (multiple collaterals)





Four pathogenic mechanisms have been described:

- directly by a siphoning effect (lobar multisegmental shape)
- portal hypoperfusion (sectorial shape) due to portal branch compression or infiltration
- thrombosis resulting in a portal branch blockade
- flow diversion caused by an arterioportal shunt

SBRT / TARE / Lenvatinib in multicentric HCC with PVTT - FMRI

Multimodality Treatment of Advanced Hepatocellular Carcinoma: A novel strategy for treating HCC with portovenous tumour thrombus with a combination of SIRT, SBRT and targeted chemotherapy

[!]Ishita Sen, [$]Saurabh Kumar, [*]Ashu Abhishek, [@]Mukesh Patekar [!]Subha Shankar Das, [!]Dharmender Malik, [*]Ashish Singhal,

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Survival

Survival was assessed starting on the day of first SIRT treatment, and the Kaplan-Meier plot is shown in Fig 1. The estimated median duration of follow up by reverse Kaplan-Meir plot was 14 months. The estimated median overall survival at the time of analysis was 13.2 months with 40% patients alive at the time of censoring. At the time of analysis, 12 patients had died, 3 of whom died as a result of primary or metastatic disease progression, whereas 9 patients died as a result of parenchymal liver failure. 1 other had progressed with extrahepatic disease but continued to survive while six continued to be in good response. with the multimodality treatment. The longest survival at the time of analysis was 20 months.

- Preliminary data : 20 cases
- HCC with PVTT
- Multi modality approach – TARE + SBRT combination

To our knowledge this is the first data demonstrating the effective combination of three modalities, SIRT, SBRT and Lenvatinib to produce not just sustainable response but also a good quality of life in patients with advanced HCC. In our cohort of patients, median survival was 13.2 months, which is marginally better than the ImBRAVE study using the combination of Atezulumab + bevacizumab which is now considered the standard of care in advanced HCC. Objective response rates by mRECIST have been found to be an independent predictor of OS in many studies of advanced HCC. In our study there was a 90% response rate by mRECIST criteria with an 85% fall in Serum AFP levels. There was also excellent patient compliance as the therapy required only two episodes of day care admission for TARE, once for mapping while the other for actual delivery of Y90 Sir sphere. The SBRT was also done as an out-patient procedure.

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New in PVTT- RT: endovascular brachytherapy

World Journal of Gastroenterology

Submit a Manuscript: http://www.wjgnet.com

World J Gastroenterol 2017 November 21; 23(43): 7735-7745

DOI: 10.3748/wjg.v23.i43.7735

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

ORIGINAL ARTICLE

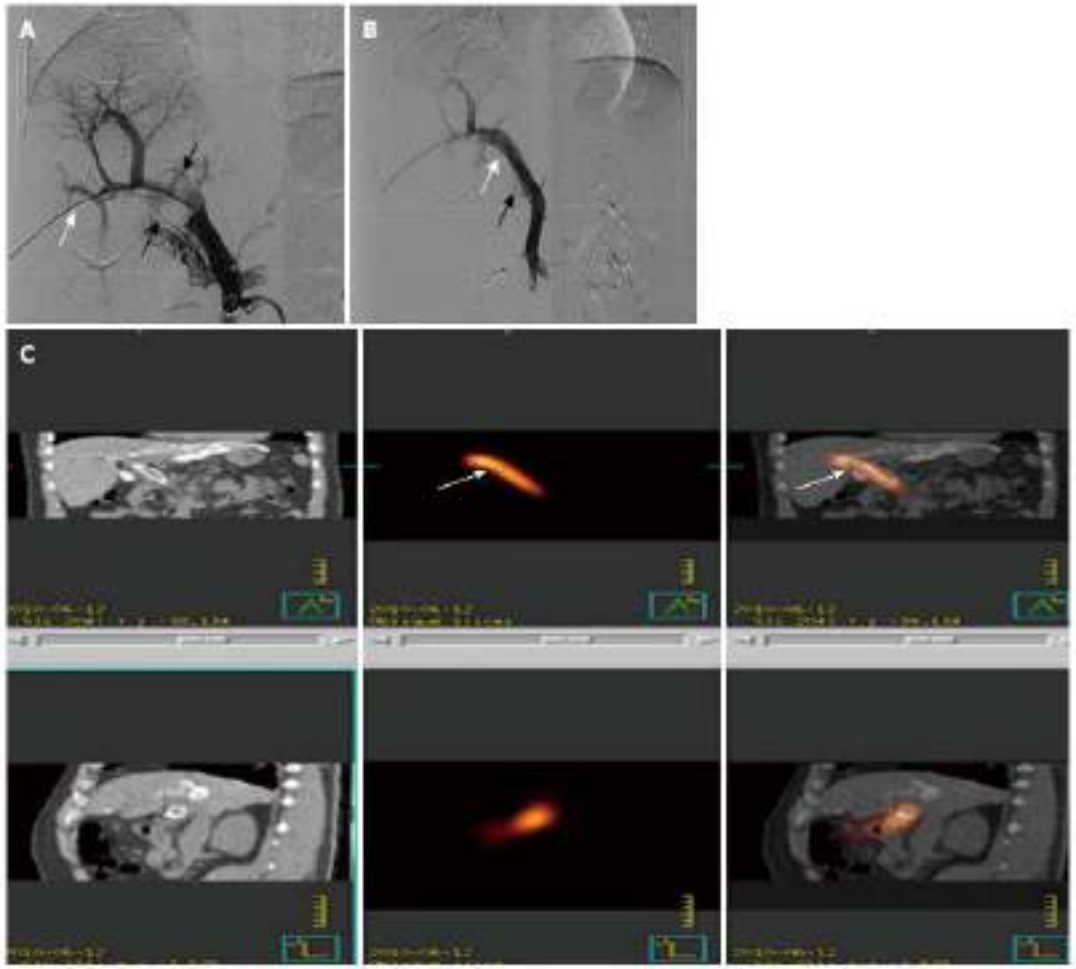
Retrospective Study

Combined endovascular brachytherapy, sorafenib, and transarterial chemobolization therapy for hepatocellular carcinoma patients with portal vein tumor thrombus

Zi-Hen Zhang, Qing-Xin Liu, Wen Zhang, Jing-Qin Ma, Jian-Hua Wang, Jian-Jun Luo, Ling-Xiao Liu, Zhi-Ping Yan

CONCLUSION

EVBT combined with stent placement, TACE, and sorafenib might be a safe and effective palliative treatment option for MPVTT.



Fortis

New in PVTT- RT: endovascular brachytherapy

www.impactjournals.com/oncotarget/ Oncotarget, 2017, Vol. 8, (No. 7), pp: 12108-12119

Research Paper

Endovascular brachytherapy combined with portal vein stenting and transarterial chemoembolization improves overall survival of hepatocellular carcinoma patients with main portal vein tumor thrombus

Tian-Zhu Yu[1,2,*], Wen Zhang[1,2,*], Qing-Xin Liu[3,*], Wen-Hui Li[4,*], Jing-Qin Ma[1,2], Zi-Han Zhang[1,2], Min-Jie Yang[1,2], Jian-Hua Wang[1,2], Bing Chen[1], Shao-Chong Zeng[1], Jian-Jun Luo[1,2], Ling-Xiao Liu[1,2], Zhi-Ping Yan[1,2]

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Ling-Xiao Liu, **email:** Liu.lingxiao@zs-hospital.sh.cn
Zhi-Ping Yan, **email:** Yan.zhiping@zs-hospital.sh.cn

Keywords: hepatocellular carcinoma, main portal vein, tumor thrombus, endovascular brachytherapy, three-dimensional conformal radiotherapy

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ABSTRACT

Hepatocellular carcinoma (HCC) patients with main portal vein tumor thrombus have a median survival time of only about 4 months. We therefore compared the safety and efficacy of endovascular brachytherapy (EVBT) and sequential three-dimensional conformal radiotherapy (3-DCRT). From a cohort of 176 patients, we treated 123 with EVBT using iodine-125 seed strands (group A) and the remaining 53 with sequential 3-DCRT (group B). Overall survival, progression free survival and stent patency characteristics were compared between the two groups. Our analysis demonstrated a median survival of 11.7 ± 1.2 months in group A versus 9.5 ± 1.8 months in group B (p = 0.002). The median progression free survival was 5.3 ± 0.7 months in groupA versus 4.4 ± 0.4 months in group B (p = 0.010). The median stent patency period was 10.3 ± 1.1 months in group A versus 8.7 ± 0.7 months in group B (p = 0.003). Therefore, as compared to sequential 3-DCRT, EVBT combined with portal vein stenting and TACE improved overall survival of HCC patients with main portal vein tumor thrombus.

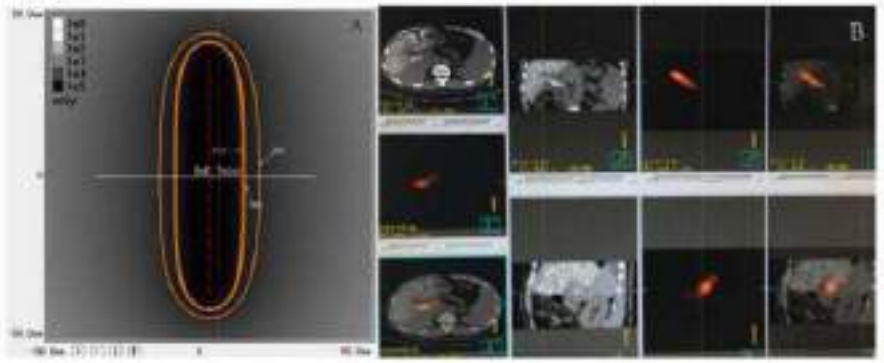

Figure 4: Images of dosimetry of a iodine-125 seeds strand and SPECT/CT. A. Dosimetry of a seed strand containing 16 Iodine-125 seeds. The isodose contours are: 100% (62.5Gy, reference point, red dot), 90% (56.2Gy), and 50% (31.2Gy). The 240 day accumulation dose was141.6Gy. **B.** Image of a SPECT/CT scan performed 1 day after the procedure. Stent and I-125 seed strands were implanted correctly in the MPV without displacement. Radiation emitted by a I-125 seed strand was distributed homogeneously and completely covered the tar

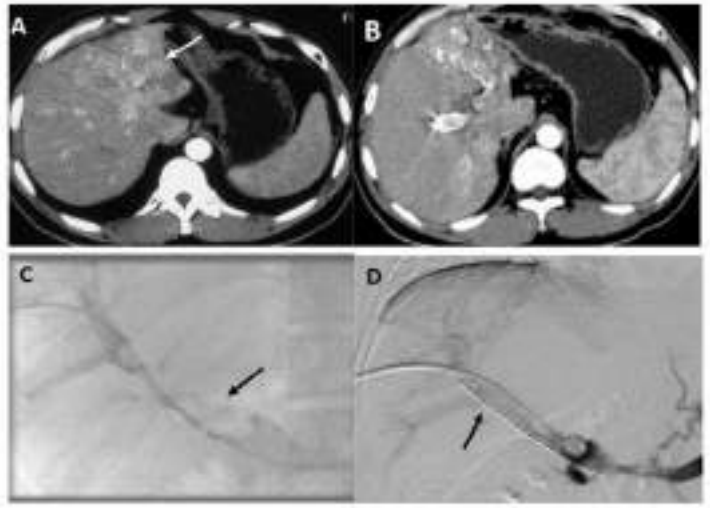

Figure 5: Images of portal vein stenting and TACE combined with endovascular brachytherapy performed in a 29-year-old male patient (group A). A. An invasive HCC (white arrow) detected on the left lobe by the enhanced abdominal CT scan before therapy. B. Image of an enhanced abdominal CT scan performed one month after the first therapy. Atrophic left lobe of liver and partial response of HCC to TACE was observed. C. The tumor thrombus (black arrow) in his MPV was observed on the direct portography after his right parent intrahepatic portal vein branch was punctured. D. Image captured after a 14/100 mm stent and iodine-125 seed strand that was loaded with 20 radioactive seeds (black arrow) had been implanted in his MPV showing restoration of the flow of the obstructed MPV.

HCC – RT

Gains…

HCC - PVTT

- 42 inoperable cases
- Expected survival – 2.7 to 10 months

SBRT Bridge of Hope

- 17 operable + 6 awaiting
- Post transplant 29 + months
- Curative cases: 15 + months

Inoperable multicentric HCC – median survival 6-9 months

Median survival - > 13 months
longest > 20 months

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RT in the HCC management guidelines

Guidelines	Mention of RT as a treatment option
APASL (2009)	No
KLCSG (2009)	Consolidate TACE, Portal invasion, Symptom palliation
JSH (2005/2007/2010)	2005/palliative RT aimed at pain relief
AASLD (2005/2010)	2005/one of non-curative treatment 2010/alleviate pain in bone metastasis
NCCN (2012)	Unresectable (unable to transplant), Inoperable local disease
EASL-EORTC (2012)	No evidence/under investigation
Chinese Society of Liver Disease	Vascular invasion/Extrahepatic spread

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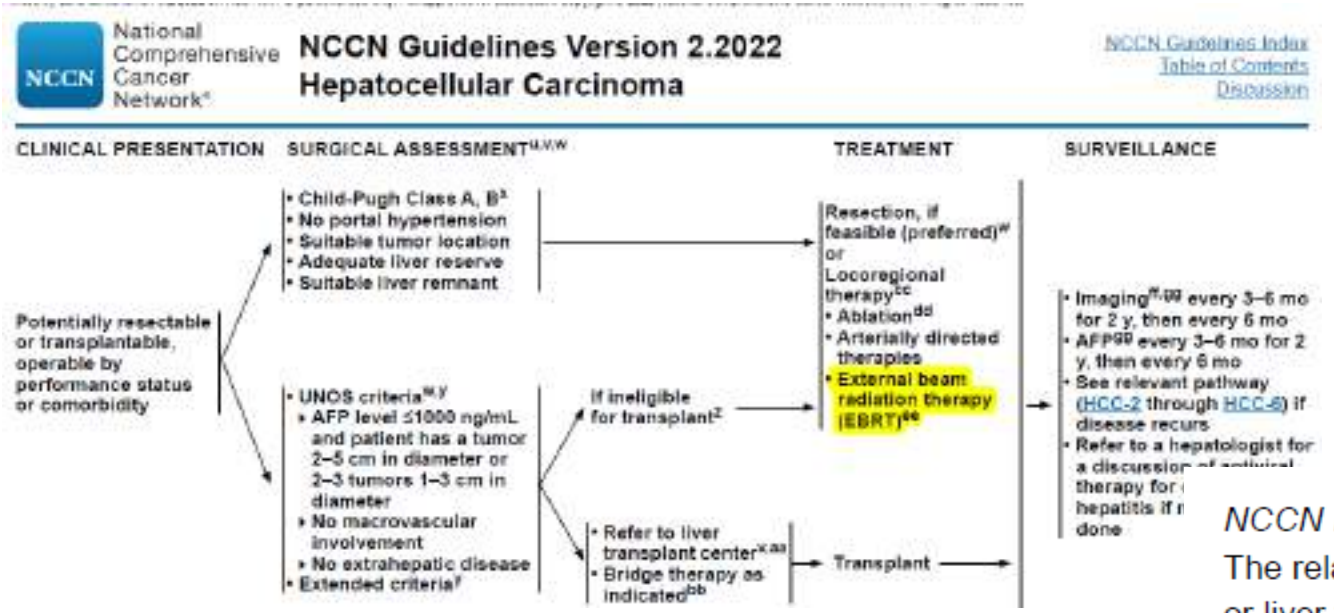
2022 NCCN



NCCN Recommendations for Locoregional Therapies

The relative effectiveness of locoregional therapies compared to resection or liver transplantation in the treatment of patients with HCC has not been established. The consensus of the panel is that liver resection or transplantation, if feasible, is preferred for patients who meet surgical or transplant selection criteria since these are established potentially curative therapies. Locoregional therapy (eg, ablation, arterially directed therapies, EBRT/SBRT) is the preferred treatment approach for patients who are not amenable to surgery or liver transplantation.

All tumors considered for ablation should be amenable to complete treatment with a margin of normal tissue around the tumor. Tumors should

NCCN Guidelines. Hepatobiliary Cancer. V2.2022. Available at: www.nccn.org

Chinese Society of Liver Disease 2019

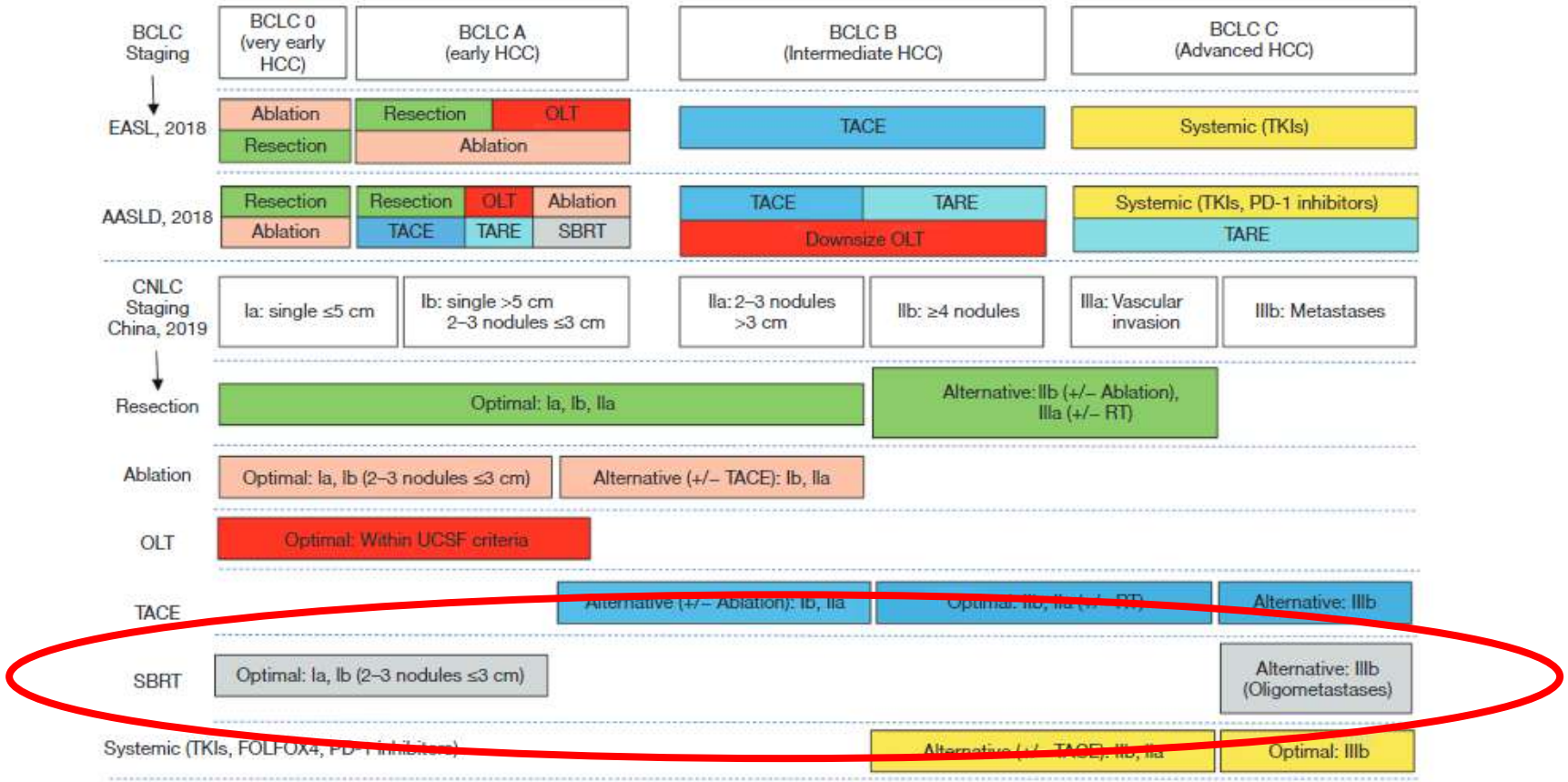
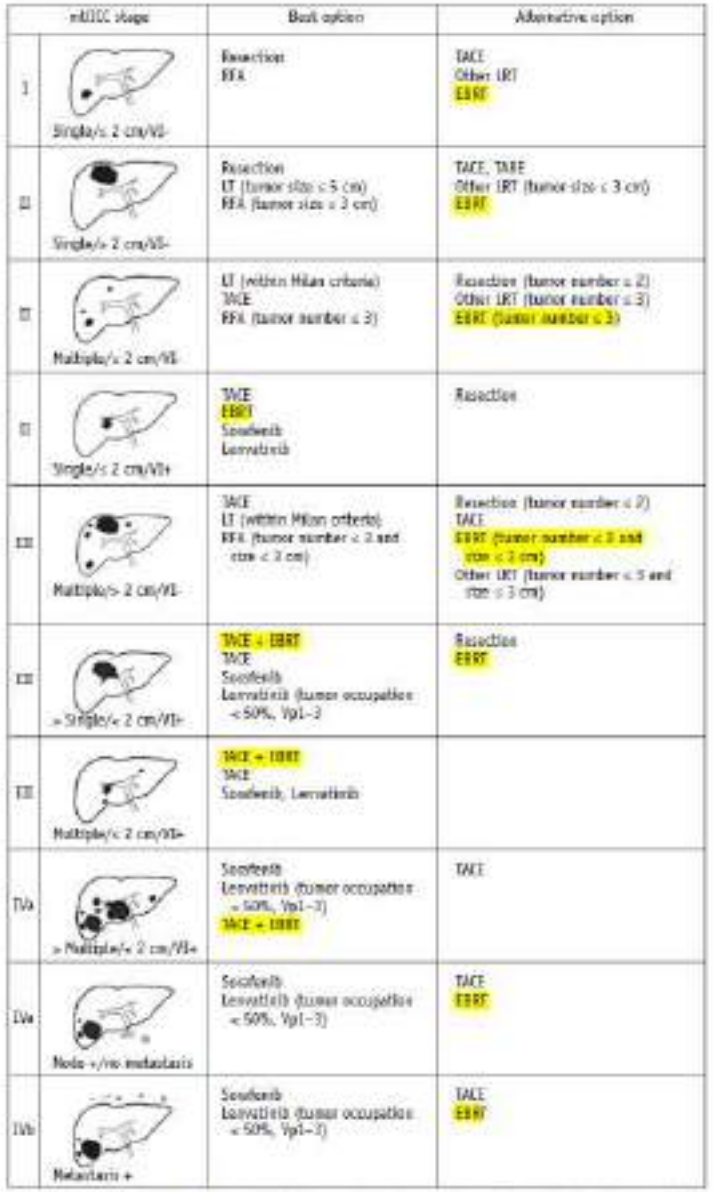


Figure 1 Comparisons of staging and treatment algorithms of HCC among 2018 EASL, 2018 AASLD, and 2019 Chinese guidelines. BCLC, Barcelona Clinic Liver Cancer; EASL, European Association for the Study of the Liver; AASLD, American Association for the Study of Liver Diseases; CNLC, China liver cancer staging; OLT, orthotopic liver transplantation; TACE, transarterial chemoembolization; TARE, transarterial radioembolization; TKIs, tyrosine kinase inhibitors; PD-1, programmed cell death-1; SBRT, stereotactic body

2018 Korean Liver Cancer Study Group

KJR



mHCC stage		Best option	Alternative option
I	Single/≤ 2 cm/VI-	Resection RFA	TACE Other LRT EBRT
II	Single/> 2 cm/VI-	Resection LT (tumor size ≤ 5 cm) RFA (tumor size ≤ 3 cm)	TACE, TARE Other LRT (tumor size ≤ 3 cm) EBRT
III	Multiple/≤ 2 cm/VI-	LT (within Milan criteria) TACE RFA (tumor number ≤ 3)	Resection (tumor number ≤ 2) Other LRT (tumor number ≤ 3) EBRT (tumor number ≤ 3)
III	Single/≤ 2 cm/VI+	TACE EBRT Sorafenib Lenvatinib	Resection
III	Multiple/> 2 cm/VI-	TACE LT (within Milan criteria) RFA (tumor number ≤ 2 and size ≤ 3 cm)	Resection (tumor number ≤ 2) TACE EBRT (tumor number ≤ 3 and size ≤ 3 cm) Other LRT (tumor number ≤ 3 and size ≤ 3 cm)
III	> Single/≤ 2 cm/VI+	TACE + EBRT TACE Sorafenib Lenvatinib (tumor occupation ≤ 50%, Vp1–3	Resection EBRT
III	Multiple/≤ 2 cm/VI+	TACE + EBRT TACE Sorafenib, Lenvatinib	
IVa	> Multiple/≤ 2 cm/VI+	Sorafenib Lenvatinib (tumor occupation ≤ 50%, Vp1–3) TACE + EBRT	TACE
IVa	Node +/no metastasis	Sorafenib Lenvatinib (tumor occupation ≤ 50%, Vp1–3)	TACE EBRT
IVb	Metastasis +	Sorafenib Lenvatinib (tumor occupation ≤ 50%, Vp1–3)	TACE EBRT

Fig. 5. First-line treatment recommendations from 2018 Korean Liver Cancer Association-National Cancer Center, Korea Practice Guidelines for Patients with HCC, Child-Pugh class A, no portal hypertension, and Eastern Cooperative Oncology Group 0–1.
EBRT = external beam radiation therapy, LRT = locoregional therapy, LT = liver transplantation, mHCC = modified Union for International Cancer Control, other LRT = percutaneous ethanol injection, microwave ablation, and cryoablation, RFA = radiofrequency ablation, TACE = transarterial chemoembolization, TARE = transarterial embolization, VI = vascular or bile duct invasion, Vp = portal vein invasion

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Thank You....

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