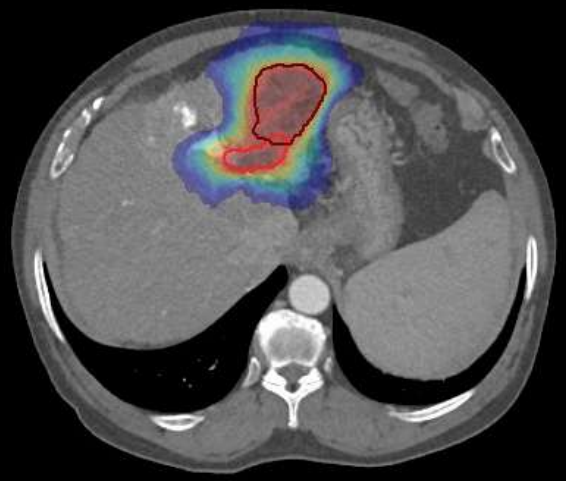

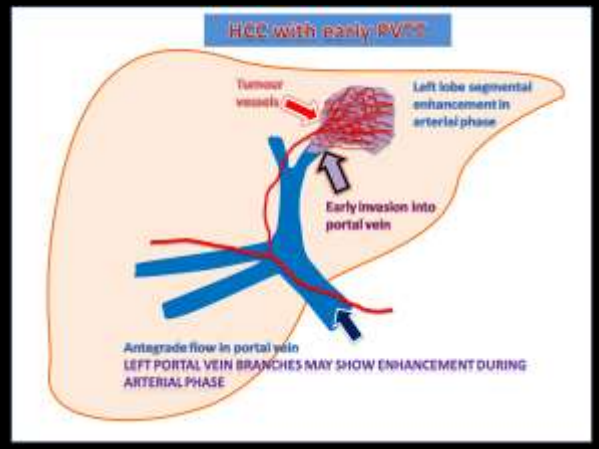

SBRT in hepato-biliary / pancreatic malignancies

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Disclaimers/ Conflicts..

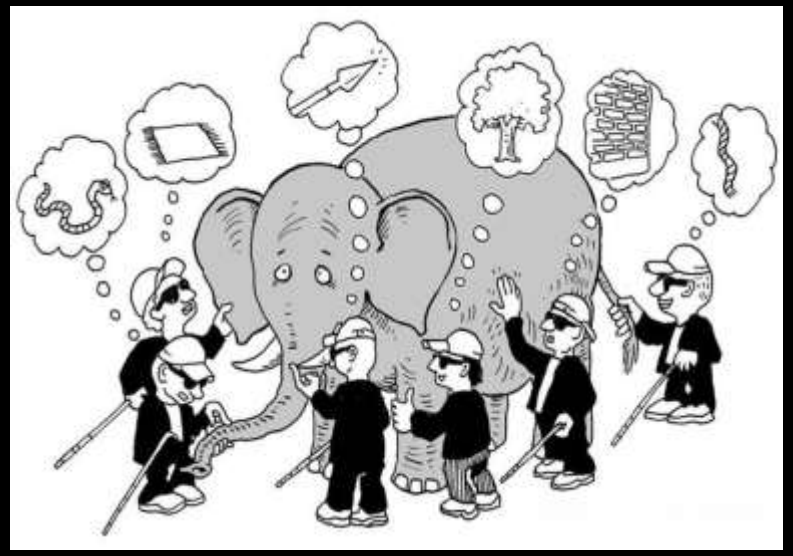
None...

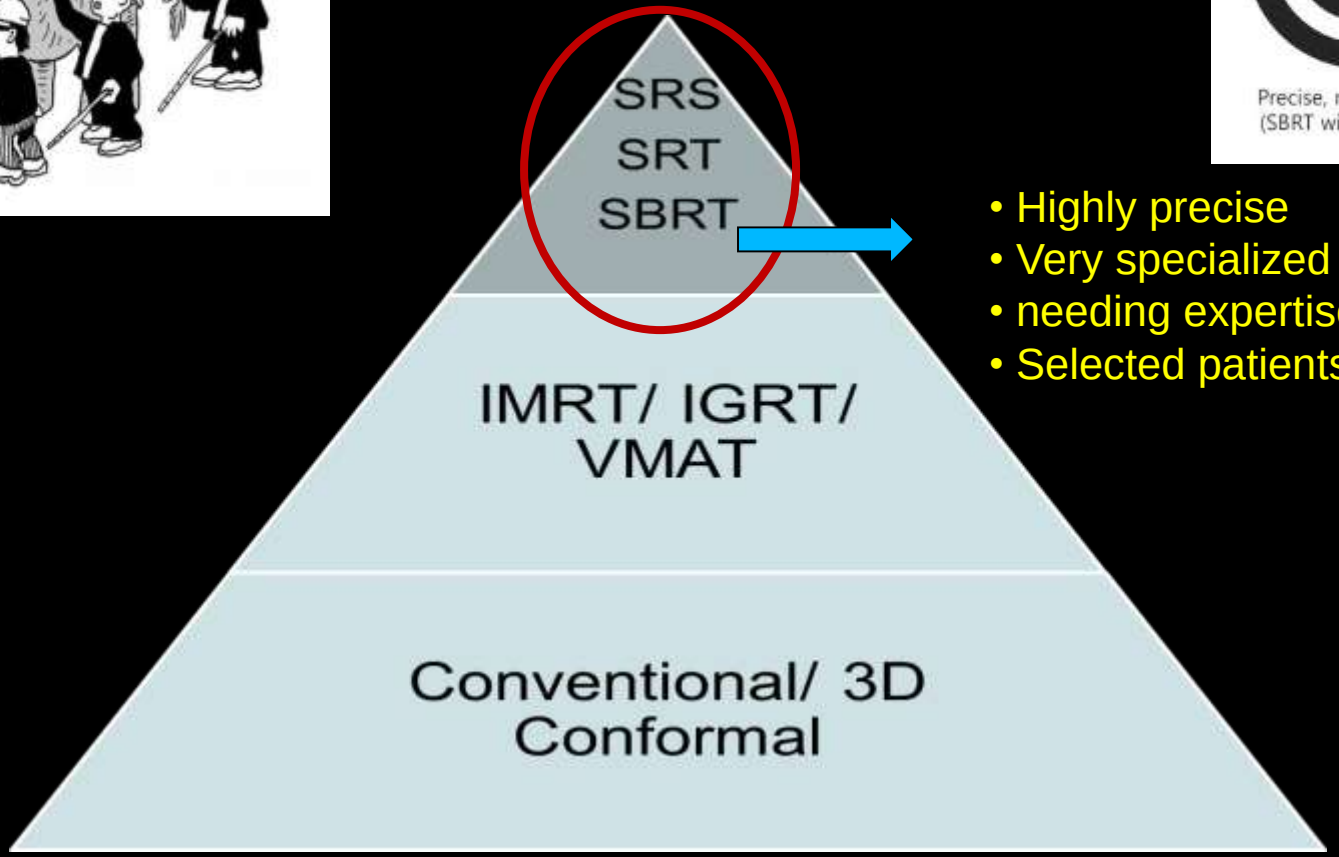
Slides...

- ✓ Available literature
- ✓ Previous & present institutes

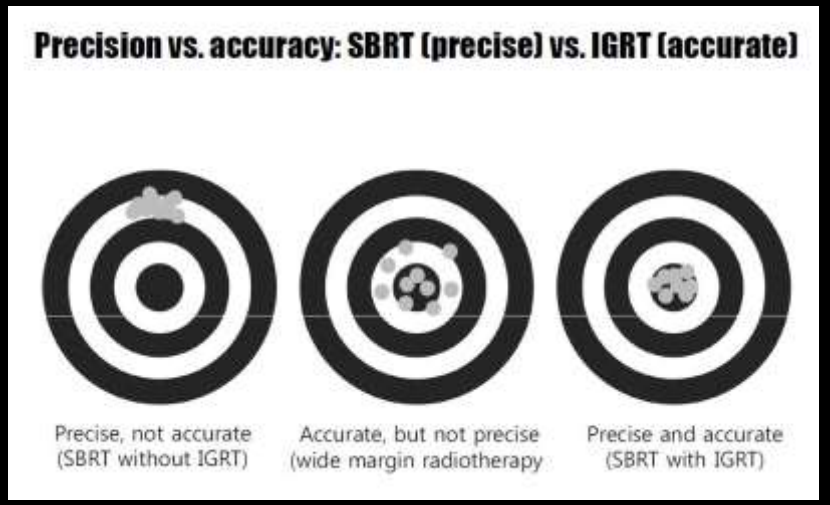
a) Medanta – The Medicity, Gurugram – acknowledged & thanks
b) Fortis memorial research institute, Gurugram - acknowledged & thanks
c) Apollo Proton Cancer center, Chennai

What is SBRT?





- Highly precise
- Very specialized
- needing expertise
- Selected patients

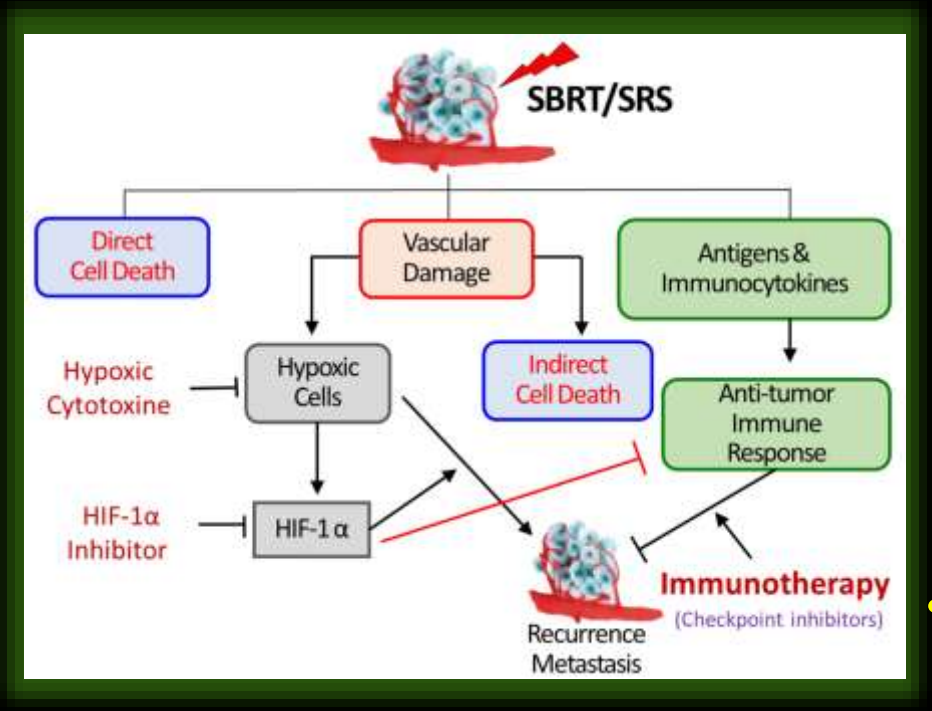


SBRT: points to remember

- Doses are very potent and biologically damaging

- Tissue response depends on:
  - Dose delivered
  - Volume exposed
  - Tissue radio-sensitivity

- High dose per fraction, thus:
  - Care for geographical misses
  - Target volumes - small
  - Critical structure tolerances



Serial organs

- Spinal cord
- Esophagus
- Bowel
- Ducts
- vessels

SBRT has limited benefit

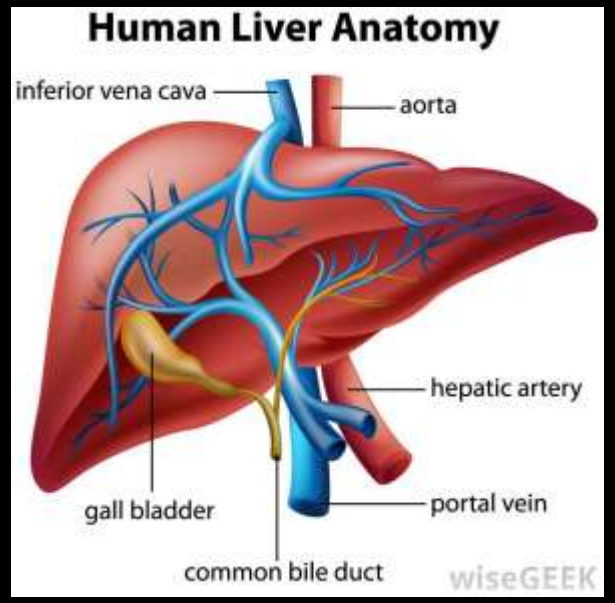
Parallel organs

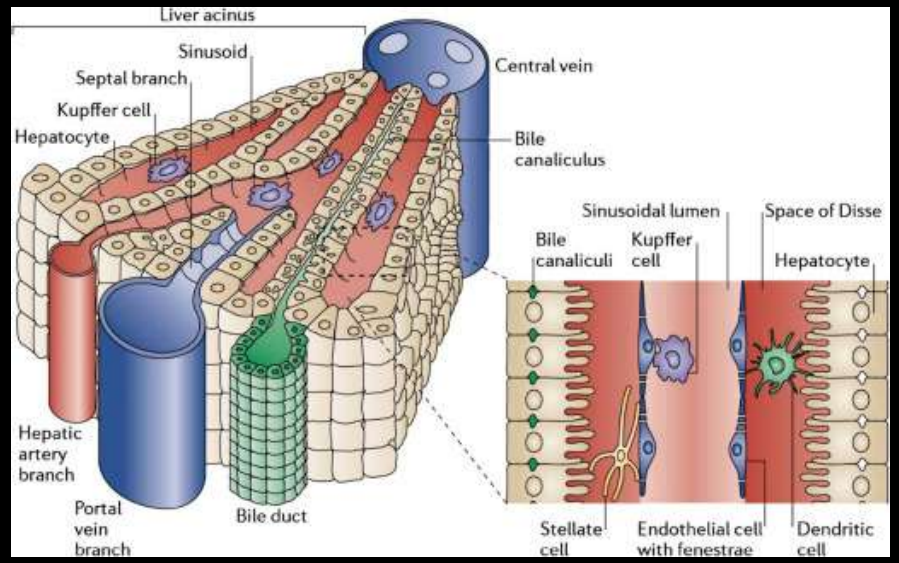
- Peripheral Lung
- Peripheral Liver
- Kidney
- Pancreas
- Prostate

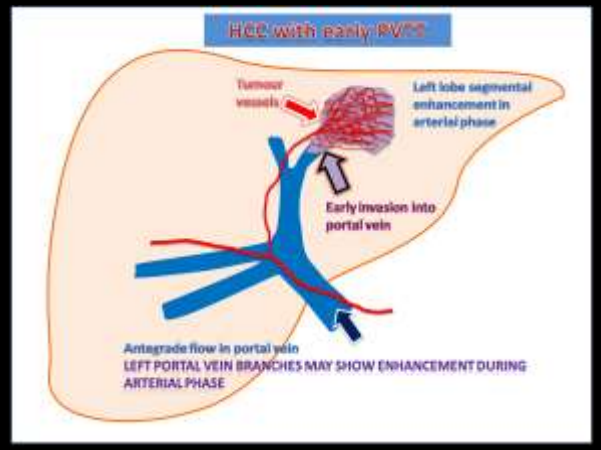
- Small volume – SBRT best

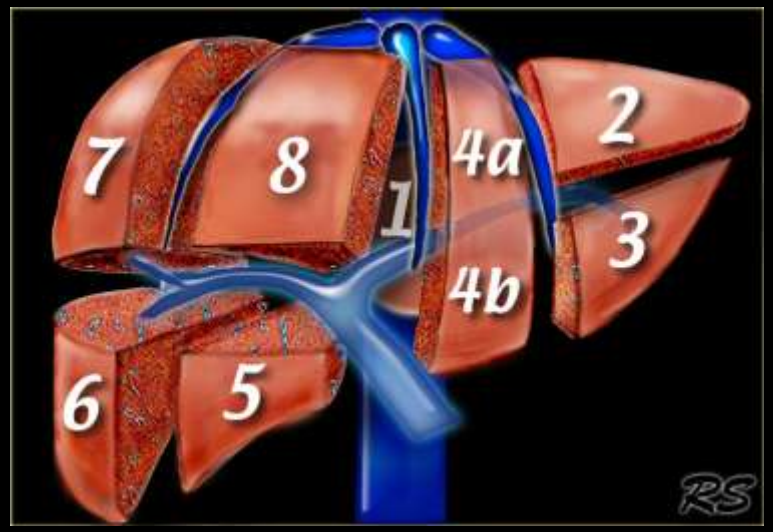
HCC – SBRT : understanding basics…….

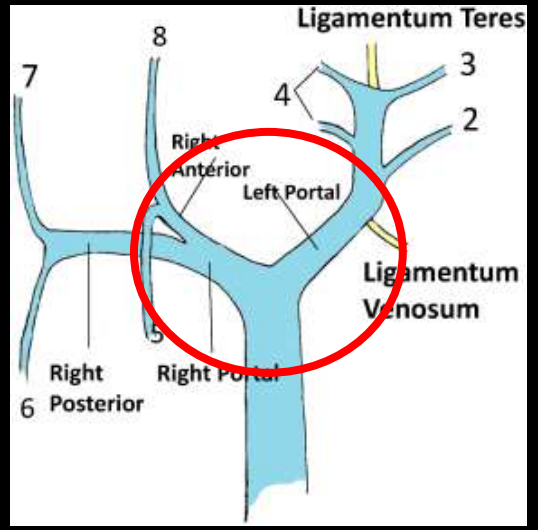
Liver : Anatomy











HCC: Treatment principle

Popcorn effect: background of Cirrhosis

Transplant candidate

HCC cells – average doubling time – 6 months

Locoregional / ablation candidate

Surgery / Transplant – Gold standard – 5 yr OS 70%

Only 20% fit for surgery

HCC: Treatment

- HCC: 3rd M/c cancer

- **Surgery**
  - Resection: 85% recurrence
  - **Transplant: Limited donor → 20-40 % dropouts**

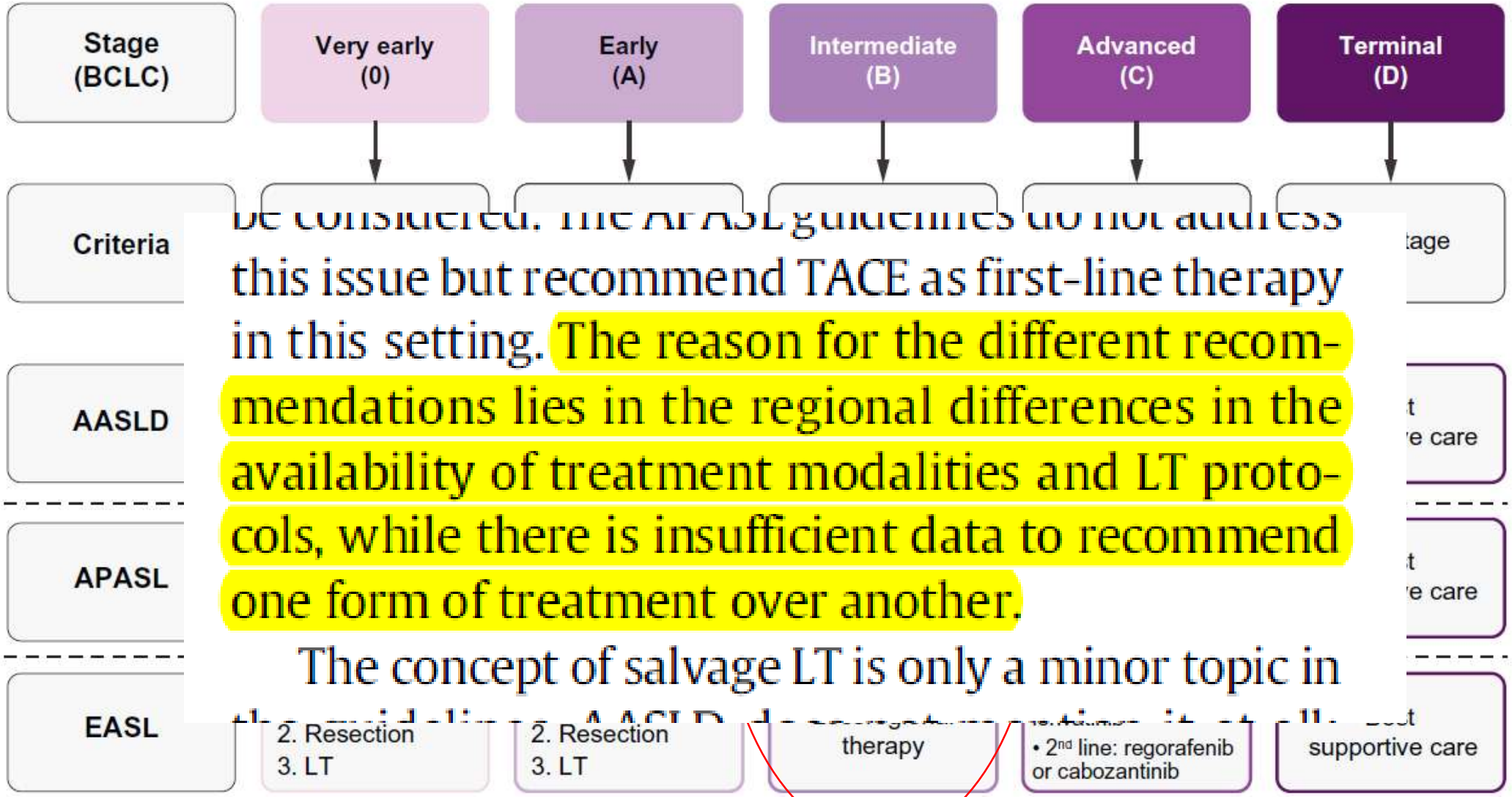
Non surgical Local management – as alternative

- **Local therapy for waitlist**
- **alternative to surgery**

- "bridge" → until a donor organ is available

- Traditionally : RFA and TACE → neoadjuvant/ downstaging
  - RFA usable < 40% of cases – < 3 cm/ not close to vessels
  - TACE → only 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



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

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.

RT in guidelines

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

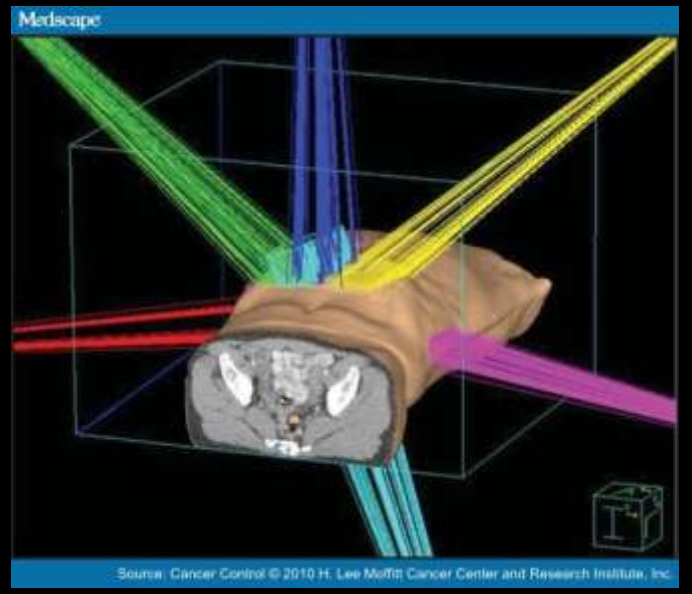
	AASLD	APASL	EASL
Surveillance	US every 6 months, AFP optional	US + AFP every 6 months	US every 6 months
CEUS	Not recommended	As sensitive as CT/MRI	Suitable for nodules ≥1 cm in cirrhosis
Biopsy	No routine use	For indeterminate nodules ≥1 cm	Required in non-cirrhotic HCC
Bridging	Recommended for T2	No 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.

Issues with liver RT in past……..

Liver – Radiotherapy - ? ineffective

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



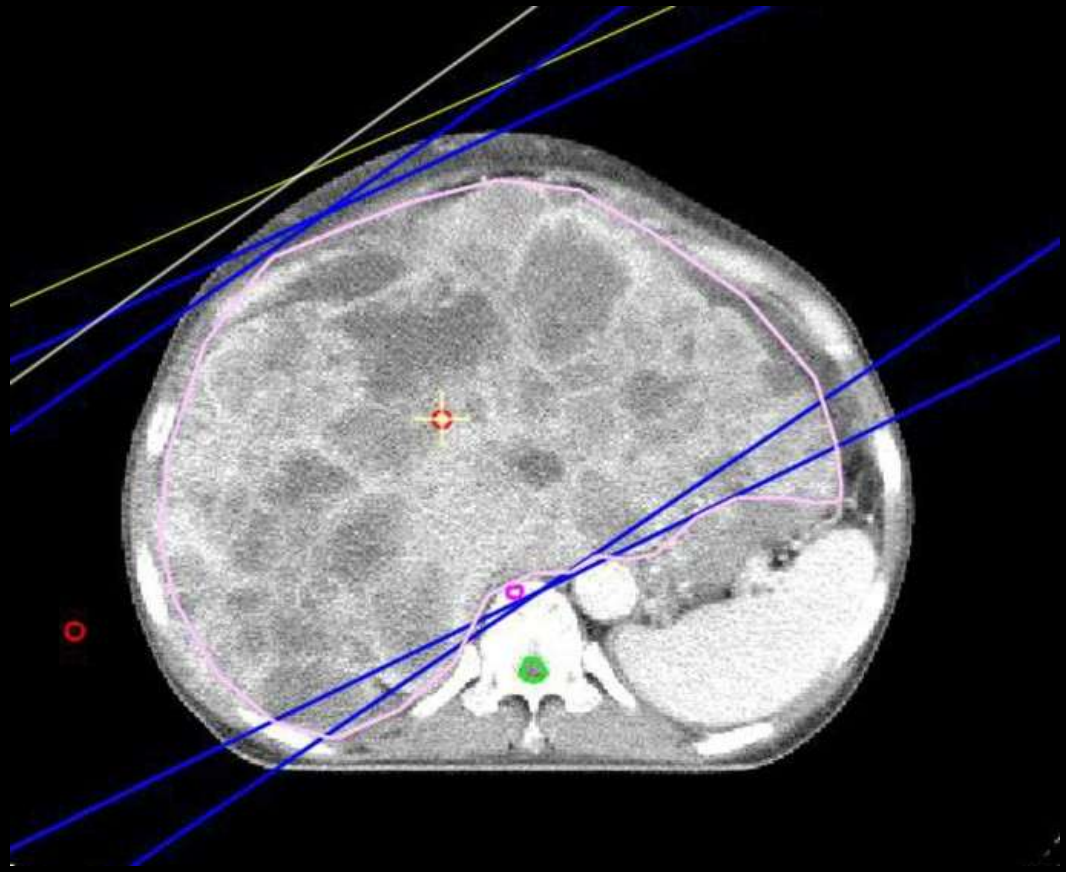
- ? Radio resistance
- ? Fear of RILD
- ? Poor tolerance - whole liver
- ? partial liver radiation tolerance – unknown?
- ? modern radiation techniques for delivery
- ? motion management techniques
- ? Lack of faith in effectiveness of radiation
- ? No multi disciplinary approach

Initial Experience of Radiation therapy in liver

RT – Historical Perspective

Liver tolerance:

- Hepatocyte – well diff cell / low repair capacity ($\alpha/\beta = 1.5$)
  - Whole liver tolerance
    - @ conventional fractionation **25 Gy (5% RILD) & 35 Gy (50%)**
    - 3 Gy/ fr: **21-24 Gy / 2.5 Gy/ fr - 24 Gy / 1.5 Gy / fr - 30 Gy**



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

Table 1 Challenges and opportunities in HCC RT

Challenge	Barrier	Opportunity
Late presentation	Lack of screening of high-risk patients	Patient/physician education Improved screening techniques
Concurrent liver disease	Competing risks of from hepatitis/ cirrhosis vs HCC	Cross-disciplinary collaboration
Patient selection for RT	Lack of level 1 evidence Limited dissemination of RT literature to non-RT experts	Randomized trials Multidisciplinary education
Tumor identification	Imaging requires technical expertise	Standardize imaging protocols Radiation oncology education/radiology collaboration Radiology/pathology correlative research Functional imaging
RT contour variability	Few published guidelines	Consensus guidelines
Appropriate RT dose	Uncertainty in dose-response	Clinical studies to improve dose-outcome models Deformable image registration and dose accumulation Research of high dose per fraction biologic effects
Conforming dose to tumor	Not enough liver	Advanced RT planning - Stereotactic body RT - Volume-modulated arc therapy - Charged particle therapy
	Identifying tumor at treatment	Image-guided radiation therapy
Luminal gastrointestinal toxicity	Proximity of duodenum, bowel to liver	Spacers to move luminal tissue away from hepatocellular carcinoma Normal tissue protectors

Abbreviations: CBCT = cone beam computed tomography; HCC = hepatocellular carcinoma; linac = linear accelerator; RT = radiation therapy.

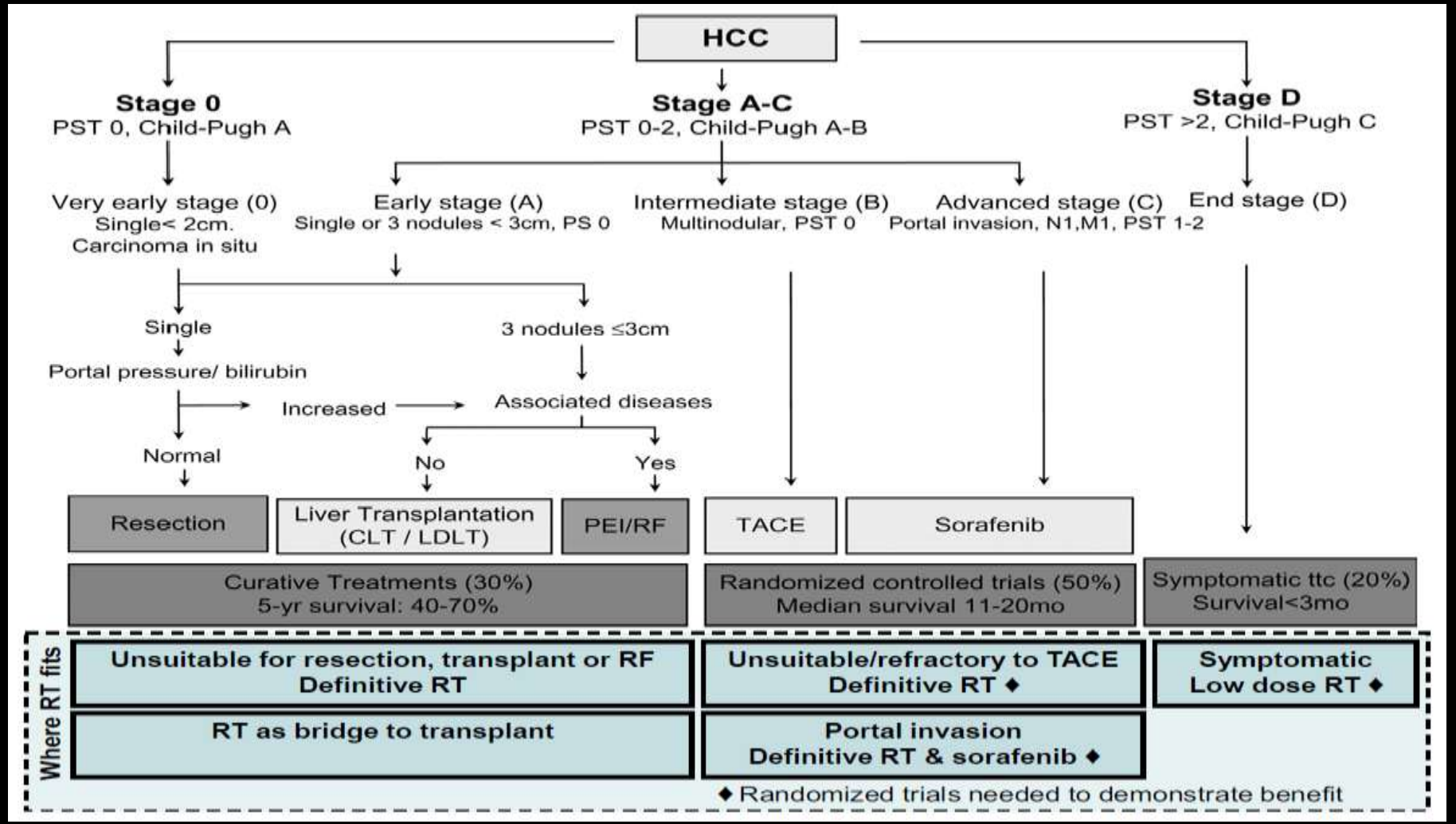
Modern Radiotherapy:
Overcoming challenges of past

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

Exploring Liver RT : partial volume & functional liver

Redefined role of RT in HCC



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

Key to modern Liver RT success:

Adequate normal liver / minimize irradiated liver - RILD

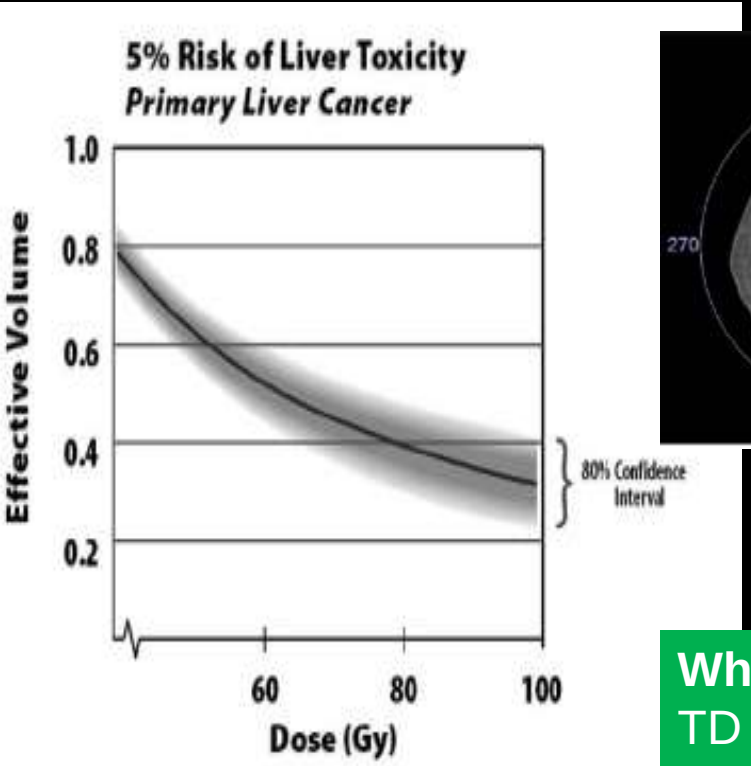
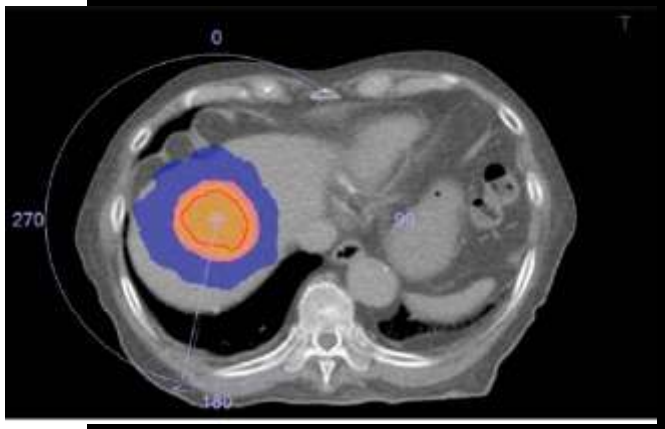


Figure 2 The Lyman-Kutcher-Burman NTCP model displaying iso-NTCP curves, with 80% confidence limits, for patients w primary liver cancer. Effective volume (the organ volume tha irradiated to the prescribed dose uniformly would be associat with the same NTCP as the nonuniform dose distribution) ver normalized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



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

- Base line normal liver > 700 cc
- Case selection
  - safe anatomy / safe functions
- Technical improvement
  - **SBRT**
  - **Motion management**
  - Targeting – surrogate fiducials

*Dawson, Seminars in Rad Onc, 2005

Functioning normal liver sparing

Contents lists available at ScienceDirect

Clinical Radiology

journal homepage: www.clinicalradiologyonline.net

Review

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

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

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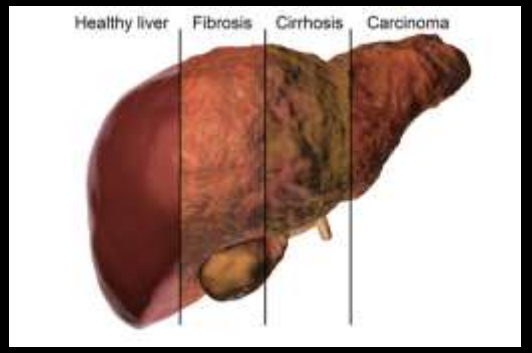
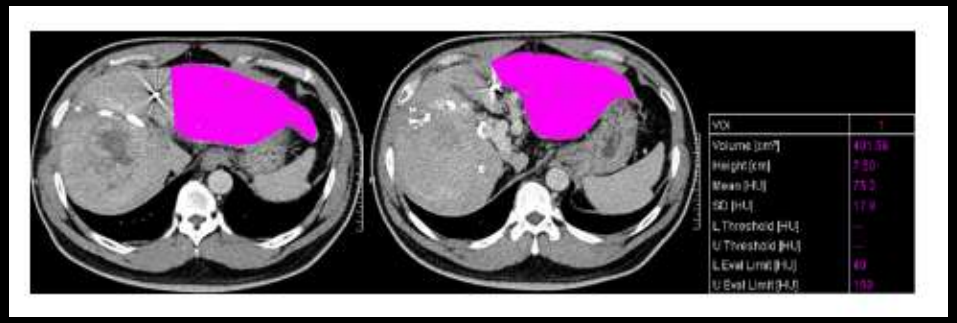
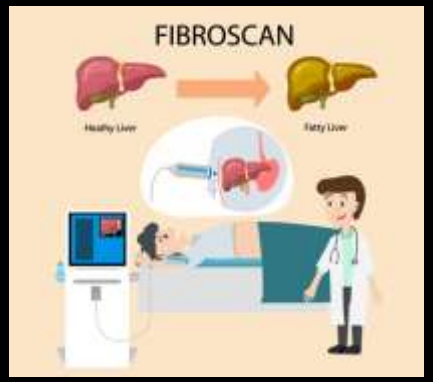
[b] School of Computer Engineering, Nanyang Technological University, Block N4 Nanyang Avenue #02a-32, Singapore 639798, Singapore
[c] University Surgical Cluster, National University Hospital, 5 Lower Kent Ridge Road, Singapore 119074, Singapore

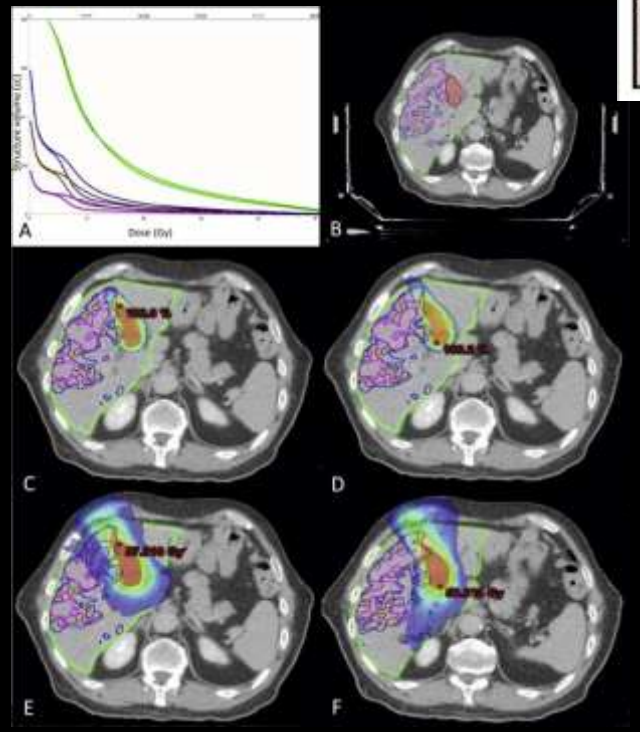


Clinical and Lab Criteria	Points*		
	1	2	3
Encephalopathy	None	Mild to moderate (grade 1 or 2)	Severe (grade 3 or 4)
Ascites	None	Mild to moderate (diuretic responsive)	Severe (diuretic refractory)
Bilirubin (mg/dL)	< 2	2-3	>3
Albumin (g/dL)	> 3.5	2.8-3.5	<2.8
Prothrombin time			
Seconds prolonged	<4	4-6	>6
International normalized ratio	<1.7	1.7-2.3	>2.3

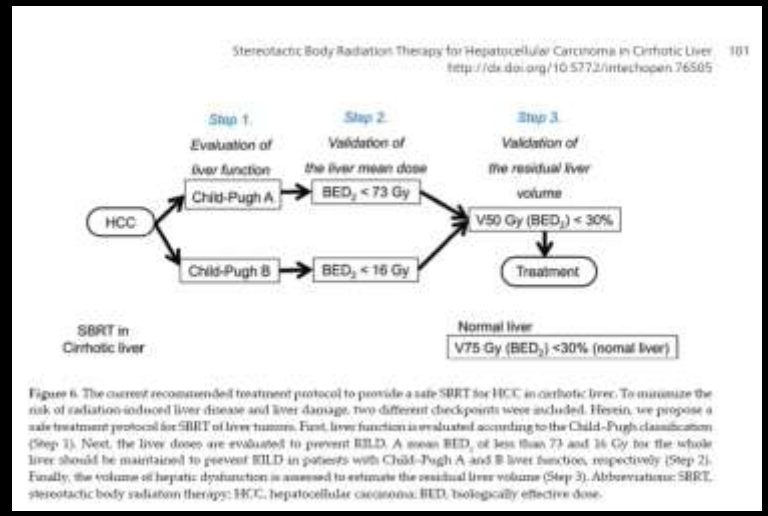
Child-Turcotte-Pugh Class obtained by adding score for each parameter (total points)
Class A = 5 to 6 points (least severe liver disease)
Class B = 7 to 9 points (moderately severe liver disease)
Class C = 10 to 15 points (most severe liver disease)







FDG galactose based functional liver



Stereotactic Body Radiation Therapy for Hepatocellular Carcinoma in Cirrhotic Liver 101
http://dx.doi.org/10.5772/intechopen.76505

Figure 6. The current recommended treatment protocol to provide a safe SBRT for HCC in cirrhotic liver. To minimize the risk of radiation-induced liver disease and liver damage, two different checkpoints were included. Herein, we propose a safe treatment protocol for SBRT of liver tumors. First, liver function is evaluated according to the Child–Pugh classification (Step 1). Next, the liver doses are evaluated to prevent RILD. A mean BED$_2$ of less than 73 and 16 Gy for the whole liver should be maintained to prevent RILD in patients with Child–Pugh A and B liver function, respectively (Step 2). Finally, the volume of hepatic dysfunction is assessed to estimate the residual liver volume (Step 3). Abbreviations: SBRT, stereotactic body radiation therapy; HCC, hepatocellular carcinoma; BED, biologically effective dose.

Advances…

Imaging

Motion mitigation

SBRT delivery

Imaging : Planning & delivery

Table 1
In-room imaging modalities available for image-guided radiotherapy

Modality	Volumetric	Ionising	Real-time (>2 Hz [13])	Additional equipment	Observations
kV/MV fluoroscopy	No	Yes	Yes (≈1–10 Hz)	No	High geometric fidelity, isocentric with respect to linac, MV image quality lower than kV. Fiducial may be needed.
CBCT	Yes	Yes	No (acquisition time ≈1 min)	No	Blurry structures due to motion
Four-dimensional CBCT	Yes	Yes	No (acquisition time >1 min)	No	Less blurry than CBCT. >1 reconstructed volume. Possible streaking due to view aliasing.
Gated CBCT	Yes	Yes	No (acquisition time >1 min)	No	Less blurry than CBCT. Less dose than four-dimensional CBCT. 1 reconstructed volume.
Surface imaging	No	No	Yes (up to ≈30 Hz)	Yes	Three-dimensional surface with 6 degrees of freedom displacement information
Hybrid (ExacTrac, Synchrony)	No	Yes	Yes (up to ≈30 Hz)	Yes	Compromise between imaging dose and reliance on internal–external correlation.
MR	Yes	No	Yes for two-dimensional (≈1–4 Hz)	Yes	Excellent soft-tissue contrast. Compromise in spatial versus temporal resolution. Dedicated machine (MR-linac) or MR-suite. No electron density information.
On-rail computed tomography	Yes	Yes	No	Yes	High image quality. Electron density information.

CBCT, cone-beam computed tomography; MR, magnetic resonance.

PVTT: Filling defect

SBRT delivery - Wall mounted Linac

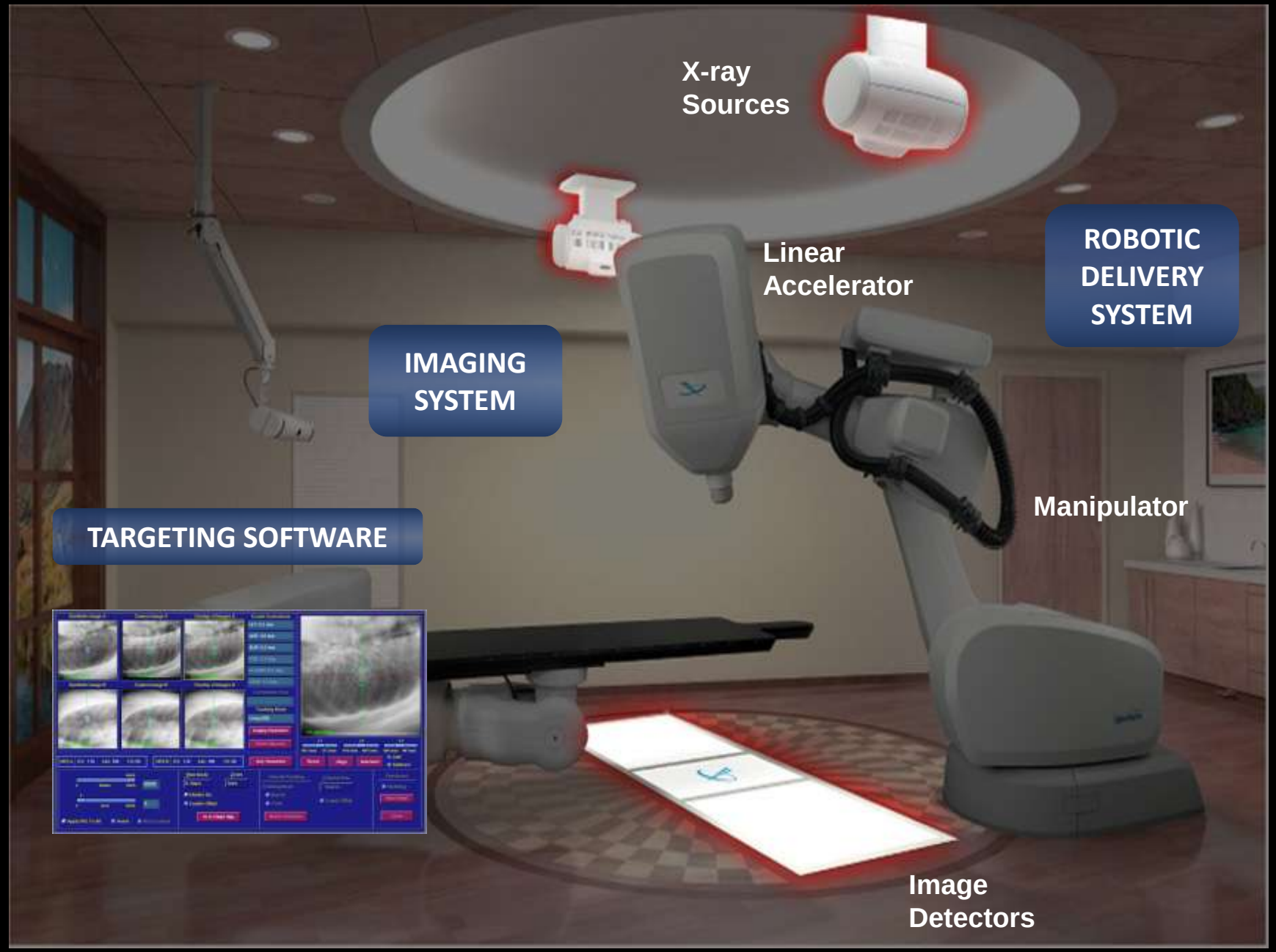
SABR

- Gamma-knife-SABR (G-SABR)
- Liner-accelerator-SABR (L-SABR)
- CyberKnife-SABR (C-SABR)
- Tomo-SABR (T-SABR)
- Proton-SABR (P-SABR)

- ? Stereotactic ablative brachytherapy (SABT) – not EBRT

3DCRT-SBRT delivery

VMAT-SBRT delivery



Real time tracking / treatment in free breathing

Modern gadgets: MRI / Proton SBRT

Journal of Clinical Medicine

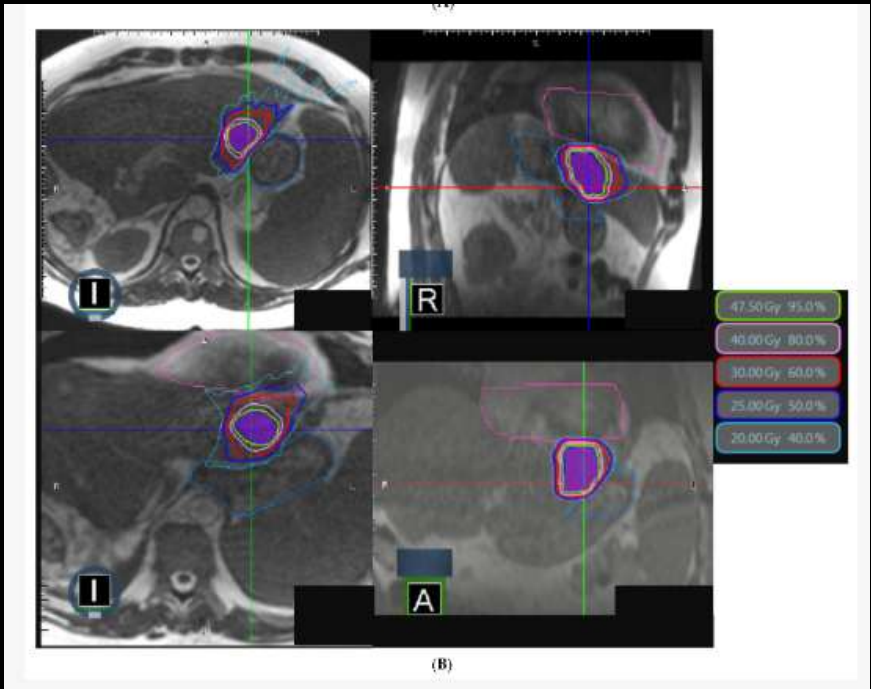
MDPI

Article

Stereotactic MR-Guided Radiotherapy for Liver Metastases: First Results of the Montpellier Prospective Registry Study

Karl Bordeau [1], Morgan Michalet [1], Aicha Keskes [1], Simon Valdenaire [1], Pierre Debuire [1], Marie Cantaloube [1], Morgane Cabaillé [1], William Jacot [2], Roxana Draghici [1], Sylvain Demontoy [1], Xavier Quantin [2], Marc Ychou [2], Eric Assenat [3], Thibault Mazard [2], Ludovic Gauthier [4], Marie Dupuy [3], Boris Guiu [5], Céline Bourgier [1], Norbert Ailleres [1], Pascal Fenoglietto [1], David Azria [1] and Olivier Riou [1,*]

J. Clin. Med. **2023**, *12*, 1183. https://doi.org/10.3390/jcm12031183



(B)

Small moving targets

Radiotherapy and Oncology

Contents lists available at ScienceDirect

journal homepage: www.thegreenjournal.com

Original Article

Clinical implementation of pencil beam scanning proton therapy for liver cancer with forced deep expiration breath hold

Francesco Fracchiolla [a,*], Francesco Dionisi [a], Roberto Righetto [a], Lamberto Widesott [a], Irene Giacomelli [a], Giorgio Cartechini [b], Paolo Farace [a], Mattia Bertolini [a], Maurizio Amichetti [a], Marco Schwarz [a,c]

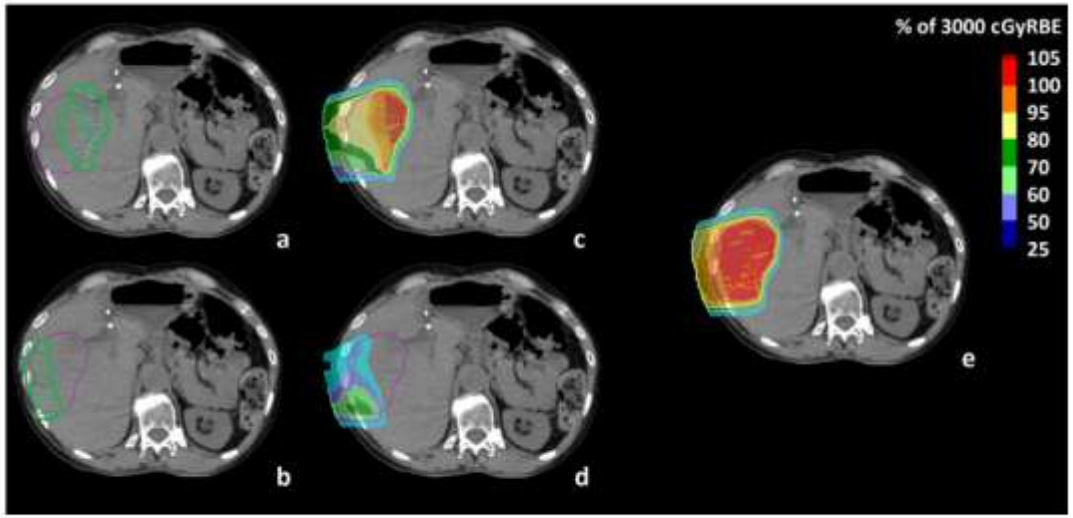
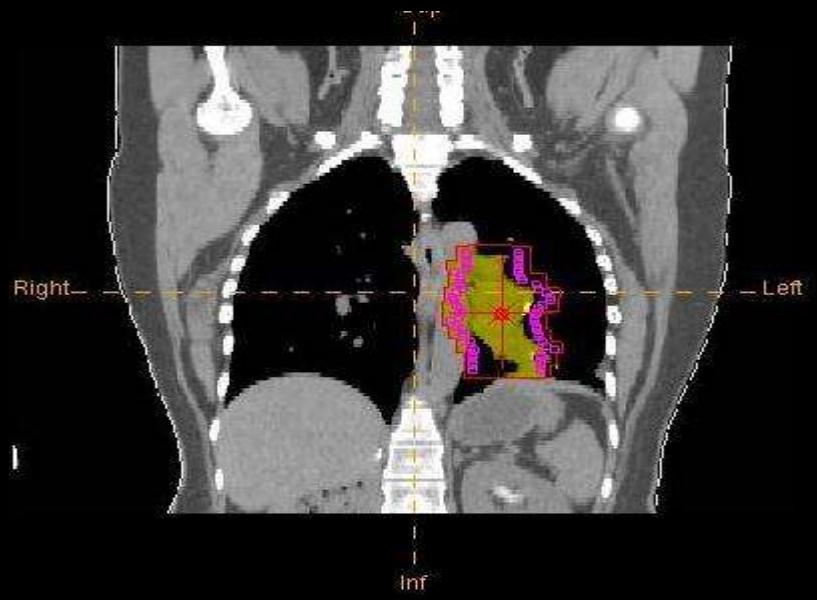
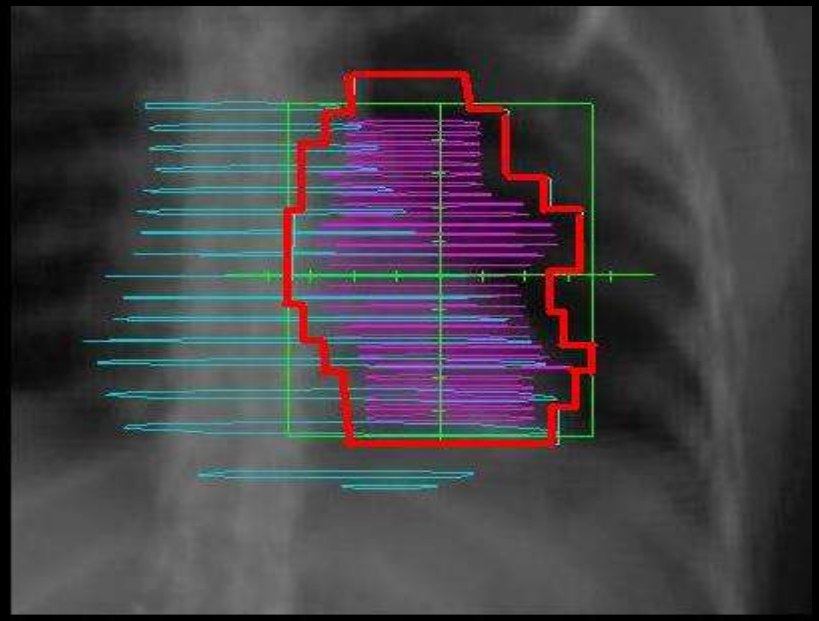


Fig. 2. Splitting technique used for each beam direction. (a and b): spot distribution (green crosses in the green area) of the distal beam (a) and the proximal beam (b). (c and d): dose distributions of the distal beam (c) and the proximal beam (d). (e): total dose distribution. The prescription dose for this patient was 60 GyRBE. The dose here is normalized to half of the prescription. The remaining 30 GyRBE will be delivered by the second pair of fields.

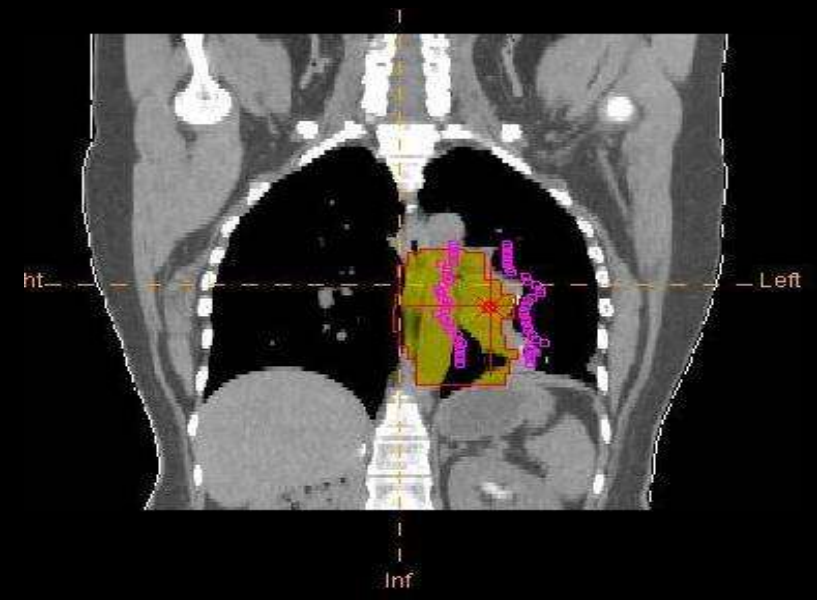
Larger targets / cirrhotic liver

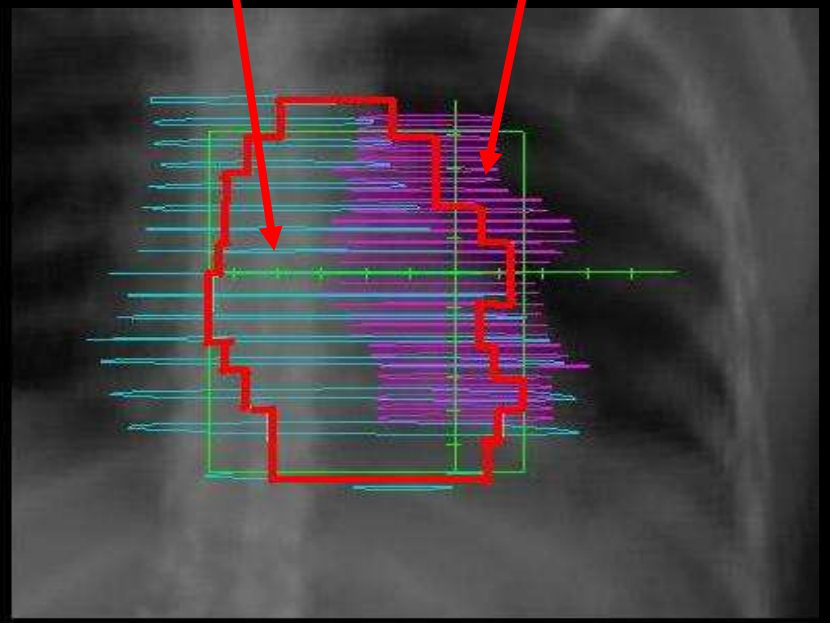
Motion mitigation strategies : Key to modern liver RT ……



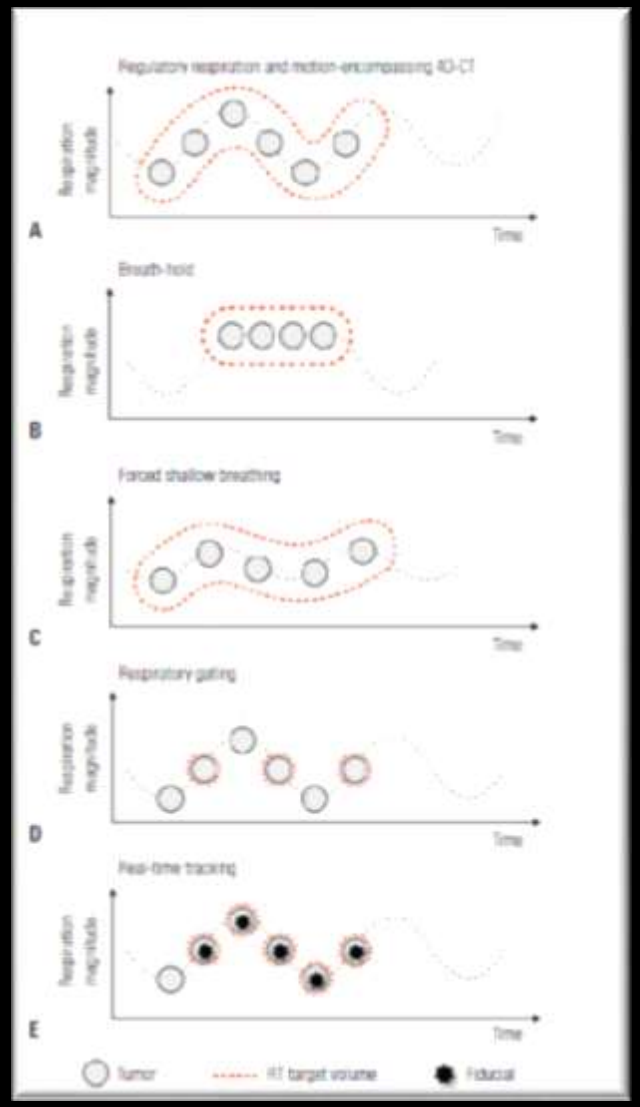


Problems with respiratory movement: Organ Hit & Tumor miss

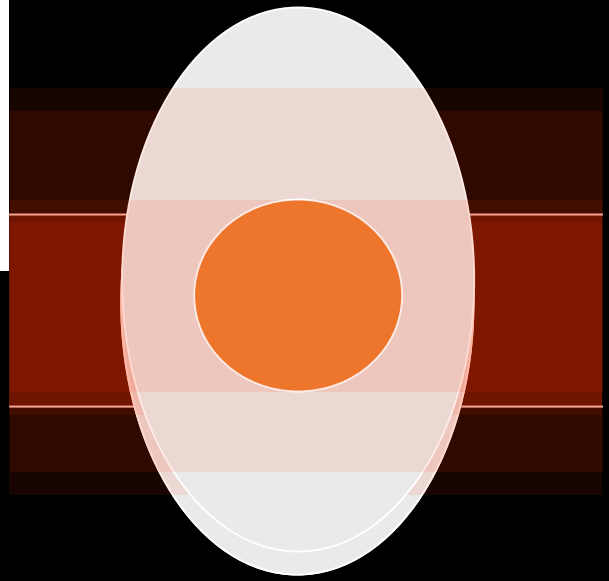




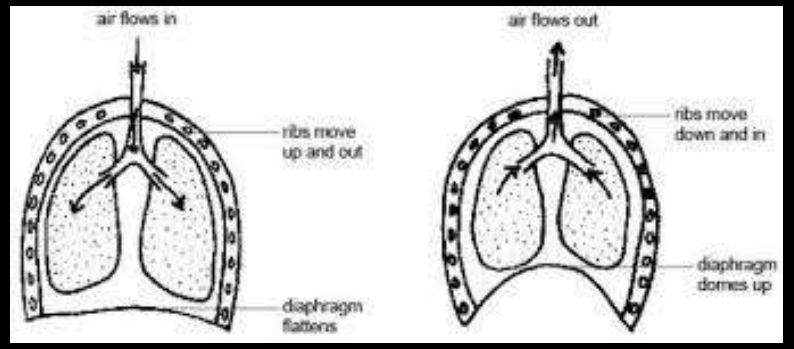
Respiratory motion management: compression devices



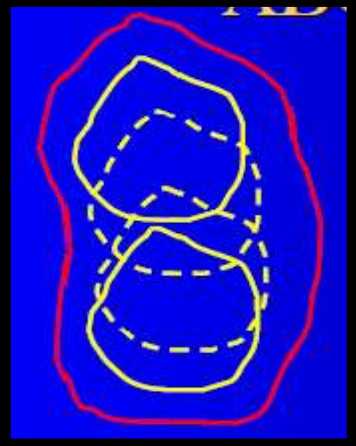
Change / mitigate breathing pattern



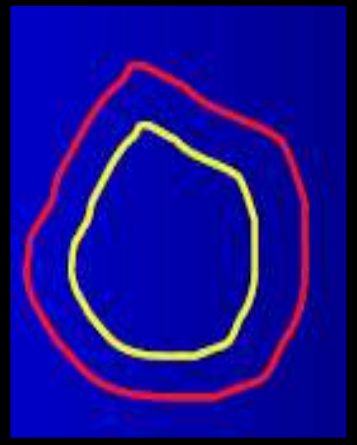
Respiratory motion management: Breath Holding

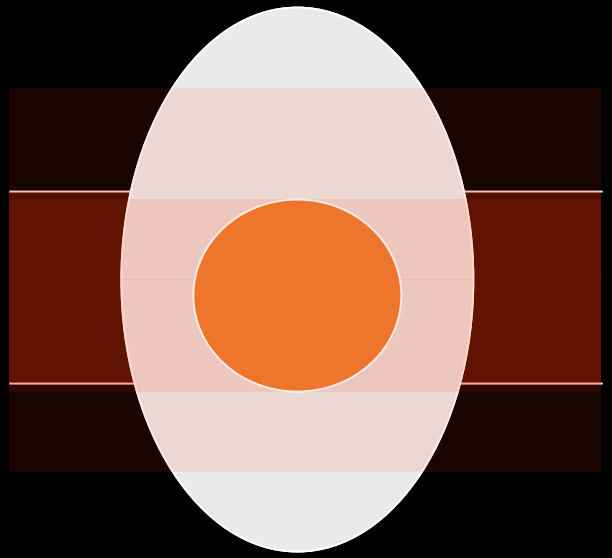


Free Breathing

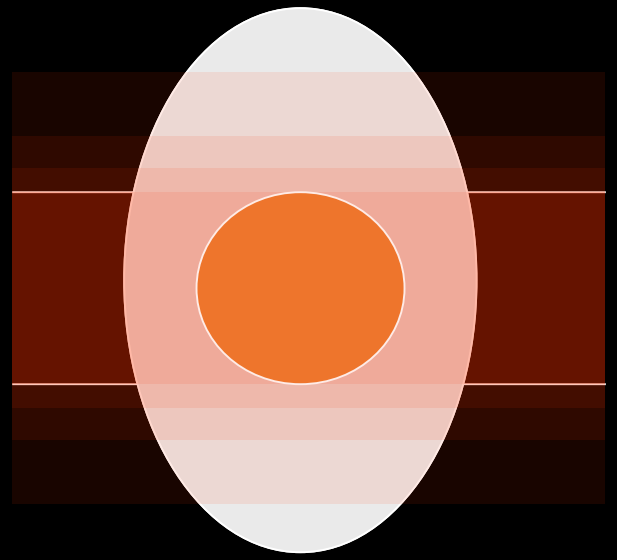


Breath-Hold





Respiratory motion management: Gating

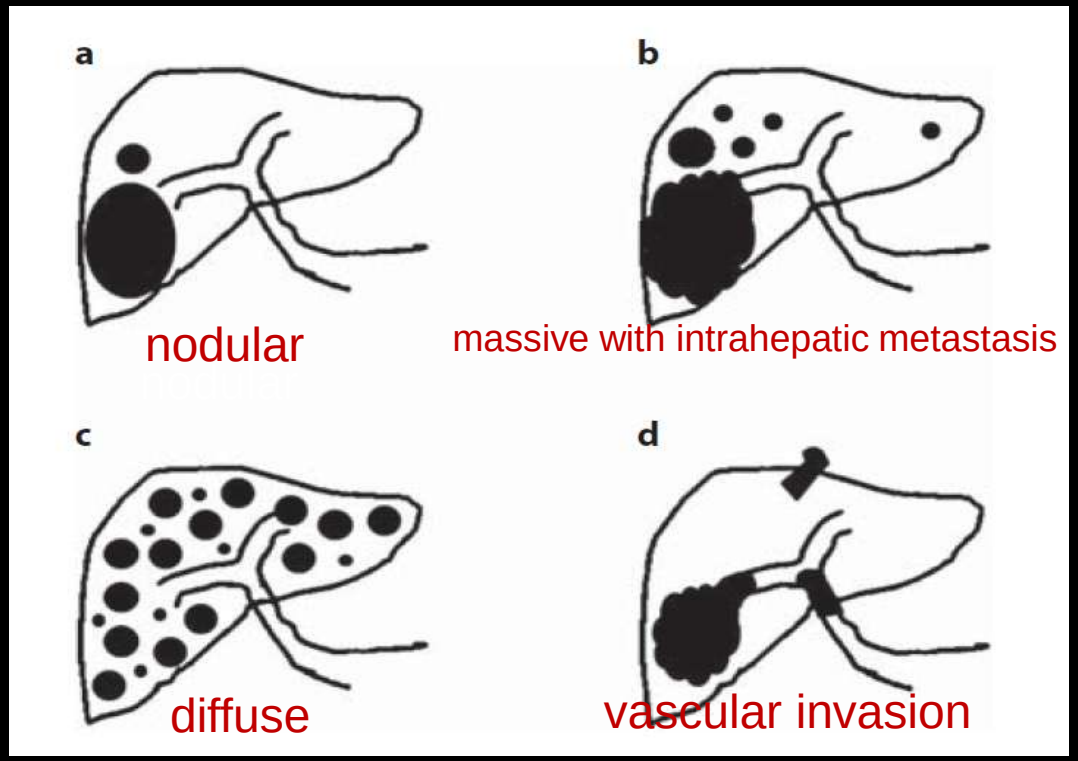


Synchrony® Respiratory Tracking System

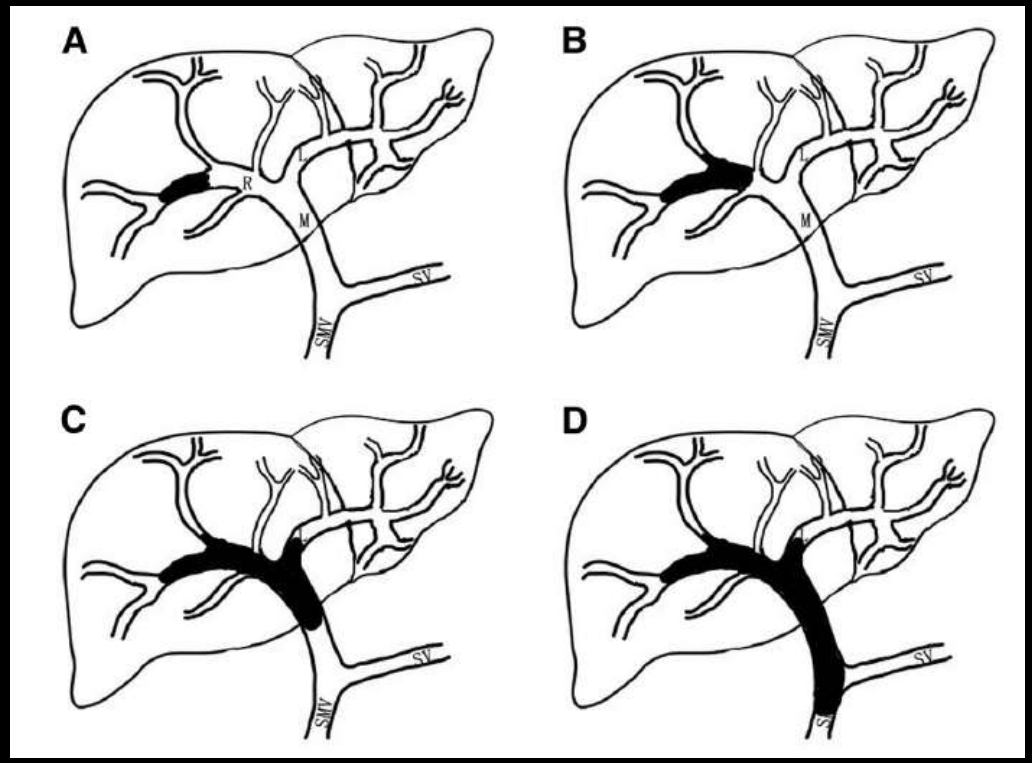
Beam tracking

MLC tracking

Sub-classification of Locally advanced HCC



HCC



PVTT

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 #	++	+	+++	++	++

*Proton, protons or any other charged practical therapy.
GI tissues, luminal gastrointestinal tissue (eg, stomach, duodenum)
Abbreviations : CRT stereotactic radiation therapy; brachy, Brachytherapy; Yttrium-90 hepatic arterial Yttrium-90

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

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 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

Literature review: RT in HCC / PVTT – growing evidence

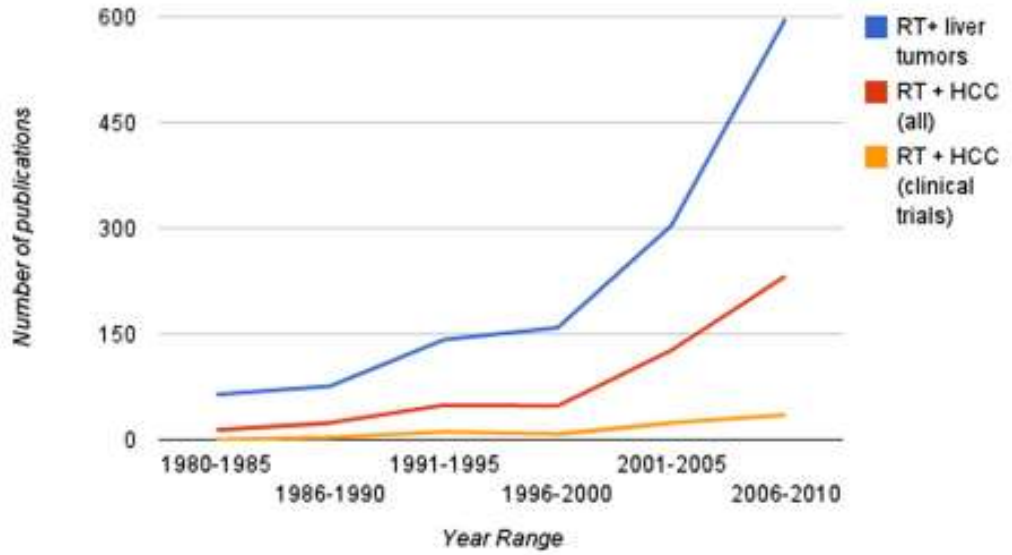


Fig. 2. Graph of number of liver cancer RT publications over time. Citation count based on a search of the MEDLINE database limited to each 5-year period. Blue line: search for "radiation therapy" and "liver neoplasms." Red line: search for "radiation therapy" and "hepatocellular carcinoma." Orange line: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

World Journal of Gastroenterology

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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

[2014]

Naoko Sanuki, Atsuya Takeda, Etsuo Kunieda

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
Damage to the liver	High	Low	Low-moderate	Low-moderate

SBRT: Stereotactic body radiation therapy; TACE: Transarterial chemoembolization.

Kim *et al.*, 2019[36]	32	Prospective Phase I/II trial	A-B	36-60 Gy/4#	27m	2y LC: 87% 2y OS: 81.2%	None	SBRT
Hara *et al.*, 2019[37]	143	Retrospective	0-C	35-40Gy/5#				

Table 1. Select prospective and retrospective series showing outcome with stereotactic body radiotherapy.

Study	Patient number	Quality/type of study	Indication/ stage (BCLC)	Dose and fractionation	Follow up	Outcomes (LC/OS)	Toxicity (Grade 3 liver/GI)	Study conclusion	Level of Evidence*
Kim *et al.*, 2021[30]	72	Phase III randomised trial- Proton vs RFA	0-C	66Gy/10Fr (Protons)	51.6m	2y LC: 92.8% 2y OS: 91.7%	none	Proton beam therapy was non-inferior to RFA and was tolerable.	II
Yoon *et al.*, 2020[31]	50	Prospective Phase II trial	0 and A (small HCC)	45 Gy/3#	47.8 m	5y LC: 97.1% 5y OS: 77.6%	4%	SBRT showed good results for ablation of small HCC with minimal toxicity.	IV
Labrunie *et al.*, 2020[32]	43	Prospective Phase II trial	A-C	45 Gy/3#	4 y	2y LC: 94% 2y OS: 69%	5%	LC and OS was promising in HCC treated with SBRT.	IV
Jang *et al.*, 2020[33]	65	Prospective Phase II trial	0-C	60 Gy/3#	41m	2y LC:97% 2y OS: 84%	2%	SBRT for HCC was well tolerated.	IV
Park *et al.*, 2020[34]	290	Prospective Phase II trial	0-A	30-60Gy/3#	38.2m	5y LC: 91.3% 5y OS: 44.9%	8.8%	SBRT is an ablative option for small HCC.	IV
Mathew *et al.*, 2020[35]	297	Retrospective	0-D	27-60Gy/3-6#	19.9m	3y LC: 87% 3y OS: 39%	16%	SBRT provides good LC and OS in HCC when it is unsuitable or refractory to other locore-	VI
								SBRT provides promising response and LC.	IV
				Gy/3-5#	27m	2y LC: 90% 2y OS: 67%	20%	SBRT is safe non-invasive option for HCC <6cm	IV

SBRT Bridge: Data

- Scarce data in past → ? local fibrosis/ vascular damages
  - (i) difficult dissection
  - (ii) anastomosis-related complications
  - (iii) increased perioperative morbidity

Table 3
HCC treated with SBRT as pre-transplant therapy.

Author	Design	Child-pugh/ BCLC grade	Number of patients	Dose fractionation scheme	Local control until transplant	Median survival
Sandroussi [51] 2010	Retrospective	A B C /A-B,D	4 5 1	23–54 Gy in 5–6 fractions	100% (2 delisted)	Not reported
Andolino [34] (Transplant) 2011	Retrospective	A B /A-B	12 11	3 × 12–16Gy 5 × 8Gy	100%	Not reached
Facciuto [53] 2011	Retrospective	A,B /A	27	2 × 12–18Gy 4 × 7Gy	100% (10 delisted)	32 months
Katz [52] 2011	Retrospective	A B C Unknown /A-B,D	3 8 4 3	10 × 5Gy	100% (6 delisted)	Not reported
O'Connor [60] 2012	Retrospective	A B C /A-B, D	7 2 1	3 × 11–18Gy	100%	Not reached

PMH series: ***Sandroussi C, Dawson LA, et al 2010***

10 patients → 3D-CRT as a bridge to OLT

33 Gy (range:8.5–54 Gy)/ 1–6 fractions→ 100% LC & 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

SBRT as bridge/ down-size –Pittsburgh group

19 - within Milan / 8 outside milan (downsized)
→ bridge to transplantation

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

- 27 HCC with cirrhosis → SBRT with intent for OLT [since 2010 @ Allegheny Health Network
- Bridge-to-transplant:
  - 18/19 (95%) pts - successfully controlled with SBRT
  - 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

Overall success
95% - bridge-to-transplant
63% - downsizing
100% local control to SBRT

SBRT Vs others

Review

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

Stephanie K. Schaub, MD[1], Pehr E. Hartvigson, 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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Volume 17: 1–19
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2018

Comparison: SBRT vs others

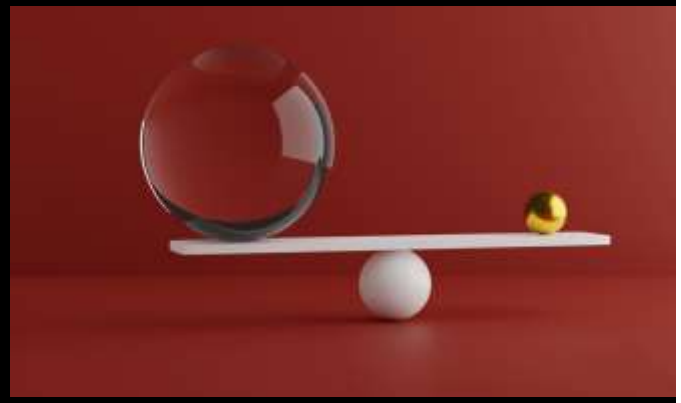


Table 5. Summary of Key Clinical Data of SBRT Compared to Other Liver-Directed Therapies.

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} ≥ 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

HEPATOLOGY

AASLD

HEPATOLOGY, VOL. 74, NO. 5, 2021

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

Tiffany Cho-Lam Wong [1,2] Victor Ho-Fun Lee,[3,4] Ada Lai-Yau Law,[5] Herbert H. Pang,[6] Ka-On Lam,[3,4] Vince Lau,[7] Tracy Yushi Cui,[2] Adrianna Sze-Yin Fong [1] Sarah Wai-Man Lee,[5] Edwin Chun-Yin Wong,[5] Jeff Wing-Chiu Dai,[1,2] Albert Chi-Yan Chan,[1,2] Tan-To Cheung,[1,2] James Yan-Yue Fung [8,9] Rebecca Mei-Wan Yeung,[5] Mai-Yee Luk,[3,4] To-Wai Leung,[3,4] and Chung-Mau Lo[1,2]

2021

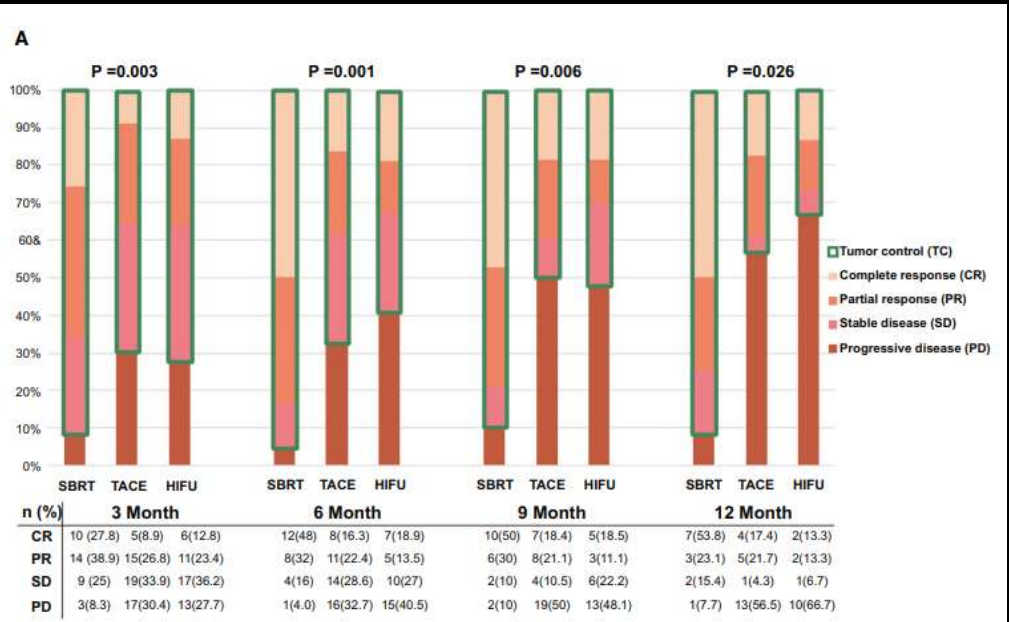
BACKGROUND AND AIMS: There are no prospective data on stereotactic body radiation therapy (SBRT) as a bridge to liver transplantation for HCC. This study aimed to evaluate the efficacy and safety of SBRT as bridging therapy, with comparison with transarterial chemoembolization (TACE) and high-intensity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



n (%)	3 Month			6 Month			9 Month			12 Month		
CR	10 (27.8)	5(8.9)	6(12.8)	12(48)	8(16.3)	7(18.9)	10(50)	7(18.4)	5(18.5)	7(53.8)	4(17.4)	2(13.3)
PR	14 (38.9)	15(26.8)	11(23.4)	8(32)	11(22.4)	5(13.5)	6(30)	8(21.1)	3(11.1)	3(23.1)	5(21.7)	2(13.3)
SD	9 (25)	19(33.9)	17(36.2)	4(16)	14(28.6)	10(27)	2(10)	4(10.5)	6(22.2)	2(15.4)	1(4.3)	1(6.7)
PD	3(8.3)	17(30.4)	13(27.7)	1(4.0)	16(32.7)	15(40.5)	2(10)	19(50)	13(48.1)	1(7.7)	13(56.5)	10(66.7)

SBRT better for :

✓LC @ 1 yr

✓Dropouts @ 1 & 3 yrs

✓Pathological response

frontiers in Oncology

2020

ORIGINAL RESEARCH
published: 24 March 2020
doi: 10.3389/fonc.2020.00347

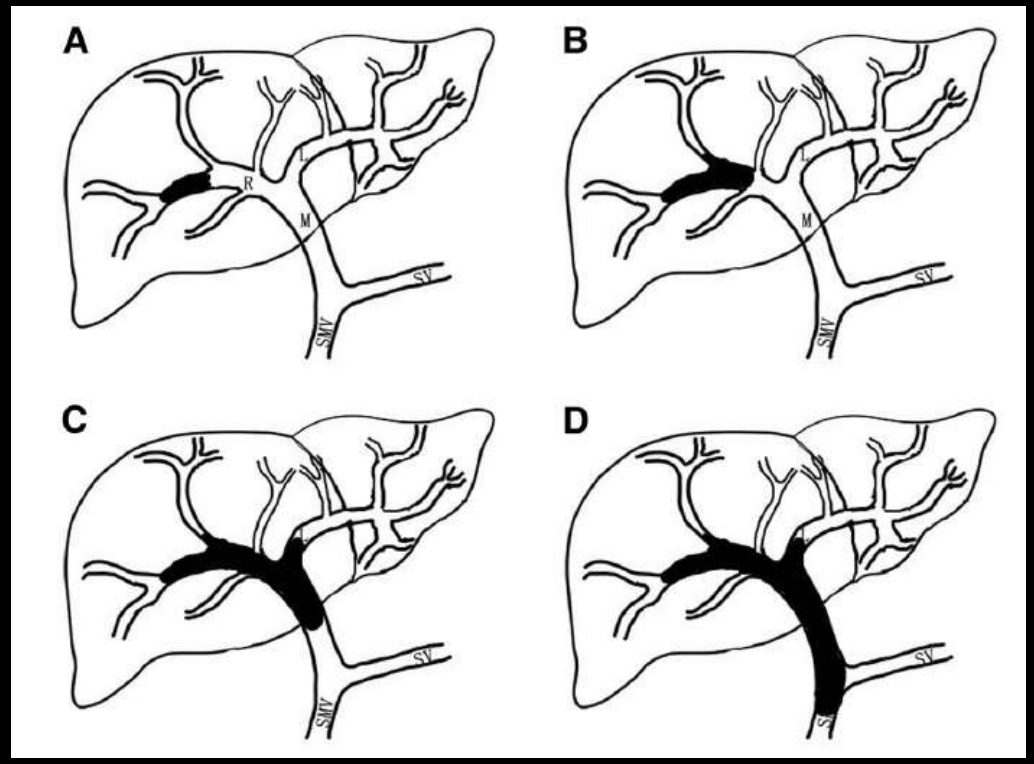
Stereotactic Body Radiation Therapy vs. Transarterial Chemoembolization in Inoperable Barcelona Clinic Liver Cancer Stage a Hepatocellular Carcinoma: A Retrospective, Propensity-Matched Analysis

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; $P = 0.009$).

HCC with PVTT



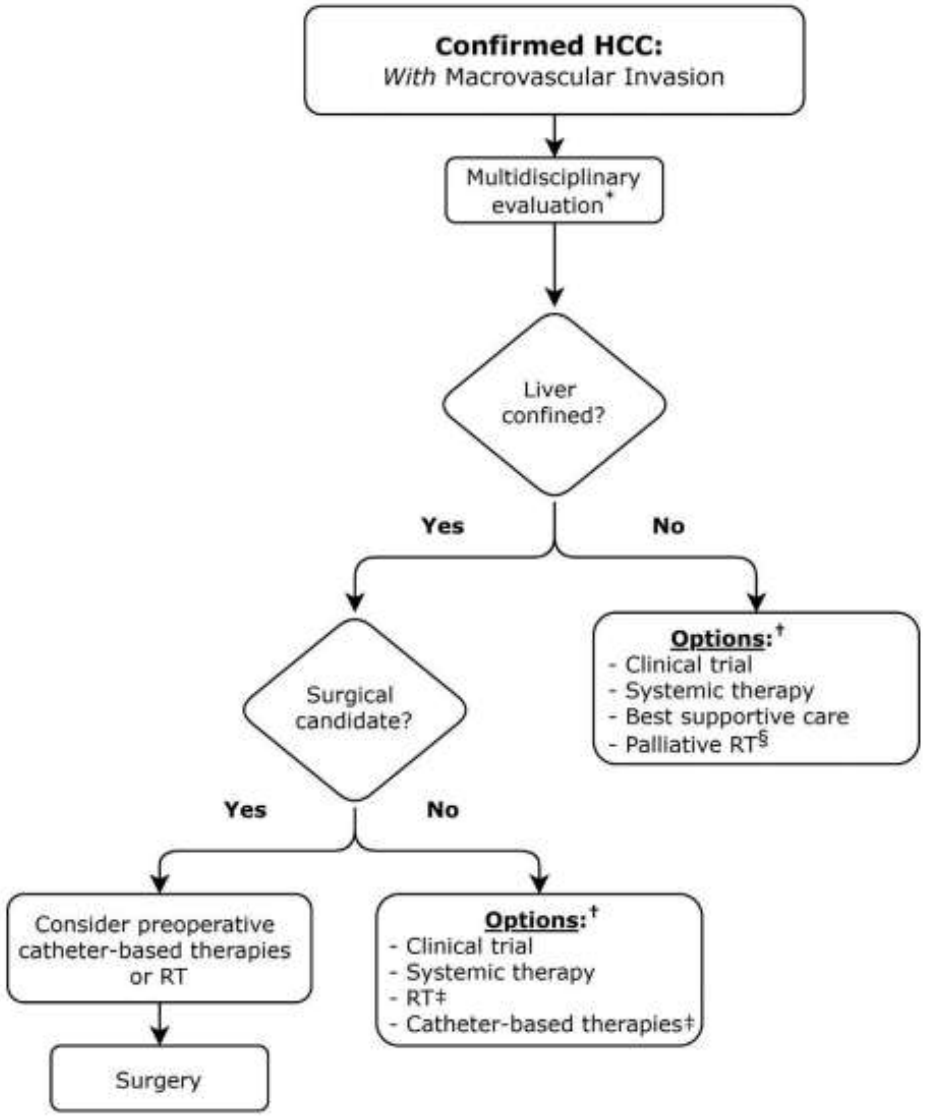
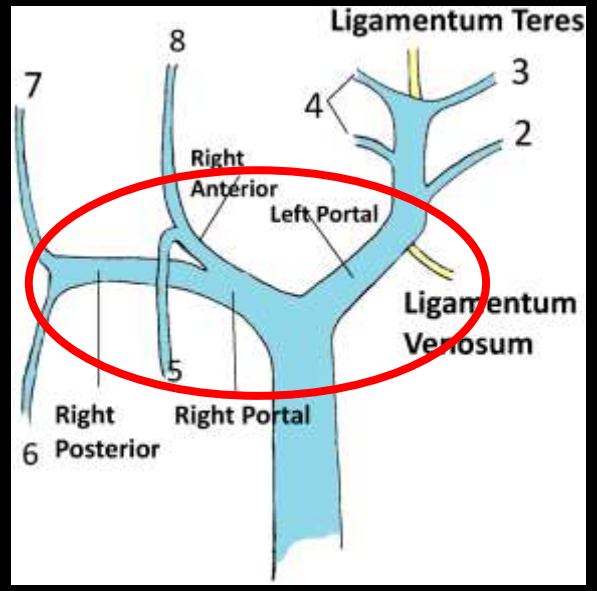


Figure 2 Algorithm for HCC with macrovascular invasion.

HCC & PVTT

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



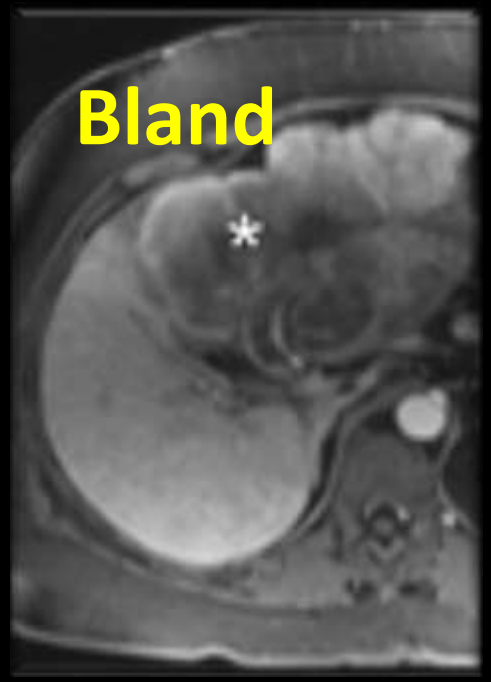
Presence of PVTT:

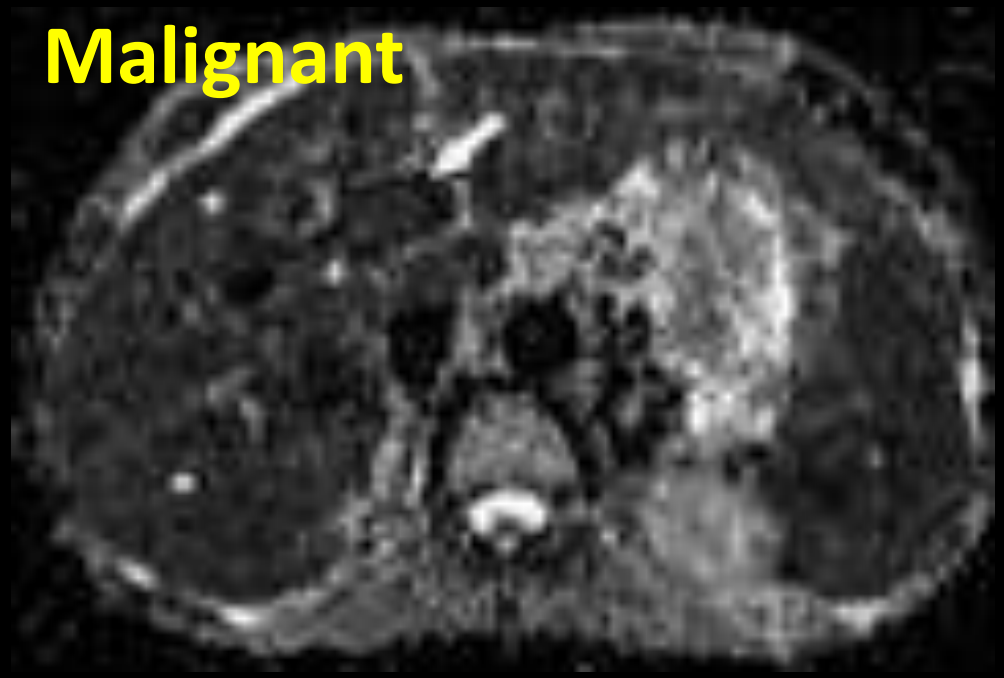
- outside MILAN- BCLC C- No transplant
- Standard therapies (TACE) – challenging
- Increased risk of : complications
- Poor prognosis
- Median survival: 2.7 months (PVTT+) Vs 10-24 months [No PVTT]

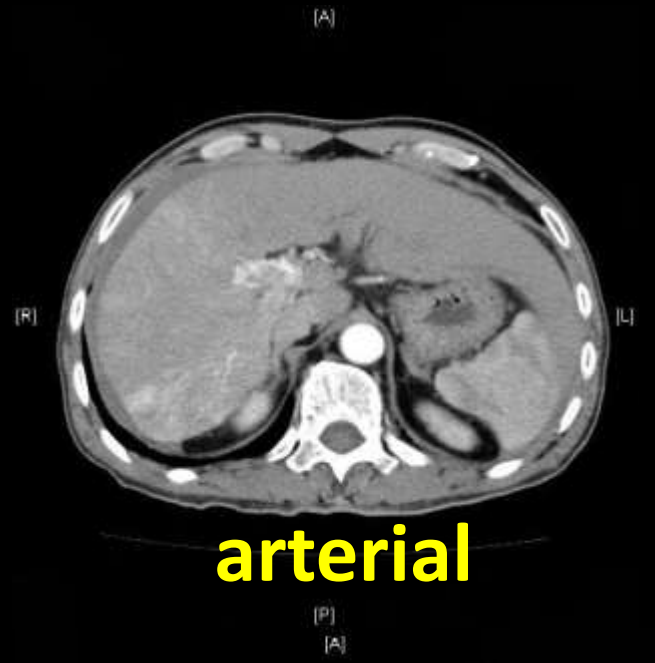
Cheung TK, Lai CL, Wong BC, Fung J, Yuen MF. Clinical features, biochemical parameters, and virological profiles of patients with hepatocellular carcinoma in Hong Kong. Aliment Pharmacol Ther2006; 24: 573-583

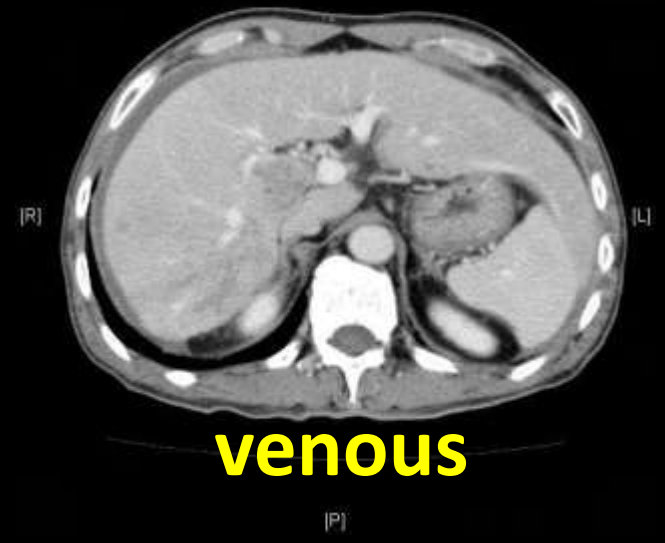
Minagawa M, Makuuchi M. Treatment of hepatocellular carcinoma accompanied by portal vein tumor thrombus. World J Gastroenterol2006; 12: 7561-7567

PVTT - radiology

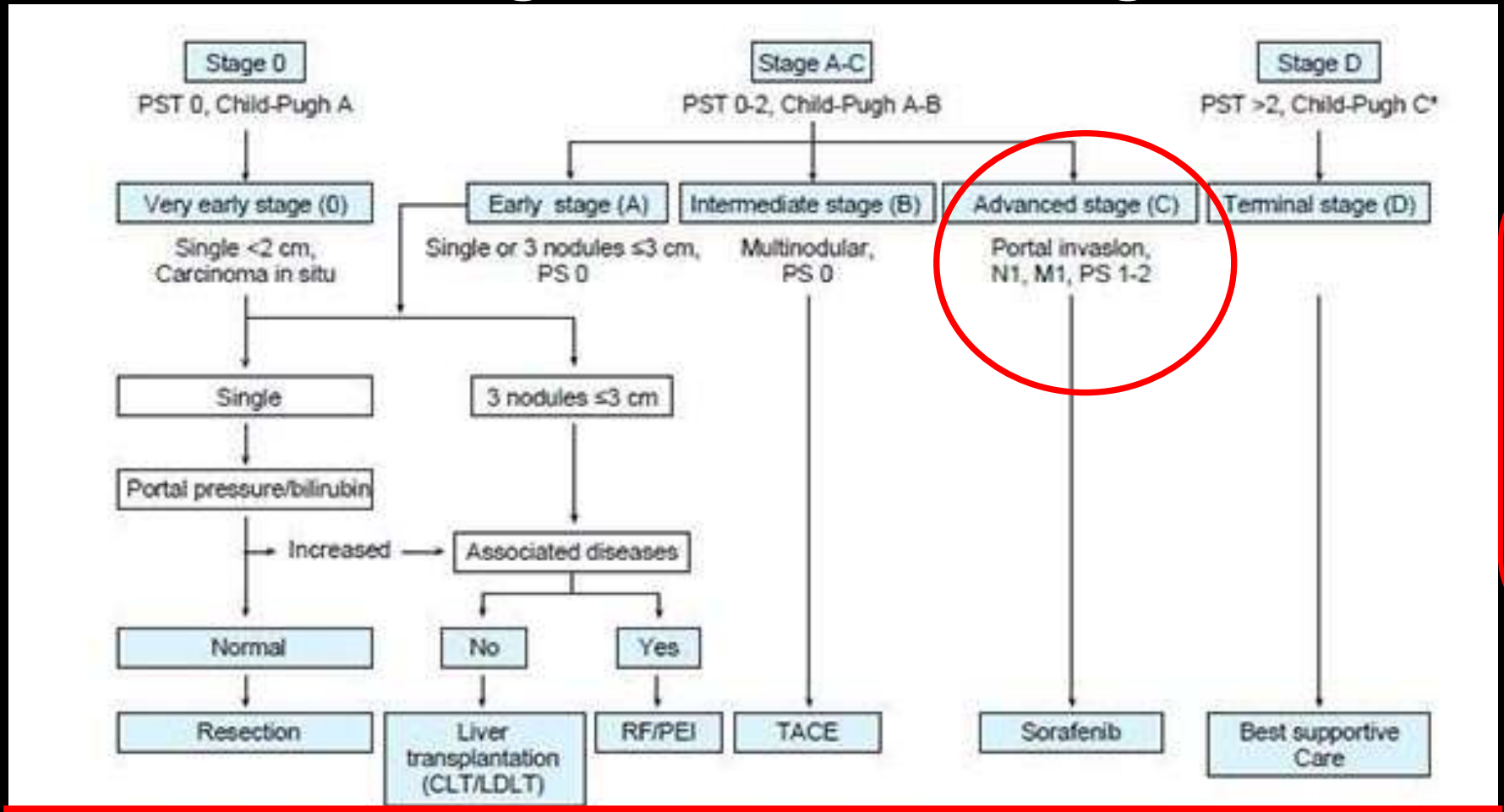








PVTT – significance on stage/ treatment



SABR/HypoFx RT/TACE+RT
- Inoperable
- Inaccessible
- To bridge before LT
- Salvage recurrence

TACE+RT/CCRT
- Consolidate TACE
- Salvage TACE refractoriness (SABR)
- Portal invasion

Palliative RT
- Symptom control
- Prevention of cancer related morbidity
- Oligometastasis

Support from evidence-making clinical trial efforts

Transplant: Contraindicated
Resection: Controversial
RFA: unsafe/ less effective
TACE: embolic effect – induces hepatic necrosis

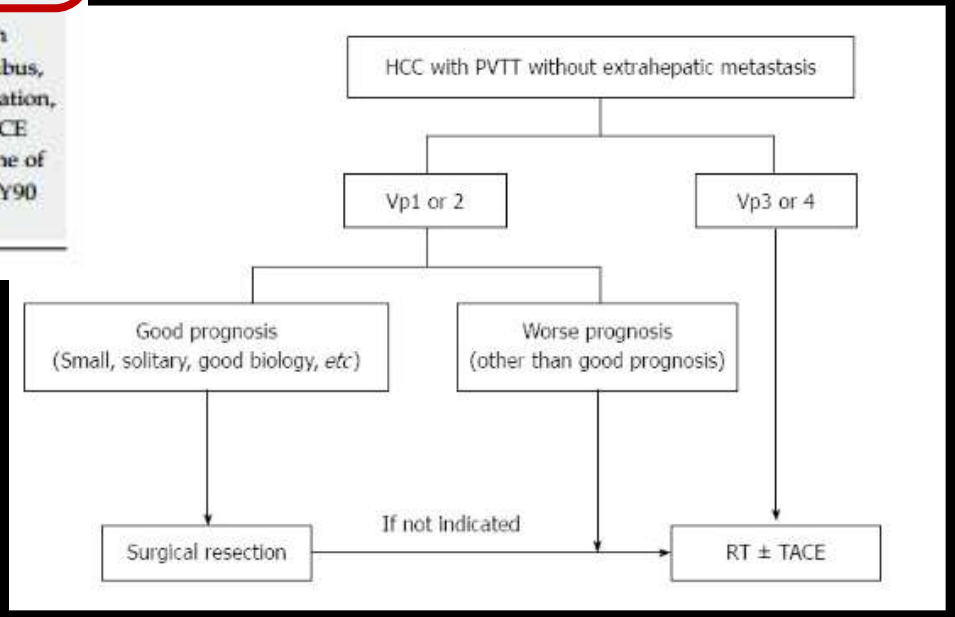
Dawson L, Semin Rad Onco; 2011 : 21

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*[48]	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*[70], Hilgard *et al*[69], Sangro *et al*[71]	Currently, PVT is one of the indications for Y90



Is All PVTT the same?

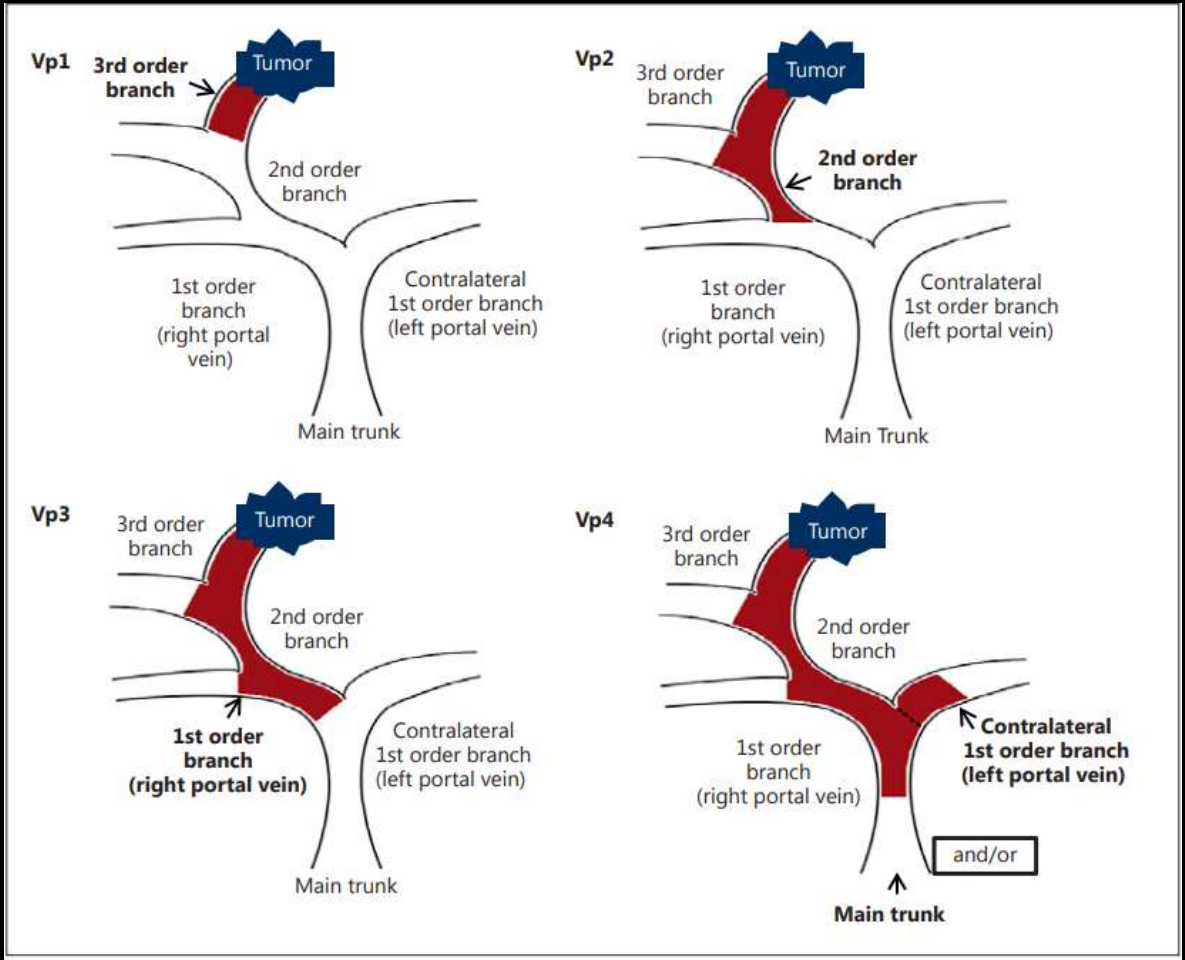


Fig. 1. Classification for hepatocellular carcinoma with portal vein tumor thrombosis according to the Liver Cancer Study Group of Japan classification.

- 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)

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

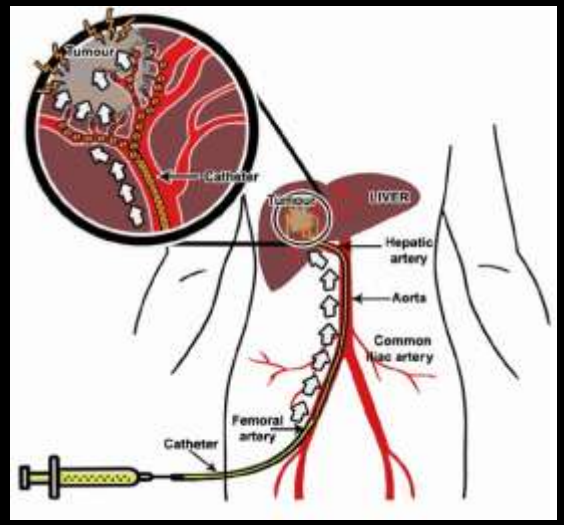
	Survival data (months)			Adverse events
	Overall survival	Main PVTT	Branch PVTT	
Supportive care[5]	2-4			
Surgical resection[6]	9-33	9-10		Operative mortality; 0-6%
TACE[23]	7-10			Liver failure, postembolization syndrome
External radiation therapy[26]	9.2			Radiation induced liver disease
HAIC[42,43]	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.

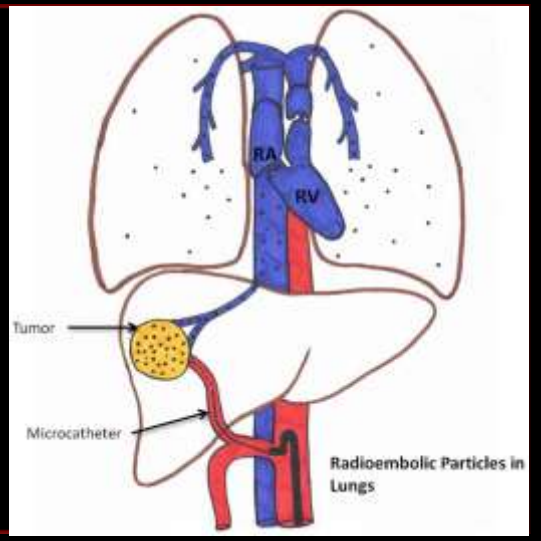
Hyun Young Woo, Clinical and Molecular Hepatology 2015;21:115-121

TACE & TARE

- TACE : M/C - unresectable HCC
- Usually contraindicated in Vp4 or Vp3 : fear of hepatic ischemia
- **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

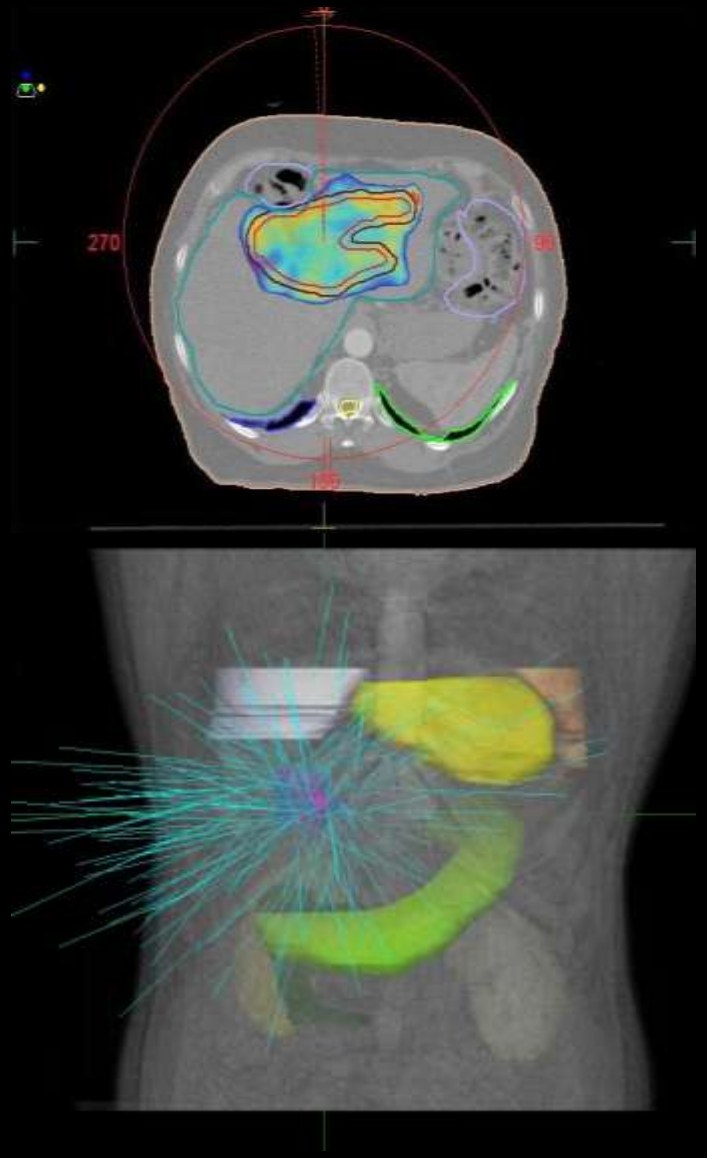


- TARE: New therapeutic modality
- Effective dose may vary from 100 Gy to 3000 Gy
- weaker embolic effect → use in PVTT
- Alternative or superior to TACE in unresectable – diffuse/ multifocal
- **Need prior mapping – rule out lung shunt/ mesenteric anomalous branching**

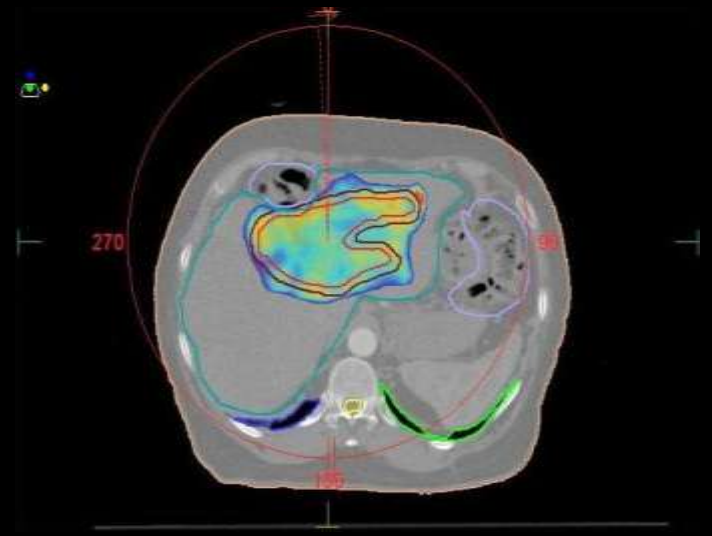


HCC with PVTT

- 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



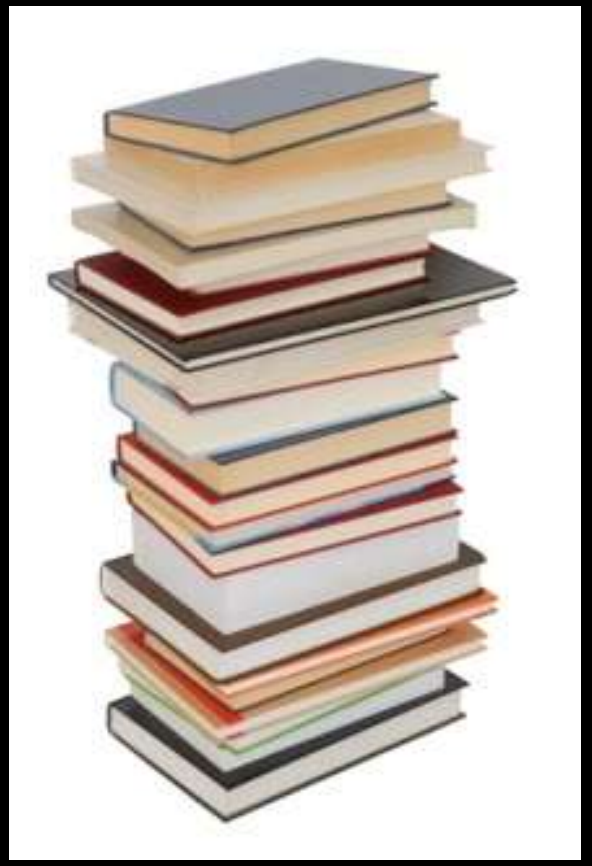


Table 1. Stereotactic body radiotherapy outcomes for hepatocellular carcinoma **2006 - 2013**

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%

PVTT down-staging → Transplant feasible

Original Clinical Science—Liver

JCO 2019

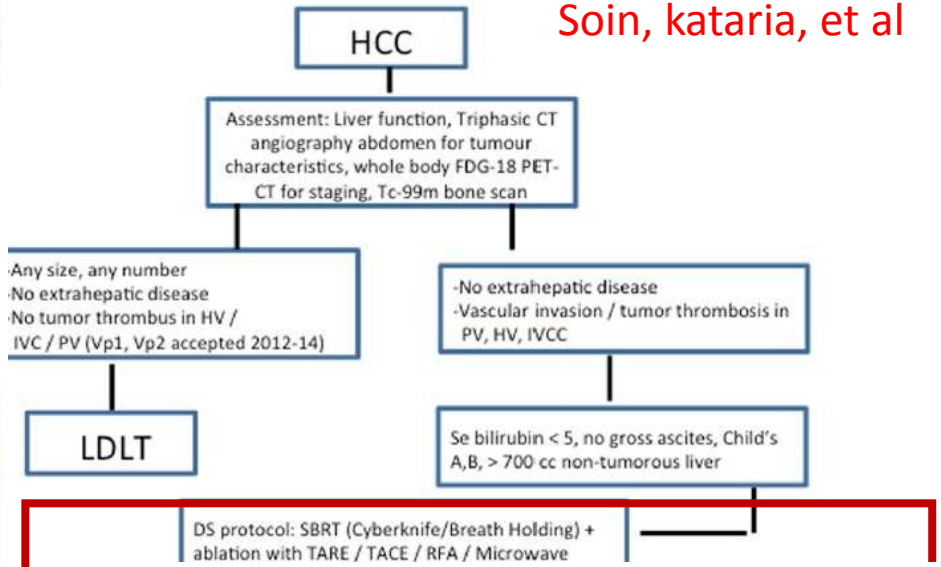
Experience With LDLT in Patients With Hepatocellular Carcinoma and Portal Vein Tumor Thrombosis Postdownstaging

Arvinder S. Soin, MS, FRCS,[1] Prashant Bhangui, MS,[1] Tejinder Kataria, MD,[2] Sanjay S. Baijal, MD,[3] Tarun Piplani, MD,[3] Dheeraj Gautam, MD,[4] Narendra S. Choudhary, DM,[1] Srinivasan Thiagarajan, MS,[1] Amit Rastogi, MS,[1] Neeraj Saraf, MD,[1] and Sanjiv Saigal, DM[1]

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 82%, 57%, and 77%, 51%, respectively, comparable to survival in 382 HCC patients without PVTT undergoing upfront LDLT (5-y OS 65%, $P = 0.06$; 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—48%/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: 2334–2345).

Soin, kataria, et al



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).

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%.

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*[31]
Sorafenib	6.5-8.1			Llovet *et al*[9], 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*[29], Nakazawa *et al*[30]
TARE	6-16.9	7.7	16.9	Salem *et al*[47], Kulik *et al*[48], Sangro *et al*[49], Memon *et al*[50]
TACE plus sorafenib	11-13	3	13-15	Pan *et al*[58], Zhu *et al*[59]
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.

Open Access Full Text Article

ORIGINAL RESEARCH

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

This article was published in the following Dove Press journal:
Therapeutics and Clinical Risk Management
22 December 2016
Number of times this article has been viewed

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Purpose: Numerous studies have tried to combine transarterial chemoembo or hepatic arterial infusion chemotherapy (HAIC) with radiotherapy (RT) fo hepatocellular carcinoma (HCC) patients with portal vein tumor thrombus (P the efficacy of TACE or HAIC combined with RT versus TACE or HAIC alon 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 systemati 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.

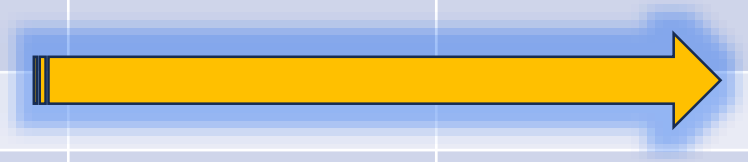
Results: Eight studies with a total of 1,760 patients were included in this meta-analysis. The pooled results showed that intra-arterial chemoembolization combined with RT significantly improved ORR of PVTT (OR, 4.22; 95% CI, 3.07–5.80; $P<0.001$) and OS (HR, 0.69; 95% CI, 0.57–0.83; $P=0.001$), but 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.

PVTT – expected response assessment

	1 mth	3 mth	6 mth	9 mth	12 mth
CR	0%	6%	32%	56%	66.7%
PR	77.4%	43%	51%	43%	33.3%
SD	15.1%	4 %	6%		
PD	7.5%	14%	3%		
LC	92.5%	85.5%			
Sr AFP	56% > 50% decrease in AFP @ 4-6 weeks				



Mean PTV – 390 cc

Dose – 40 Gy in 5 fr SBRT

3-6 months ideal for assessment

Stereotactic body radiotherapy based treatment for hepatocellular carcinoma with extensive portal vein tumor thrombosis

Yongjie Shui, Wei Yu, Xiaoqiu Ren, Yinglu Guo, Jing Xu, Tao Ma, Bicheng Zhang, Jianjun Wu, Qinghai Li, Qiongge Hu, Li Shen, Xueli Bai, Tingbo Liang & Qichun Wei

Radiation Oncology **13**, Article number: 188 (2018) | Cite this article

Response evaluation

Available online at www.sciencedirect.com
ScienceDirect
journal homepage: http://www.elsevier.com/locate/rpor

Original research article

Evaluation of response after SBRT for liver tumors

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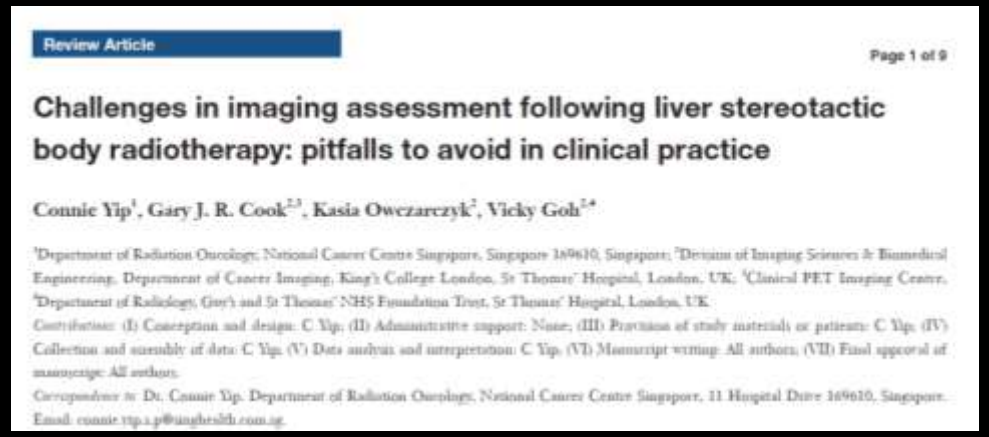

Review Article

Page 1 of 9

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

Connie Yip[1], Gary J. R. Cook[2,3], Kasia Owczarczyk[2], Vicky Goh[2,4]

[1]Department of Radiation Oncology, National Cancer Centre Singapore, Singapore 169610, Singapore; [2]Division of Imaging Sciences & Biomedical Engineering, Department of Cancer Imaging, King's College London, St Thomas' Hospital, London, UK; [3]Clinical PET Imaging Centre, [4]Department of Radiology, Guy's and St Thomas' NHS Foundation Trust, St Thomas' Hospital, London, UK

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

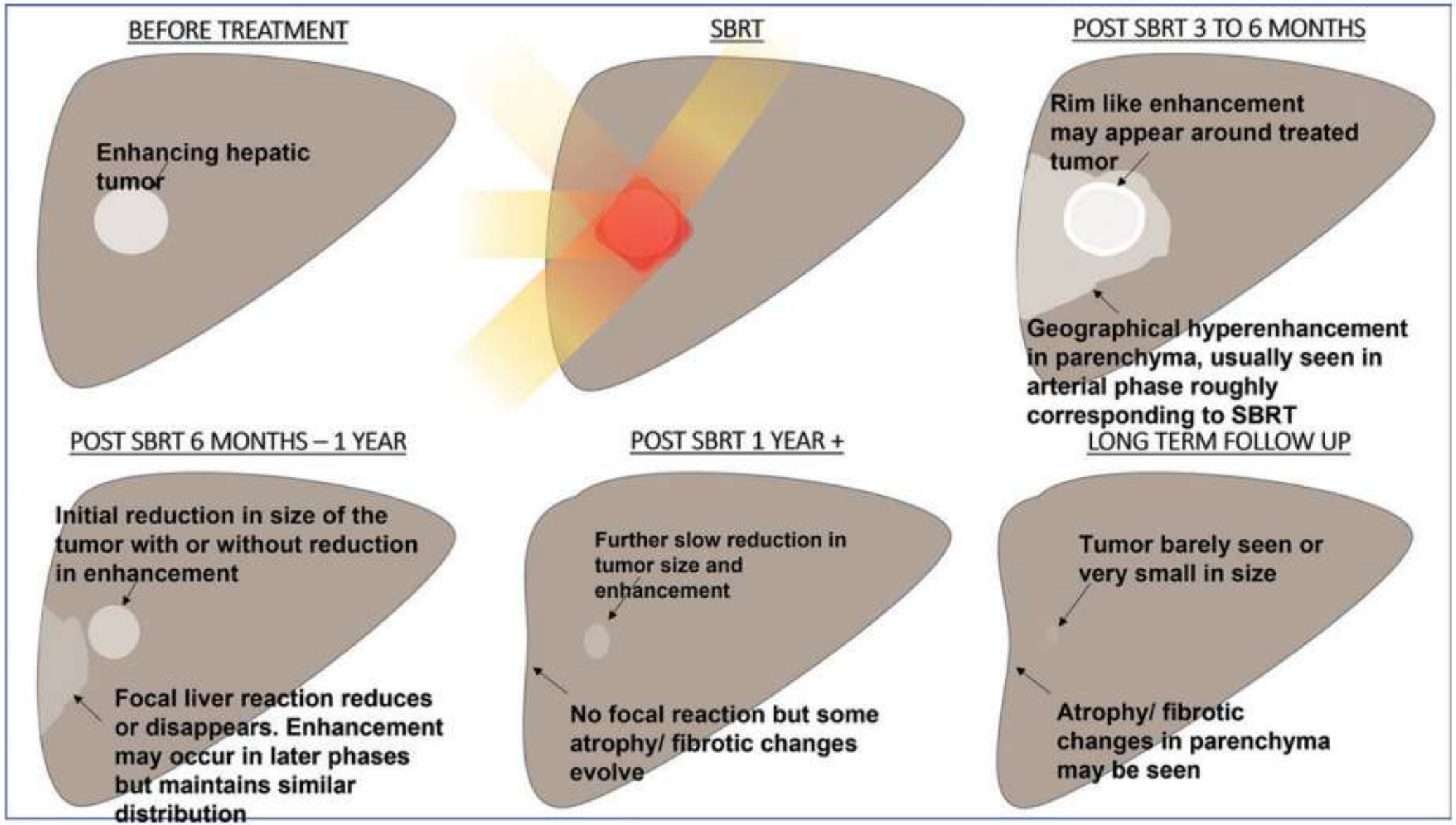
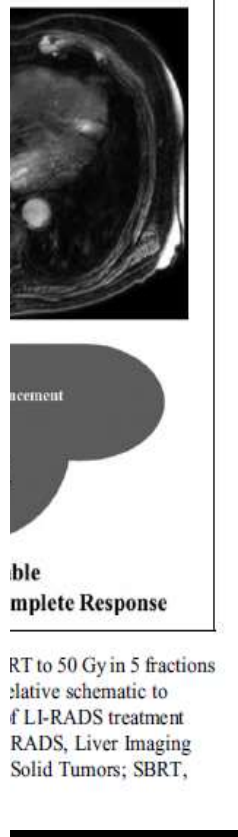


Figure 6. Diagram shows expected changes after SBRT.



RT to 50 Gy in 5 fractions
elative schematic to
f LI-RADS treatment
RADS, Liver Imaging
Solid Tumors; SBRT,

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

What dose and how much toxicity is expected??

Table 6 Recommended EBRT doses and fractionation for HCC and IHC*

Fractionation Regimen	Total dose/fractionation	BED_{10}	References
Ultrahypofractionation	**Noncirrhotic (primarily IHC): 4000-6000 cGy/3-5 fx**†	7200-18,000 cGy	110
	CP class A: 4000-5000 cGy/3-5 fx	7200-12,500 cGy	24,27,28,30,34,43, 44,61,86,101,111
	CP class B7: 3000-4000 cGy/5 fx	4800-7200 cGy	28,36,86,94,101
	4000-5400 cGy/6 fx	6700-10,300 cGy	65,93
	5000-6600 cGy/10 fx	7500-11,000 cGy	57,59,83,90,100,112
Moderate hypofractionation	4800 cGy/12 fx	6720 cGy	110
	4500-6750 cGy/15 fx	5900-9800 cGy	42,46,50,62,90,113,114
	6000 cGy/20 fx	7800 cGy	57
	6600-7200 cGy/22 fx	8600-9600 cGy	57-59,112
Standard fractionation	**5040 cGy/28 fx**†	5947 cGy	114,115
	6000 cGy/30 fx†	7200 cGy	114,115
	7700 cGy/35 fx	9400 cGy	58,59

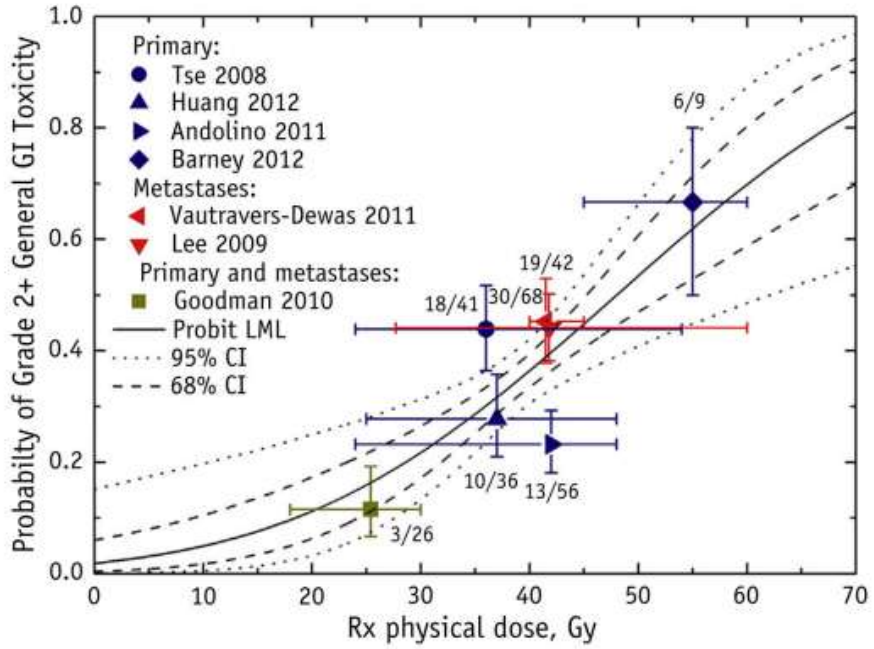


Fig. 2.

Grade ≥2 general gastrointestinal (GI) toxicity as a function of the prescription (Rx) physica dose to the target, with the probit model result (maximum likelihood parameter fitting) and 95% and 68% confidence intervals (CIs). General GI toxicities were defined as fatigue, nausea, diarrhea, gastritis, ulcers, GI area pain, and colitis. The target Rx dose definition is provided in Table 2. Each data point was placed at the reported mean or median dose and reported complication rate; horizontal error bars represent the reported ranges, and the vertical error bars represent binomial 68% CIs. The number of patients who developed toxicity of the total number of patients for each study is displayed next to the data point. Th study by Andolino et al (14) did not distinguish between grade 1 and 2 general GI toxicities *Abbreviation:* LML = log maximum likelihood.

of the target, and the null hypothesis of no dose response was not rejected ($P = .10$); therefore, we could not exclude that the incidence of liver enzyme complications wa independent of the dose; the probit model fit is displayed for reference. *Abbreviatio* = log maximum likelihood.

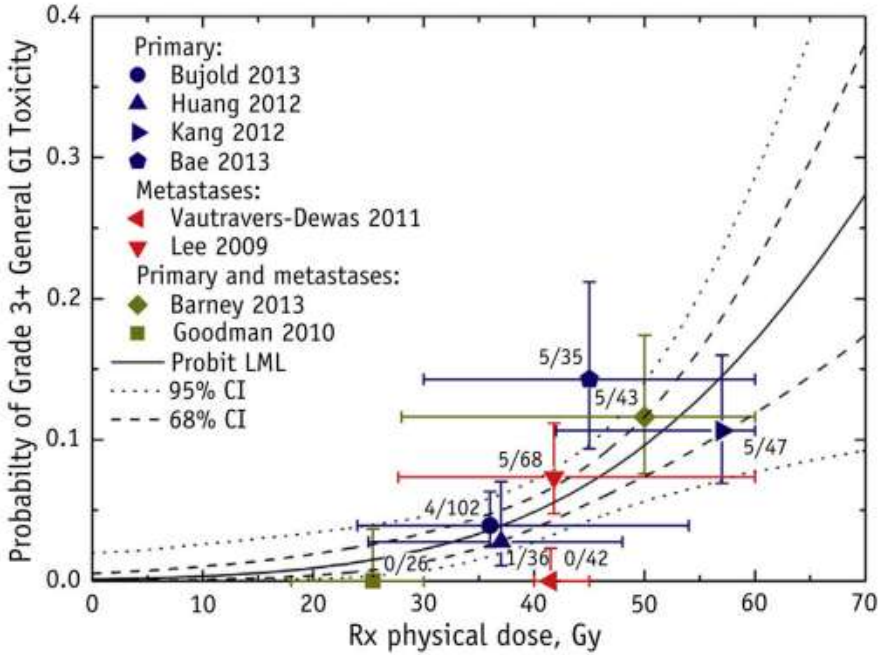
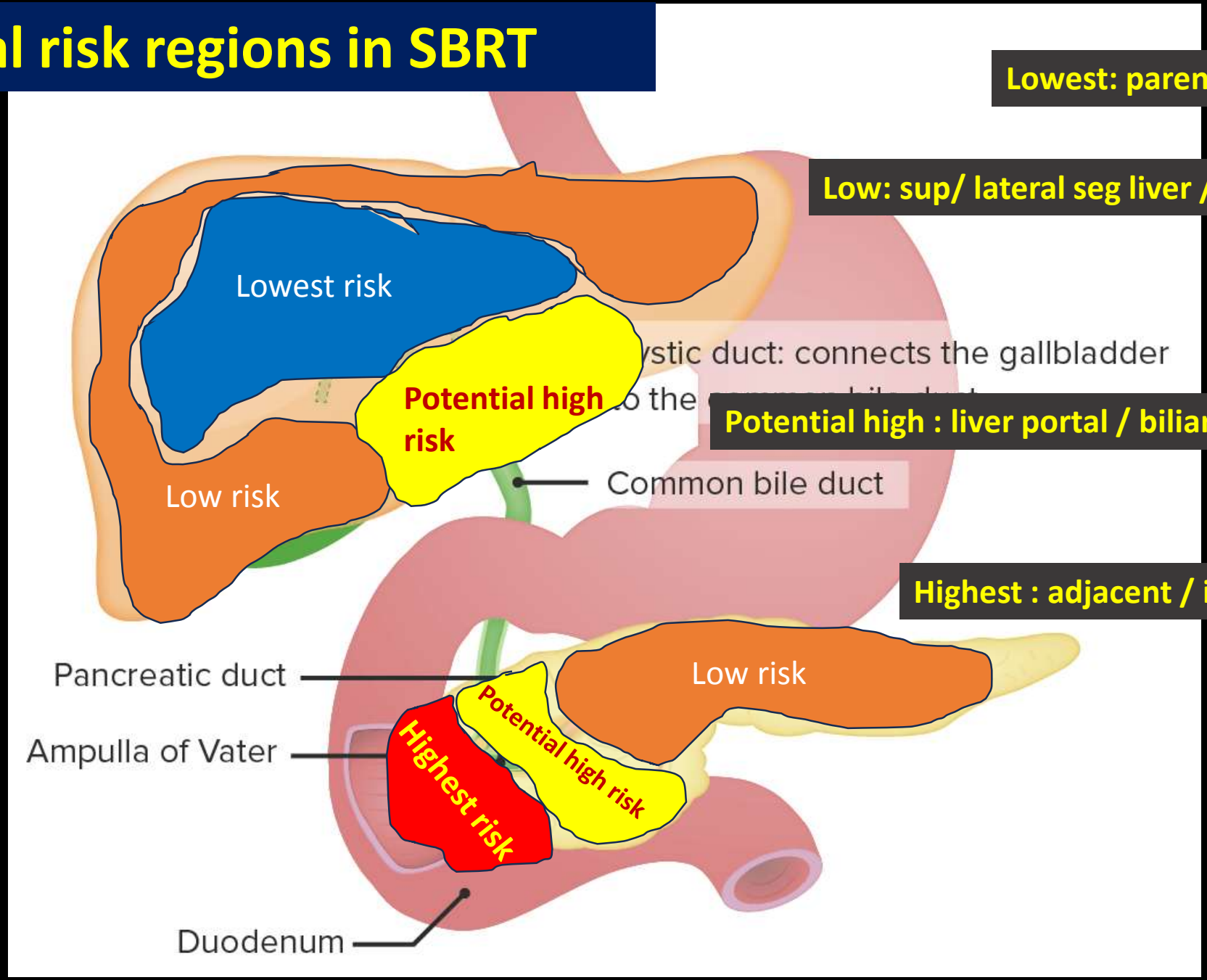


Fig. 3.

Grade ≥3 general gastrointestinal (GI) toxicity as a function of the prescription (Rx) physical dose to the target, with the probit model result (maximum likelihood parameter fitting) and 95% and 68% confidence intervals (CIs). General GI toxicities were defined as fatigue, nausea, diarrhea, gastritis, ulcers, GI area pain, and colitis. The target RX dose definition is provided in Table 2. Each data point is placed at the reported mean or median dose and reported complication rate; the horizontal error bars represent the reported ranges, and the vertical error bars represent binomial 68% CIs. The number of patients who developed toxicity out of the total number of patients for each study is displayed next to the data point. *Abbreviation:* LML = log maximum likelihood.

Anatomical risk regions in SBRT



Lowest: parenchymal

Low: sup/ lateral seg liver / tail body pancreas

Potential high : liver portal / biliary / pancreas head

Highest : adjacent / invading lumen

SBRT case selection: risk based on segment & function

REPORTS OF PRACTICAL ONCOLOGY AND RADIOTHERAPY 20 (2015) 417–424

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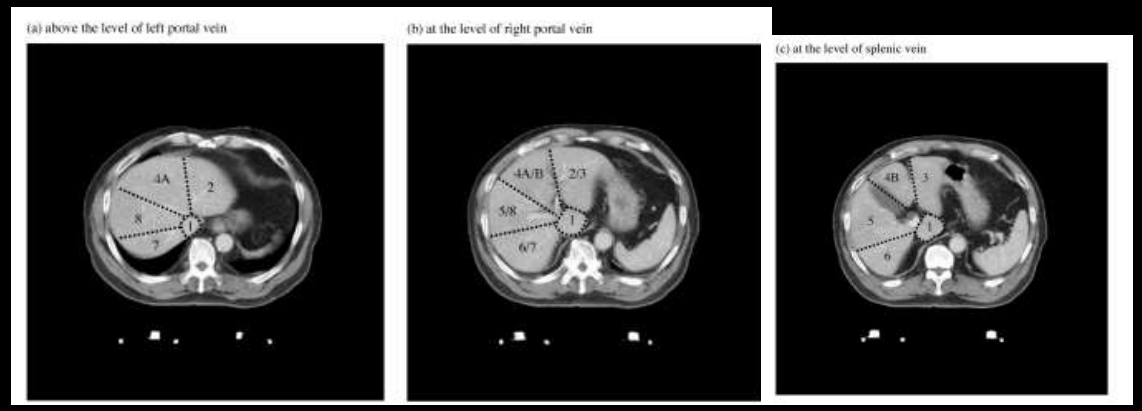
[c] Radiotherapy and Radiosurgery Department, Humanitas Cancer Center, Istituto Clinico Humanitas, Rozzano, Milano, Italy

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



- **FUNCTION based**
  - CP [Child Pugh] score better than CP stage
  - CP-A5 better OS than CP-A6
  - CP-A6 – more inflammation/fibrogenecity than CP-A5

Better functioning liver – better outcomes

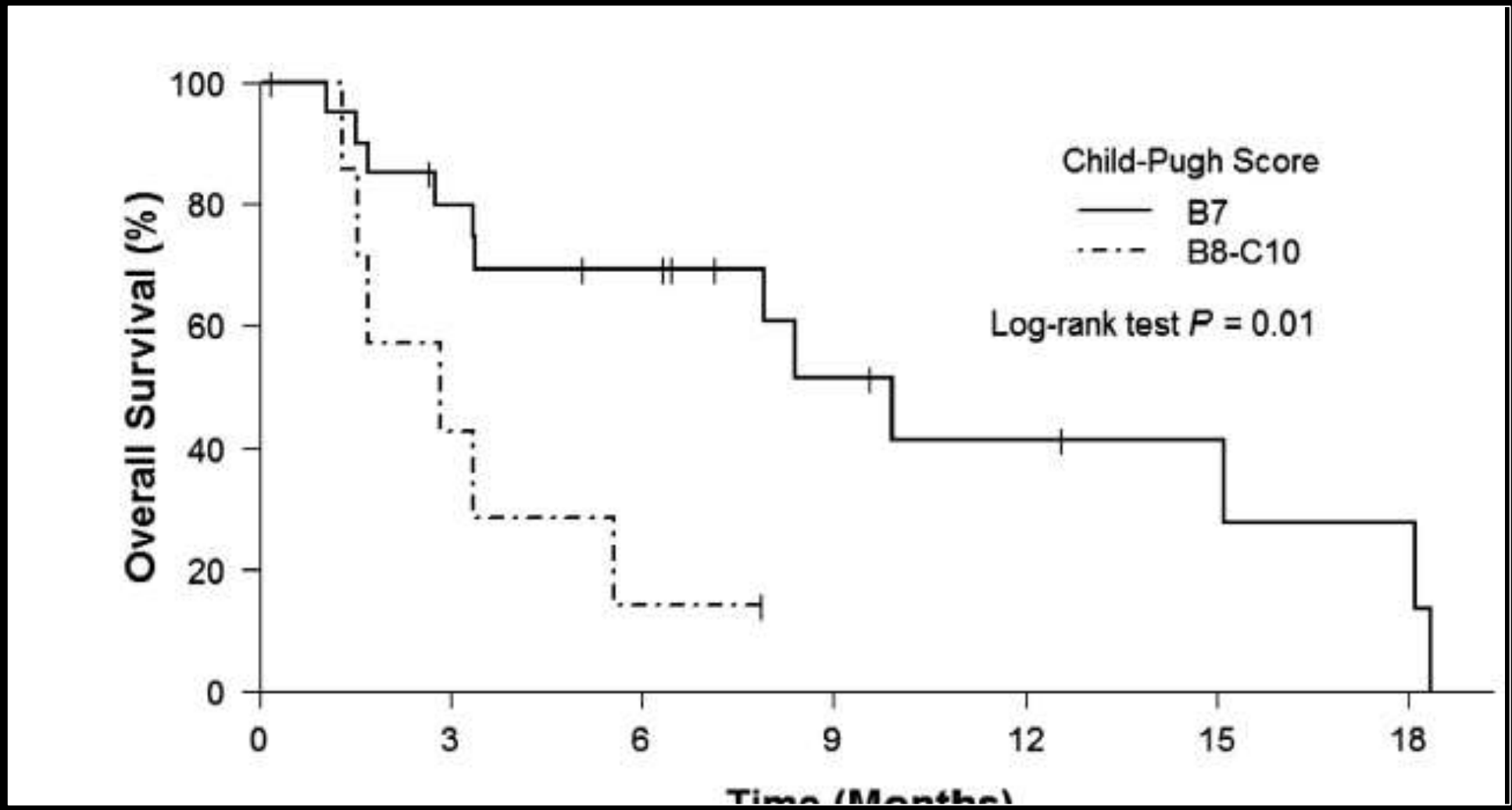


Table 1
Individual scores and associate prognostic estimates at

Day Score Acute parameters	2 Value	Prognosis
APACHEII	11	In hospital mor 15%
SOFA	7	In hospital mor 33%
ACLF grade*	0	–
CLIF-C consortium ACLF score (used if ACLF grade≥ 1)	–	
CLIF-C consortium AD score (used if ACLF grade=0)	47	Mortality: 1 month - 2% 3 month - 6% 6 month - 11 12 month- 21
C-SOFA	6	
Chronic parameters		
CPS	C10	Mortality 1yr- 55% 2yr- 65%
MELD	20	Mortality 3 month –20
UKELD	61	Mortality 1 yr - 50%

* ACLF grade progressed from 0 to 2 by Day 7 sugges

Table 1. Equation for calculating each grade including CTP score, MELD score, ALBI grade and PALBI grade.

CTP score	Adding points of five categories below		
CTP class	Class A, 5–6 points	Class B, 7–9 points	Class C, 10–15 points
	1 point	2 points	3 points
Albumin (g/dL)	> 3.5	2.8–3.5	< 2.8
Bilirubin (mg/dL)	< 2	2–3	>3
INR	<1.7	1.7–2.3	>2.3
Ascites	None	Mild	Severe
Encephalopathy	None	Grade I or II	Grade III or IV
MELD score	3.78 x $\log_e$ serum bilirubin (mg/dL) + 11.20 x $\log_e$ INR + 9.57 x $\log_e$ serum creatinine (mg/dL) + 6.43		
MELD grade	Grade 1, <10	Grade 2, 10–14	Grade 3, >14
ALBI score	($\log_{10}$ bilirubin × 0.66) + (albumin × -0.085), where bilirubin is in μmol/L and albumin in g/L		
ALBI grade	Grade 1, ≤-2.60	Grade 2, >-2.60 to ≤-1.39	Grade 3, >-1.39
PALBI score	2.02 × $\log_{10}$ bilirubin − 0.37 × ($\log_{10}$ bilirubin)^2 − 0.04 × albumin − 3.48 × $\log_{10}$ platelets + 1.01 × ($\log_{10}$ platelets)^2		
PALBI grade	Grade 1, ≤-2.53	Grade 2, >-2.53 to ≤-2.09	Grade 3, >-2.09

CTP, Child-Turcotte-Pugh; INR, International normalized ratio; MELD, Model for end-stage liver disease; ALBI, albumin-bilirubin; PALBI, platelet-albumin-bilirubin

https://doi.org/10.1371/journal.pone.0216173.t001

Central liver toxicity - SBRT

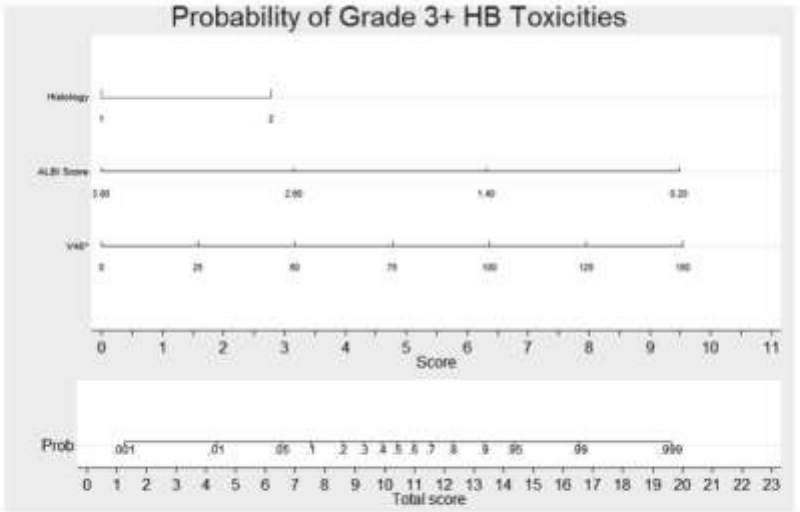


Fig. 2. Nomogram to predict the occurrence of grade 3 or higher HB toxicity after SBRT among primary liver cancer patients. *Abbreviations:* HB = hepatobiliary; SBRT = stereotactic body radiotherapy. *Volume of central hepatobiliary tract (created from a 15 mm expansion from the portal vein) receiving a biologically effective dose of 40 Gy with an α/β ratio of 10. Histology (1 = HCC and 2 = CCA). (A nomogram calculator is available online at http://web.stanford.edu/~akoong/nomogram.html.)

Histology:

- HCC (good) vs CCA (bad)

ALBI score

- 1 - 3

V40 Gy:

- $VBED_{10}40$ – 37 cc
  $VBED_{10}$ 30 – 45 cc [3 #]
- V26 < 37 cc
  V21 < 45 cc
  Dmean < 19 Gy [5#]

FORMULA

ALBI = ($\log_{10}$ bilirubin × 0.66) + (albumin × -0.085), where bilirubin is in µmol/L and albumin in g/L.

FACTS & FIGURES

Interpretation:

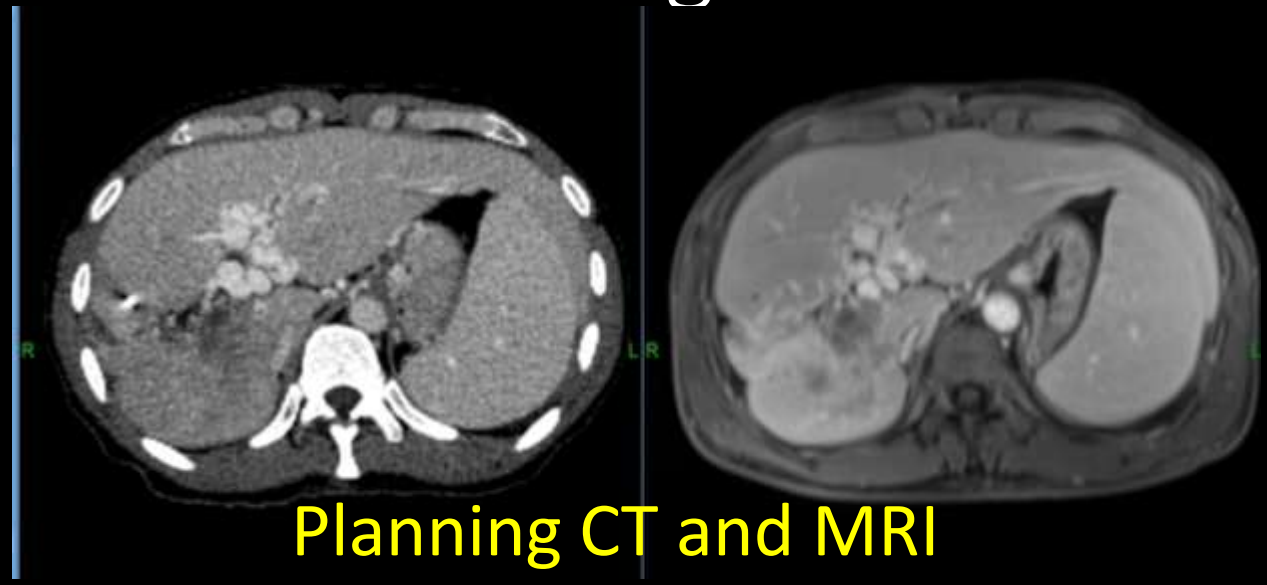
ALBI Score	Grade	Median survival
≤-2.60	1	18.5-85.6 months
>-2.60 to ≤-1.39	2	5.3-46.5 months
>-1.39	3	2.3-15.5 months

Table 4
Multivariate analysis for predictors of grade 3 or higher HB toxicity after SBRT for primary liver cancer patients.

Predictor	*p* value	OR	95% CI	
Histology	0.017	8.1267	1.4437	45.7450
Albumin–Bilirubin score	0.011	0.1377	0.0297	0.6374
$V_{BED10}40$	0.001	1.0490	1.0201	1.0788

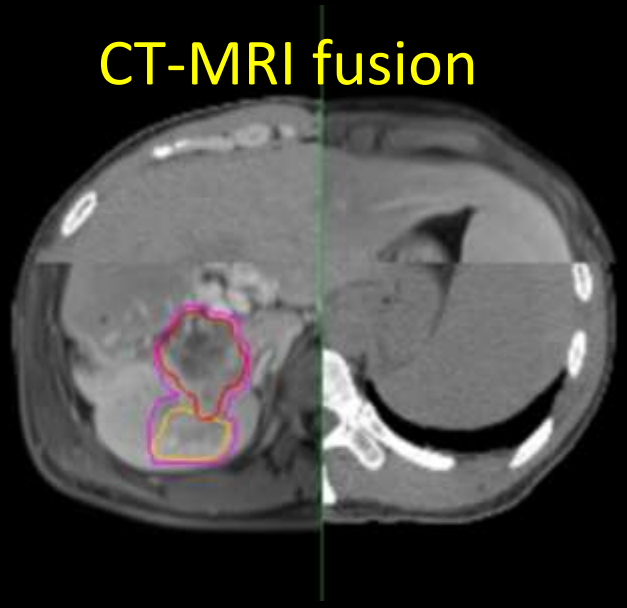
Abbreviations: HB = hepatobiliary; SBRT = stereotactic body radiation therapy; OR = odds ratio; CI = confidence interval; $V_{BED10}40$ = volume of central hepatobiliary tract (created from a 15 mm expansion from the portal vein) receiving a biologically effective dose of 40 Gy with an α/β ratio of 10.

Target delineation: Image Fusion

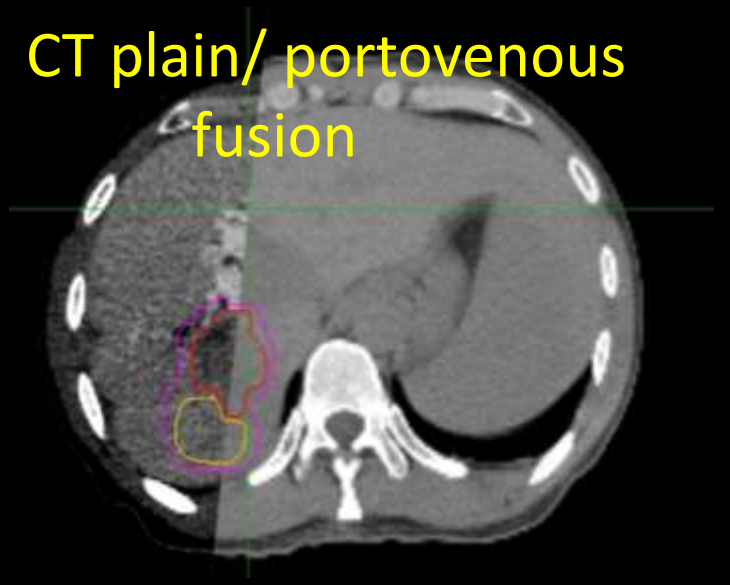


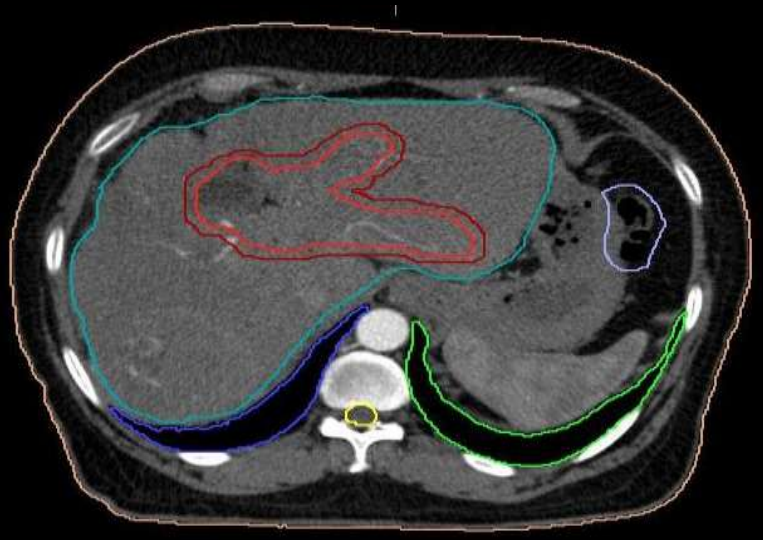
Planning CT and MRI

CT-MRI fusion



CT plain/ portovenous fusion





Target delineation:

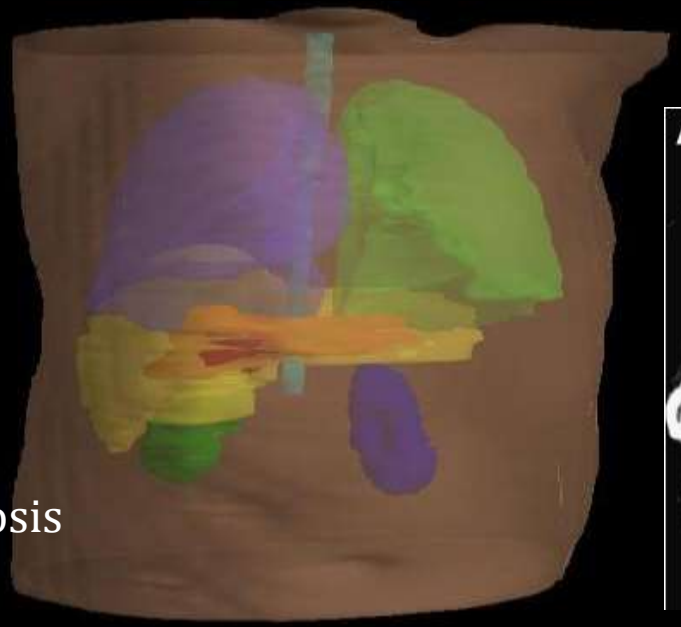
- GTV: PVTT +/- HCC on planning CT
- Additional fused MRI/ PET-CT used
- PTV:
  - Cyberknife: 3 mm radial and 5 mm cranio-caudal
  - DIBH: 5 mm radial and 7 mm cranio-caudal

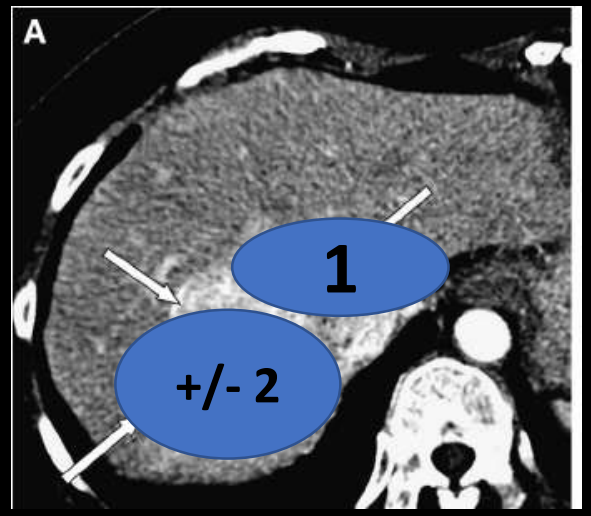
GTV :

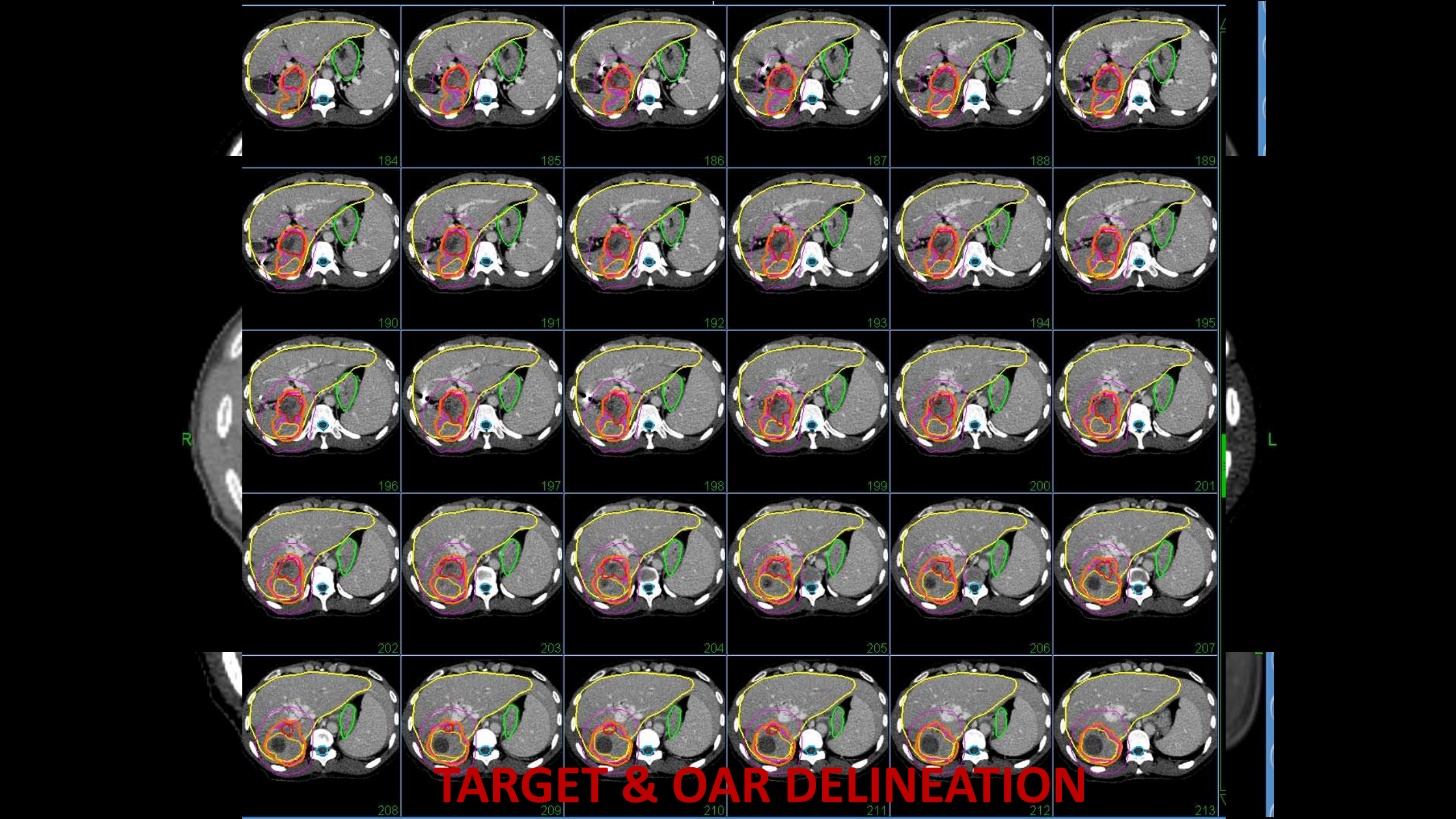
- ✓ *capsulated growth pattern*
- ✓ *pushing growth pattern*
- ✓ *infiltrative growth pattern*

Tumor/normal liver interface **(TNI) –**

Post chemo – residual – peripheral thickness → prognosis



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TARGET & OAR DELINEATION

Dose selection & outcomes

- Liver SBRT : HCC TD 50 ~ 53 Gy EQD2 Vs Metastases 70 Gy EQD2
- 2
- L
- I
- A
  - Individualize maximum dose / for specific toxicity risk levels

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%

Initiating the liver SBRT program – Toxicity dilemma

- **RILD** – not a limiting factor
- other non-RILD toxicities:
  - **gastroduodenal damage**
  - Chest wall and rib injury
  - Esophageal ulceration
  - Renal failure
  - Reactivation of viral hepatitis
  - Cardiac injury
  - Pneumonitis
  - Skin necrosis.

Table 2. Dose constraints for stereotactic body radiation therapy planning.

Organ at risk	Constraint for 3 fractions	Constraint for 5 fractions
Uninvolved liver (non-cirrhotic)[137]		
Mean dose	<12-15 Gy	<15-18 Gy
Dose to ≥700 cm^3	<19 Gy	<21 Gy
Uninvolved liver (Child-Pugh class A)[40,85,138]		
Mean dose	<10-12 Gy	<13-15 Gy
Dose to ≥700 cm^3	–	<15 Gy
Uninvolved liver (Child-Pugh class B)[40,85,138]		
Mean dose	None	<8-10 Gy
Dose to ≥500 cm^3		<10 Gy
Stomach[137]		
D 0.03 cm^3	<22 Gy	<32 Gy
D 10 cm^3	<16.5 Gy	<18 Gy
Duodenum[137,139]		
D 0.03 cm^3	<22 Gy	<32 Gy
D 5 cm^3	<16.5 Gy	<18 Gy
Small bowel[137,139]		
D 0.03 cm^3	<22 Gy	<32 Gy
D 5 cm^3	<18 Gy	<19.5 Gy
Large bowel[137,139]		
D 0.03 cm^3	<28 Gy	<34 Gy
D 20 cm^3	<24 Gy	<25 Gy
Common bile duct[88]		
D 0.5 cm^3	40 Gy	40 Gy

LIVER[HCC.METS

1.	NAME	
2.	DIAGNOSIS	
3.	PRIOR TREATMENT	
4.	MOTION MANAGEMENT	
5.	NUMBER OF LESIONs	
6.	CHILD SCORE[BEAP]	
7.	LIVER VOLUME	
8.	LOCATION	SIDE
	1.	
	2.	
	3.	
	4.	
	5.	
9.	PLAN TYPE-[3DCRT/VMAT	
10	PRESCRIBED MARGIN	

	LESION 1	
D_{MAX}	LESION 1	
D95%	LESION 1	
D100%	LESION 1	
V95%	LESION 1	
V100%	LESION 1	
V120%	LESION 1	
V130%	LESION 1	

DISTANCE BETWEEN 80% ISODOSE AND 60% ISODOSE-[<2mm]

	LESION 1		LESION 2		LESION 3		LESION 4		LESION 5	

DISTANCE BETWEEN 80% ISODOSE AND 40% ISODOSE-[<8mm]

	LESION 1		LESION 2		LESION 3		LESION 4		LESION 5	

CONFIRMITY INDEX [IDEAL 1] VOLUME OF PRESCRIPTION ISODOSE/VOLUME OF PTV

	LESION 1		LESION 2		LESION 3		LESION 4		LESION 5	

HOMOGENITY INDEX [BETWEEN 1.1-1.3] MAX DOSE/ PRESCRIPTION DOSE

	LESION 1		LESION 2		LESION 3		LESION 4		LESION 5	

GRADIENT INDEX[BETWEEN 0.3-0.9][RADIUS OF PRESCRIPTION ISODOSE - RADIUS OF HALF PRESCRIPTION ISODOSE]

	LESION 1		LESION 2		LESION 3		LESION 4		LESION 5	

PRESCRIPTION DOSE	LIVER-GTV [>700CC]			
	NEEDED	ACCEPTABLE	UNACCEPTABLE	ACHIEVED
50 Gy	≤13 Gy	13-13.2 Gy	> 13.2 Gy	
45 Gy	≤15 Gy	15-15.2 Gy	> 15.2 Gy	
40 Gy	≤15 Gy	15-15.2 Gy	> 15.2 Gy	
35 Gy	≤15.5 Gy	15.5-15.7 Gy	> 15.7 Gy	
30 Gy	≤16 Gy	16-16.2 Gy	> 16.2 Gy	
27.5 Gy	≤17 Gy	17-17.2 Gy	> 17.2 Gy	

11 NON LIVER OAR CONSTARINTS	NEEDED	ACCEPTABLE	UNACCEPTABLE	ACHIEVED
Esophagus max (to 0.5 cc):	32 Gy	> 32 but ≤34 Gy	> 34 Gy	
Stomach max (to 0.5 cc):	30 Gy	>30 but ≤32 Gy	> 32 Gy	
Duodenum max (to 0.5 cc):	30 Gy	>30 but ≤32 Gy	> 32 Gy	
Small bowel max (to 0.5 cc):	30 Gy	>30 but ≤32 Gy	> 32 Gy	
Large bowel max (to 0.5 cc):	32 Gy	>32 but ≤34 Gy	> 34 Gy	
Cord + 5 mm max (0.5cc):	25 Gy	>25 but ≤28 Gy	> 28 Gy	
Kidneys: Bilateral mean	≤10 Gy	>10 but ≤12 Gy	> 12 Gy	
Chest wall				
Gall bladder				
CBD	<50Gy			

CBD	<50Gy				

Stereotactic Body Radiation Therapy for Hepatocellular Carcinoma in Cirrhotic Liver

Hiroshi Doi, Hiroya Shiomi and Ryoong-Jin Oh

Solutions that Enable Ablative Radiotherapy for Large Liver Tumors: Fractionated Dose Painting, Simultaneous Integrated Protection, Motion Management and CT Image Guidance

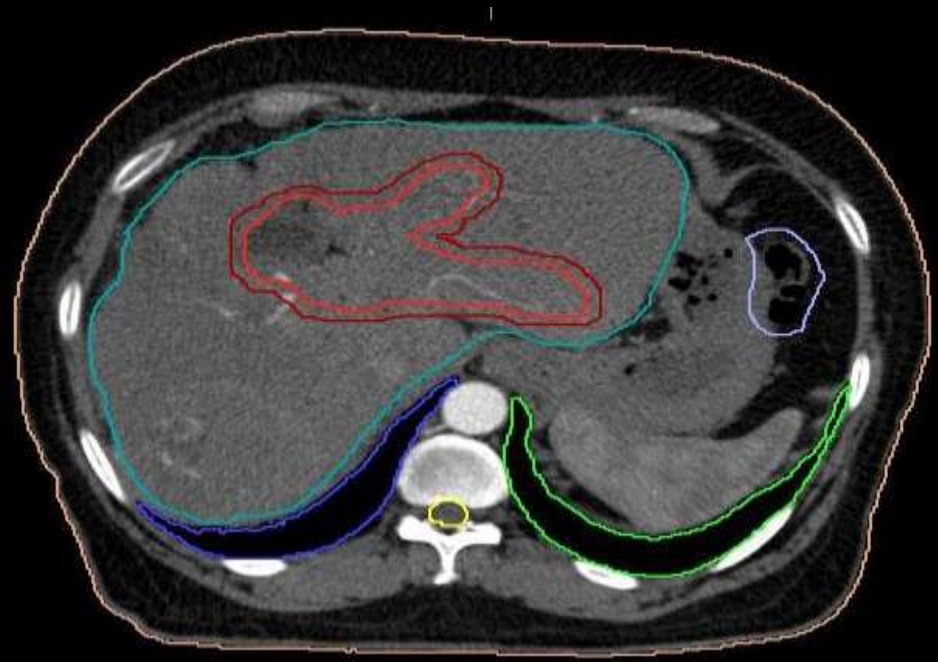
Christopher H. Crane, M. D. and **Eugene J. Koay, MD., Phd.**
Department of Radiation Oncology of The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Large tumors

- Issues : liver failure

(intrahepatic progression before extrahepatic disease)

- Reasons of death – inoperable large HCC:
  - tumor related liver failure / underlying liver disease
  - inadequate intrahepatic control
  - functional liver parenchymal loss, biliary/ vascular obstruction- ischemia



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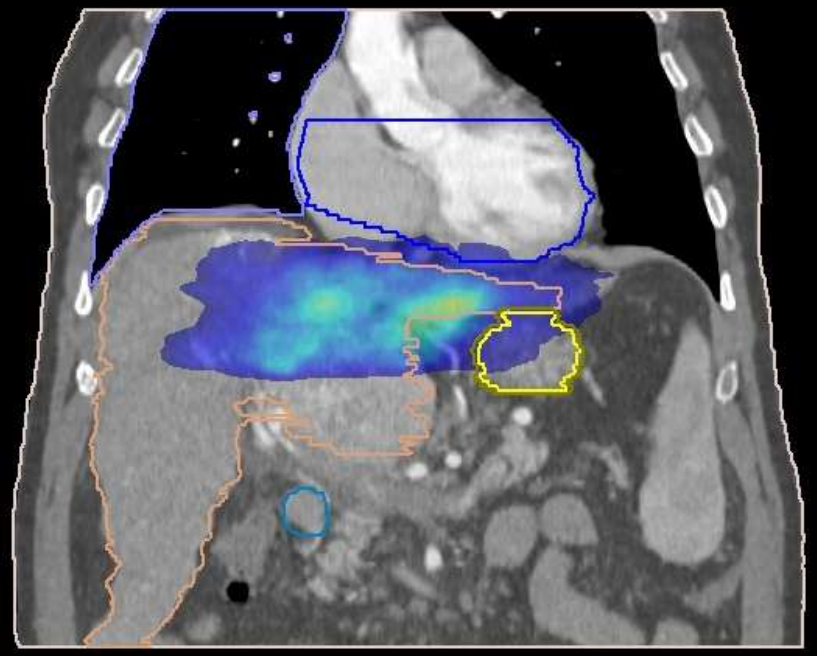
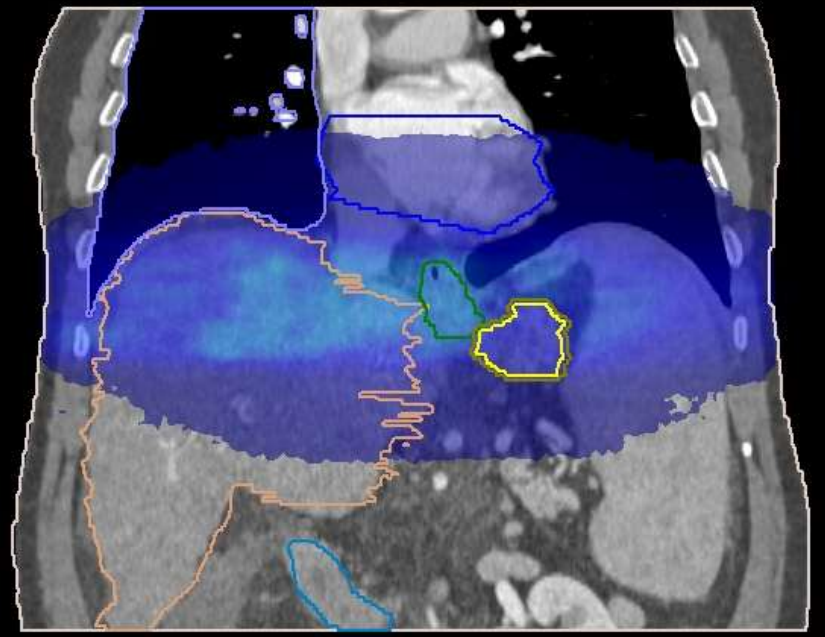




se (cGy)	Cold Ref. (cGy)	Volume < (cm³)	Volume < (%)	Hot Ref
5913.8				
5882.9				
5433.7				
1067.5				
1116.6				
1046.3				
1283.8				
274.8				
202.4				
473.0				
30.8				
1110.5				

DVH Statistics (Total Volume) @monaco2 - [11857811, SURJIT SINGH, CT20072022port, P2]

Statistics | Display

Structure	Volume (cm³)	Min. Dose (cGy)	Max. Dose (cGy)	Mean Dose (cGy)	Cold Ref. (cGy)	Volume < (cm³)	Volume < (%)	Hot Ref. (cGy)	Volume > (cm³)	Volume > (%)	% in Volume	Is in SS	Heterogeneity Index	Conformity Index
GTV 56 PVTT	15.256	4759.0	6716.0	5913.8				**6440.0**	0.276	1.81	100.00	yes	1.15	0.11
GTV 56 HCC	99.912	4288.7	6766.5	5882.9				**6400.0**	2.380	2.38	100.00	yes	1.18	0.67
PTV 42	219.720	2750.5	6766.5	5433.7				4162.9	**208.734**	**95.00**	100.00	yes	1.50	0.85
PRV stomach	220.328	369.9	2745.1	1067.5				2036.5	**10.000**	**4.54**	100.00	yes	4.37	0.01
esophagus	40.280	242.6	2159.2	1116.6				1676.7	**5.000**	**12.41**	100.00	yes	5.87	0.01
LIVER - GTV	2331.816	4.2	6153.0	1046.3				204.5	**1631.000**	**69.95**	100.00	no	144.55	
LIVER_1	2529.280	4.2	6766.5	1283.8							100.00	no	203.97	
R. LUNG	2324.864	10.2	1671.6	274.8							100.00	no	28.20	
duodenum	67.408	8.9	565.8	202.4							100.00	no	23.59	
heart	614.896	83.8	5380.2	473.0				1670.9	**15.000**	**2.44**	100.00	yes	8.55	
right kidney	210.592	5.5	128.7	30.8							100.00	no	4.58	
stomach	171.408	407.9	2654.2	1110.5				1953.0	**10.000**	**5.83**	100.00	yes	3.92	

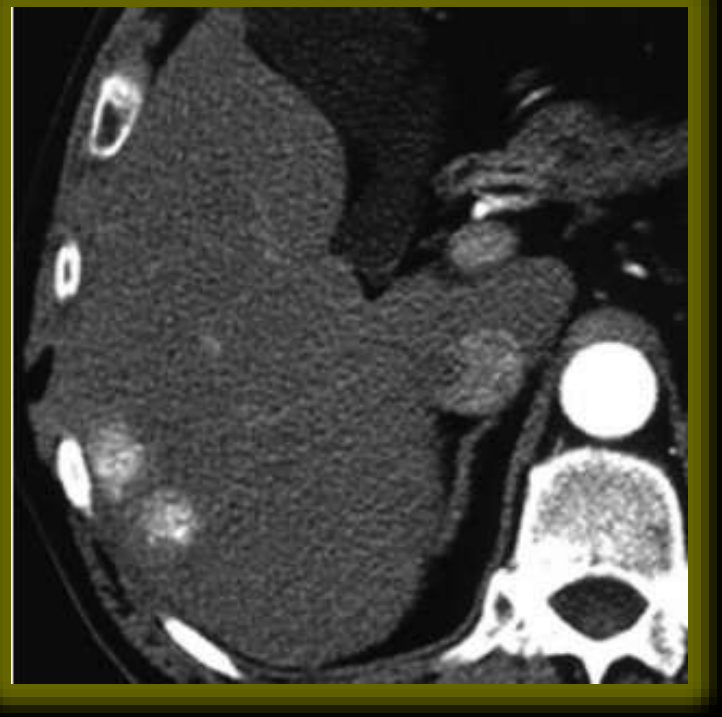
Print | OK

Centrifugal effect of dose

SBRT liver mets

Table 1 Selection Criteria for SBRT for Oligometastases

	Selection for Stereotactic Body Radiation Therapy for Oligometastases
Patient characteristics	Patients capable of self-care with controlled or absent primary tumors.
Tumor characteristics	Four or fewer tumors typically less than 5 cm ideally from colon, breast, sarcoma, or renal-cell primary tumors. Tumors should be well demarcated without significant risk of occult spread.
Imaging requirements	Extent of tumor identifiable on primary treatment planning imaging or able to be accurately fused from other imaging platform.
Dosimetry requirements	Normal tissue tolerance to particularly serially functioning tissues (eg, tubular structures) must be respected. Tumors next to hollow viscous including major bronchi and major ducts should be avoided. Dose should be concentrated in the tumor with rapid fall-off in all directions by using multiple field techniques akin to intracranial radiosurgery.



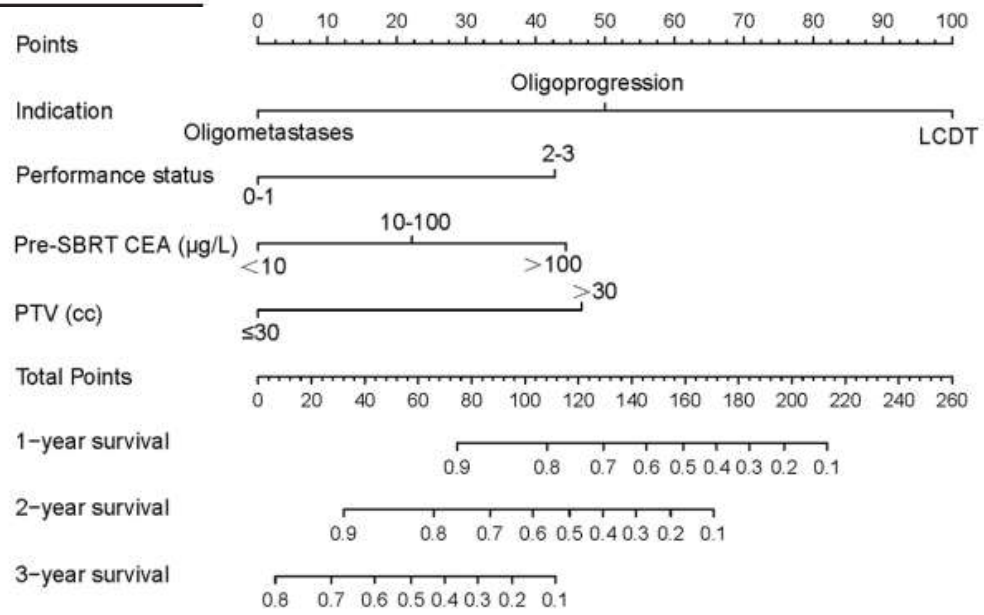
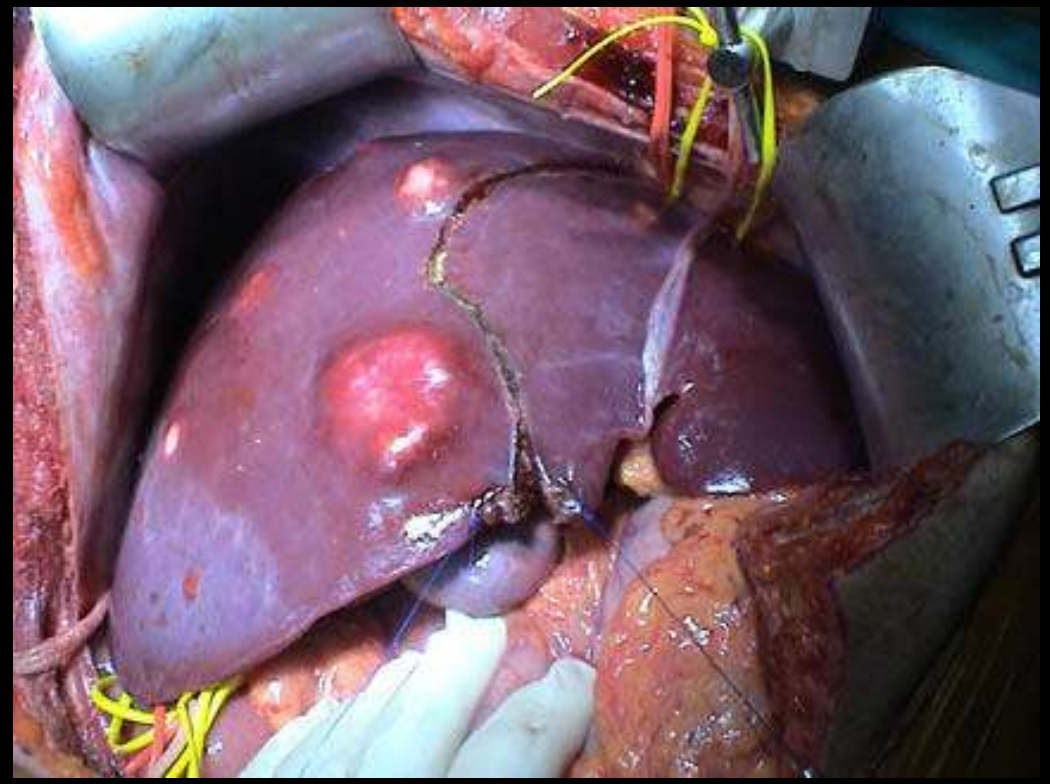


FIGURE 3 | mCRC survival nomogram. (To use the nomogram, the value of each patient was on each variable axis, and a line was drawn upward to determine the number of points received for each variable value. The sum of these numbers was on the Total Points axis. A line was drawn downward to the survival axes to determine the likelihood of 1, 2- or 3-year survival). mCRC, metastatic colorectal cancer; SBRT, stereotactic body radiotherapy; LCDT, local control of dominant tumors; CEA, carcino-embryonic antigen; PTV, planning tumor volume.

Mets : Surgery



Oncological factors:

- node-positive primary
- disease-free interval (< 12 months)
- number of hepatic metastases (> 1)
- hepatic metastasis (> 5 cm)
- CEA (> 200 ng/mL)

< 2 factors – 5 Yr ~ 50%, 10 yr OS ~ 17-25%

Anatomical factors:

- Latest imaging: accurate diagnosis and staging
- Both primary/ mets resectable
- Post op preserved hepatic functions

Patient tolerance:

- adequate liver function
- Performance status / comorbidities
- Post op - ~ 20–25% normal liver with adequate inflow, outflow, and biliary drainage

SBRT liver mets: selection of cases

Table 1 Risk factors affecting survival for patients with surgical resection of liver metastases from colorectal cancer

Variable	Low risk	High risk
Number of lesions	$N \leq 3$	$N > 3$
Size (largest diameter)	< 5 cm	≥ 5 cm
Disease-free interval	> 12 months	≤ 12 months
CEA level	< 200 mg/m	≥ 200 ng/ml
Resection margins	Negative (R0)	Positive (R ≥ 1)

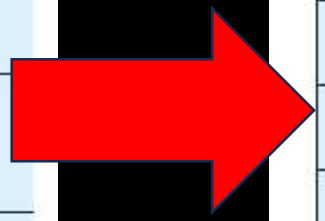
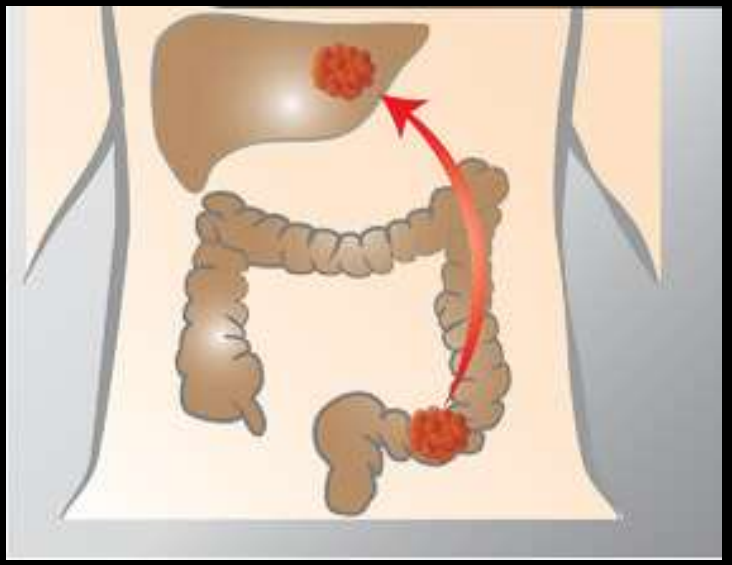


Table 2 Favorable patient characteristics for trials testing stereotactic radiotherapy for liver metastases

Variable
Colorectal or breast cancer primaries
No extrahepatic disease
≤ 3 liver lesions
≤ 6 cm largest diameter
> 1.5 cm from luminal gastrointestinal organs
No or minimal prior systemic therapy
Locally controlled or potentially treatable primary tumor
Good performance status and life expectancy ≥ 6 months

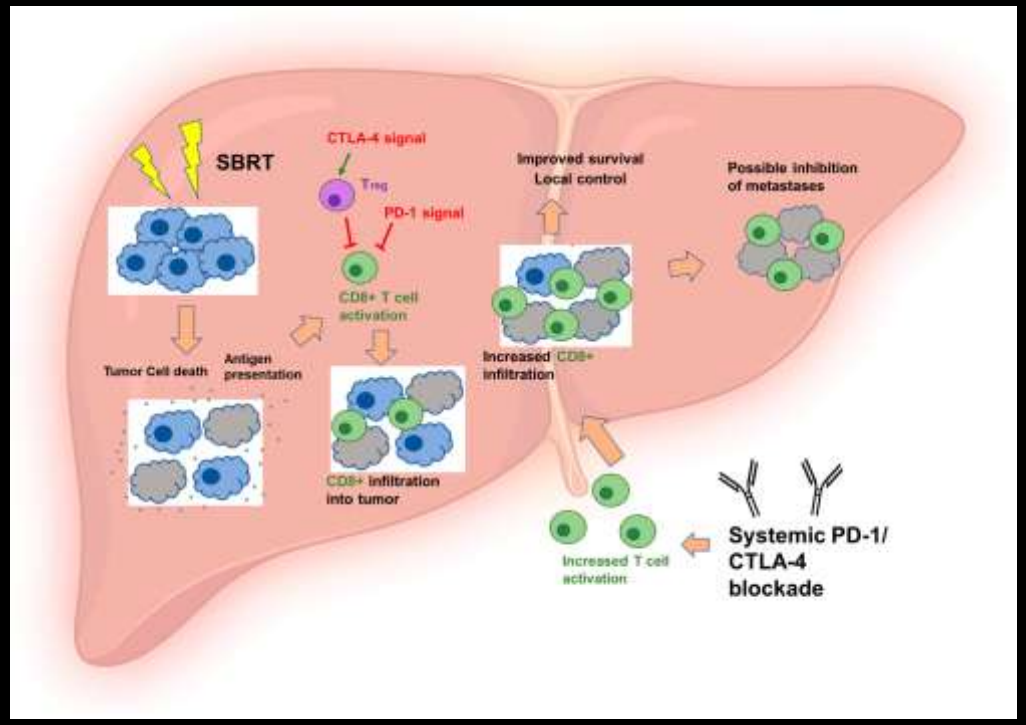
Liver mets: SBRT – dose selection

- Spectrum of dose ranges in literature
- 14 -30 Gy / 1 fr -→ 30-75 Gy/ 3-5 fr , occasionally 48-60 Gy / 6-8 fr
- Difficult to compare: heterogeneity in
  - dosimetric planning
  - dose prescription
  - patient selection
  - primary tumor number/ volume
  - systemic treatments before/ after SBRT
  - Definition of LC



- Usual local control 56% to 100% at 2 years
- Higher doses – better LC / although dose response curve – uncertain
- *Chang et al. - colorectal liver mets*
  - $BED_{10\ Gy}$ for 90% LC - @ 1 yr - 117 Gy_{10}.
  - ~ 46- 52 Gy in 3 fractions [LQ model]
  - ~ 55 Gy in 5 fractions
  - Better outcomes with non colorectal mets

SBRT in era of Immunotherapy : Systemic effects of local Radiation



Immunotherapy :

evolution 1st line for locally advanced inoperable HCC

SBRT :

antitumor immune response + immunogenic cell death

necroptosis, i.e. caspase-independent apoptosis → increased PDL1

PD-L1 blockade by immunotherapy - potent synergistic treatment

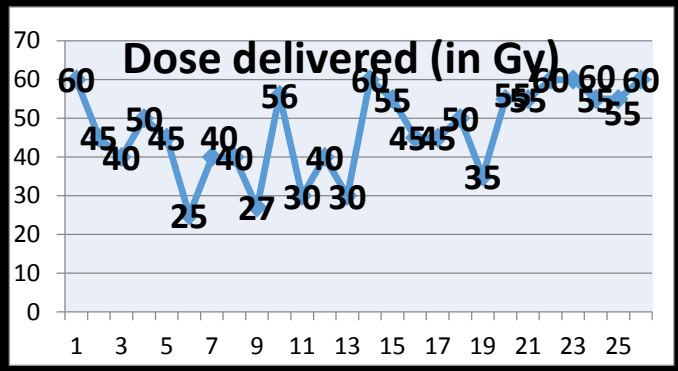
Phase I/II trials: SBRT with immunotherapy
(NCT03482102, NCT03203304, NCT03316872, NCT03817736).

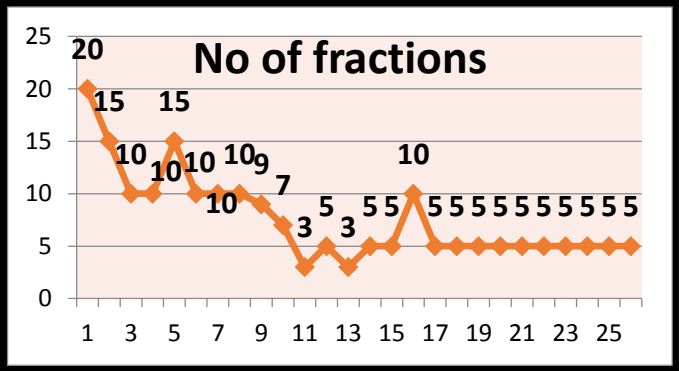
SBRT Liver – our Experience

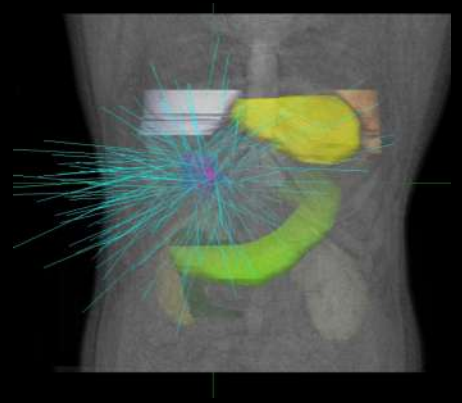
Courtesy: Medanta (kataria et al)

Treatment planning/ delivery

SBRT : breath-hold ABC

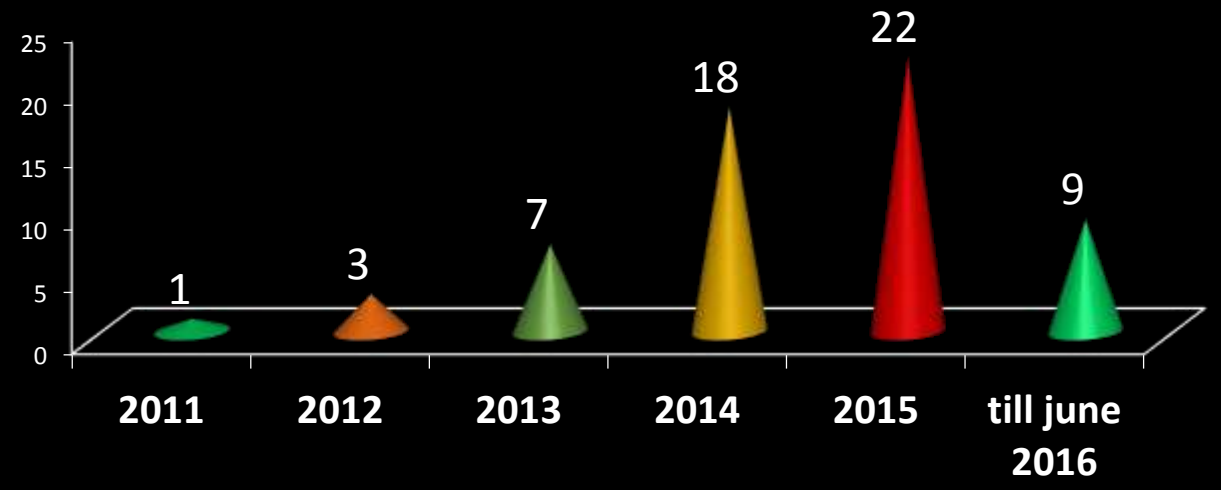






SBRT : tracking Cyberknife

Yearly case referral pattern



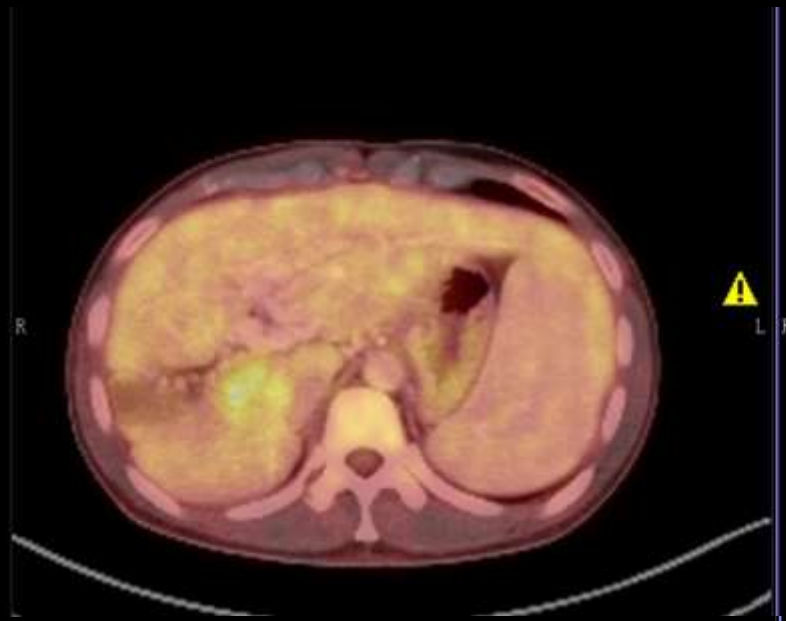
HCC – PVTT case

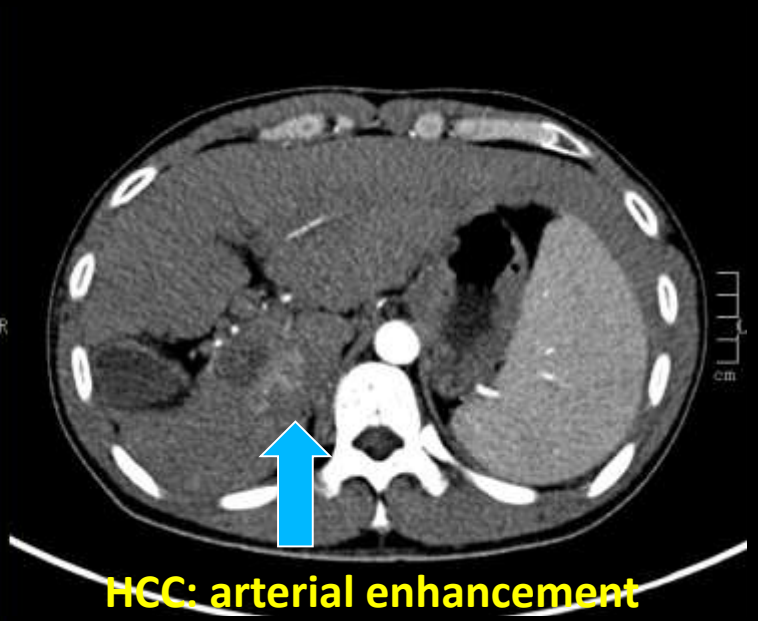
Courtesy: Medanta (kataria et al)

- 38/M
- Hep B / multifocal HCC – 2012
- RFA for 3 lesions – 2012 [Singapore]
- TARE in 2014 [another facility]
- 2015 with:
  - AFP- 78.1
  - PECT – CT: SOL seg V/ VI + Rt PVTT
- Impression:

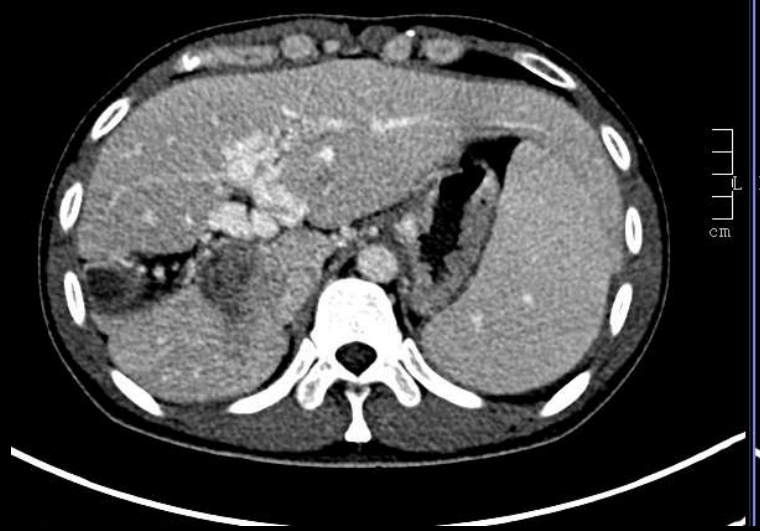
  HCC with PVTT

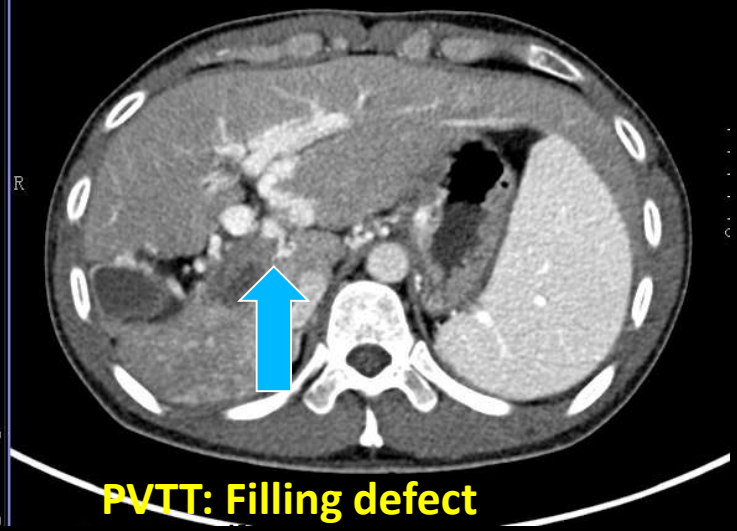
  Outside Milan - poor prognosis





HCC: arterial enhancement

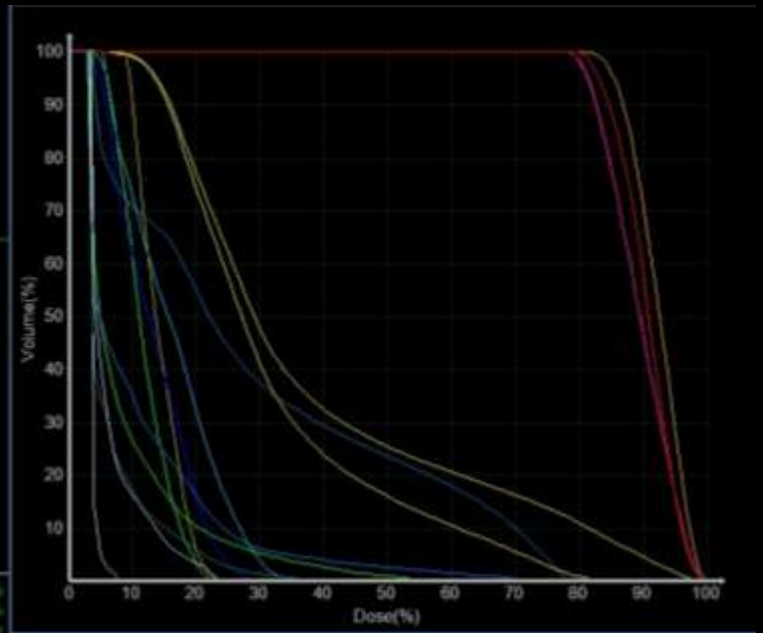




PVTT: Filling defect

Planned - 48 Gy in 3 fractions (BED 124 Gy)

Courtesy: Medanta (kataria et al)



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

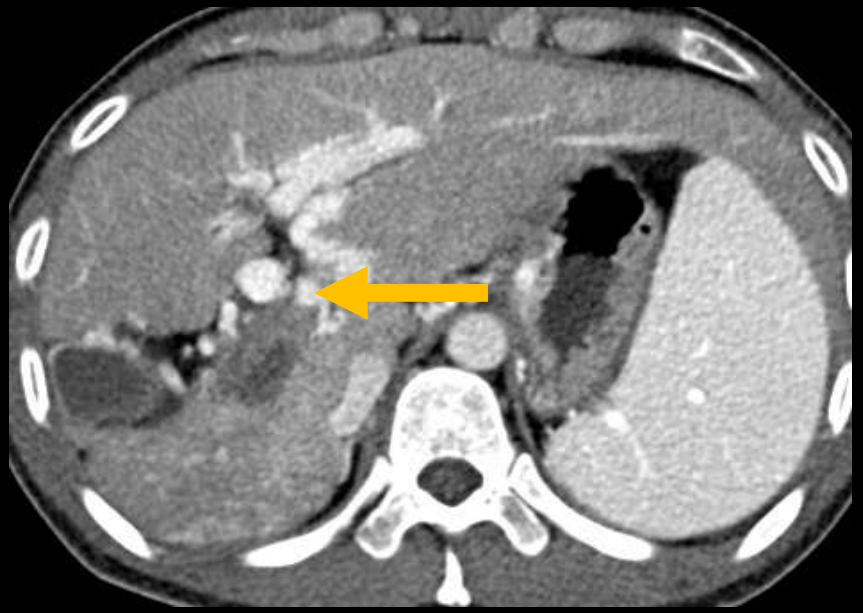
Estimated Treatment Time Per Fraction (minutes) 69

Dose Statistics Table | Dx Vx Values | Plan Information

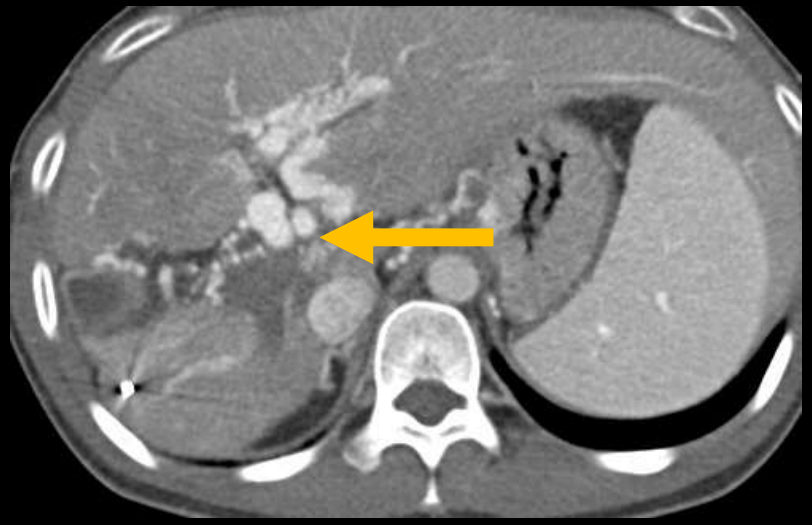
Name	Min (cGy)	Mean (cGy)	Max (cGy)	CI	nCI	HI	Coverage (%)
GTV PVTT	4763.29	5438.13	5978.48	5.67	5.68	1.25	99.88
GTV arterial	4771.34	5539.44	6000.00	2.86	2.86	1.25	99.97
PTV	4530.56	5367.43	6000.00	1.24	1.27	1.25	98.15
liver	231.82	2302.47	6000.00	n/a	n/a	n/a	n/a
stomach	230.72	700.76	1504.33	n/a	n/a	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

Post SBRT : response

Courtesy: Medanta (kataria et al)



Pre- SBRT



Post- SBRT: Recanalization of filling defect

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.*

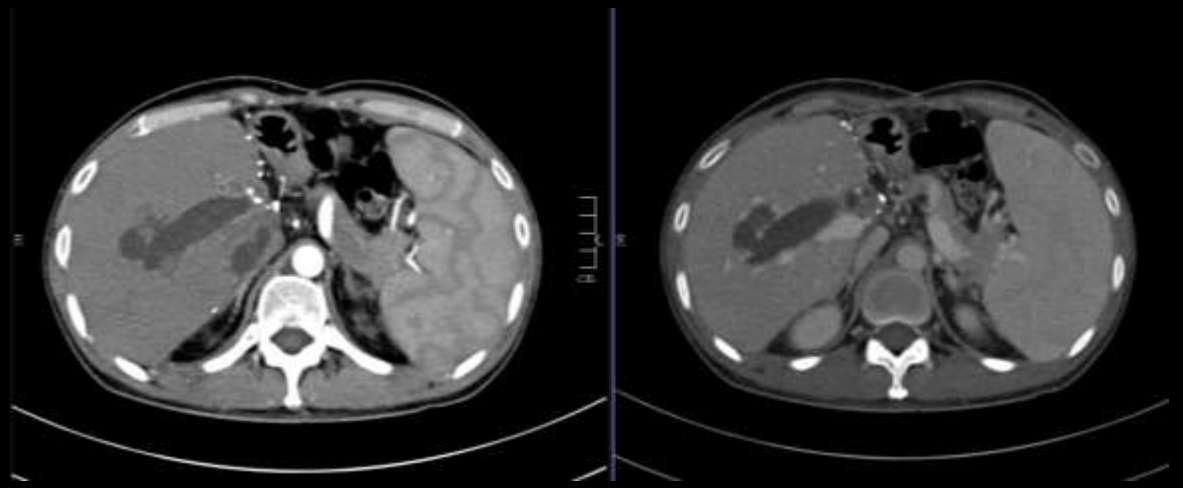
TISSUE SUBMITTED FOR MICROSCOPY:
A, B : Tumor with capsule
C to E : Tumor proper
F, G : 2nd lesion with ?portal V thrombus
H, I : Suspicous area in segment V
J : Right lobe periphery
K : Right lobe centre
L : Left lobe random
M : Caudate lobe
N : Hilum
More Sections Taken:
MS1 to MS4 : 1st lesion
MS5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

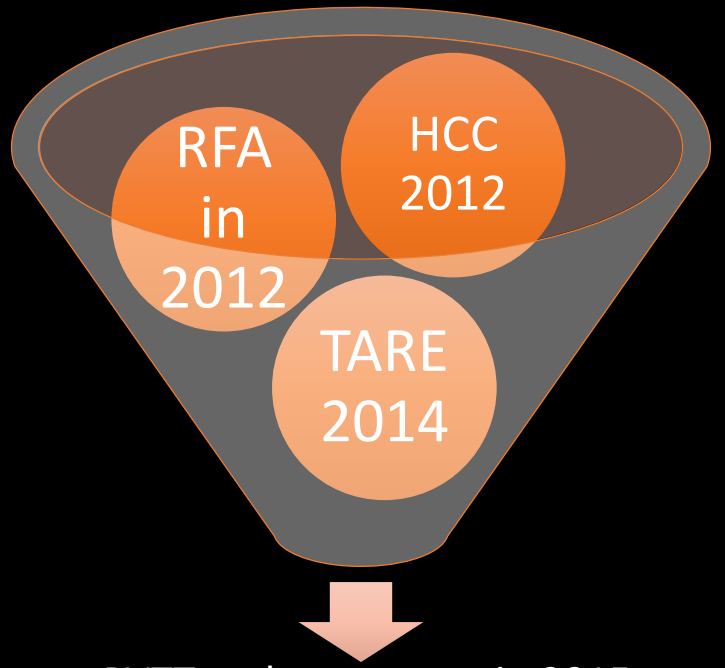
IMPRESSION: *Explant hepatectomy :*

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

Courtesy: Medanta (kataria et al)



Post Transplant CECT



PVTT and recurrence in 2015

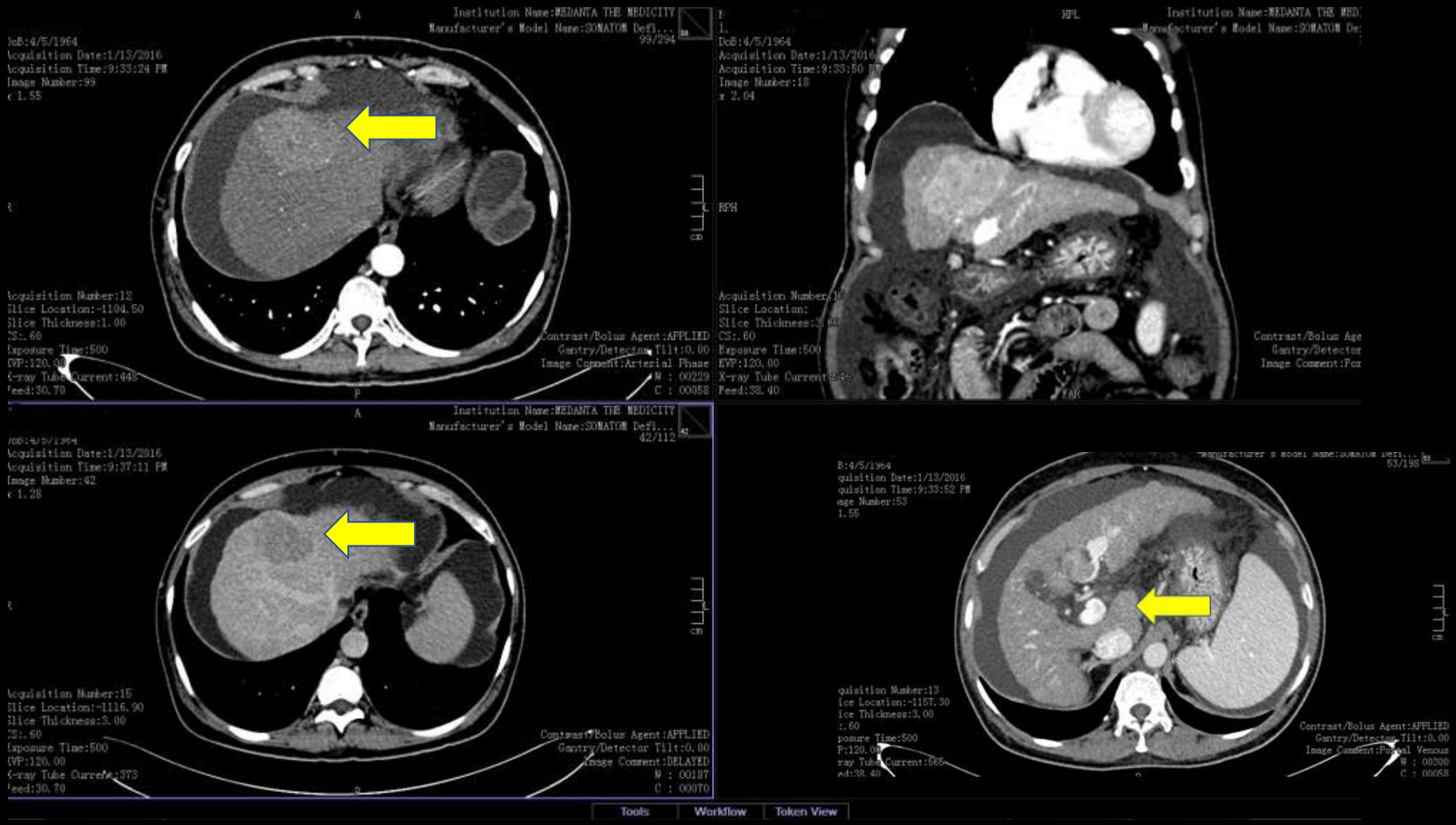
SBRT PVTT – Dec 2015

Transplant – LDLT- Feb 2016

Post transplant – 5 year – alive & healthy

Case 2: multifocal HCC with PVTT

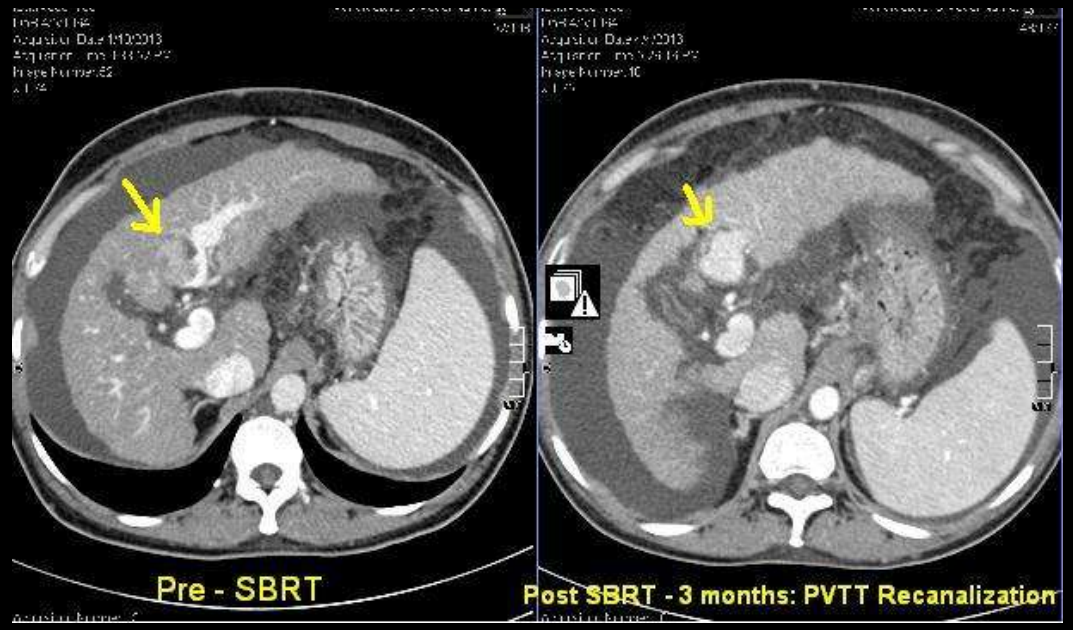
Courtesy: Medanta (kataria et al)



- ***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

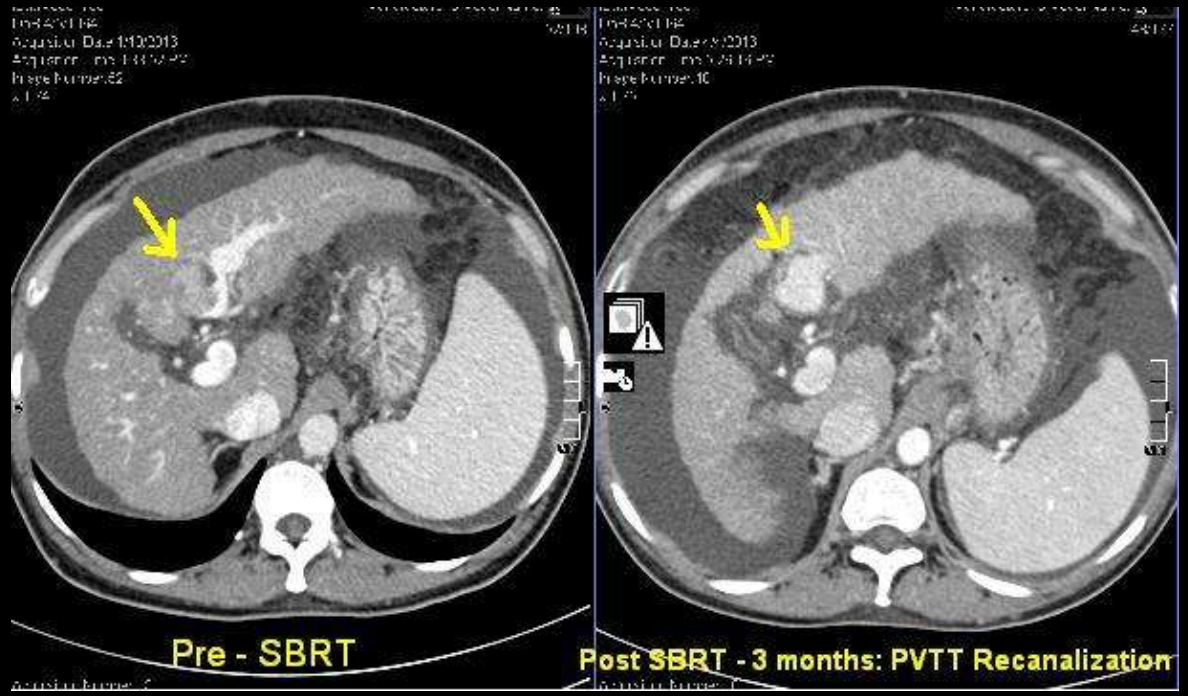
Macroscopic Venous (Large vessel) Invasion (V) -Not identified
Microscopic (small vessel) Invasion (L) -Present
Organised thrombus present in portal vein
PERINEURAL INVASION - Not identified
TUMOUR NECROSIS - 45-50%
CAPSULAR INVASION - Not seen
PORTAL VEIN THROMBUS : Seen
PATHOLOGIC STAGING (pTNM): y(post-treatment)
Primary Tumor (pT) -
pT1: Solitary tumor with vascular invasion
ADDITIONAL PATHOLOGIC FINDINGS -
Fibrosis score: VI
Cirrhosis (Ishak score 5-6) (F1) - Present
Gall bladder - Appears unremarkable

IMPRESSION: Liver with Gall Bladder -
- Moderately differentiated Hepatocellular carcinoma
- ypT1 (Post TARE)
- Portal vein thrombosis present
- Margin is free of tumor
- Gall bladder appears Unremarkable.

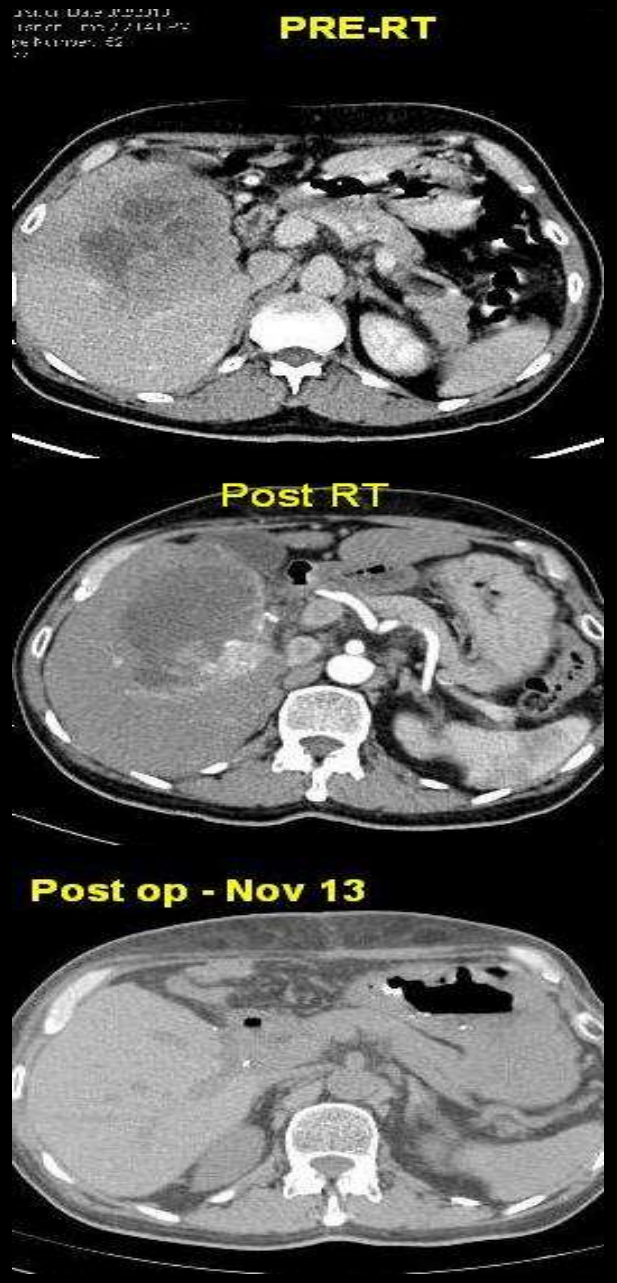
***** END OF REPORT *****

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

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]

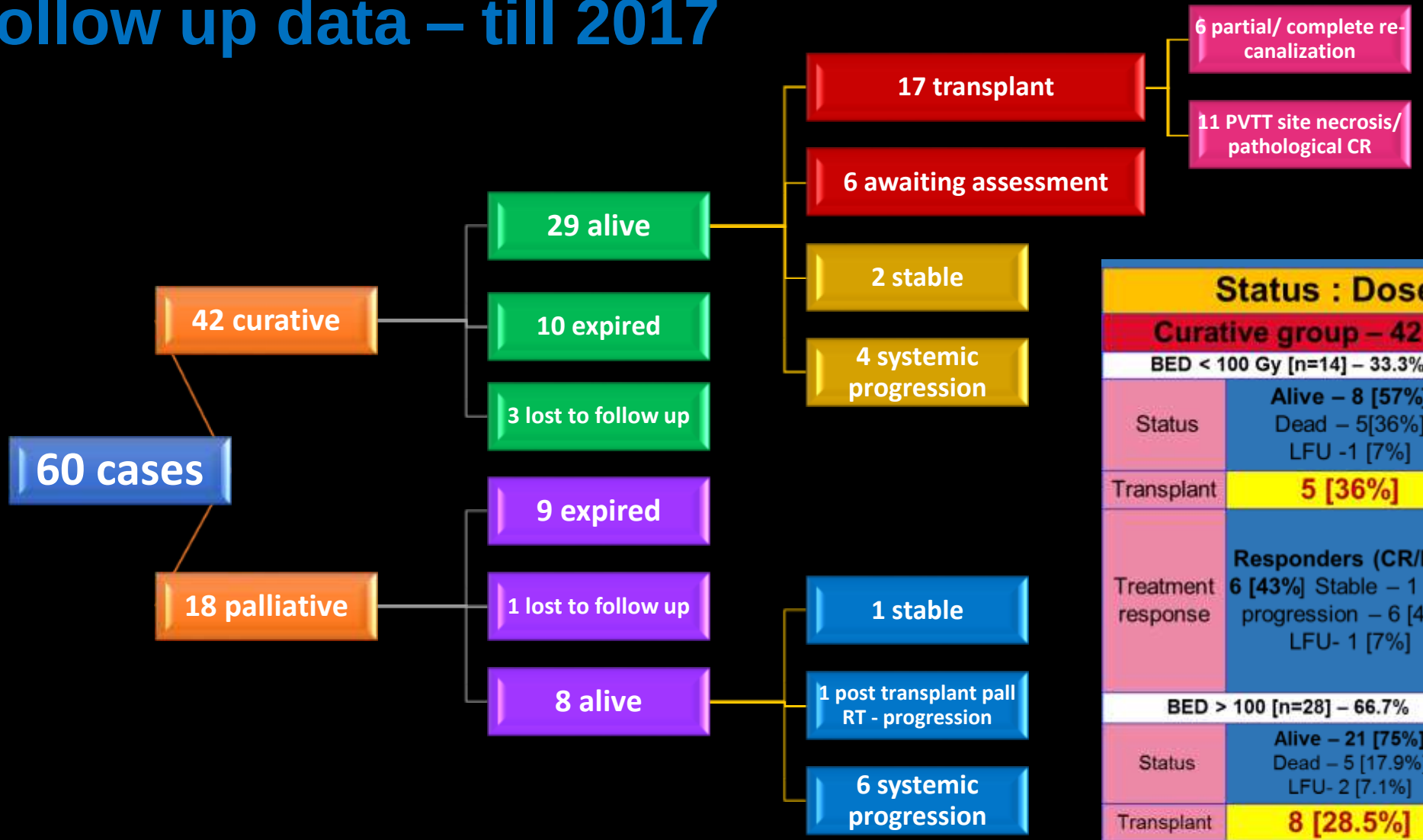


PVTT recanalization



Post Transplant

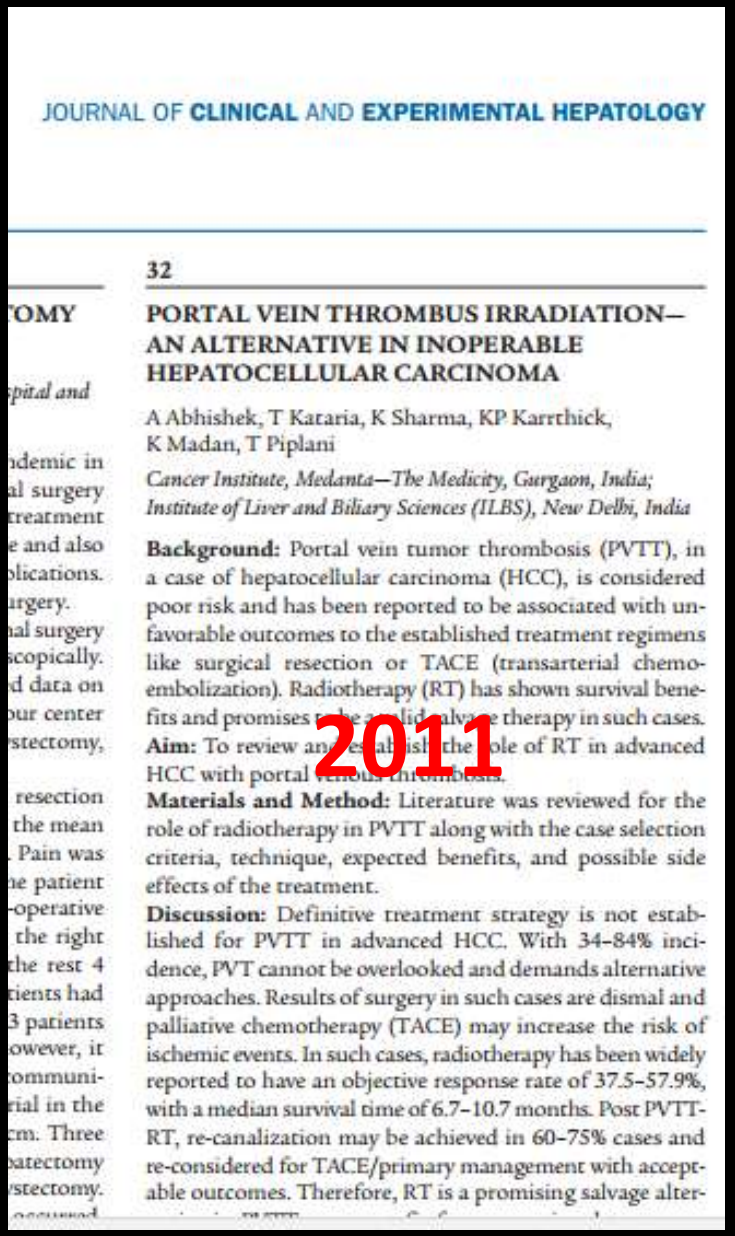
Follow up data – till 2017



Status : Dose (BED) Vs Intent			
Curative group – 42		**Palliative group –18**	
BED < 100 Gy [n=14] – 33.3%		**BED < 100 Gy [n=9] – 50 %**	
Status	**Alive – 8 [57%]** Dead – 5[36%] LFU -1 [7%]	Status	Alive – 2 [22.2%] Dead – 6[66.7%] LFU -1 [11.1%]
Transplant	**5 [36%]**	Transplant	0
Treatment response	**Responders (CR/PR)- 6 [43%]** Stable – 1 [7%] progression – 6 [43%] LFU- 1 [7%]	Treatment response	Responders (CR/PR)- 0 Stable – 2 [22.2%] progression – 6 [66.7%] LFU- 1 [11.1%]
BED > 100 [n=28] – 66.7%		**BED > 100 [n=9] – 50 %**	
Status	**Alive – 21 [75%]** Dead – 5 [17.9%] LFU- 2 [7.1%]	Status	Alive – 6 [66.7%] Dead – 3 [33.3%]
Transplant	**8 [28.5%]**	Transplant	0
Treatment response	**Responders (CR/PR)- 12 [42.8%]** stable - 7 [25%] Progression – 7 [25%] LFU- 2 [7.2%]	Treatment response	Responders (CR/PR)- 1 [11.1%] stable - 1[11.1%] Progression – 7 [77.8%]

Courtesy: Medanta –The Medicity

Role of SBRT in HCC – PVTT: Medanta Experience



JOURNAL OF CLINICAL AND EXPERIMENTAL HEPATOLOGY

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PORTAL VEIN THROMBUS IRRADIATION—AN ALTERNATIVE IN INOPERABLE HEPATOCELLULAR CARCINOMA

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

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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

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Portal Vein Tumor Thrombus: Role of External Beam Radiotherapy

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DOI: http://dx.doi.org/10.1016/j.ceh.2014.03.022

2014

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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

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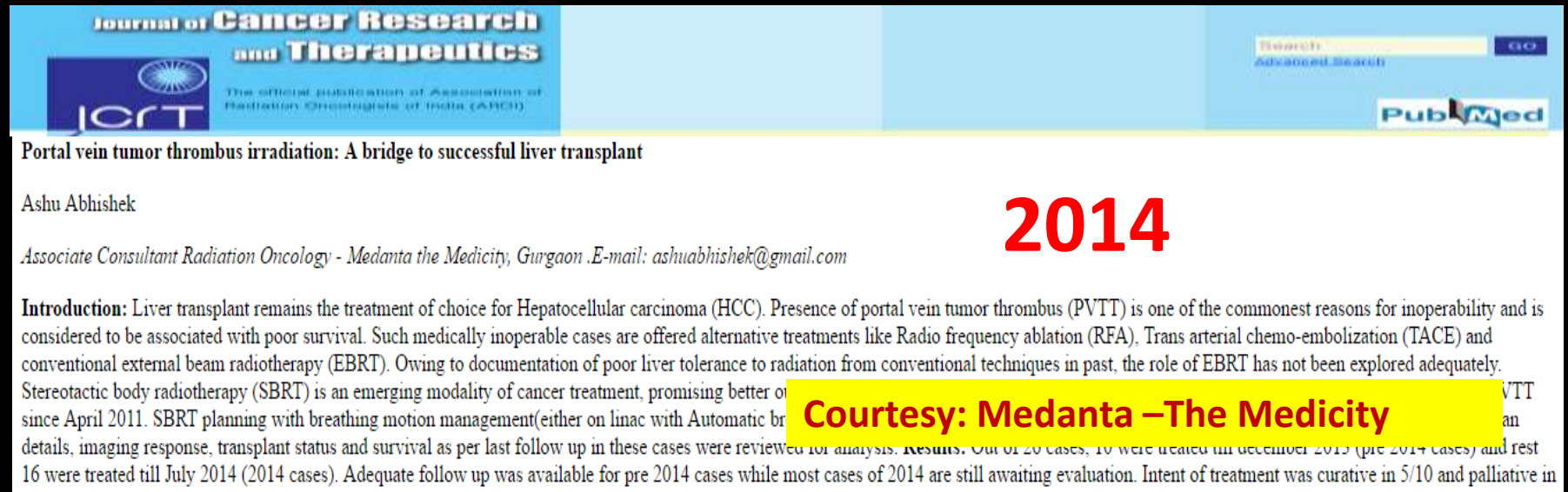
2401

Altmetric 0

DOI: http://dx.doi.org/10.1016/j.ijrobp.2016.06.1004

2016



Journal of Cancer Research and Therapeutics

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

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2014

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 26 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

Courtesy: Medanta –The Medicity

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

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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[1,3], 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.

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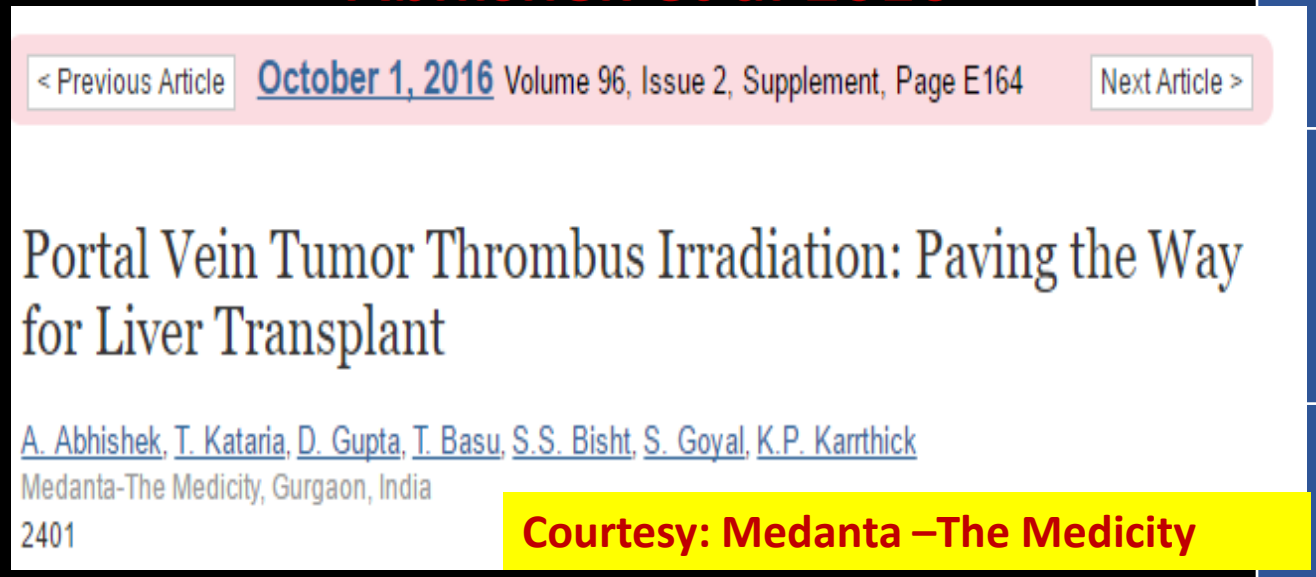
Abhishek et al 2016



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

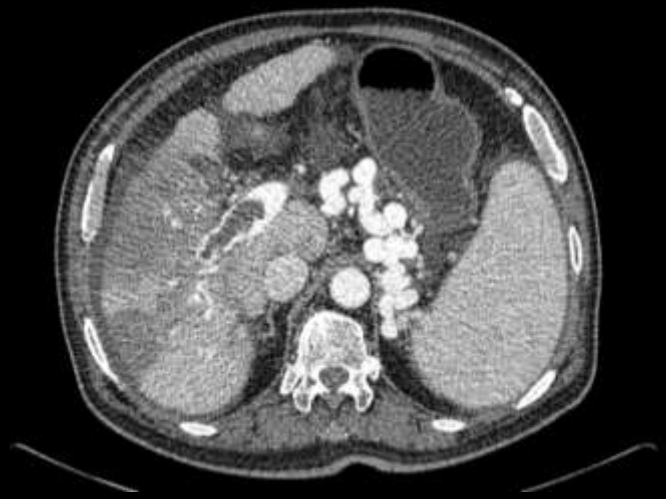
A. Abhishek, T. Kataria, D. Gupta, T. Basu, S.S. Bisht, S. Goyal, K.P. Karrthick
Medanta-The Medicity, Gurgaon, India

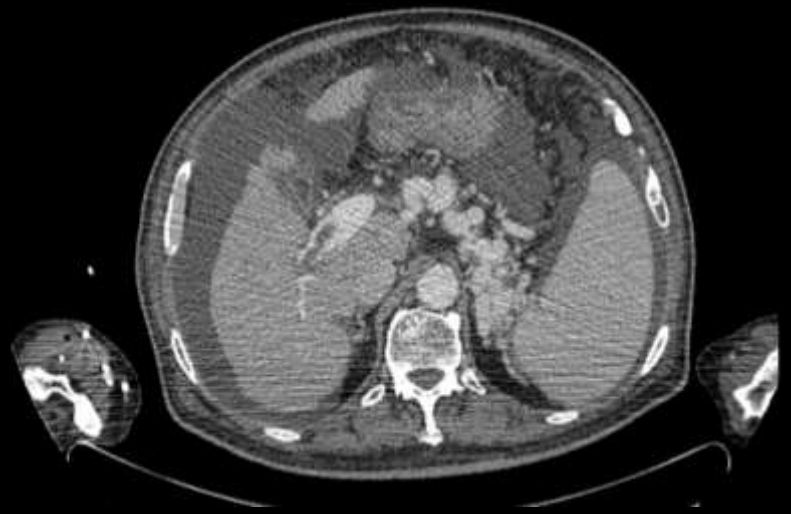
2401

Courtesy: Medanta –The Medicity

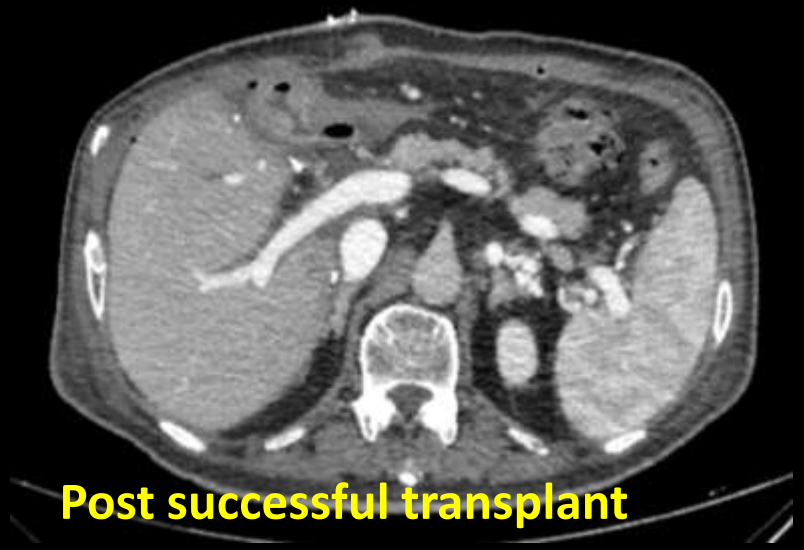
	Korea	Abhishek et al
No of cases	8	40
No of transplant	8	17
Awaiting assessment	N/A	11
Responders	N/A	18 (CR or PR) -43% 8 (stable) – 20%
Median survival (transplant cases)	33 months	29 mths (6-55 mths)
Tumor recurrence	3 @ median 17 mths	1 @ 8 mths

HCC –PVTT : SBRT + TARE → Transplant



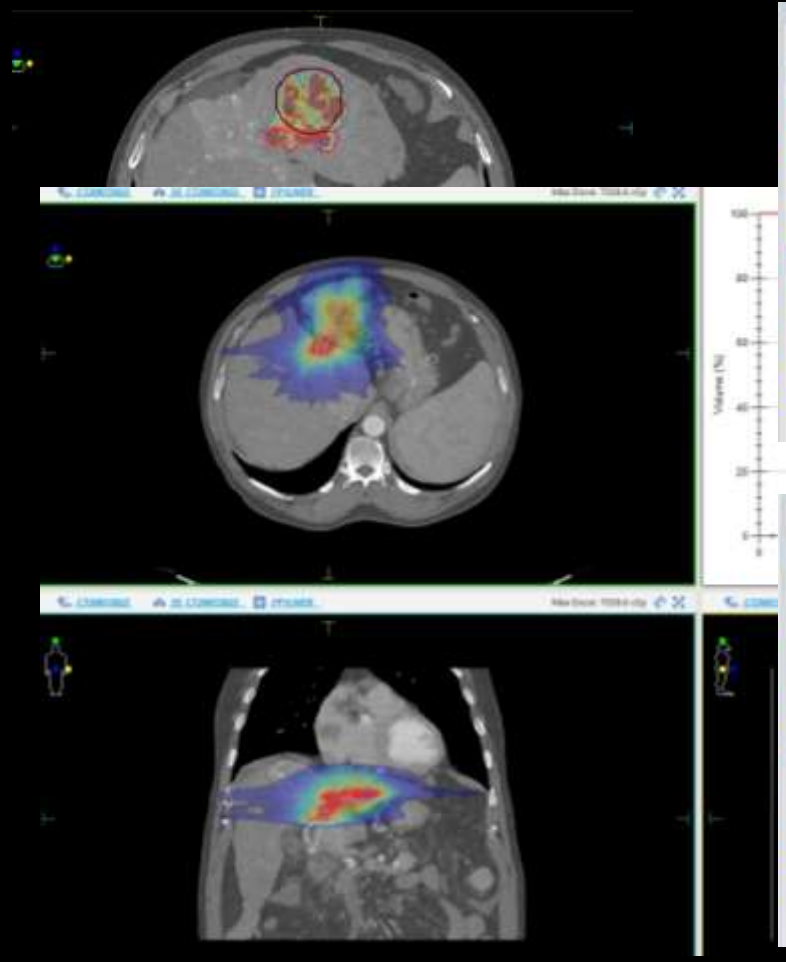


FMRI



Post successful transplant

HCC – PVTT – unfit for TARE (multiple collaterals)



DVH Statistics

Dosimetric Criteria | Statistics | Display

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	14.493	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	4363.2		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
esophagus	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	5085.6	485.1	1.000	0.16	3351.7		100.00	yes	7.56	0.00
LIVER - GTV	2331.816	3.1	6728.9	1111.5	685.536	29.40	1505.0		100.00	no	152.18	
LIVER_1	2529.280	3.1	6946.5	1350.8					100.00	no	211.92	
R. LUNG	2324.864	7.2	1834.6	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	1699.6		100.00	yes	3.52	

Dosimetric Criteria | Statistics | Display

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
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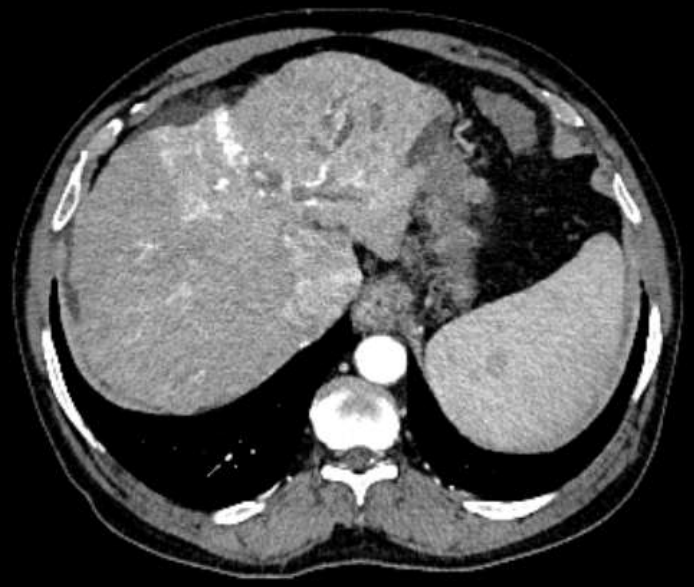
FMRI

56 Gy / 7 fr alt days

HCC – PVTT – unfit for TARE (multiple collaterals)



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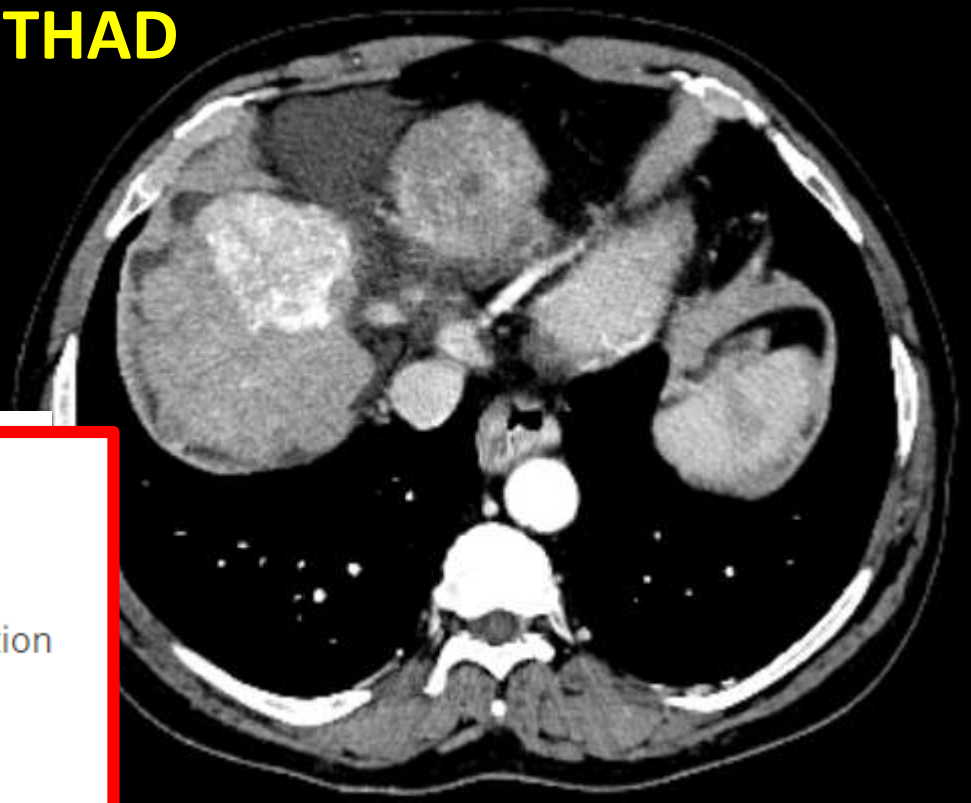
THAD



FMRI

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 muticentric 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

[1]Ishita Sen, [5]Saurabh Kumar, *Ashu Abhishek, [##]Mukesh Patekar [1]Subha Shankar Das, [1]Dharmender Malik, [#]Ashish Singhal,

*Department of Radiation Oncology, FMRI

[#]Department of Liver Transplant, Fortis Healthcare

[1]Department of Nuclear Medicine, FMRI

[5]Department of Interventional Radiology, FMRI

[##]Department of Medical Oncology, FMRI

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.

HCC – RT

Gains…

HCC - PVTT

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

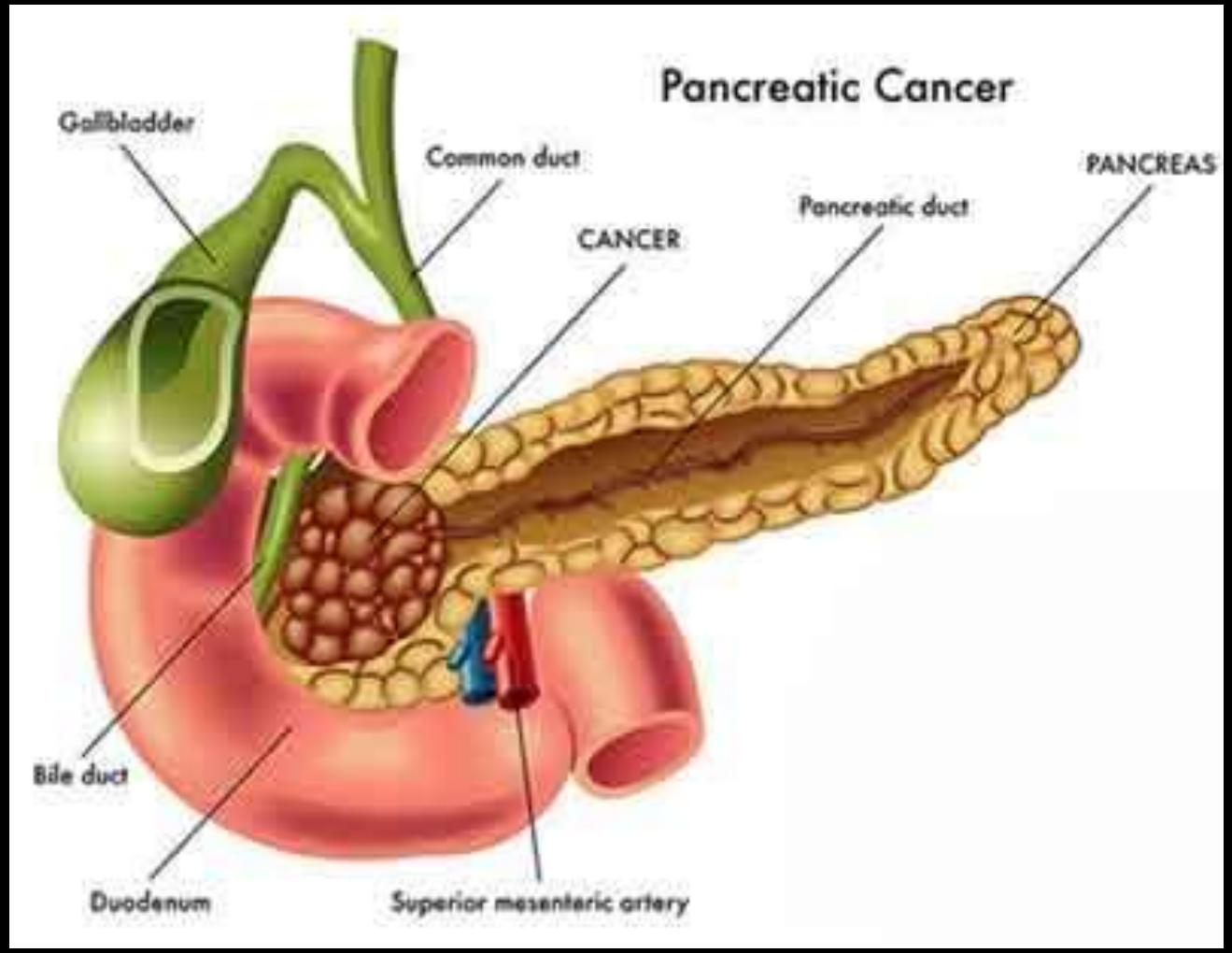
SBRT Bridge of Hope

- 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

SBRT Pancreas



Decreased utilization of Radiation for Pancreatic cancer

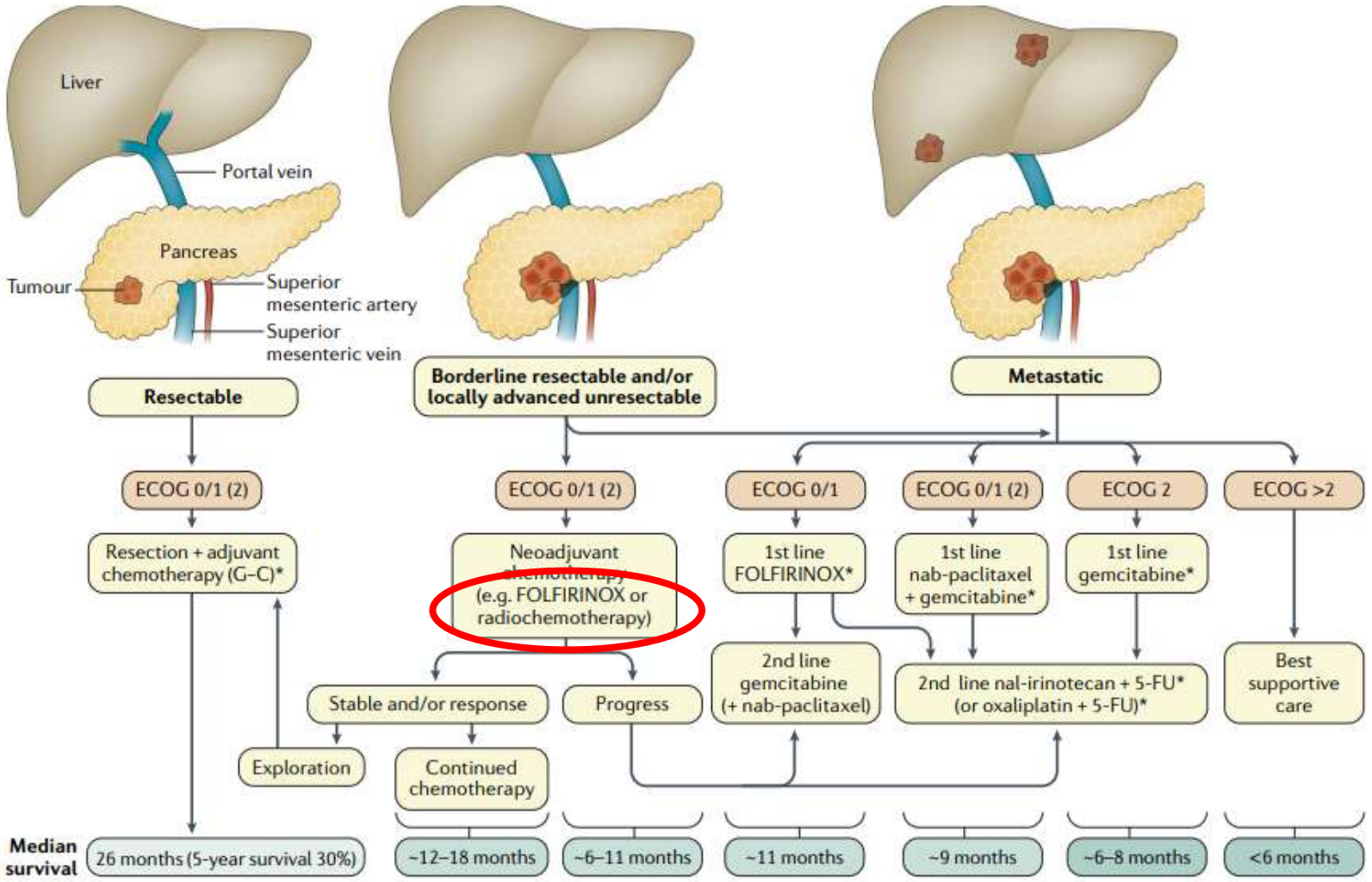


Fig. 1 | **Suggested treatment algorithm for patients with pancreatic cancer.** Patients are stratified according to tumour stage (resectable, borderline resectable and locally advanced unresectable, metastatic) and performance status (defined by the Eastern Cooperative Oncology Group (ECOG) score). Median survival values are) estimates from published data, mainly from small, single-arm or retrospective trials. In the metastatic setting, survival data are from trials of first-line therapy. This treatment algorithm represents the expert opinion of the authors. 5-FU, 5-fluorouracil; FOLFIRINOX, folinic acid, fluorouracil, irinotecan and oxaliplatin; G–C, gemcitabine–capecitabine; nab, nanoparticle albumin-bound; nal, nanoliposomal. *Approaches are based on evidence from RCTs. Other depicted treatment algorithms are current approaches, but they are not evidence based and are not standard of care worldwide.

Conventional or SBRT ?

Original Article

Conventionally Fractionated Radiation Therapy Versus Stereotactic Body Radiation Therapy for Locally Advanced Pancreatic Cancer (CRiSP): An International Systematic Review and Meta-Analysis

Leila T. Tchelebi, MD [1]; Eric J. Lehrer, MD [2]; Daniel M. Trifiletti, MD [3]; Navesh K. Sharma, DO[1]; Niraj J. Gusani, MD, MS [5,6]; Christopher H. Crane, MD[4]; and Nicholas G. Zaorsky, MD [1,6]

In conclusion, locally advanced, unresectable pancreatic cancer is an incurable disease with poor outcomes. This meta-analysis suggests that SBRT may offer a modest improvement in OS compared with CFRT, with a more favorable toxicity profile. Further study into the use of SBRT for patients with LAPC is needed to improve outcomes for these patients.

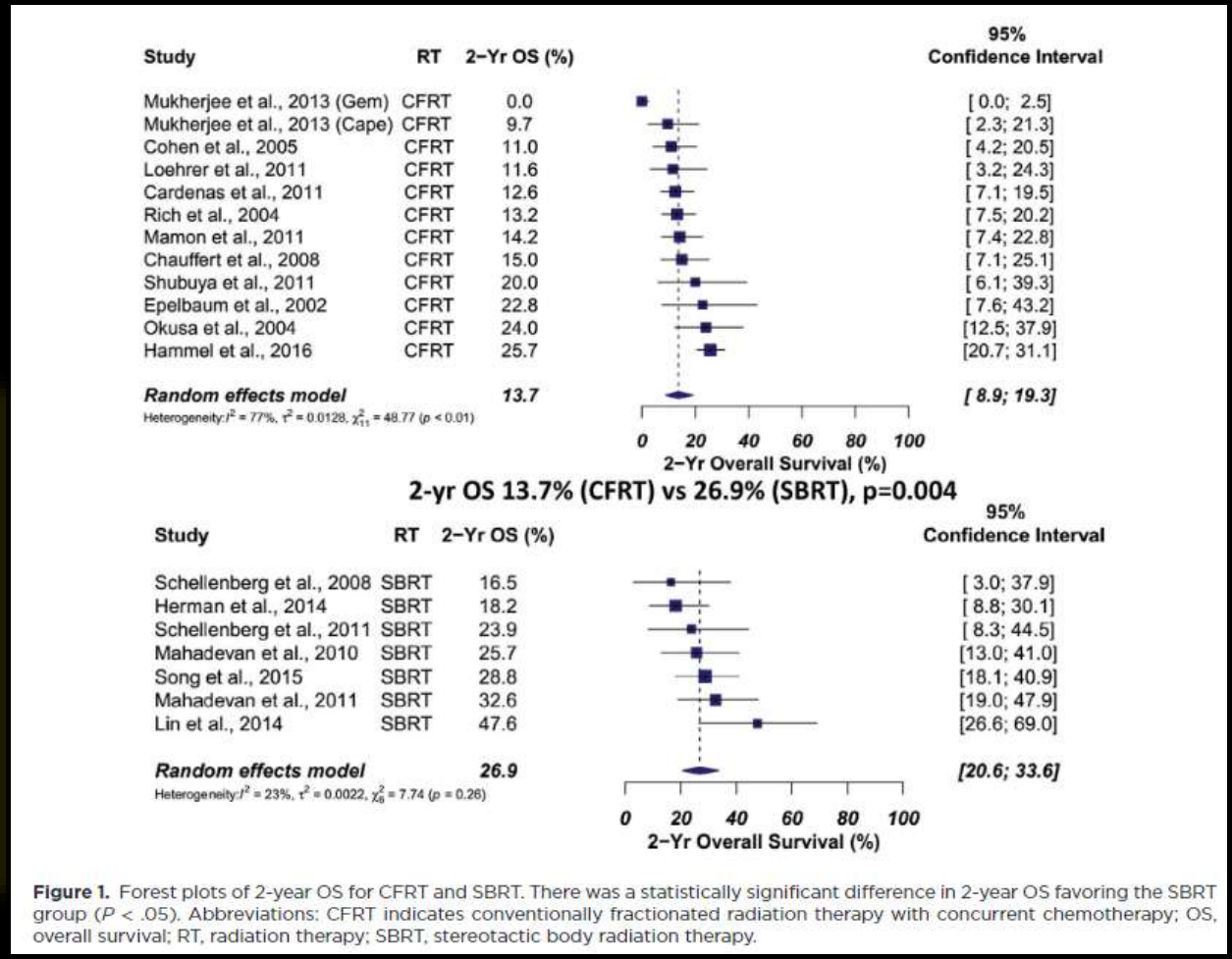


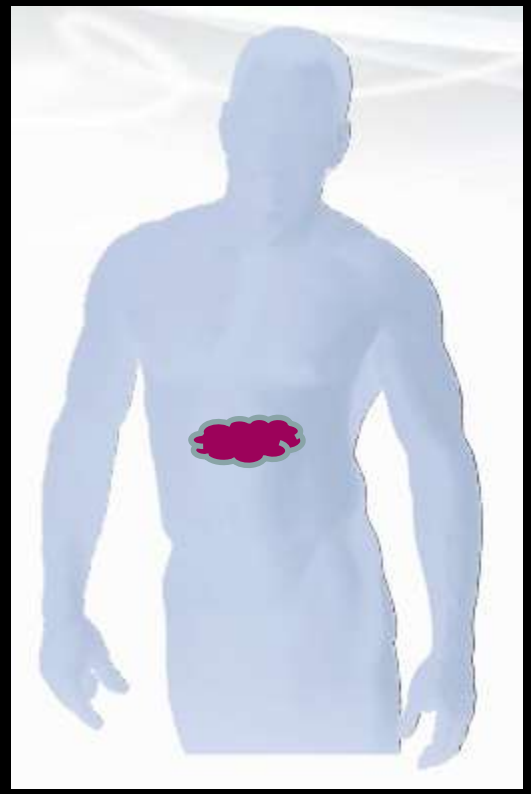
Figure 1. Forest plots of 2-year OS for CFRT and SBRT. There was a statistically significant difference in 2-year OS favoring the SBRT group (P < .05). Abbreviations: CFRT indicates conventionally fractionated radiation therapy with concurrent chemotherapy; OS, overall survival; RT, radiation therapy; SBRT, stereotactic body radiation therapy.

Limited / well delineated with safe OAR location

Pancreas SBRT

Why SBRT –Pancreas?

- Aggressive / 20% operable, 40% locally advanced
- 60% - local progression
- Local management : Non surgical
  - Symptom control
  - Local control / PFS
  - conversion → operable
- SBRT : No delay in systemic therapy

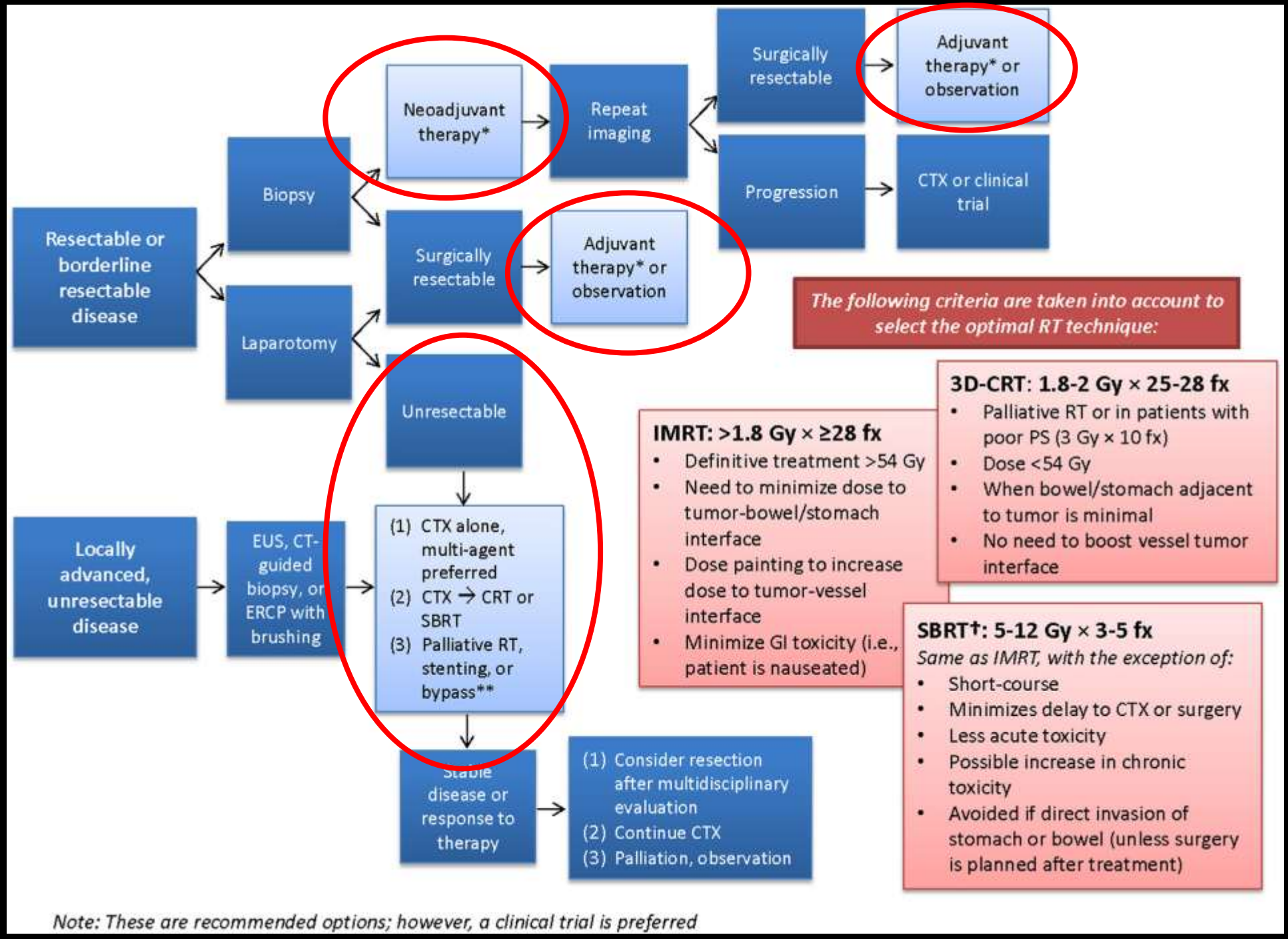


Indications/ benefit:

- **Inoperable cases** – unfit Sx
- As **boost** for high risk / post op
- **Avoid delay** in systemic
- **Recurrent** disease
- **Oligometastatic** Mets
- **Palliation** : Pain / Biliary obstruction

	Vascular Structure	Localised and Resectable	Borderline Resectable	Locally Advanced
Pancreatic Head	Arteries	No arterial abutment, clear fat plane with CA, CHA and SMA	CHA abutment or encasement; no extension to the celiac axis < 180 degree SMA, no CA encasement	> 180 degree abutment of SMA or any CA abutment Aortic invasion
	Veins	No venous abutment, clear fat plane with MPV and SMV	MPV or SMV encasement with reconstructible MPV or SMV	Unreconstructible MPV or SMV
Pancreatic Body or Tail	Arteries	No arterial abutment, clear fat plane with CA, CHA and SMA	< 180 degree SMA, or CA encasement	> 180 degree abutment of SMA or CA abutment
	Veins	No venous abutment, clear fat plane with MPV and SMV	Reconstructible MPV or SMV	Unreconstructible MPV or SMV

Table 1 National Comprehensive Cancer Network guidelines on resectability criteria
Legend: *CA: celiac axis, CHA: common hepatic artery, SMA: superior mesenteric artery, MPV: main portal vein, SMV: superior mesenteric vein*


Resectable or borderline resectable disease
Biopsy
Laparotomy
Neoadjuvant therapy*
Surgically resectable
Repeat imaging
Surgically resectable
Adjuvant therapy* or observation
Progression
CTX or clinical trial
Adjuvant therapy* or observation
Unresectable
Locally advanced, unresectable disease
EUS, CT-guided biopsy, or ERCP with brushing
(1) CTX alone, multi-agent preferred
(2) CTX → CRT or SBRT
(3) Palliative RT, stenting, or bypass**
Stable disease or response to therapy
(1) Consider resection after multidisciplinary evaluation
(2) Continue CTX
(3) Palliation, observation
The following criteria are taken into account to select the optimal RT technique:
3D-CRT: 1.8-2 Gy × 25-28 fx
• Palliative RT or in patients with poor PS (3 Gy × 10 fx)
• Dose <54 Gy
• When bowel/stomach adjacent to tumor is minimal
• No need to boost vessel tumor interface
IMRT: >1.8 Gy × ≥28 fx
• Definitive treatment >54 Gy
• Need to minimize dose to tumor-bowel/stomach interface
• Dose painting to increase dose to tumor-vessel interface
• Minimize GI toxicity (i.e., patient is nauseated)
SBRT†: 5-12 Gy × 3-5 fx
Same as IMRT, with the exception of:
• Short-course
• Minimizes delay to CTX or surgery
• Less acute toxicity
• Possible increase in chronic toxicity
• Avoided if direct invasion of stomach or bowel (unless surgery is planned after treatment)
Note: These are recommended options; however, a clinical trial is preferred

SBRT Pancreas: Curative effects

- 1st experience : Stanford
  - 25 Gy / 1 fr – 100 % LC but > 25% Gr II + toxicities, ulcer, stricture, perforation
- 3-5 fractions better
  - Herman (33 Gy/5 fr) / Ryal et al / Park et al (SBRT vs IMRT)
  - Median survival 14-15 months, LC – 80%, Gr III toxicity < 10%
  - Margin negative/ LN negative resections
  - Induction chemo → SBRT → better survival / PFS in inoperable
- BRPC
  - Moningi et al.
    - 88 cases / SBRT 25 -33 Gy/ 5 fr + Gem or FOLFIRINOX chemo
    - 1 yr LC 61%, mOS 18 m
    - Those made operable – 20 m Vs 12 m , Grade 3 toxicity < 6%.
  - Mellon et al.
    - 159 cases (110 BRPC, 49 LAPC)
    - **24% surgical conversion / all margin negative , mOS 34 month**

3-5 fr better than 1

Toxicity less

Conversion in BRPC

Induction + SBRT : better PFS / survival if inoperable

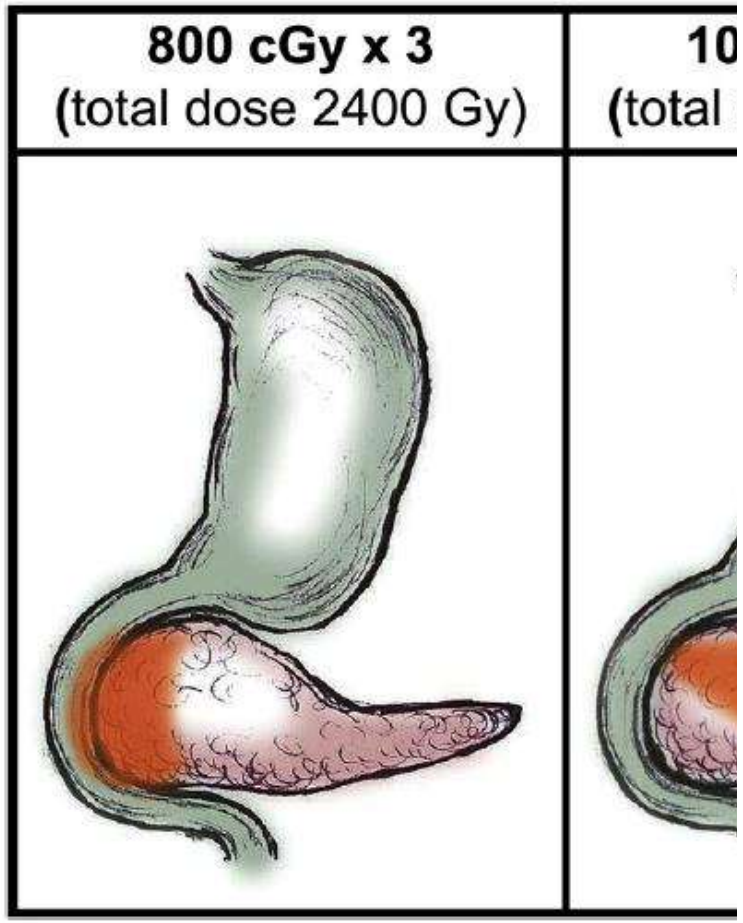


Fig. 1. Adaptive tolerance-based stereotactic body ra
ship between duodenum and pancreatic tumor (red)

Table 2 – Stereotactic body radiation therapy for locally advanced pancreatic cancer.

Study	Patients, *n*	SBRT dose (in Gy)	Grade 3+ GI toxicities (unless other wise specified)	Local control at 1 year	Median OS (months)	Median follow-up (months)
Koong et al.[16]	15	15, 20, or 25 Gy × 1	0	100%	11	5
Koong et al.[17]	19	45 Gy IMRT followed by 25 Gy × 1 boost	2 (12.5%)	94%	8.3	6
Hoyer et al.[18]	22	15Gy × 3	79% acute grade 2+	57%	5.4	Not available
Schellenberg et al.[19]	16	25 Gy × 1 after induction gemcitabine + post-SBRT gemcitabine	1 (6%) acute 2 (13%) late	100%	11.4	9.1 for all patients; 22.3 for living patients
Schellenberg et al.[20]	20	25 Gy × 1 after induction gemcitabine + post-SBRT gemcitabine	0 acute 1 (5%) late	94%	11.8	4.3
Herman et al.[21]	49	6.6 Gy × 5 after induction gemcitabine	1 (2%) acute 3 (6%) late	78%	13.9	13.9
Mahadevan et al.[24]	36	8, 10, or 12 Gy × 3 followed by adjuvant gemcitabine	5 (14%)	78%	14.3	24
Mahadevan et al.[25]	39	8–12 Gy × 3 after induction gemcitabine	0 acute 3 (9%) late	85%	20	21
Gurka et al.[26]	10	5 Gy × 5 with concurrent gemcitabine	0	40%	12.2	Not available
Polistina et al.[28]	23	10 Gy × 3 with induction and concurrent gemcitabine, ± surgery, ± maintenance chemotherapy	0	82.6%	10.6	9

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Table 2 Suggested dose constraints for pancreas SBRT

Organ	Standardized name	Parameter	Constraint		
		Constraint	Per protocol, Gy	Minor variation, Gy	Major variation, Gy
Duodenum	Duodenum	Dmax (0.5 cm^3)	<33	≤35	>35
		V30	<5*	5-10*	>10*
Stomach	Stomach	Dmax (0.5 cm^3)	<33	≤35	>35
		V30	<5*	5-10*	>10*
Small bowel	SmallBowel	Dmax (0.5 cm^3)	<33	≤35	>35
		V30	<5*	5-10*	>10*
Large bowel	LargeBowel	Dmax (0.5 cm^3)	≤35 Gy	35-38 Gy	>38
Duodenum PRV†	Duodenum_PRV	Dmax (0.5 cm^3)	<38 Gy	38-40 Gy	>40
Small bowel PRV†	SmallBowel_PRV	Dmax (0.5 cm^3)	<38 Gy	38-40 Gy	>40
Large bowel PRV†	LargeBowel_PRV	Dmax (0.5 cm^3)	<38 Gy	38-40 Gy	>40
Stomach PRV†	Stomach_PRV	Dmax (0.5 cm^3)	<38 Gy	38-40 Gy	>40
Spinal cord PRV	SpinalCord_05	Dmax (0.5 cm^3)	<20 Gy	≤25 Gy	>25
Combined kidneys	Kidneys_Comb	V12‡	<25‡	25-30‡	>30‡
Single kidney	Kidney_L Kidney_R	V10‡	<10‡	10-25‡	>25‡
Liver	Liver	V12‡	<40‡	≤50‡	>50‡

Abbreviations: Dmax = maximum dose; PRV = planning organ-at-risk volume; SBRT = stereotactic body radiation therapy.

* Unit is cm^3.

† Minimum PRV expansion should be 3 mm; however, larger expansions should be considered in a setting of increased organ movement or uncertainty.

‡ Unit is Gy.

§ Unit is percent.

Table 3

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4 CTV4
5 ITV40
6 PTV40
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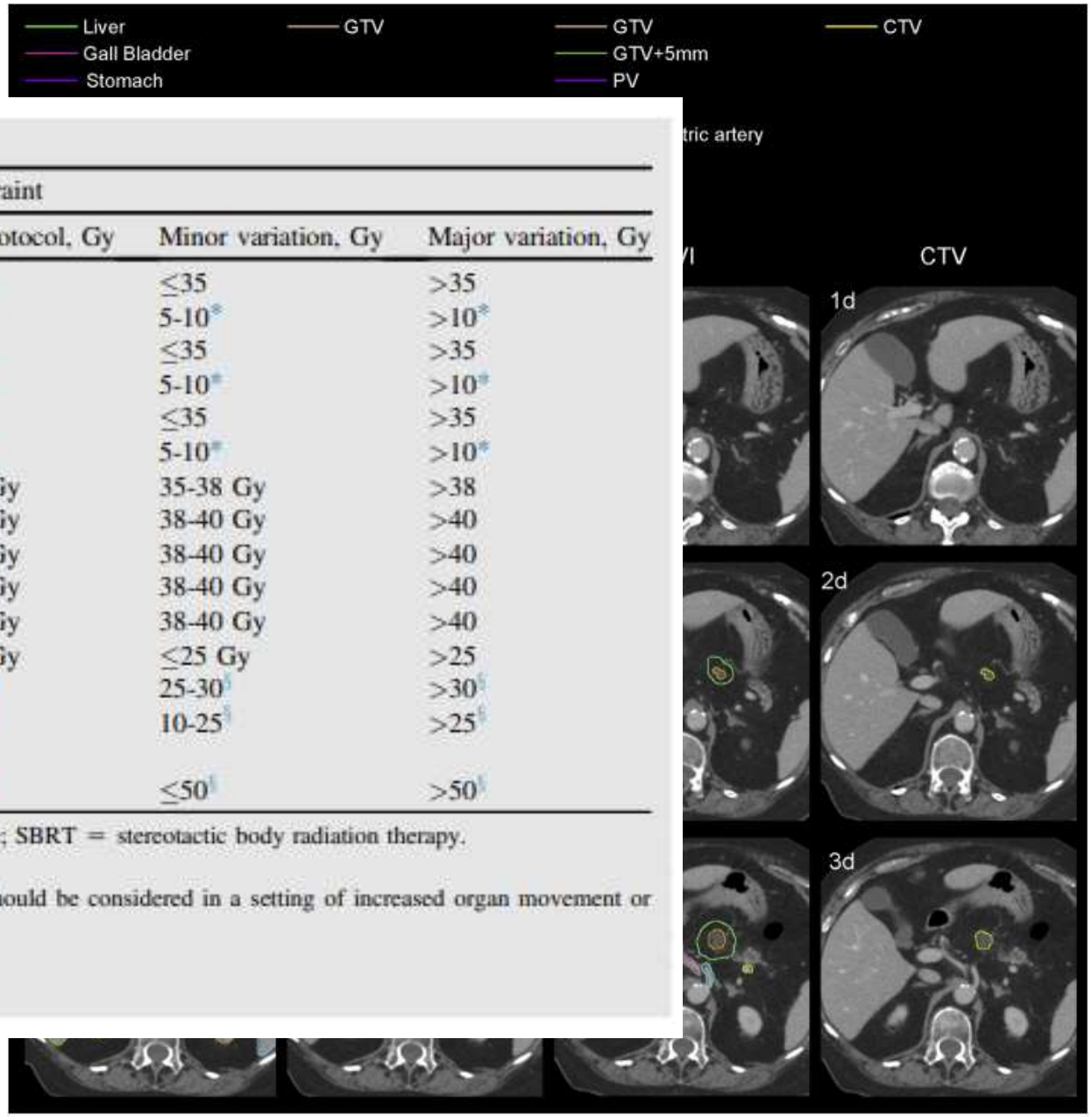

Figure 3 Contouring atlas for pancreas stereotactic body radiation therapy demonstrating formation of the tumor-vessel interface. Patient with locally advanced pancreatic cancer and aberrant left gastric artery. Abbreviations: CA = celiac artery; CTV = clinical target volume; GTV = gross tumor volume; PV = portal vein; SMV = superior mesenteric vein; SV = splenic vein.

Palliation / Pain

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CLINICAL INVESTIGATION

Impact of Short-Course Palliative Radiation Therapy on Pancreatic Cancer-Related Pain: Prospective Phase 2 Nonrandomized PAINPANC Trial

C. Paola Tello Valverde, MSc,*,† Gati Ebrahimi, MD, MBA,*,‖ Mirjam A. Sprangers, PhD,‡,‖ Konstantinos Pateras, PhD,¶,# Anna M.E. Bruynzeel, MD, PhD,†,‖ Marc Jacobs, PhD,‖ Johanna W. Wilmink, MD, PhD,‖,** Marc G. Besselink, MD, PhD,‡,†† Hans Crezee, PhD,*,‖ Geertjan van Tienhoven, MD, PhD,*,‖ and Eva Versteijne, MD, PhD†,‖

*Department of Radiation Oncology, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands; †Department of Radiation Oncology, Amsterdam UMC, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands; ‡Cancer Center Amsterdam, Treatment and Quality of Life, Amsterdam, The Netherlands; §Department of Radiation Oncology, Instituut Verbeeten, The Netherlands; ‖Department of Medical Psychology, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands; ¶University of Thessaly, Faculty of Public and One Health, Laboratory of Epidemiology & Artificial Intelligence, Karditsa, Greece; #Department of Data Science and Biostatistics, University Medical Center Utrecht, Julius Center of Primary Care, Utrecht, The Netherlands; **Department of Medical Oncology, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands; and ††Department of Surgery, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands

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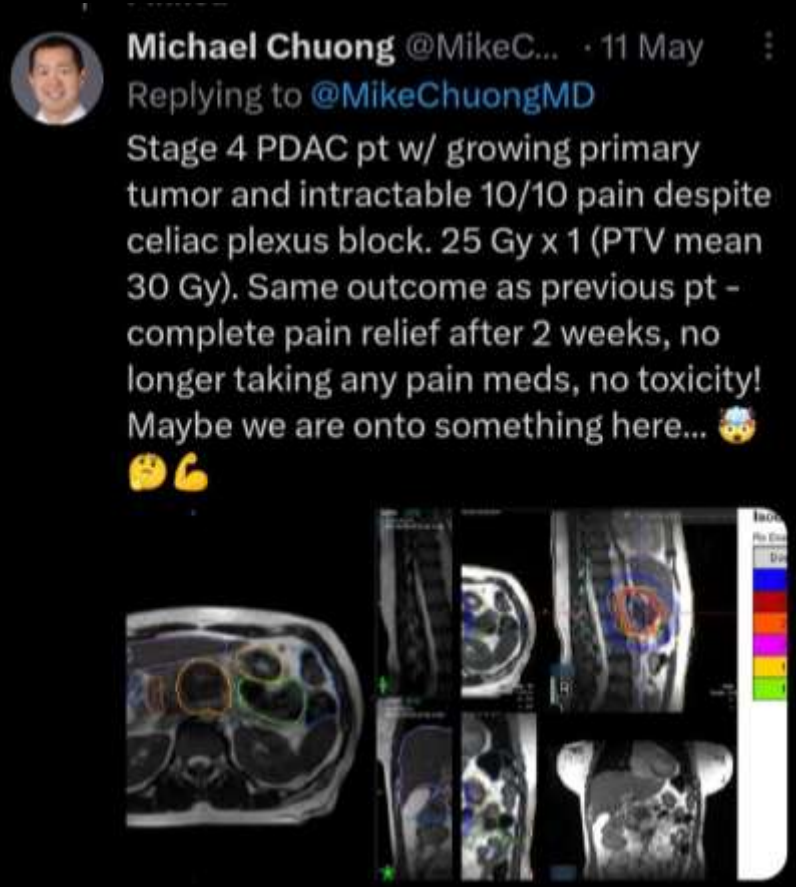
- ❑ 24 Gy / 3 fr
- ❑ 25 Gy / 5 Fr
- ❑ 25 Gy / 1 fr [MR linac]



Methods and Materials: In this prospective phase 2 single center nonrandomized trial, 30 patients with moderate-to-severe pain (5-10, on a 0-10 scale) of pancreatic cancer refractory to pain medication, were treated with a short-course palliative radiation therapy; 24 Gy in 3 weekly fractions (2015-2018). Primary endpoint was defined as a clinically relevant average decrease

Conclusions: Short-course palliative radiation therapy for pancreatic cancer-related pain was associated with rapid, clinically relevant reduction in pain severity, and clinically relevant improvement in global QoL, with mostly mild toxicity.

Re-irradiation / salvage

Original Article

Re-irradiation with stereotactic body radiation therapy as a novel treatment option for isolated local recurrence of pancreatic cancer after multimodality therapy: experience from two institutions

Aaron T. Wild[1*], Susan M. Hiniker[2*], Daniel T. Chang[2], Phuoc T. Tran[1,3], Mouen A. Khashab[4], Maneesha R. Limaye[2], Daniel A. Laheru[3], Dung T. Le[3], Rachit Kumar[1], Jonathan S. Pai[2], Blaire Hargens[2], Andrew B. Sharabi[1], Eun Ji Shin[4], Lei Zheng[3], Timothy M. Pawlik[5], Christopher L. Wolfgang[5], Albert C. Koong[2], Joseph M. Herman[1,3]

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*These two authors (ATW and SMH) contributed equally to this work.

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- ✓ Localized salvageable recurrence
- ✓ 2-6 months systemic → Re-RT
- ✓ > 9-12 mths DFS → better for local control Re-RT
- ✓ Re-RT – 5 fr SBRT 4-5 Gy/fr [20-25 ~ 30 Gy]
  - ❖ median BED early/late: 37.5/66.7 Gy

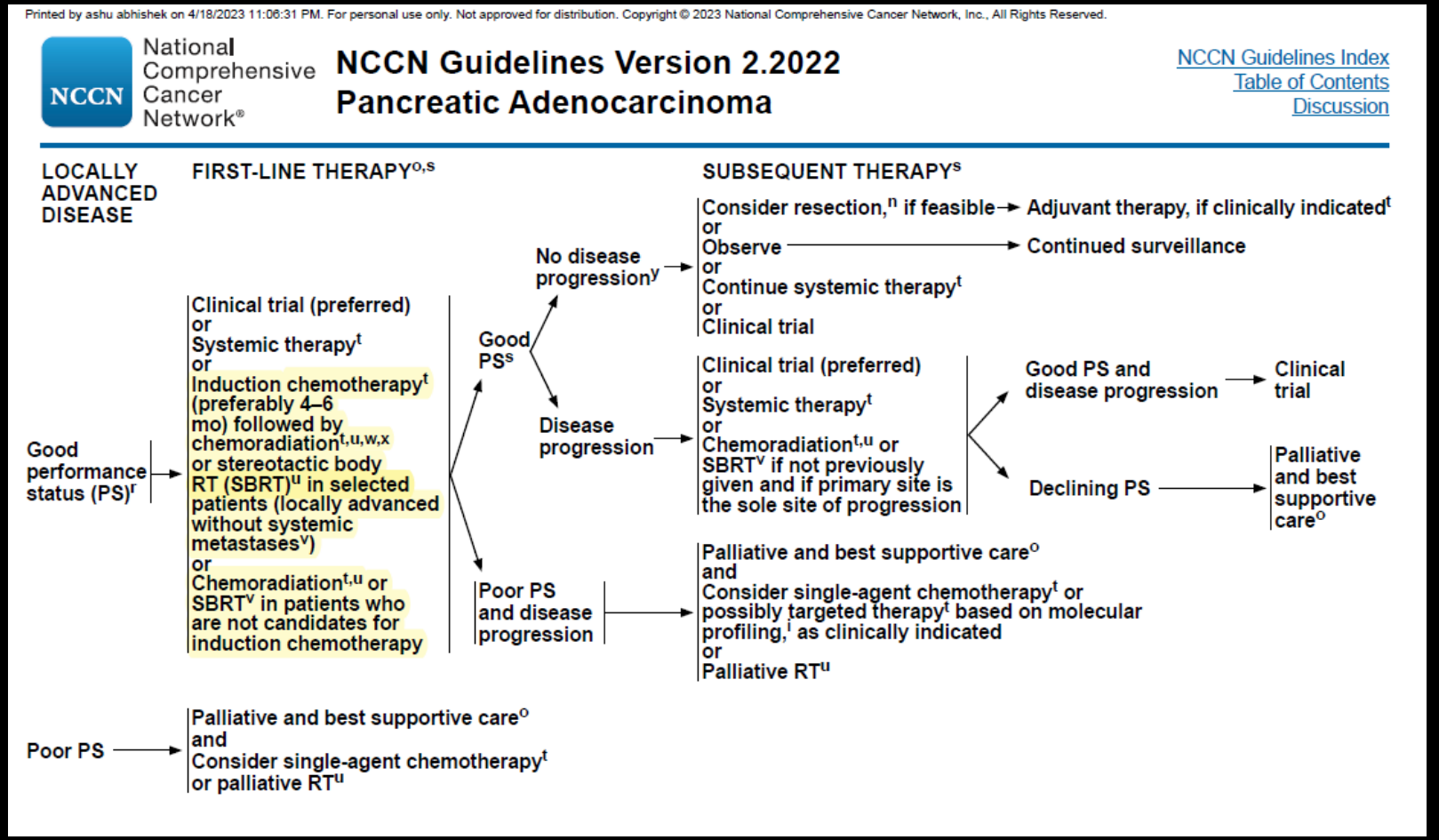
The trials examining SBRT discussed above (19-21) demonstrated excellent local control rates (81-100%), but minimal impact on median survival, which was similar to that observed in our study (8.8 months) at 7.6-11.8 months. This is likely explained by the propensity of pancreatic cancer to microscopically disseminate early (31), rendering local salvage therapy ineffective for prolonging survival due to subsequent emergence of occult distant metastases. Notably, however, two patients in our series who received a pancreatic tumor cell vaccine with ipilimumab prior to local recurrence/progression demonstrated extended survival after SBRT. While we cannot confirm the role of SBRT in prolonging survival in these cases, it is possible that these patients manifested an improved immune response to their tumors following SBRT, similar to the abscopal effect recently reported for patients with melanoma (32,33).

In order to prevent administration of futile local therapy, one strategy is to give chemotherapy for 2-6 months and reassess for metastases before administering re-irradiation with SBRT (30). While this selection approach is preferable, some patients with acute local symptoms may require a more rapid decision regarding local therapy. Our data indicate that SBRT is more effective in prolonging survival for patients who develop isolated local recurrence/progression ≥9 months after surgical resection or definitive CRT. Therefore, in patients for whom a 2-6 month course of chemotherapy is not feasible due to acute symptoms or inability to tolerate further systemic therapy, the decision to give salvage SBRT without induction chemotherapy could be based on the interval between surgery or definitive CRT and local recurrence/progression. Those recurring/progressing after a prolonged time interval (≥9 months)

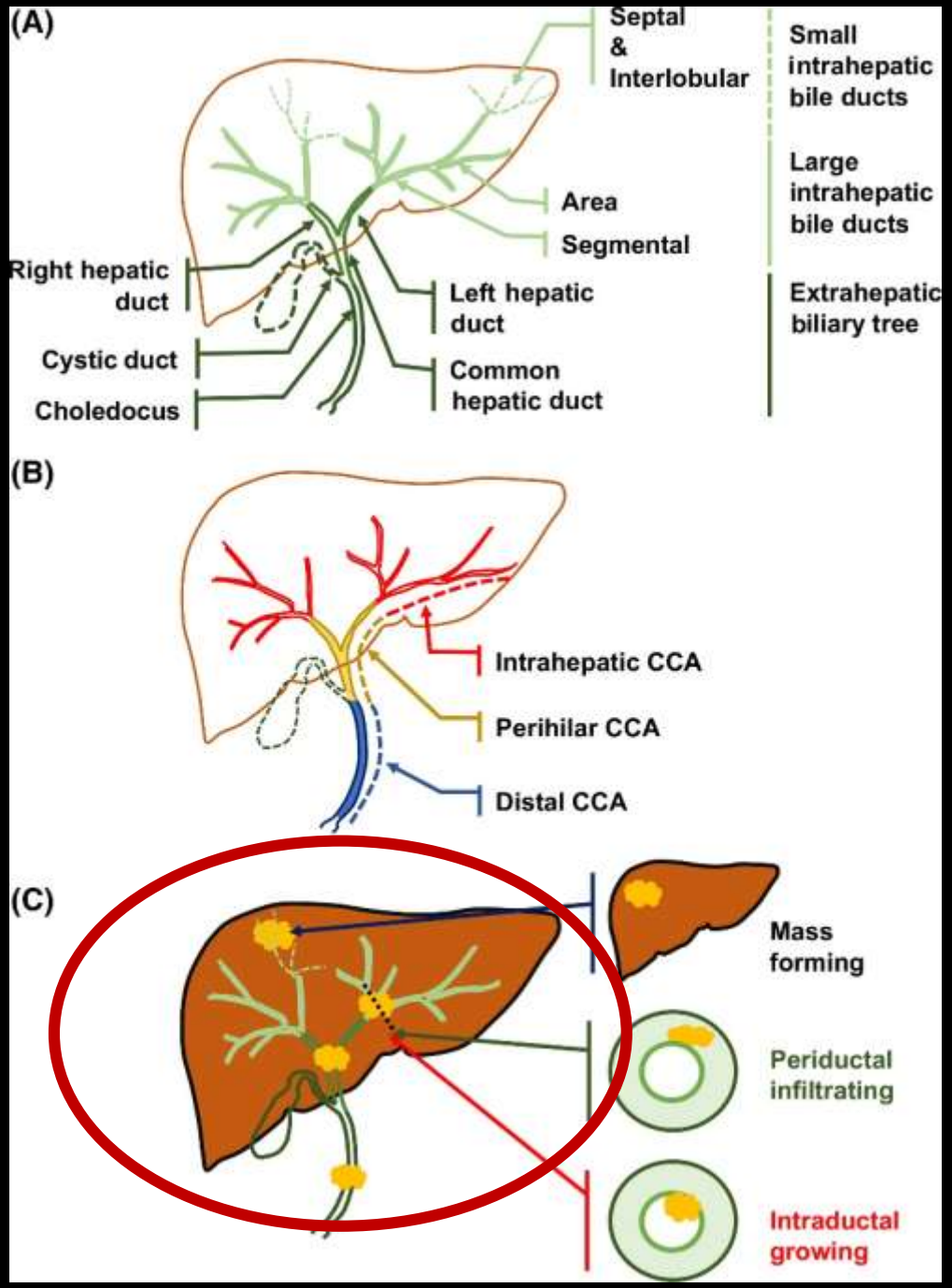
Case selection

- Mostly reserved for LAPC and BRPC
- Extent of disease / size / relationship with OARs
- Gastrointestinal mucosal / luminal infiltration - C/I - risk of bleeding and peritonitis
- Not in mets except – oligomets or large symptomatic primary post induction

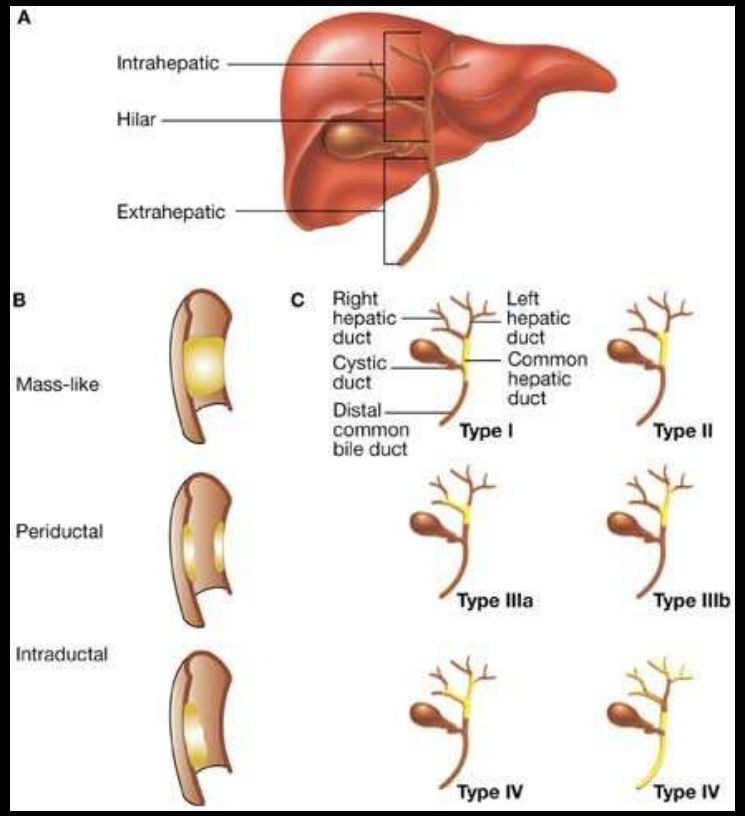
- NCCN : SBRT after induction for advanced, inoperable, and non-metastatic / unfit for chemo



Cholangiocarcinoma



Cholangiocarcinoma – SBRT – limited role



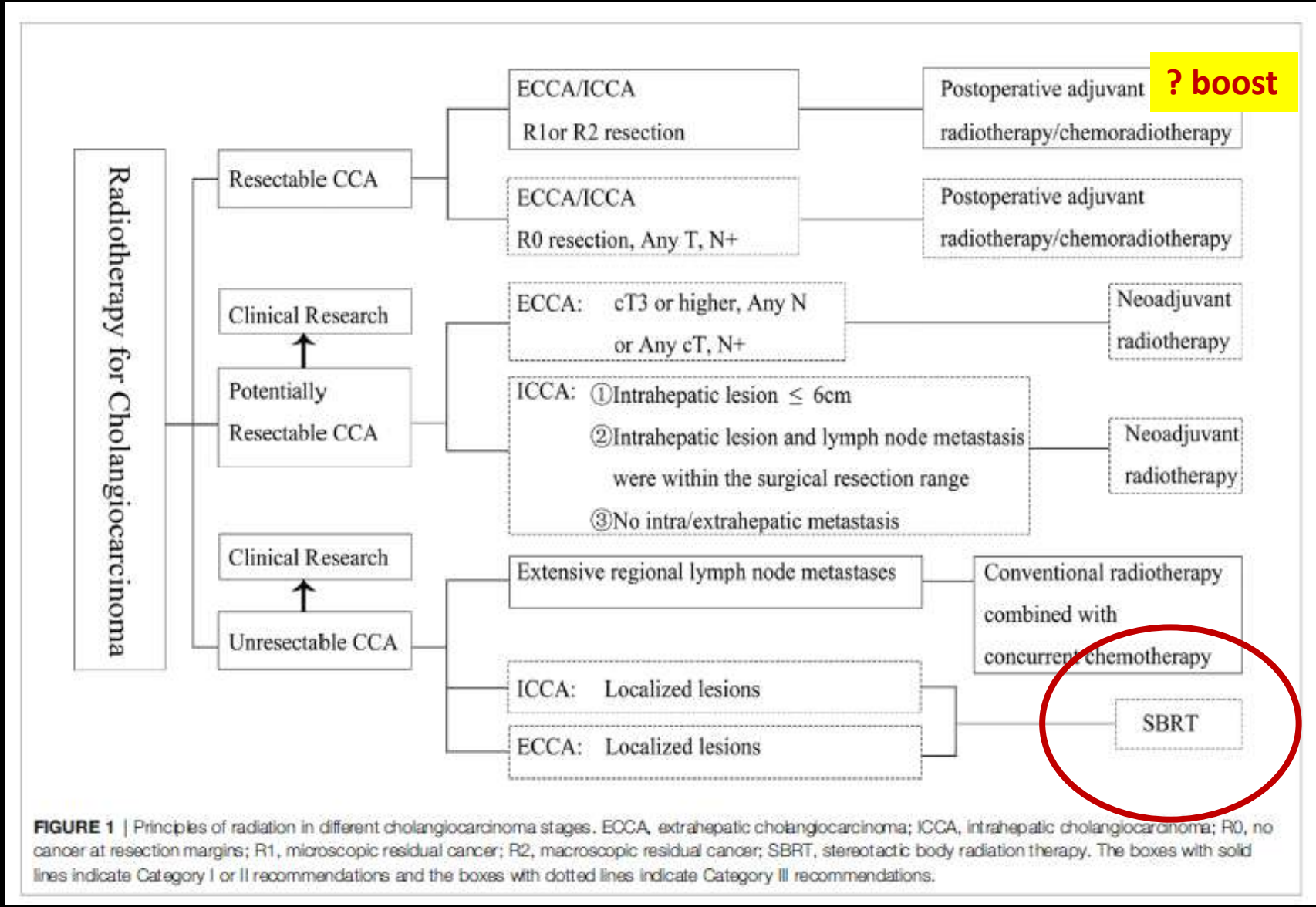


FIGURE 1 | Principles of radiation in different cholangiocarcinoma stages. ECCA, extrahepatic cholangiocarcinoma; ICCA, intrahepatic cholangiocarcinoma; R0, no cancer at resection margins; R1, microscopic residual cancer; R2, macroscopic residual cancer; SBRT, stereotactic body radiation therapy. The boxes with solid lines indicate Category I or II recommendations and the boxes with dotted lines indicate Category III recommendations.

Table 4

SBRT as definitive therapy for cholangiocarcinoma.

Author	Design	Location	Number of	RT dose scheme ± Chemo-therapy	2 y local control	2 y/median survival
Ts						
M						
Ko						
Po						
Ba						
Ju						
M						
Ta						
				fractions 75 chemo		

Table 5 Results of primary treatment for cholangiocarcinoma

Author	Study design	Number of patients	Fractionation	Median follow-up (months)	Local control	Median survival (months)	Relevant toxicity
Kopek [41]	Phase I/II prospective	26	3 × 15 Gy (isocenter)	64.8	85 % 1 year	10.6	Six ulcerations, three stenoses
Tse [73]	Phase I prospective	10	6 × 4–8 Gy	17.6	80 %	15	Two transient biliary obstructions, one bowel obstruction
Goodman [22]	Phase I prospective	5	1 × 18–30 Gy (tumor covering isodose)	17.3	na	na	None
Polistina [57]	Retrospective	10	3 × 12.5 Gy + gemcitabine (80 % isodose)	35.5	40 %	35.5	Three/ten ulcerations or stenoses
Ibarra [33]	Retrospective	11	3 × 37.5 Gy (70 % isodose)	7.8	50 %	11	Seven to 11 grade 3
Barney [6]	Retrospective	10	3–5 × 12–20 Gy	14	100 %	15.5	One grade 3 biliary stenosis, one lethal liver failure
Momm [52]	Retrospective	13	10–12 × 4 Gy	12.9	78 % (1 year); mLPFS 32.5 m	33.5	Acute: one Grade 3 Late: 0

na not available, **mLPFS** median local progression free survival

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Original Article

Stereotactic body radiotherapy dose and its impact on local control and overall survival of patients for locally advanced intrahepatic and extrahepatic cholangiocarcinoma

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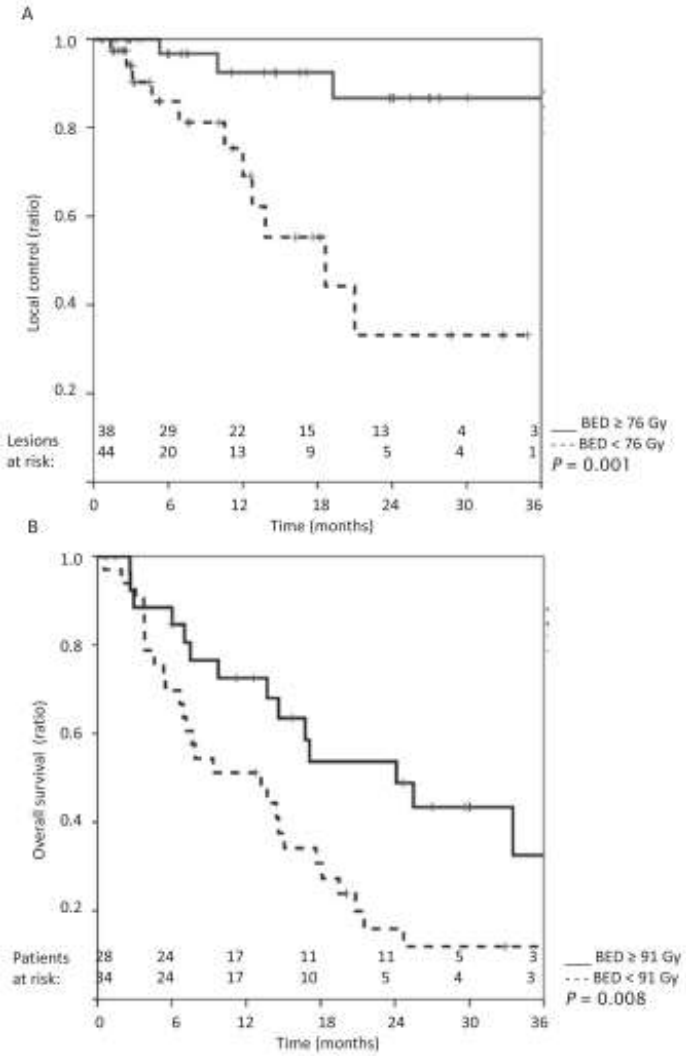

Fig. 2. (A) Effect of radiation dose on local control (LC) and (B) overall survival (OS) from the time of stereotactic body radiotherapy. Kaplan–Meier estimate of (A) LC in 82 lesions according to biologic equivalent dose (BED) of the D_{mean} less than 76 Gy or 76 Gy or more illustrate the superiority of the higher dose. (B) Kaplan–Meier estimate of OS in 64 patients with 82 lesions according to biologic equivalent dose (BED) of the D_{max} less than 91 Gy or 91 Gy or more illustrate the superiority of the higher dose.

Stereotactic radiotherapy in intrahepatic cholangiocarcinoma: A systematic review

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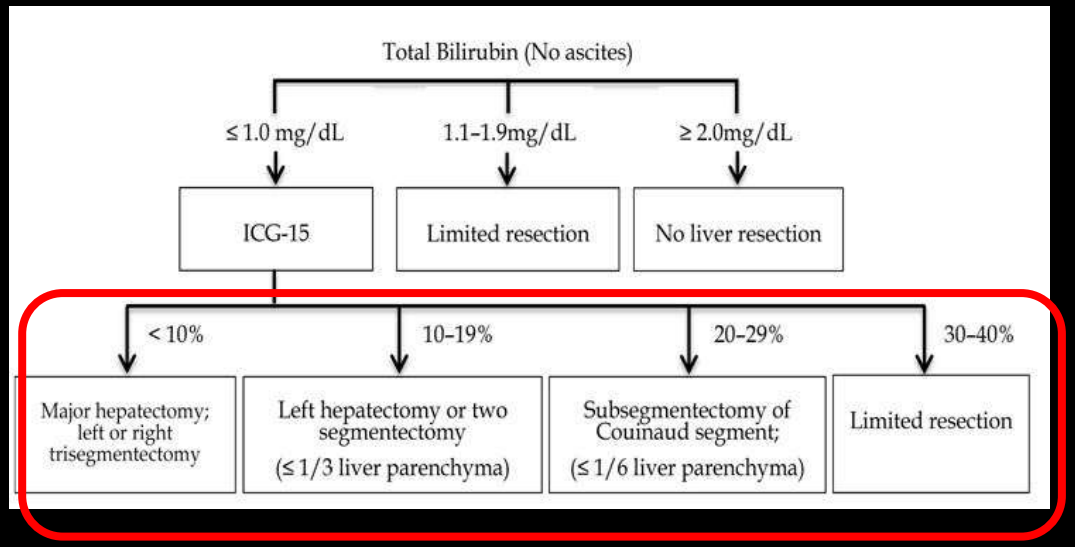
Abstract. Among biliary tract cancers, intrahepatic cholangiocarcinoma (ICC) has different characteristics compared with those in other sites. Current guidelines suggest several treatment options for ICC, including stereotactic body radiation therapy (SBRT). However, the role of SBRT in locally advanced ICC is unclear. The aim of the present study was to present a systematic review on the efficacy and safety of SBRT in ICC. A systematic review based on the PRISMA methodology was performed. Only papers reporting outcomes in terms of overall survival (OS) after SBRT in inoperable patients with ICC were included. Secondary aims were local control (LC), progression-free survival (PFS) and treatment-related toxicity. Six papers (145 patients) were included in the present analysis. SBRT was frequently used as a salvage treatment, since 28.6-66.7% of patients received previous systemic or local treatments. The median SBRT dose was 45 Gy delivered in 3-5 fractions. The median follow-up was 16 months, and median OS time was 14 months (range, 10-48 months). In one of the included studies, SBRT was significantly superior in terms of OS compared with both chemoradiation and trans-arterial-radio-embolization. The 1-year LC rate was 85% in one study, and 1-year PFS rates were 50 and 68% in two studies, respectively. Toxicity was generally not reported in detail or was reported including other sites of biliary cancers. Overall, limited evidence was available on the efficacy of SBRT in ICC, which should be further investigated in prospective studies with a larger number of patients. However, based on the available data, SBRT seems to produce similar results compared with other ICC treatments, with the advantage of being a very short and non-invasive therapy. Therefore, SBRT should be considered in selected patients with ICC.

Introduction

Intrahepatic cholangiocarcinoma (ICC) is an aggressive disease representing the second most common liver malignancy (1). The incidence of ICC is increasing worlwide (2). Surgery is considered a potential option with an overall 5-year survival of about 25-30%. (3,4). Gemcitabine-based chemo-
therapy (CT) represents the standard therapy in unresectable


Thank
you

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

Surgery & SBRT – local ablative therapies

Learning from surgical experience – partial liver radiation concept was monumental in improving response rates

- Rusthoven et al, JCO [2009]