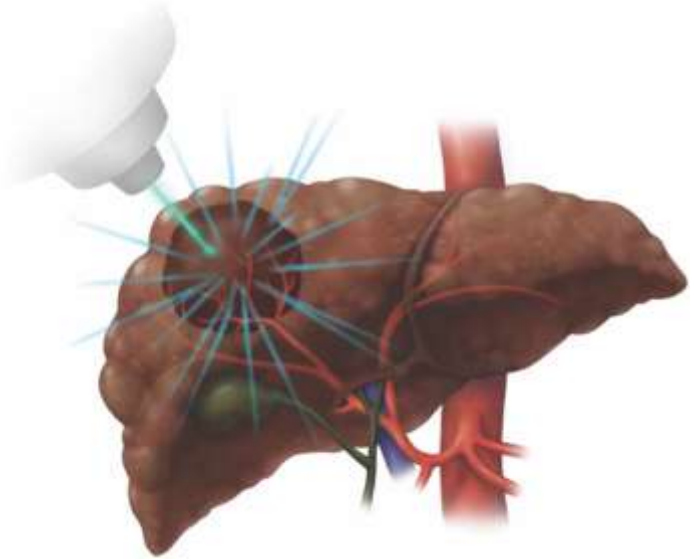

Liver SBRT

Toxicity & response Assessment

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ICRO – Proadvance – 2022, chennai

Setting the Stage

SBRT produces characteristic changes in the tumor and surrounding liver parenchyma at histology and on imaging

Knowledge of changes

correct assessment of treatment response

Intended Learning Objectives

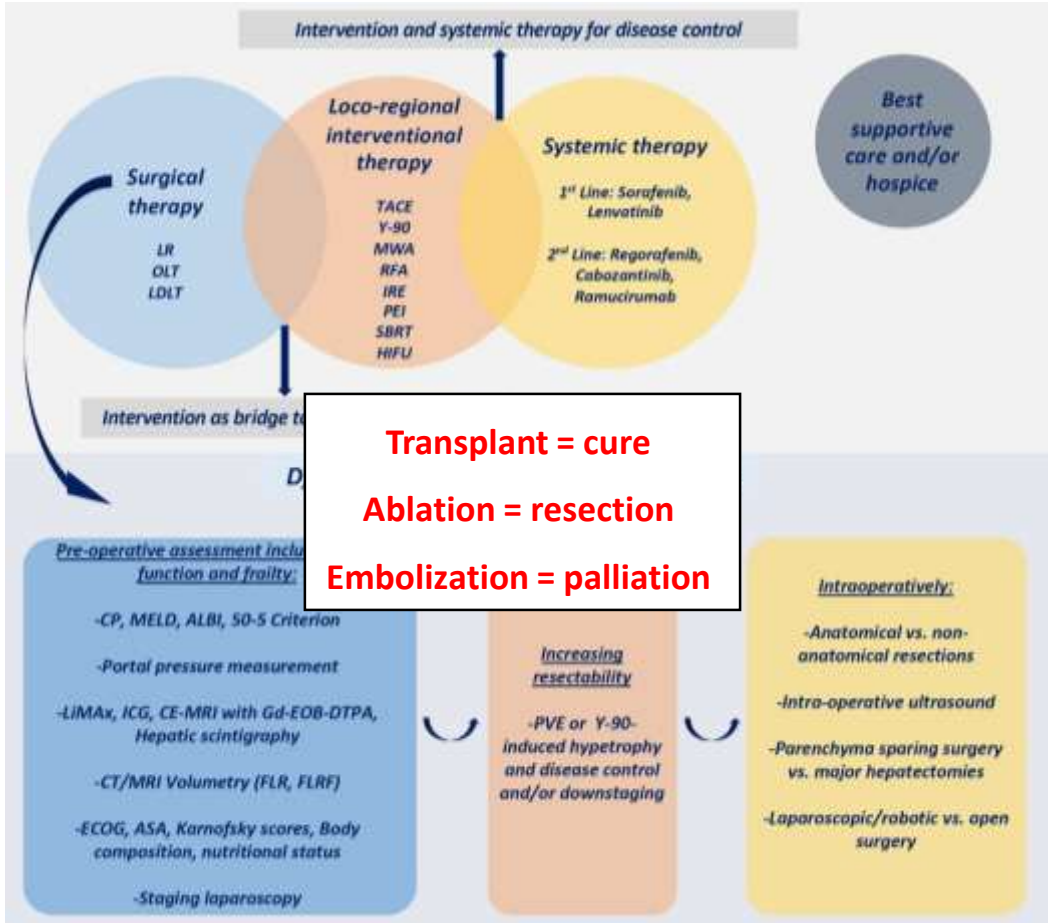
- **Basics Revisted !!**

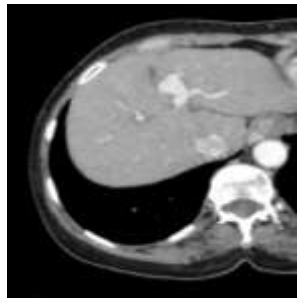
- Pathological changes after SBRT
  - Changes in liver parenchyma
  - Changes in Tumor Tissue

- Radiation Induced Liver Disease (RILD)

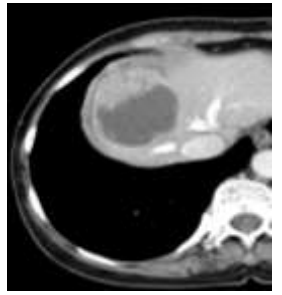
- Image Response Evaluation
  - Tools, Criteria
  - Tumor changes & Parenchymal Changes (FLC)

LDT's – Game of Locoregional Shuffle

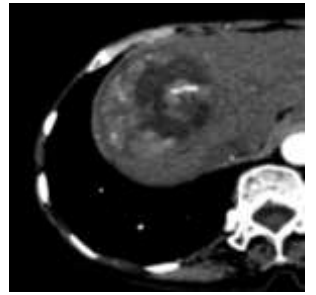




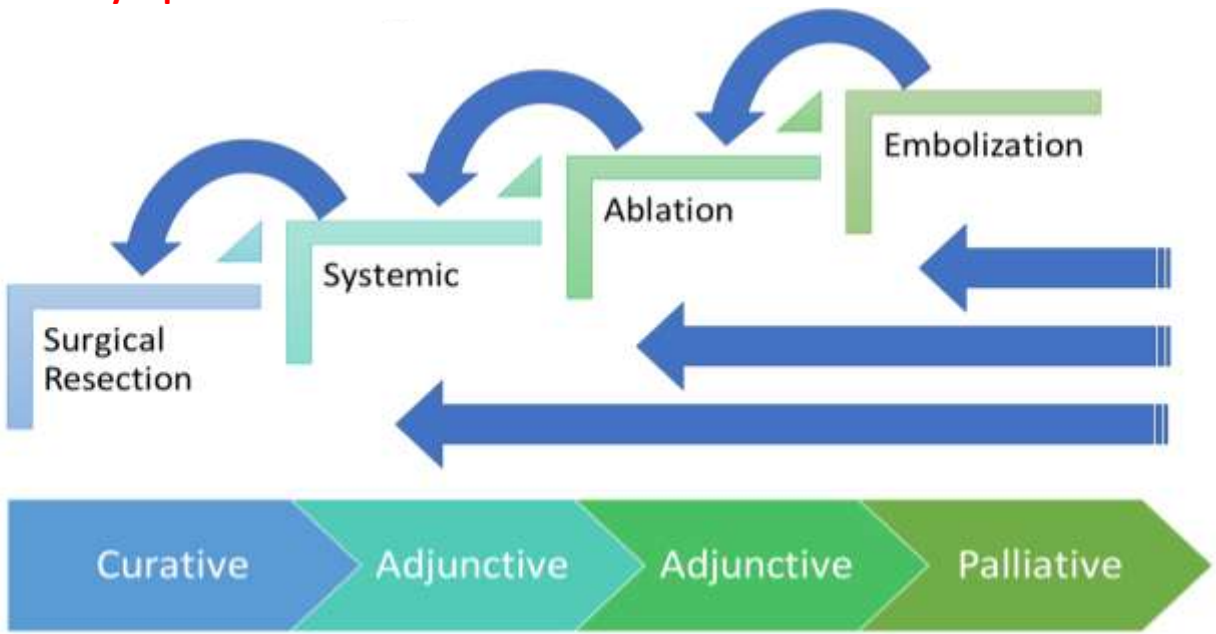
2 yrs post SBRT



Post 2 tace



Pre-Rx

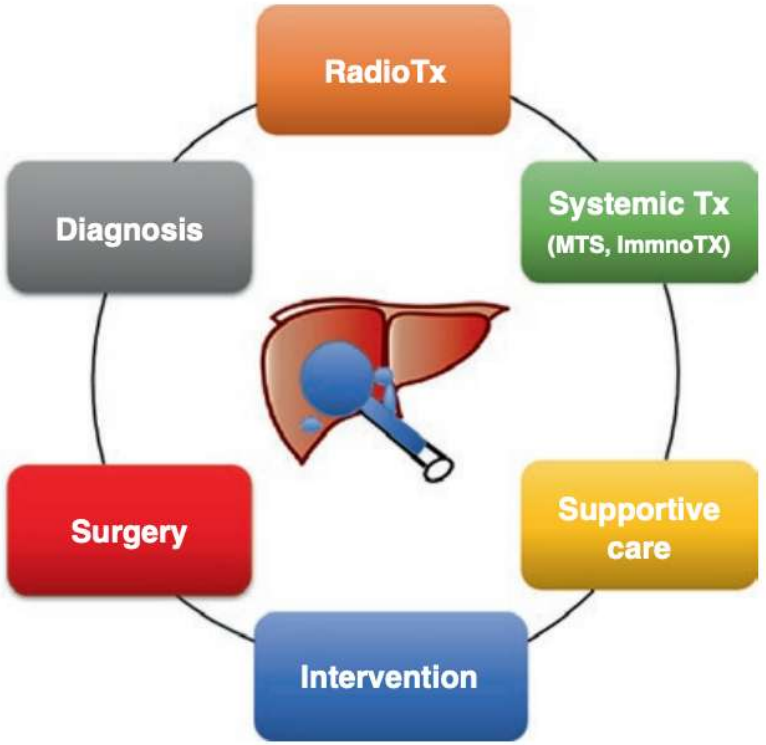


Sequencing is the Key

Management of Liver neoplasia is rarely about finding the silver bullet !!

Multidisciplinary Approach:

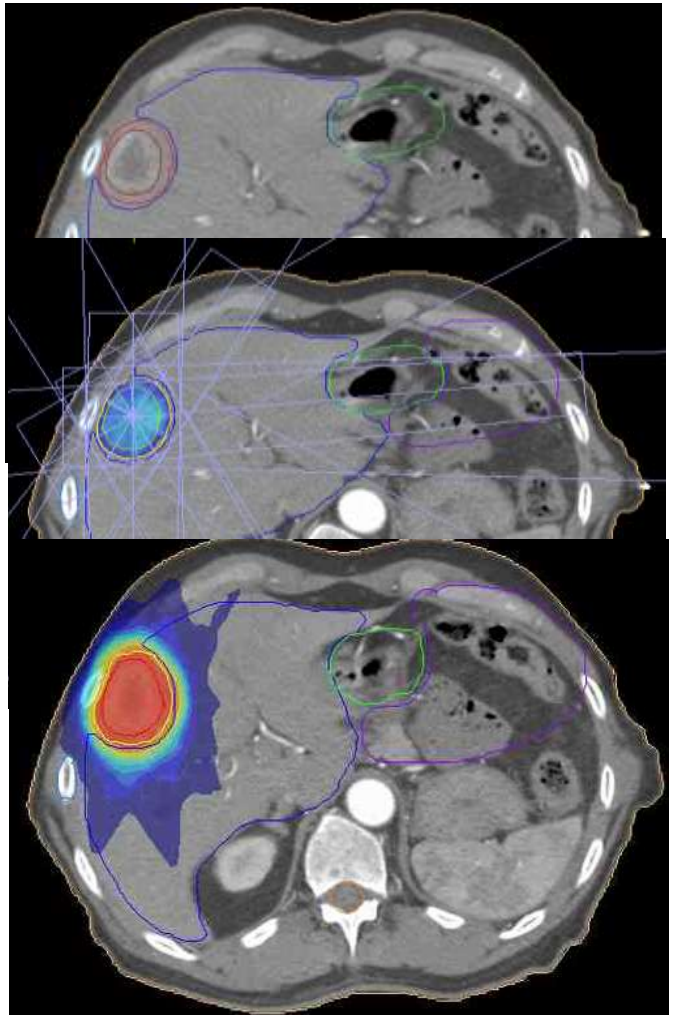
- multifocal occurrence
- underlying cirrhosis (80%) with/without active hepatitis
- high recurrence rate,
- frequent vascular invasion and intra and extra-hepatic metastasis
- Rapid growth &
- frequent metastasis after incomplete treatment and



SBRT – Thinking the Surgeon's way

High-precision image-guided RT characterized by:

- Accurate patient Positioning
- Robust Motion Management Tools
- 4-D Target Delineation (Integration of time, tumor movements)
- Multiple non-coplanar beams / Arcs therapy / Non-isocenteric beams



Allowing for:

– High Steep dose gradient

– Hypofractionation (3-6#)

– High BED - Ablative

PTV = GTV + 6- 10mm Geometric Expansion

Dose gradient outside

(Asymmetric / complex / Non-anatomical)

→ Compounded with multiple BH

Intermediate & Low Dose Spillage

Clinical Practice Guideline

External Beam Radiation Therapy for Primary Liver Cancers: An ASTRO Clinical Practice Guideline

Smith Apisarnthanarax, MD,[a,*] Aisling Barry, MD,[b] Minsong Cao, PhD,[c] Brian Czito, MD,[d] Ronald DeMatteo, MD,[e] Mary Drinane, MD,[f] Christopher L. Hallemeier, MD,[g] Eugene J. Koay, MD, PhD,[h] Foster Lasley, MD,[i] Jeffrey Meyer, MD, MS,[j] Dawn Owen, MD, PhD,[g] Jennifer Pursley, PhD,[k] Stephanie K. Schaub, MD,[a] Grace Smith, MD, PhD, MPH,[h] Neeta K. Venepalli, MD, MBA,[l] Gazi Zibari, MD,[m] and Higinia Cardenes, MD, PhD[n]

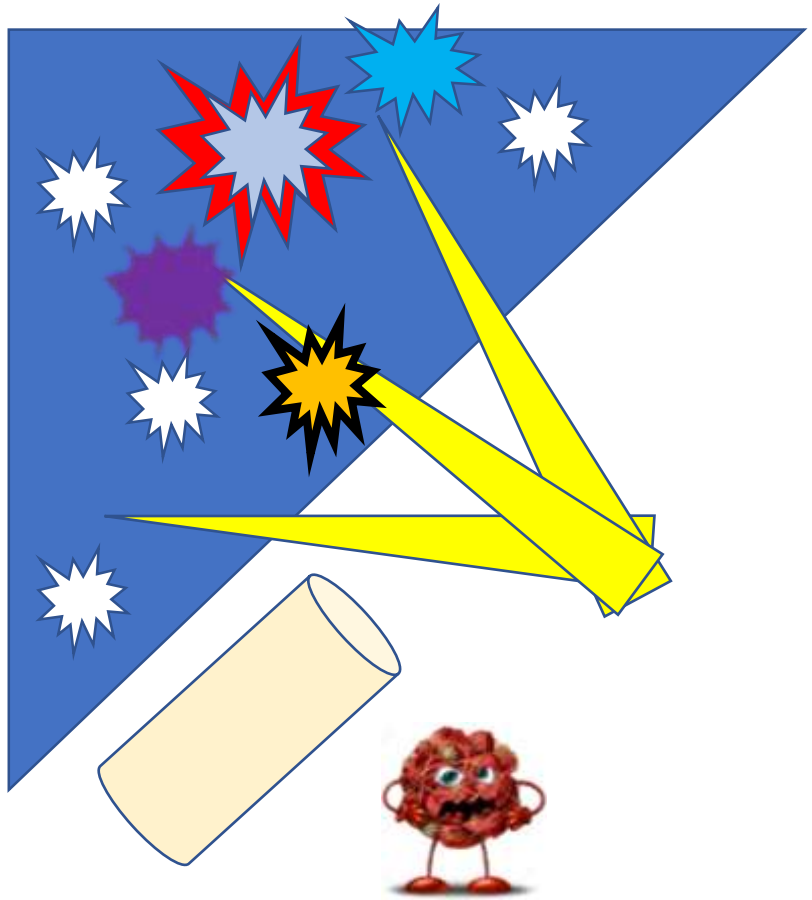
January/February 2022

https://doi.org/10.1016/j.prro.2021.09.004

Key Takeaways

- ✓ Multidisciplinary approach is key in management
- ✓ Low-to-moderate quality evidence support EBRT for definitive, consolidative, salvage & Adj.Rx
  - ➢ **Strong recommendations:** Potential first line, consolidation after LDT's and salvage options
  - ➢ **Conditional recommendations:**
    - *Limited Multifocal disease*, unresectable primary with/without macrovascular invasion
    - *Potential bridge to transplant* and neoadjuvant therapy prior to surgical options
    - *Palliative therapy* : Primary tumor & *tumor thrombus*
- ✓ Dose fractionation regimens, technique & modality personalized
- ✓ Close attention to liver dose constraints

SBRT Preferred – RFA Unpreferred Tumors



- Too Big (3-5cms)
- Too Close (To vascular or central strucs) –
  Hep.Portovenous conflunces
- Subscapular (High Dome, Posterior)
- Not Well Defined (Invisible on USG – Obesity.Fatty liver)
- Too Many (>3 lesions)
- Star burst , circumferential Recurrence / Failure – Post TACE
- Near the luminal gastrointestinal tract
- Bleeding Tendency → Platelets < 50k / Current Anticoagulants

Dose Fractionation considerations

Moderate Hypofractionation

- 300-500cgy/fr → 12-20#

Ultrahypofractionation

- >500cgy/fr → < 10frcs

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

Abbreviations: BED_{10} = biologically effective dose assuming an $\alpha/\beta = 10$; CP = Child-Pugh; EBRT = external beam radiation therapy; fx = fractions; HCC = hepatocellular carcinoma; IHC = intrahepatic cholangiocarcinoma.

* Bolded regimens are the most common prescriptions used, based on consensus of the task force. Dose constraints in Table 7 pertain to these most common dose fractionations.

† Lower doses recommended for central lesions in which the maximum point dose to central bile duct(s) cannot be met.

‡ For IHC when combined with concurrent systemic therapy.

Key Determinants - Prescription Strategies

2 key questions:

Can I get a meaningful dose of radiation?

Can I deliver radiation safely?

Dose Fractionation & Appropriateness

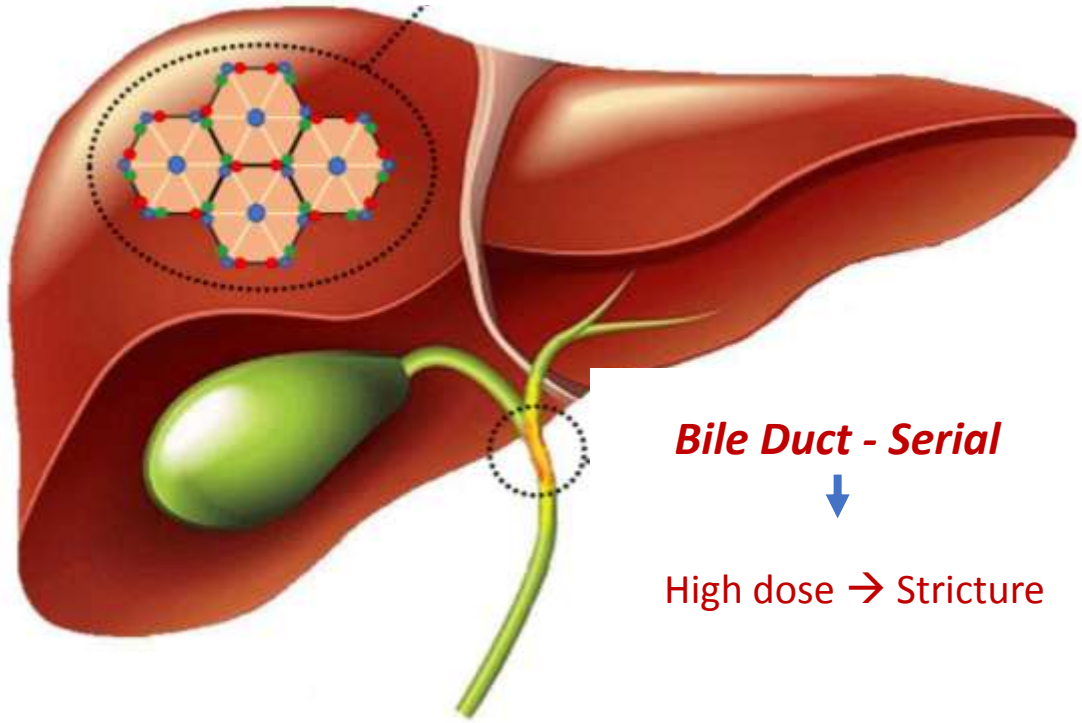
1. CP Score (baseline Liver Function)
2. Size / number of the lesion
3. Size of the liver and function
    - Can you meet Liver – GTV constraints
4. Can u meet the Nearby Critical organ constraints -

    Bowel constraints

Liver Radiobiology

Liver – Parallel (independent Lobules)

(Volume effects - Small vol. High Dose)



Bile Duct - Serial

↓

High dose → Stricture

Conventional Fractionation

Whole liver

– Mets: • ≤ 30 Gy (2 Gy) • ≤ 21 Gy (3 Gy)

– Primary Liver: • ≤ 28 Gy (2 Gy) • ≤ 21 Gy (3 Gy)

Partial Liver

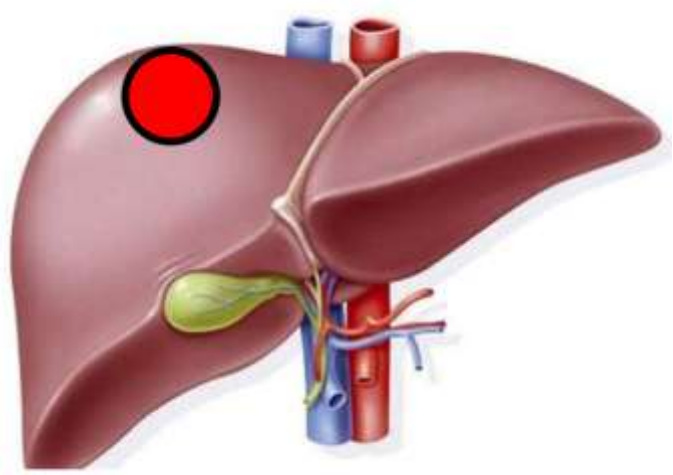
– MLD < 28 Gy (2 Gy): HCC – MLD < 32 Gy (2 Gy): mets

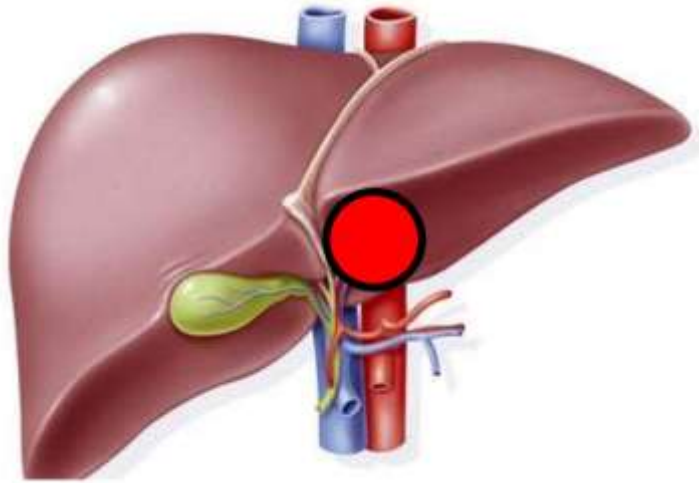
Ultra hypo Fractionation

Liver - SBRT

- HCC – MLD < 13 Gy (3 fx), < 15 MLD < 15 Gy (3 fx),
- Mets – MLD < 15 MLD < 15 Gy (3 fx)

45-54 Gy/3 fxs

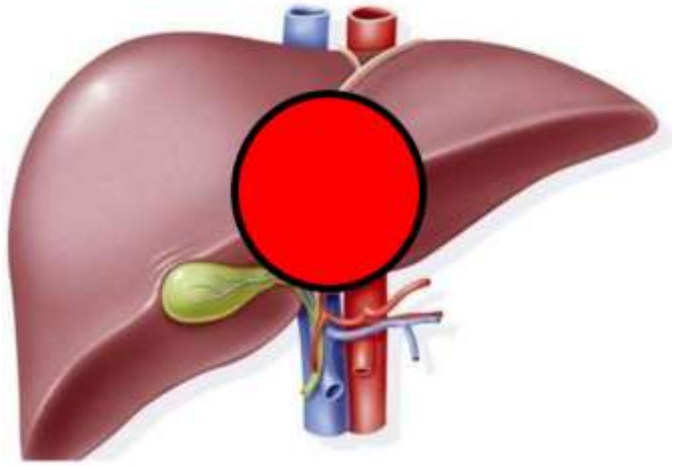


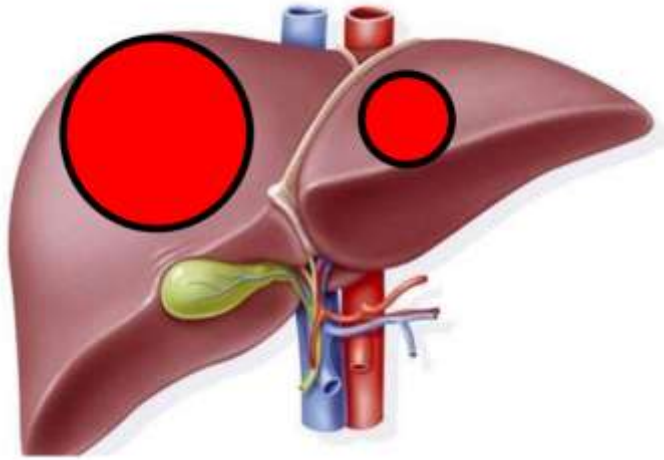


40-45 Gy/5 fxs

55 to 84 Gy EQD2 range
70 – 100 gy BED

30-40 Gy/5 fxs





Combine modalities 30-40 Gy/5 fxs

SABR Biology – Vascular Effects !!

Single Dose (>8-10gy)

Endoth. Memb.Lipid rafts .

SM

ASMase

VEGF
b-FGF

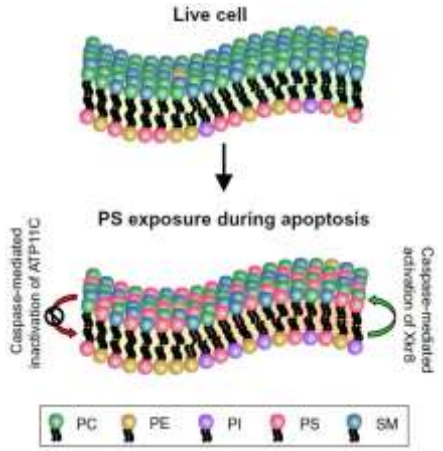
Ceramide

Endothelial Apoptosis

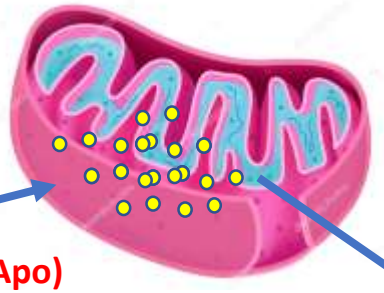
Tumor cell damage

Tumor cell death

Tumor response



Mitochondrial Pores



++ BAX / BAK (Pro-Apo)

++ BIM / BID/BAD

Cyto-C Released

Binds to APF 1

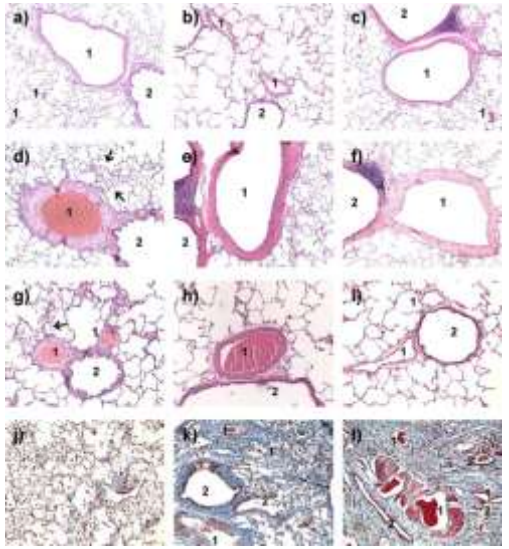
++ Initiator caspases 9

++ Executioner caspases 3,6

(-) Flippase / Flappases
(+) Scramblase

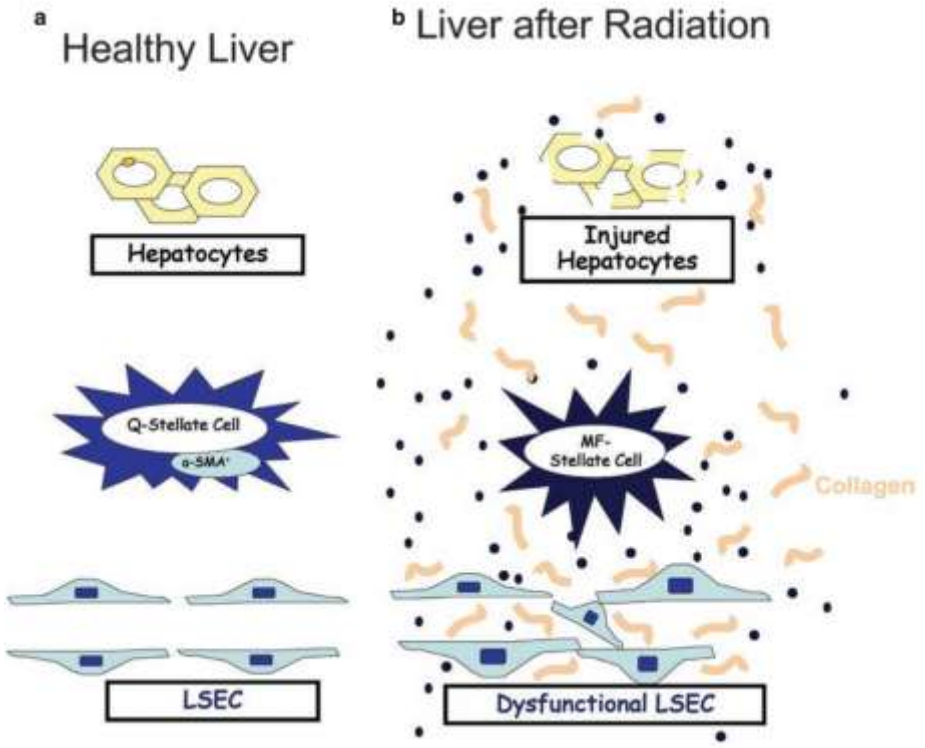
Phostidylserine expressed to Outer Leaflet

Cell Phagocytosed



- Park, Radtn Research, 2013;
- Hillmann, Radiotherapy Oncology, 2013

SABR Biology – Vascular Effects !!



Radiotherapy of Liver Cancer,

https://doi.org/10.1007/978-981-16-1815-4_2

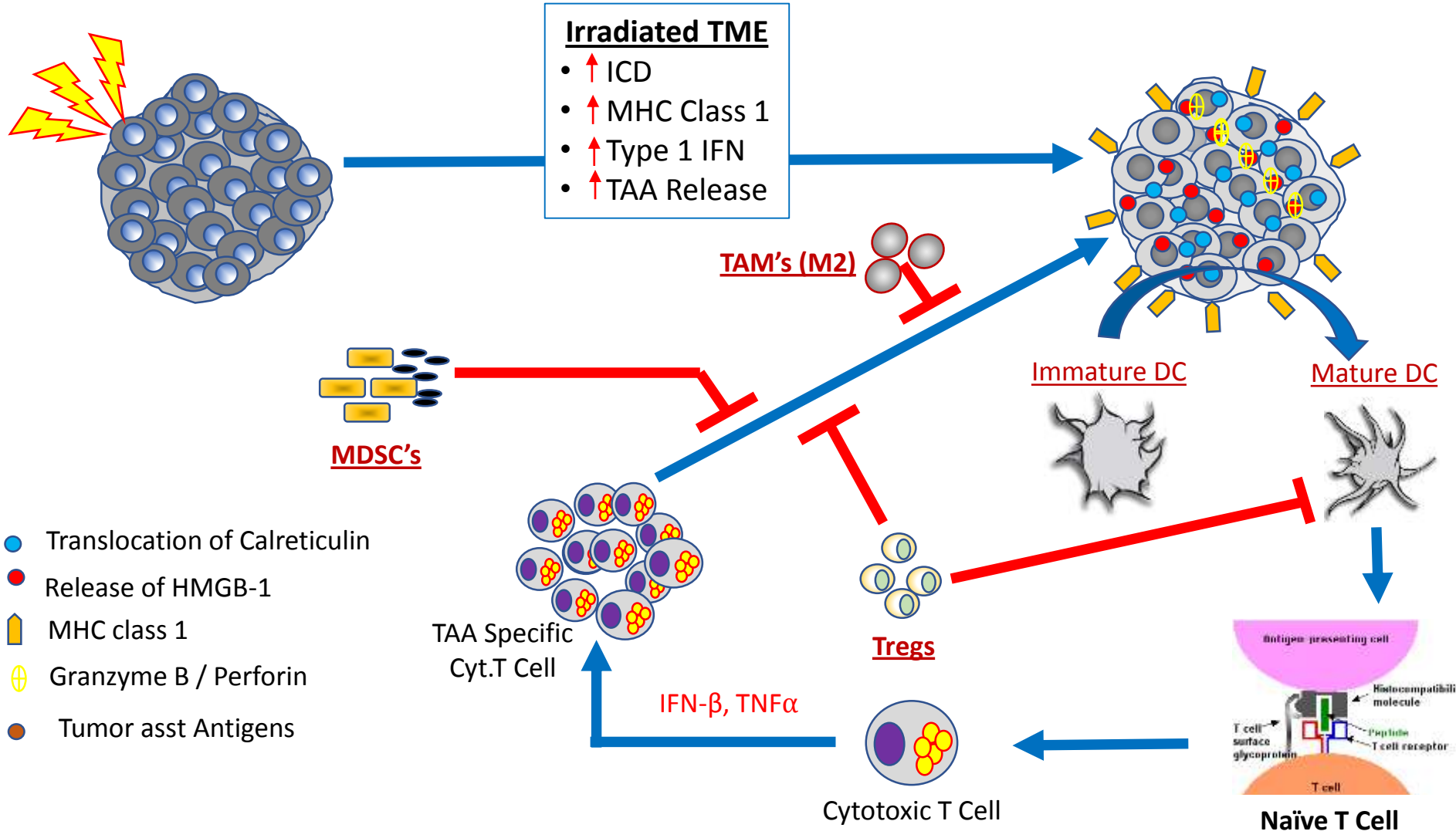
Hepatic irradiation

1. **endothelial cell damage**
2. **stellate cell activation → (MF-Stellate Cell)**

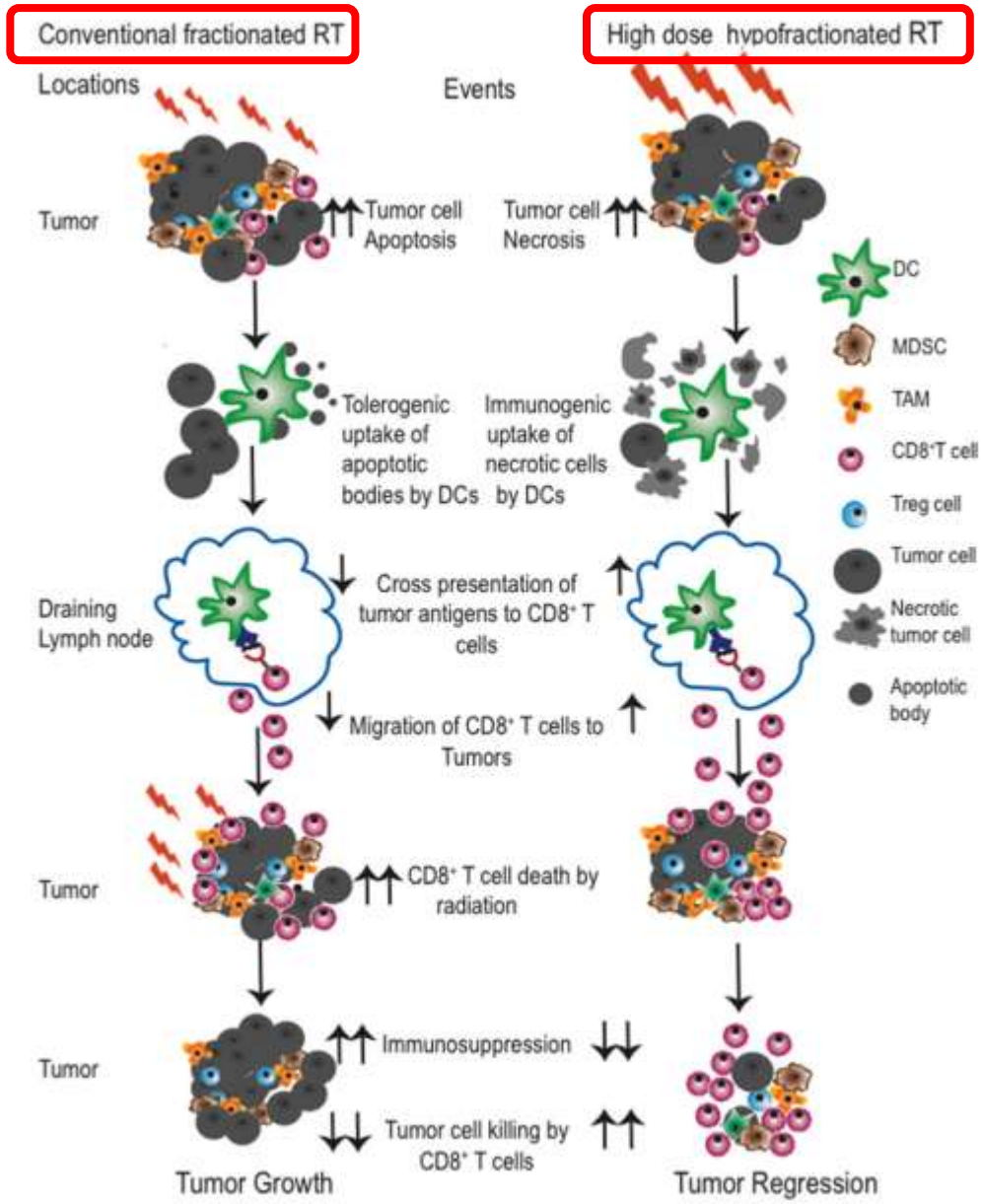
- **High dose Region - perisinusoidal and hepatic fibrosis → Atrophy**
- **Low dose region - modulation of liver regeneration**

  → Compensatory Hypertrophy

Immune Effects of Radiation – Negative



RT immunomodulatory effects



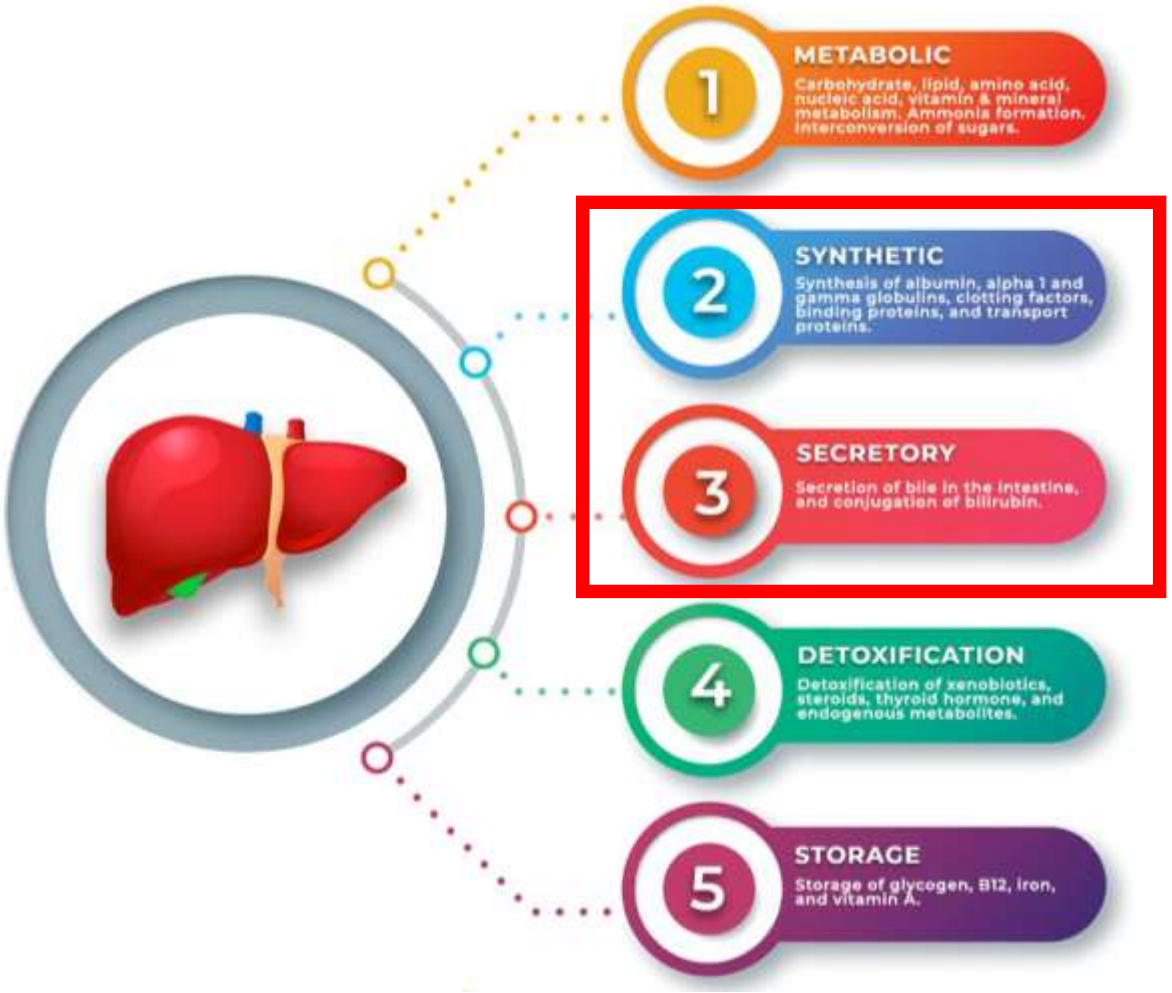
- Conventional RT kills tumor infiltrating CD8+ T cells while sparing immunosuppressive cells such as MDSCs, Treg cells, and TAMS.
- Contrast hypofractionated RT (8gy-12gy SF) the radiation schedule is completed before CD8+ T cell infiltrate the tumor

Suparna etal, https://doi.org/10.1016/j.semradonc.2019.12.006 1

Intended Learning Objectives

- Setting the Stage – Basics Revisted !!
- **Pathological changes after SBRT**
  - **Changes in liver parenchyma**
  - **Changes in Tumor Tissue**
- Radiation Induced Liver Disease (RILD)
- Image Response Evaluation
  - Tools, Criteria
  - Tumor changes & Parenchymal Changes (FLC)

Liver Function



Laboratory data

CPS - Serum albumin, bilirubin and INR.

Clinical: ascites and encephalopathy

ALBI - Serum albumin & Bilirubin

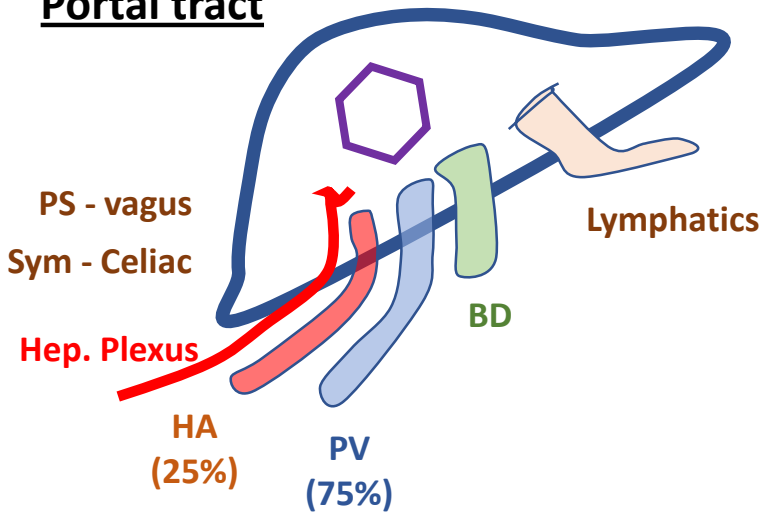
PALBI - Platelet ct., Ser.Albumin, Bilirubin

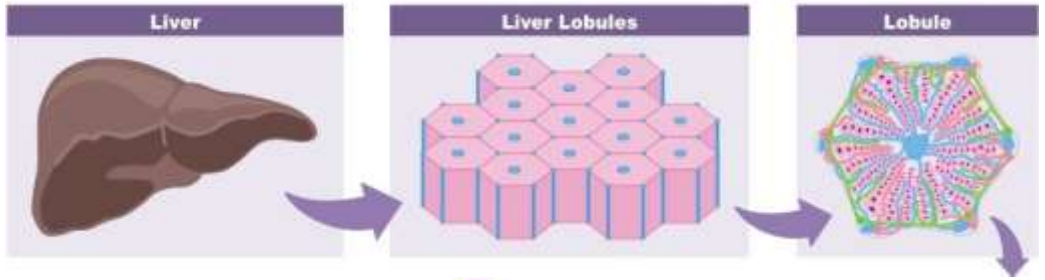
MELD: Serum bilirubin, creatinine, international normalized ratio (INR), and sodium

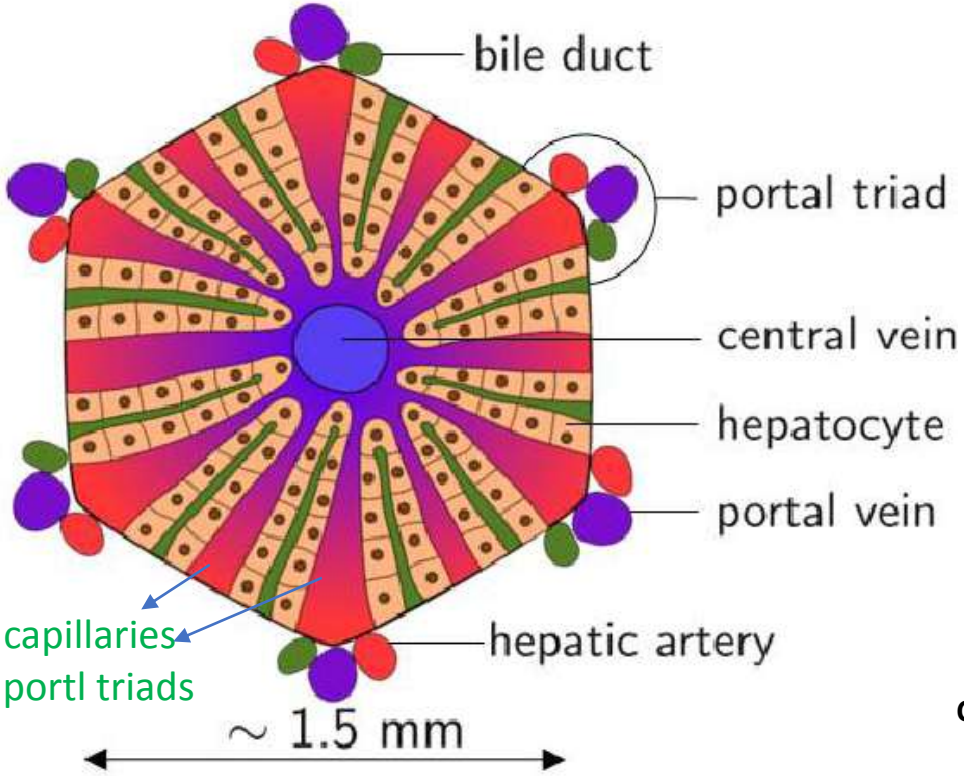
Toxicity: increase of CPS ≥2 or change in absolute (ALBI) score ≥0.5 or ALBI grade ≥1 within 6mo. After SBRT

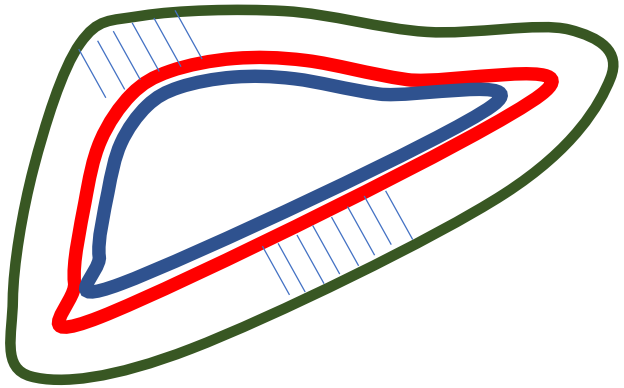
Basic Anatomy – Hepatic Lobule

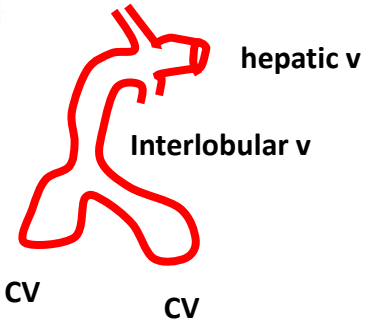
Portal tract











Basic Anatomy – Kupfer Cells – Inflammation

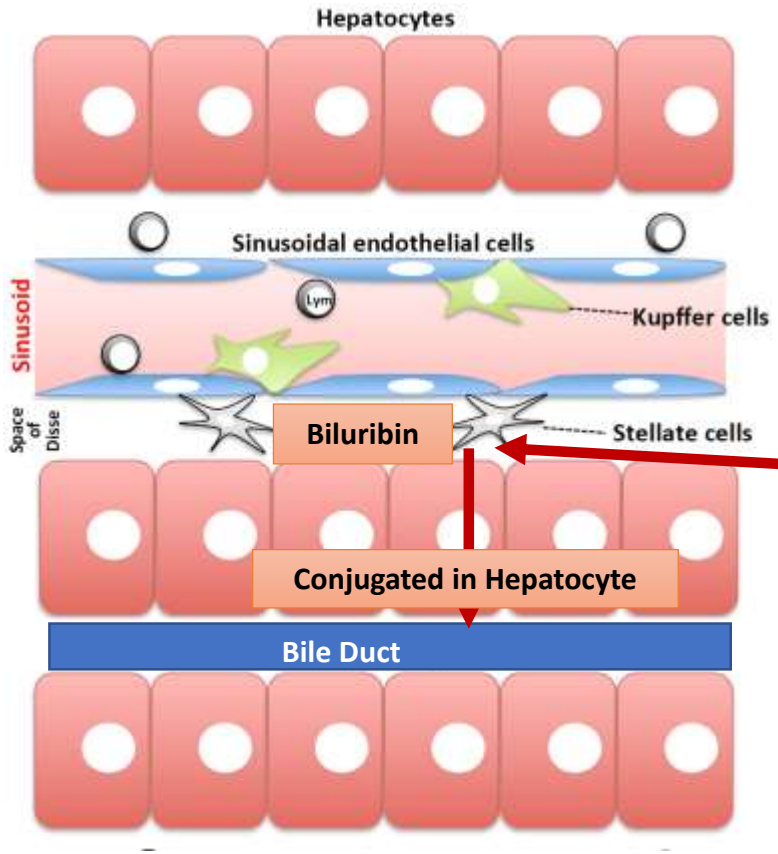
Kuppfer cells Along sinusoids have

Pattern recognition Receptors (TLR4)

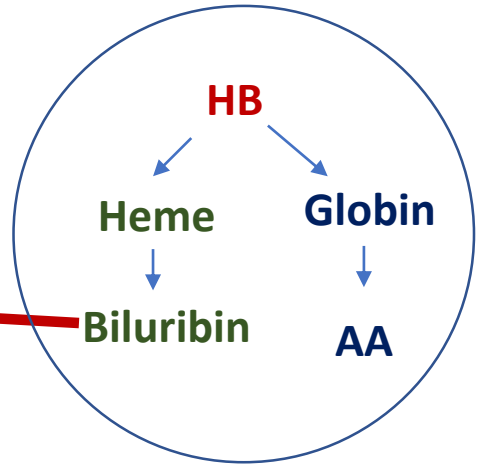
Recognize Danger signals (LPS/FFA)

Activate → Inflammatory cytokines
(TNF, IL1, IL6, ROS, TNF – β, NO, PG)

development of liver injury.

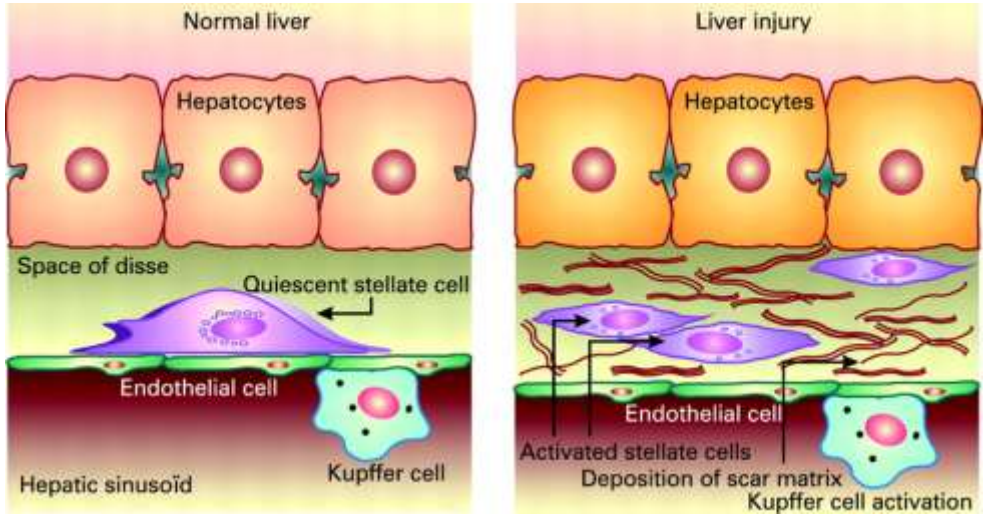


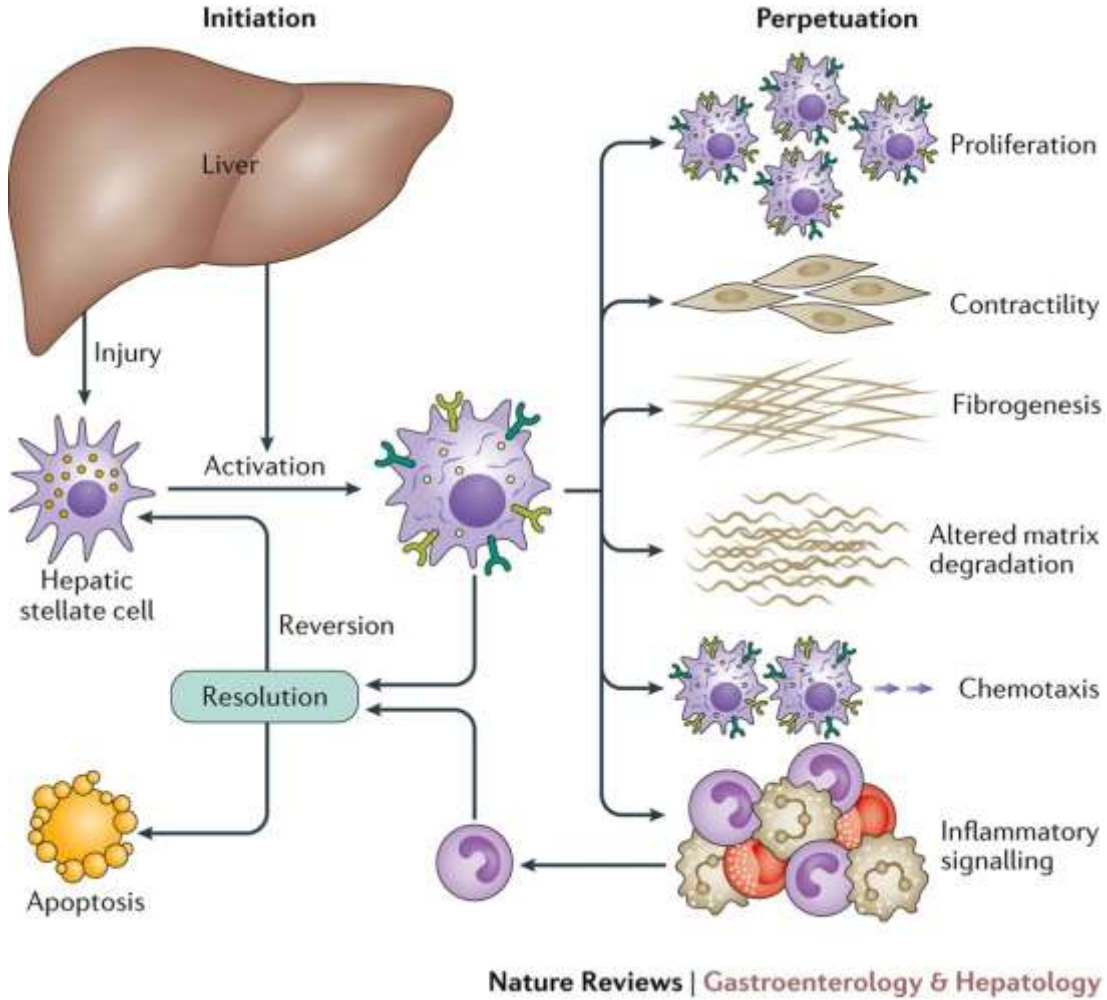
Hb Recycling



Basic Anatomy – Stellate Cells / ITO cells

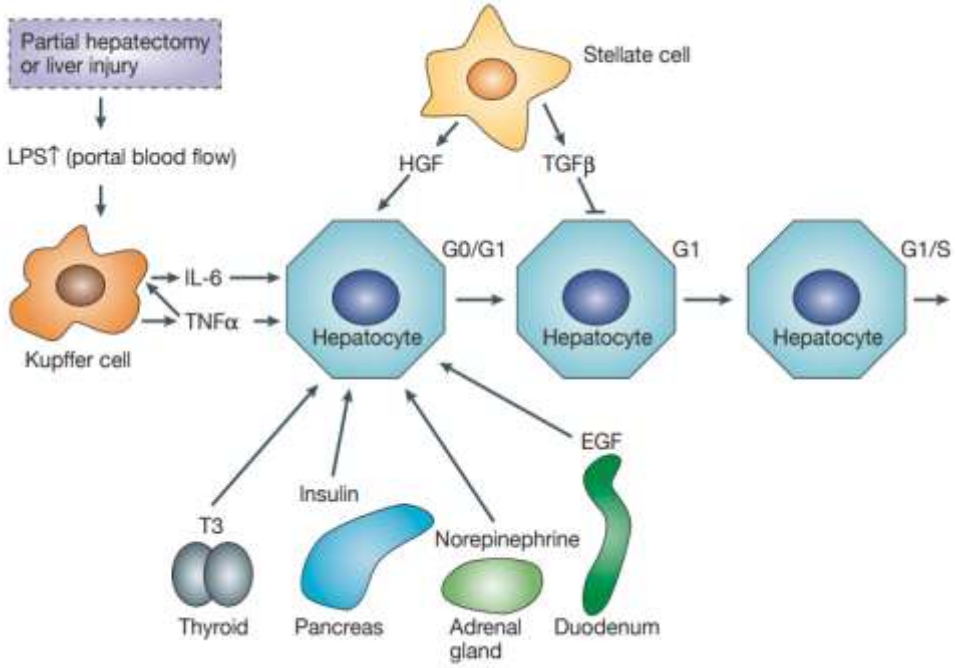
5% Liver

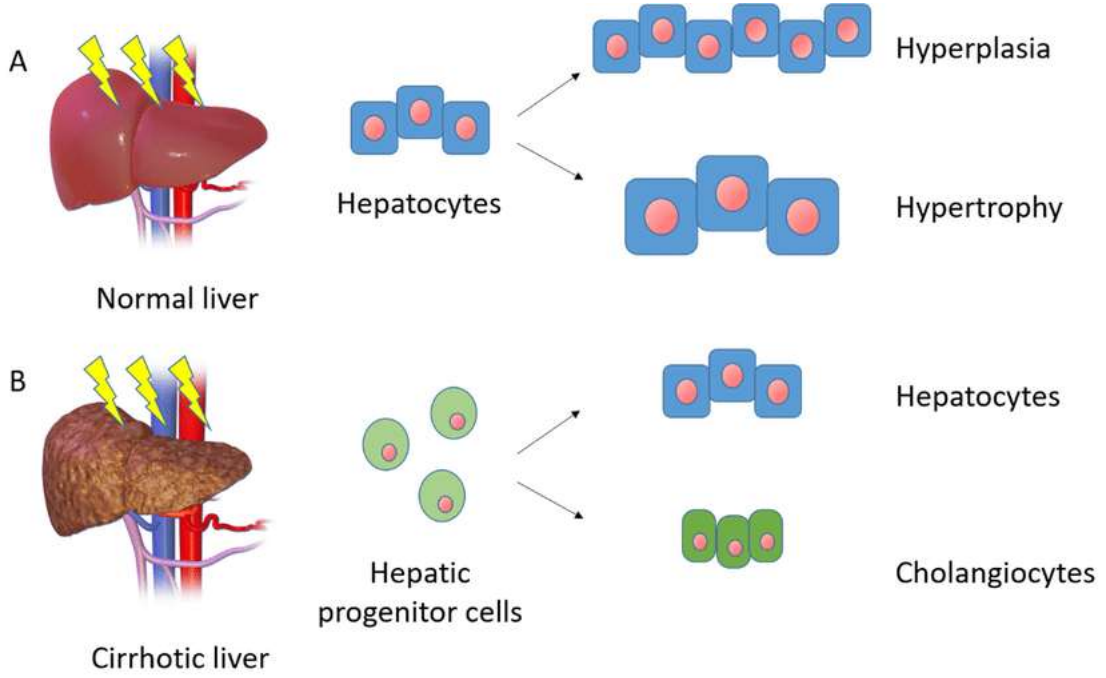




Basic Anatomy – Stellate Cells - Regeneration

Liver regeneration evolved to protect animals -from catastrophic results of liver loss that can be caused by ingested toxins.





Principal liver regen. mechanisms – Hypertrophy & Hyperplasia

Post SBRT - Liver Parenchymal Changes

Hepatic lobules : anatomical & functional units of the liver

Zone I, II, and III
periportal, transition, and pericentral areas

High dose RT

↓

endothelial cell damage

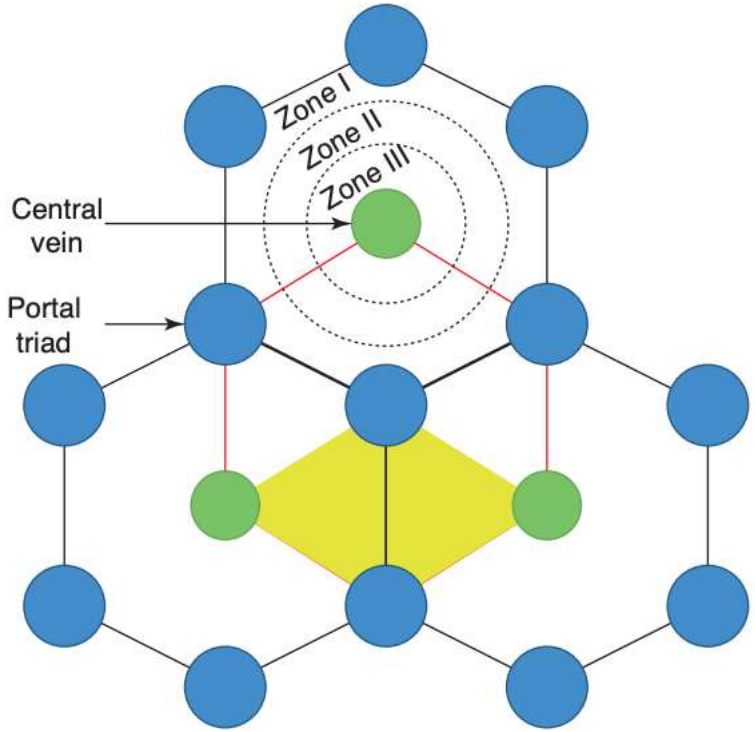
↓

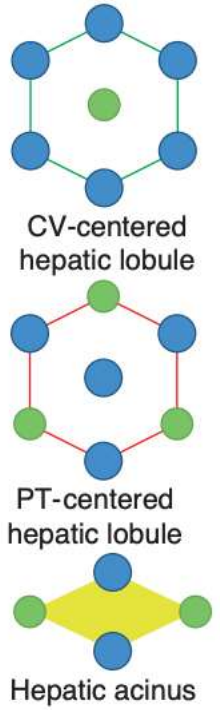
formation of thin fibrin deposits → Traps RBC
Obstruction of the central viens

↓

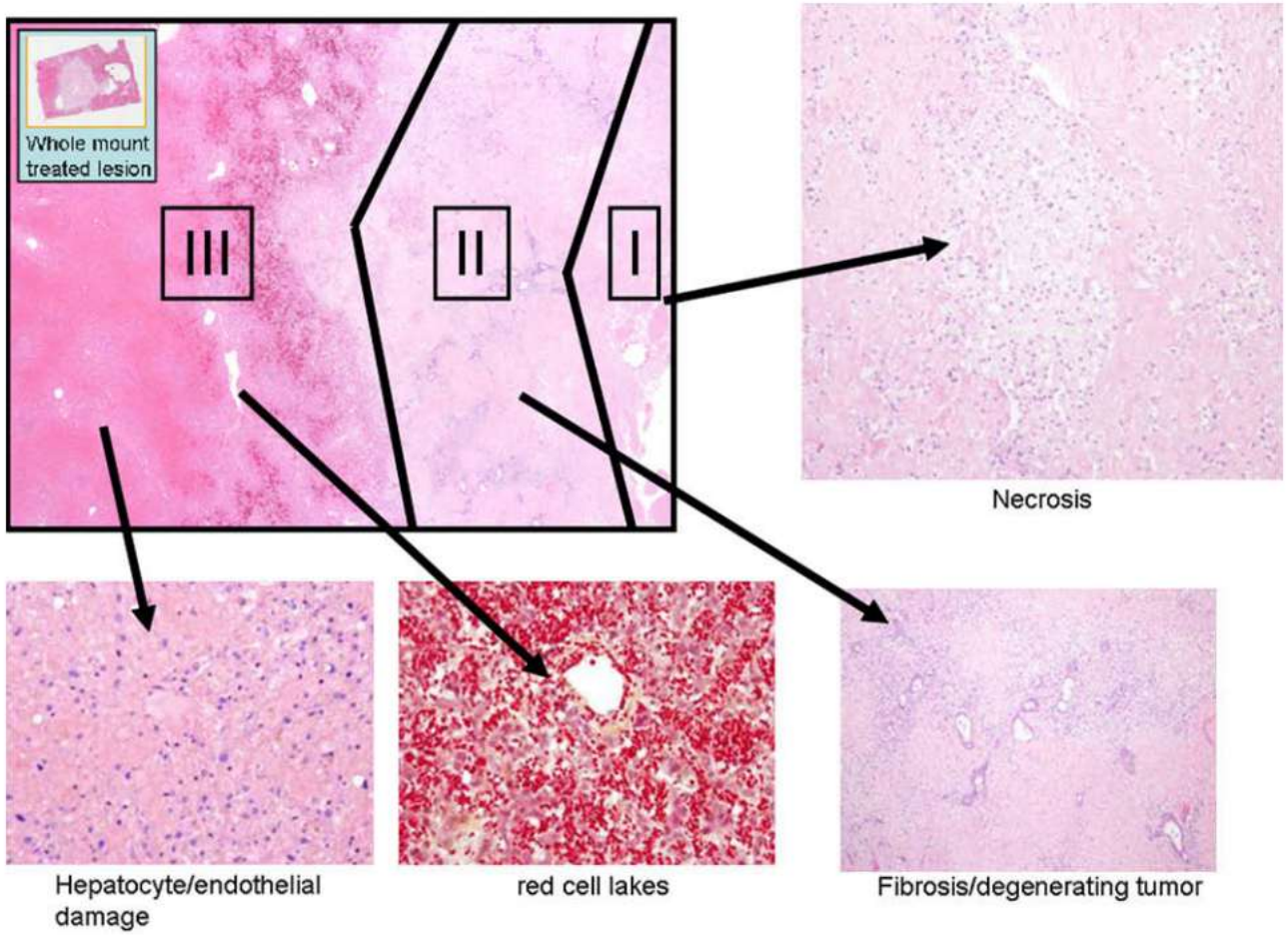
hepatic venule stenosis
sinusoidal artery congestion

ZONE III – HVOD





Zonal Injury Pattern –RILD



Zone 1 - Liquifaction necrosis → maximal total NLV reduction corresponds approx. to the time of onset of Herfarth Type I reaction.

Zone 2 - capillary rich zone (II) with more numerous lymphocytes and occasional foreign body giant cells

Zone 3 : consisted of damaged, but non-necrotic, liver tissue → characteristic of radiation-induced VOD, with marked sinusoidal congestion and disarray of the hepatic cords

Oslen et al, IJROBP,73, Number 5, 2009

Intended Learning Objectives

- Setting the Stage – Basics Revisted !!
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  - Changes in liver parenchyma
  - Changes in Tumor Tissue
- **Radiation Induced Liver Disease (RILD)**
- Image Response Evaluation
  - Tools, Criteria
  - Tumor changes & Parenchymal Changes (FLC)

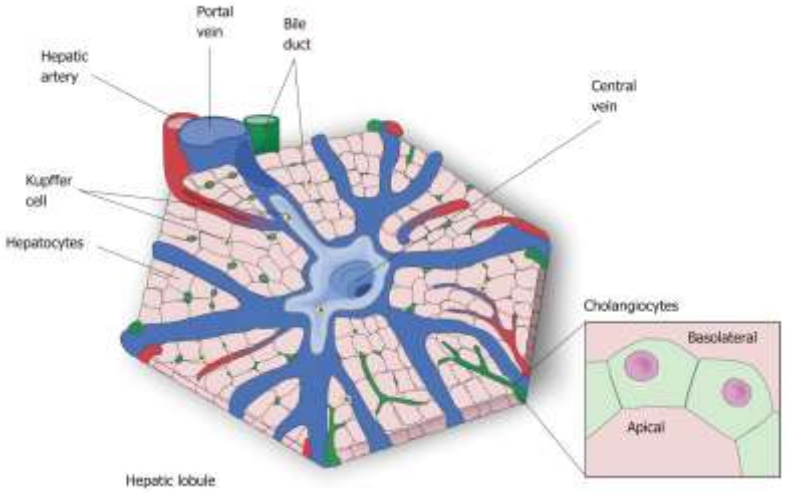
RILD – Basic Concepts

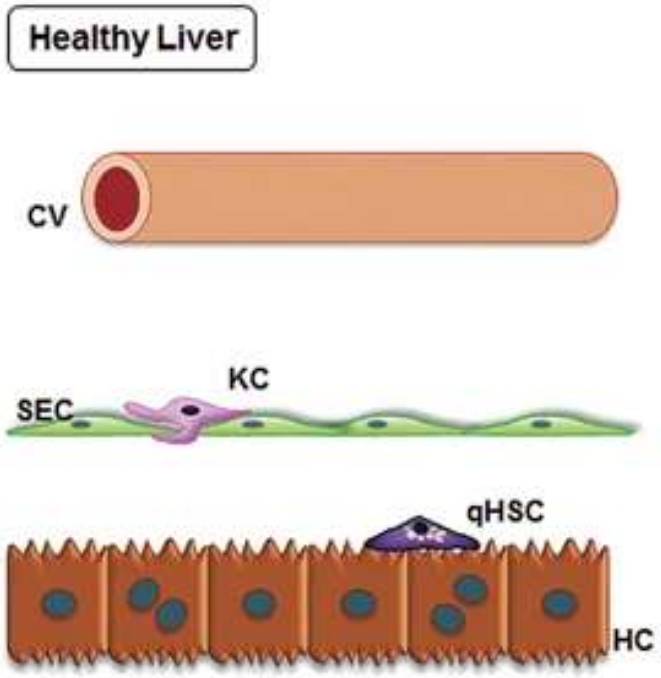
RILD → liver toxicity after high-dose radiotherapy delivered to large liver volumes or when the whole-liver tolerance dose (30–35 Gy) is exceeded during external beam radiotherapy (RT).

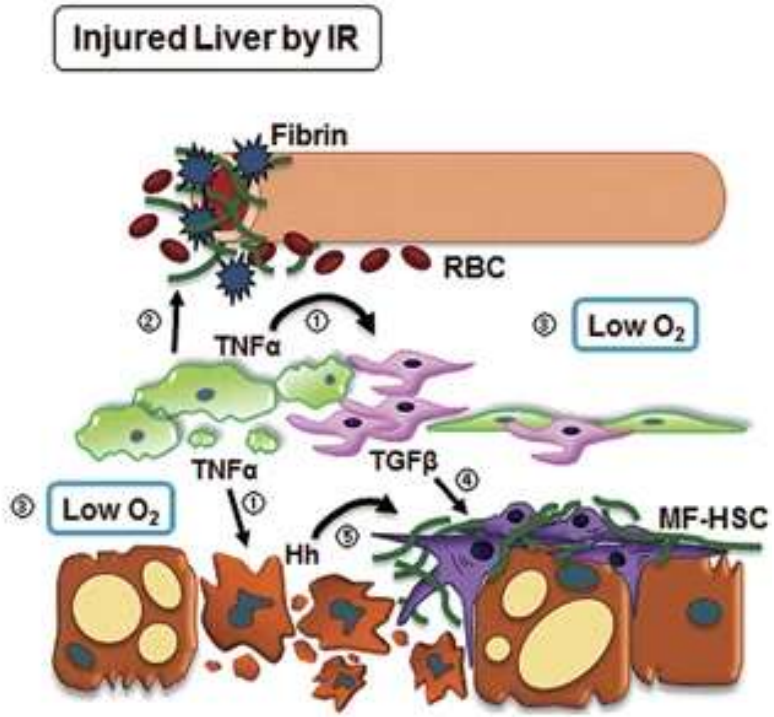
Conformal techniques → Injury occur in the liver parenchyma surrounding irradiated tumors and may be symptomatic → Focal Liver injury / Focal Liver reaction

	Chr. Liver Damage	Fatigue	Abdominal Pain	LFTs	Factors of Child Pugh Score				
					Ascites	T-Bil	Alb	NH3	Plt
Classical RILD	-	+	+	**ALP** ↑↑ (>2 UL)	+	(↑)	(↓)	(↑)	(↓)
Non-Classical RILD	+ (cirrhosis) (hepatitis)	+	-	**GOT/GPT** ↑↑ (>5 UL)	+	↑	↓	↑	↓

RILD - Pathophysiology



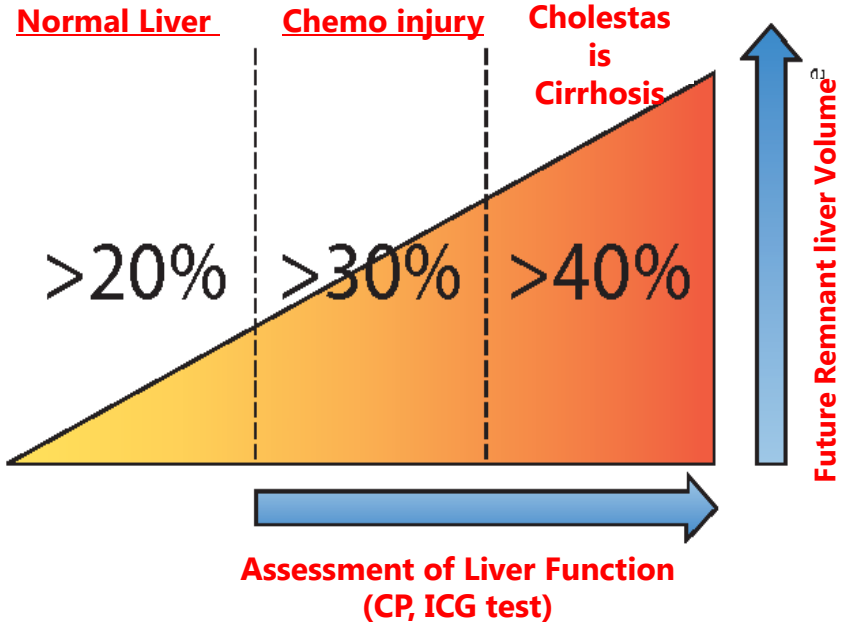




Non classic RILD – Poorly understood - involves loss of regenerating hepatocytes and reactivation of hepatitis

Avoidance - Future Remnant Liver Reserve

It's not What you Take out, "it is what you Leave behind" → sustain life & allow for hepatic regeneration



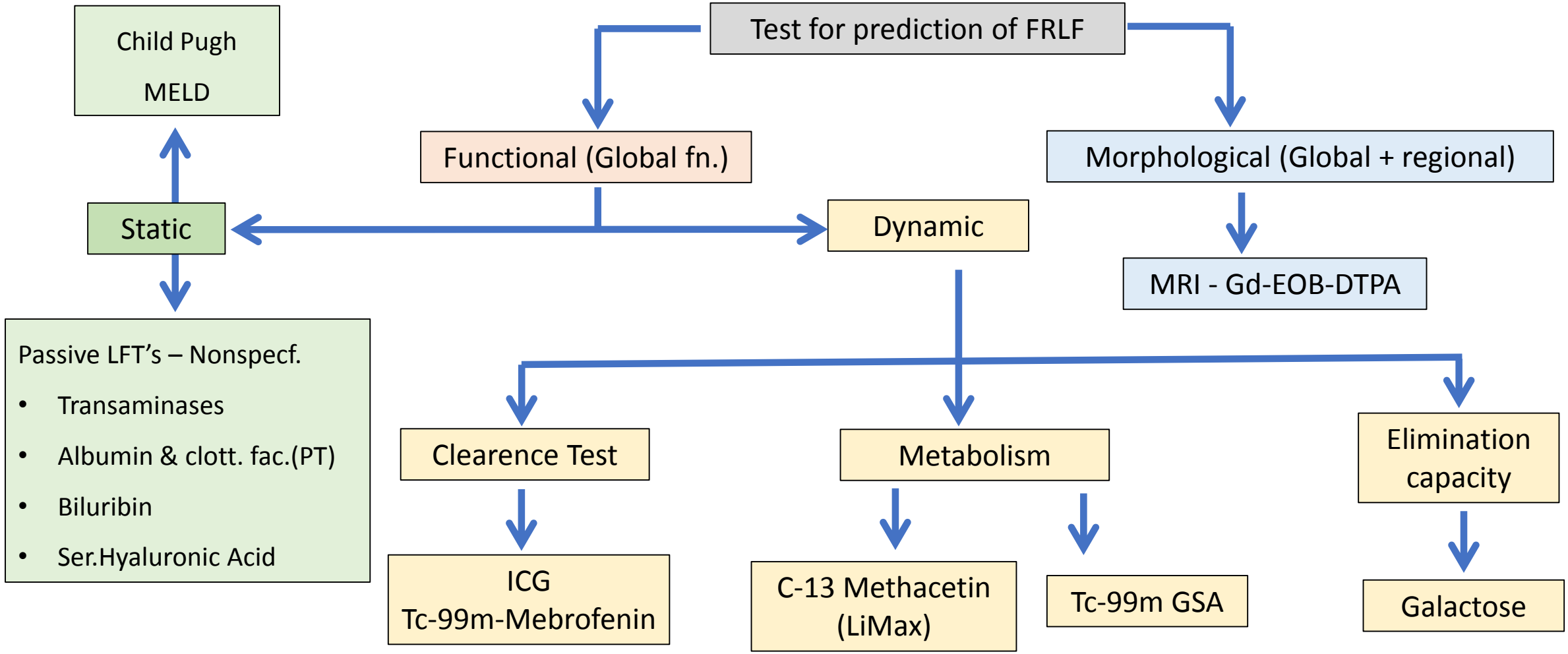
Normal Liver Volume
≒ 1600

40% Liver needs to protected
= 650cc normal Liver

Dosimetric Predictors

OAR	UF-3#	UF-5#
Uninvolved liver (Non cirrhotic)	Mean <12gy >700 cc <15gy	Mean <15gy >700 cc <21gy
Uninvolved liver (CP class A)	Mean <12gy >700 cc <15gy	Mean <13-15gy >700ccc <15gy
Uninvolved liver (CP class B)	--	Mean <10gy >700ccc <10gy >500cc <7gy
Central Liver	--	V26 <40cm3 V21 <37cm3 Mean < 19gy

Future Remnant Liver Reserve

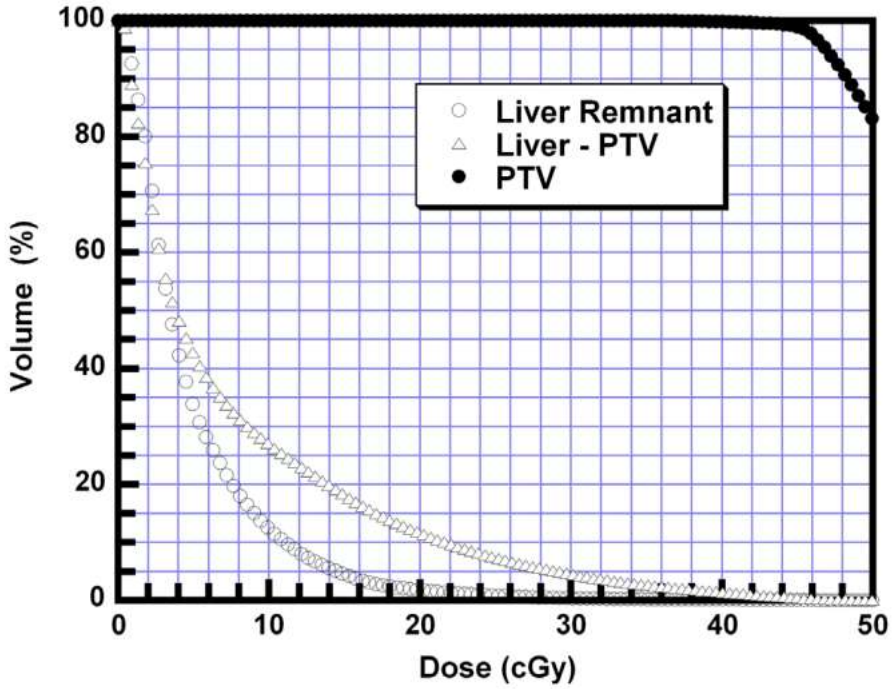


Mebrofen DHART (Differential Hepatic Avoidance RT)

Mebrofen = IAA - 2 mols. Of lidocaine

Liver – 100% Primary uptake

Voxels with higher uptake of 99mTc-mebrofenin were transferred to the planning CT as an avoidance structures.

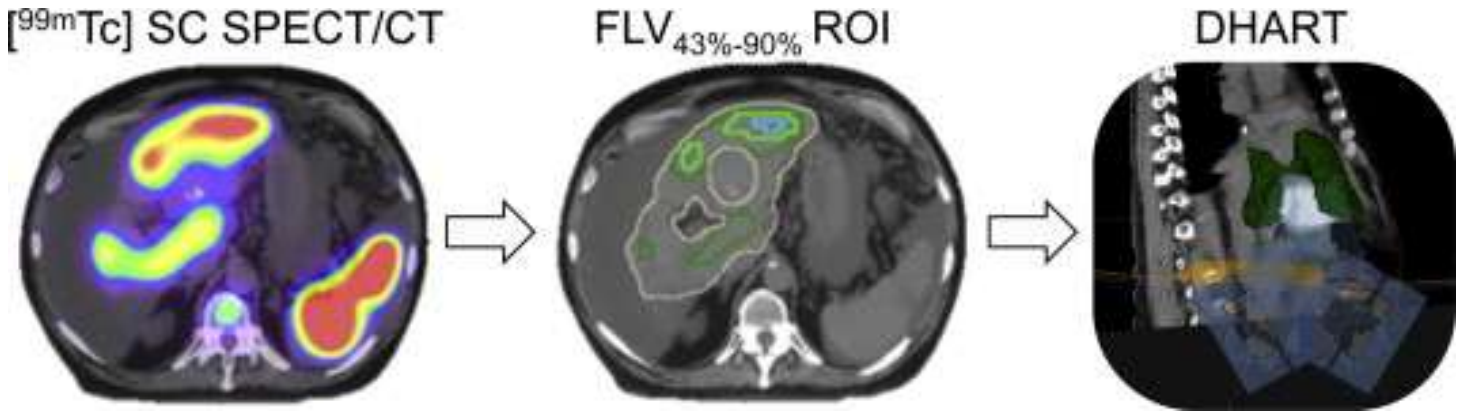


SC DHART - (Differential Hepatic Avoidance RT)

^{99m}Tc-Sulfur Colloid (SC) SPECT-CT

- Sulphur colloid → taken by RES Kupffer cells → related to hepatocyte function.
  - normal healthy liver → 80–85% isotope sequestered
  - cirrhosis or parenchymal liver damage→ depression of the reticuloendothelial system → decreased uptake of sulfur colloid

End-exhale attenuation correction SEPCT- CT – DIBH Scan

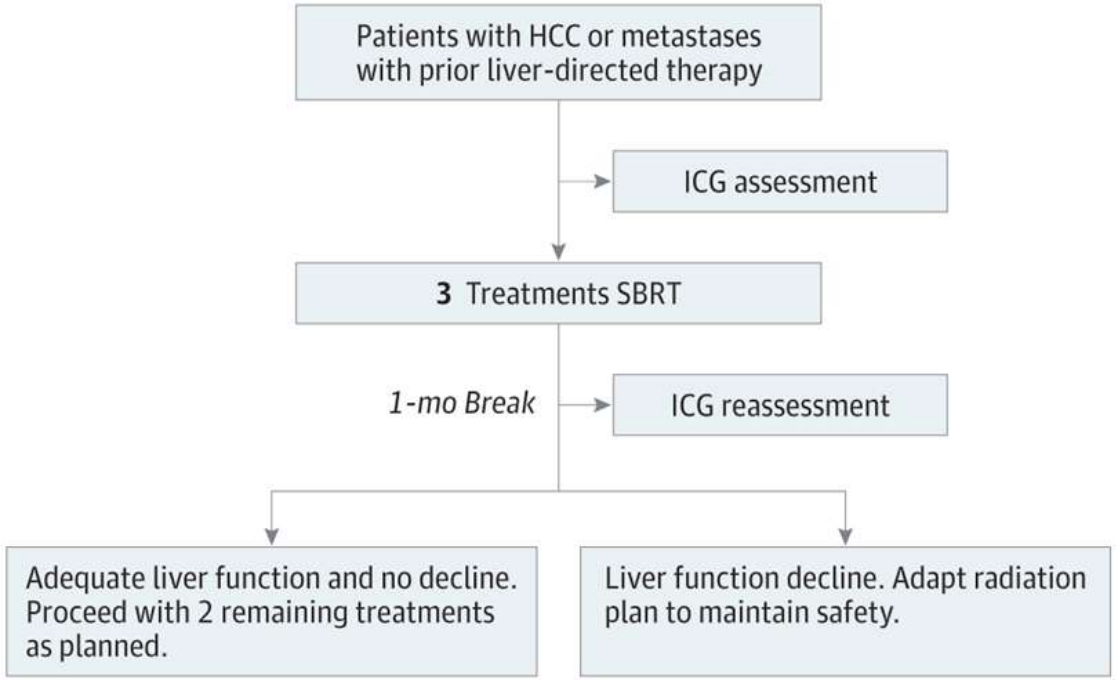


Spl Situation → Child Pugh B

Imaging Global Liver Function – Pre SBRT

Indocyanine Green

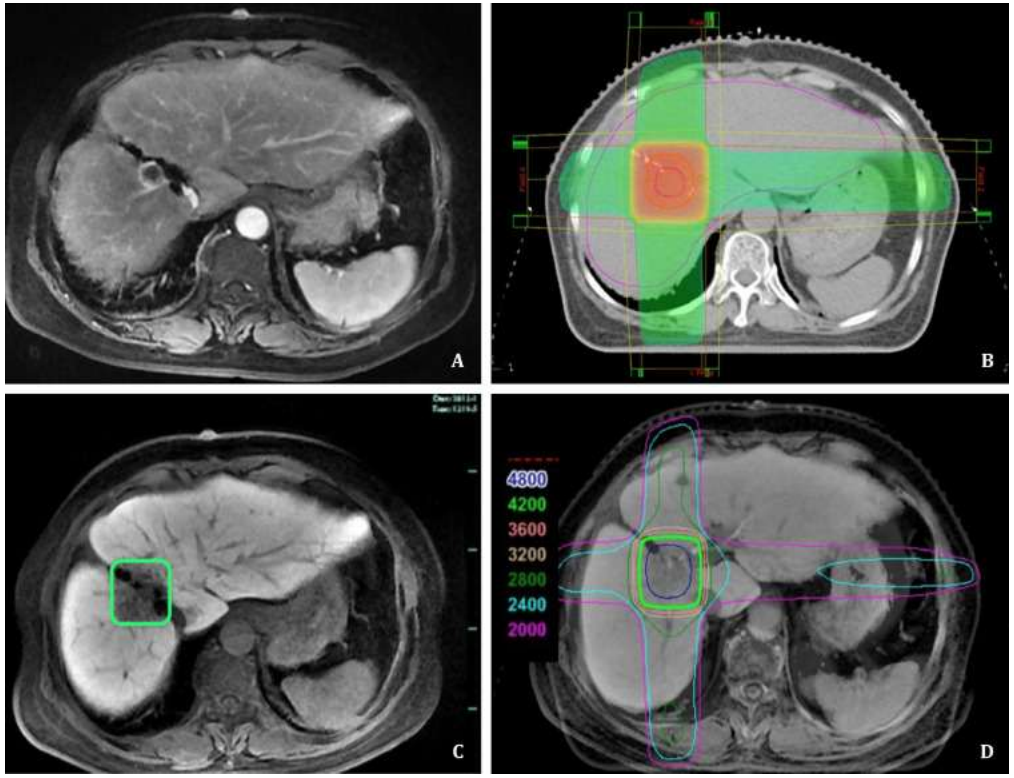
- Indocyanin green (ICG) is a water-soluble, inert compound that binds to albumin in the plasma after intravenous injection.
- ICG is selectively taken up by hepatocytes and is excreted unmetabolized into the bile in an ATP-dependent fashion.
- Because ICG is not recirculated into the enterohepatic system, its excretion rate in bile reflects the hepatic excretory function and energy status.
- Hepatic function can be assessed by measuring ICG clearance and ICG retention



JAMA Oncol. 2018;4(1):40-47. doi:10.1001/jamaoncol.2017.2303

Imaging Global Liver Function – Post SBRT

Gd-EOB-DTPA



Gd-EOB-DTPA → preferentially absorbed by hepatocytes and eventually excreted via the biliary pathway

OATP-8 and OATP-2 transporter proteins (apical membrane of hepatocytes) →facilitate the uptake area of Gd-EOB-DTPA in functioning hepatocytes.

Radiation Exposure → decrease transporter protein expression & upregulate the expression of excretion proteins → decrease in signal intensity in HPB areas

Serum Markers – Liver Toxicity

Biomarkers	
Inflammatory	TNFalpha and IL1β, IL8, sIL2R, VEGF
Endothelial	von Willebrand factor (vWF), thrombomodulin, and soluble intercellular adhesion molecule-1 (sICAM-1), PAI-1 (plasminogen activation inhibitor 1), endothelin 1, SDF-1 and CXCL12
Fibrosis	N-terminal propeptide for type III procollagen (P-III-P), TGF-β
Coagulation	Protein C, Antithrombin III, plasminogen
Circulating	Serum hyaluronic acid
Metabolomics	Plasma metabolites, regulation of amino acid and lipid metabolism, change in energy metabolism, calcium signaling, choline metabolism, pentose and purine metabolism and microbiome

- CD40L (also known as CD154) is a member of the TNF family of cytokines.
  - Platelet derived or present on a subset of T cells.
  - Low platelet counts are associated with poor liver function in patients with advanced cirrhosis.

- HGF - primary ligand for the receptor tyrosine kinase c-MET
  - Important role in liver regeneration
  - Associated with tumor invasion and metastasis

high HGF and low CD40L were potentially associated with an increase in Child-Pugh score following treatment.

↓ Alternate Liver directed therapies

↓ Decrease the dose in SBRT

RILD – Therapeutic Approaches !

Main Approach - Prevention & Risk Minimisation

Rx Mostly supportive

- ✓ diuretics to relieve fuid retention,
- ✓ analgesics for pain,
- ✓ paracentesis for tense ascites,
- ✓ correction of coagulopathy, and
- ✓ steroids to prevent hepatic congestion
- ✓ tPA/heparin → Early during the course of VOD/SOS - Avoided in patients with multi-organ failure

HBV reactivation:

- HBsAg and anti-HBc (total or immunoglobulin G) testing
  - **HBsAg +ve and anti-HBc-+ve → Anti HBV Prophylaxis**
    - **Preferred Drug** – High Resistance Barrier – Interferon α, Entecavir
    - **Not Preferrred** - lamivudine, adefovir, and telbivudine.
  - **HBsAg -ve and anti-HBc-+ve →** monitored with ALT, HBV DNA, and HBsAg with the intent for on-demand therapy

Hepatocyte Transplatation: Intraportal transplantation of LSEC with HGF

→ engraftment and gradual regeneration of the radiation-damaged hepatic sinusoidal endothelium by the donor cells.

Intended Learning Objectives

- Setting the Stage – Basics Revisted !!
- Pathological changes after SBRT
  - Changes in liver parenchyma
  - Changes in Tumor Tissue
- Radiation Induced Liver Disease (RILD)
- **Image Response Evaluation**
  - **Tools, Criteria**
  - **Tumor changes & Parenchymal Changes (FLC)**

Imaging Tumor Response – Preferred Tools

1. **Preferred Tool: Dynamic Contrast CT** except:
   - Post TACE – Lipoidal – Beam hardening → Difficulty Tumor viable enhancement
   - Post Fudicials artefactcs

CE – MRI

2. MRI : DWI with ADC Map

- biomarker of cellularity
- Decreased DWI signal – Increased ADC value – Hypocellularity - Favourable Signal

3. MRI : Hepatobil. contrast

Gd-EOB-DTPA / Primovist/Eovist

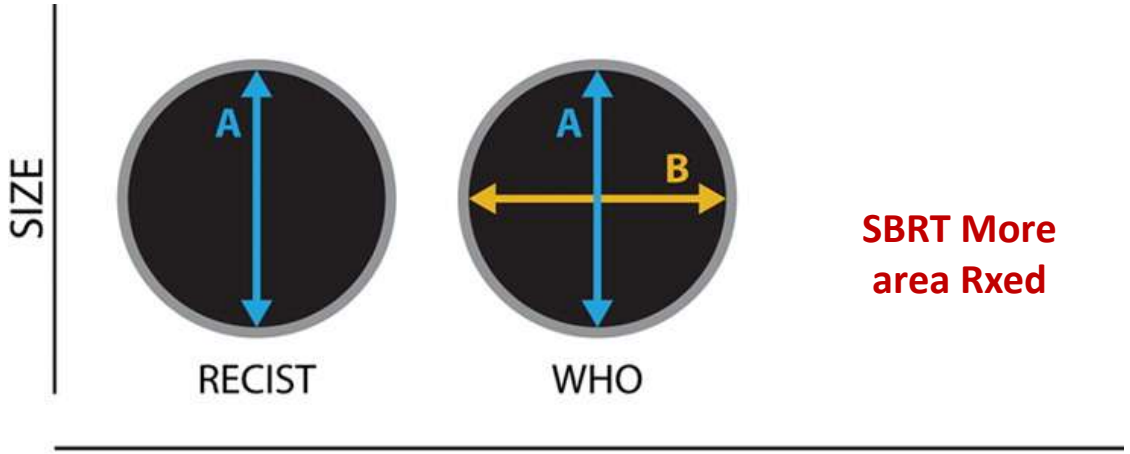
- Surrogate contrast markers of hepatocellular function → Selectively internalised by hepatocyte.
- FLR's

4. PET-CT

- poor sensitivity - 50–55% in the detection of HCC, particularly for small and/or well-differentiated tumors
- PET not mandatory for HCC.
- Nonshrinking tumors after RT → Metabolic activity tumor relative to background liver activity

Imaging Tumor Response

Classification Systems



SBRT More area Rxed

Imaging criteria Response Assessment esp. Hypervascular Tumors:

1. arterial phase hyperenhancement (APHE)
2. washout (WO) appearance,
3. enhancement similar to pretreatment, and
4. change in size.

Ideal Imaging : 3 months after Rx.

Classification Systems

Table 19.1 Comparison of imaging response evaluation criteria

Response	WHO	RECIST 1.0 and 1.1	EASL	mRECIST
Complete response	Disappearance of all target lesions	Disappearance of all target lesions	Disappearance of intratumoral arterial enhancement in all target lesions	Disappearance of intratumoral arterial enhancement in all target lesions
Partial response	≥50% decrease in the sum of the products of bidimensional diameters of the target lesions	≥30% decrease in the sum of the greatest unidimensional diameters of the target lesions	≥50% decrease in the sum of the product of bidimensional diameters of the target enhancing area	≥30% decrease in the sum of the greatest unidimensional diameters of the target enhancing area
Stable disease	Neither PR nor PD	Neither PR nor PD	Neither PR nor PD	Neither PR nor PD
Progressive disease	≥25% increase in the sum of the products of bidimensional diameters of the target lesions or development of new lesions	≥20% increase in the sum of the greatest unidimensional diameters of the target lesions or development of new lesions	≥25% increase in the sum of the product of bidimensional diameters of the target enhancing area or development of new lesions	≥20% increase in the sum of the greatest unidimensional diameters of the target enhancing area or development of new lesions

CR complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease

Reduced Enhancement

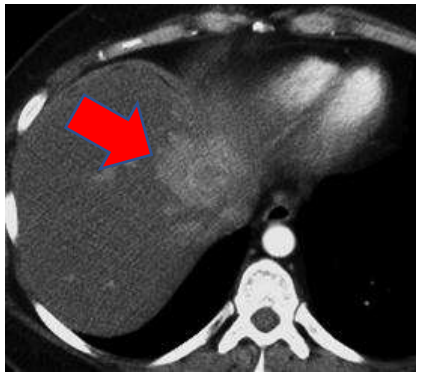
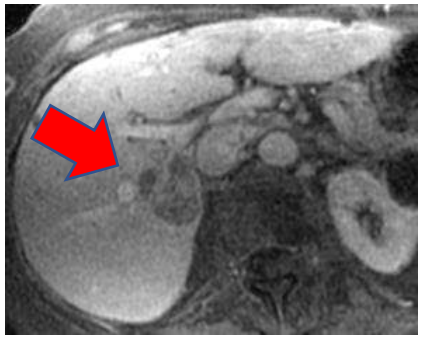
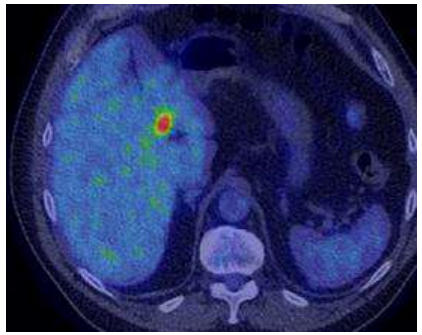
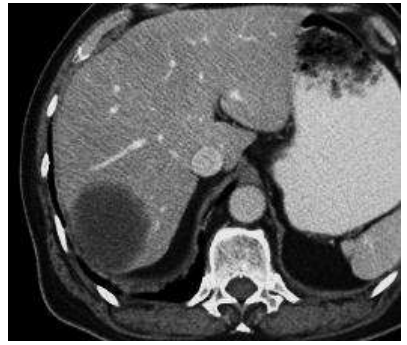
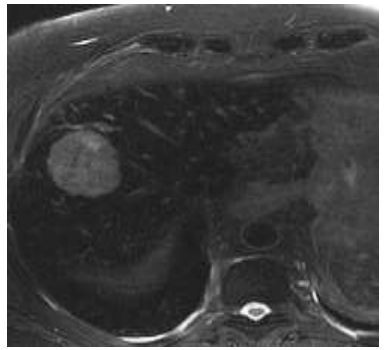
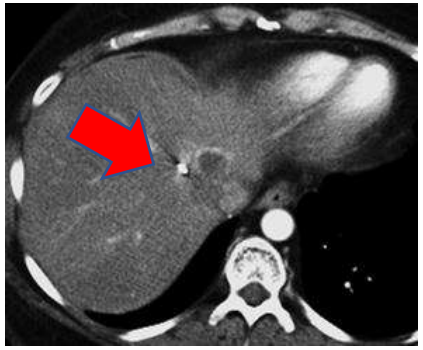
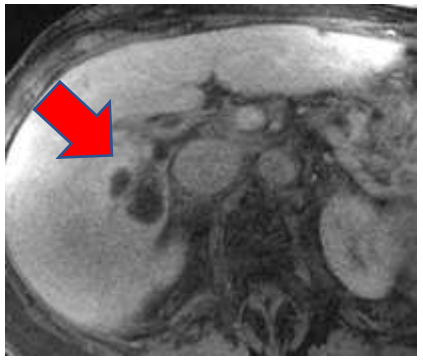
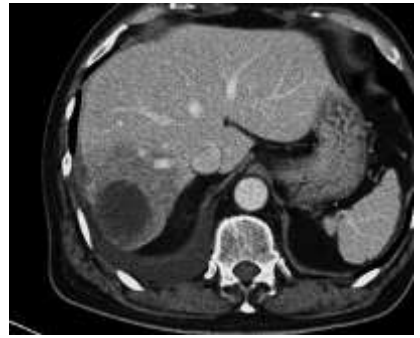
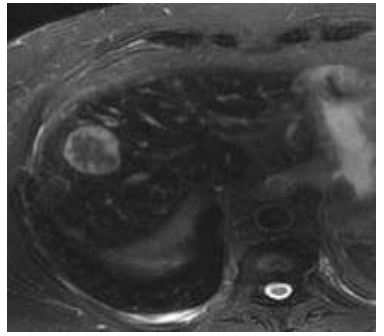
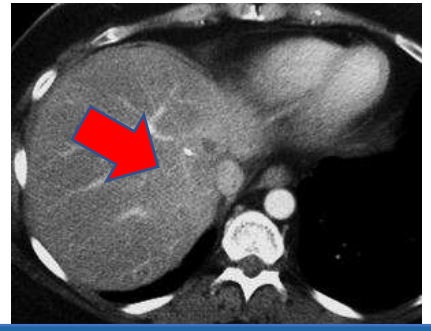
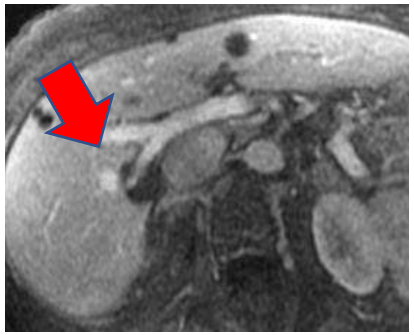
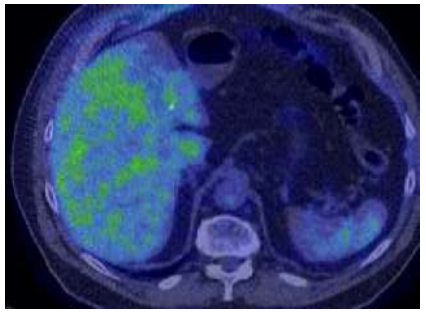
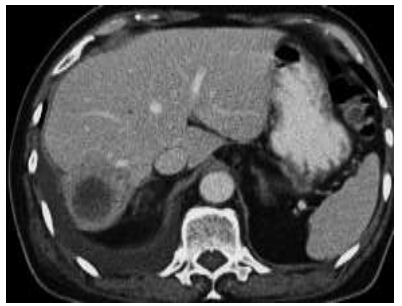
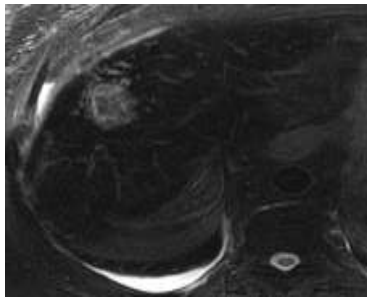
Reduced FDG Uptake

Gradual Redtn over mo.

Pre-Rx

3mo.

6 mo.

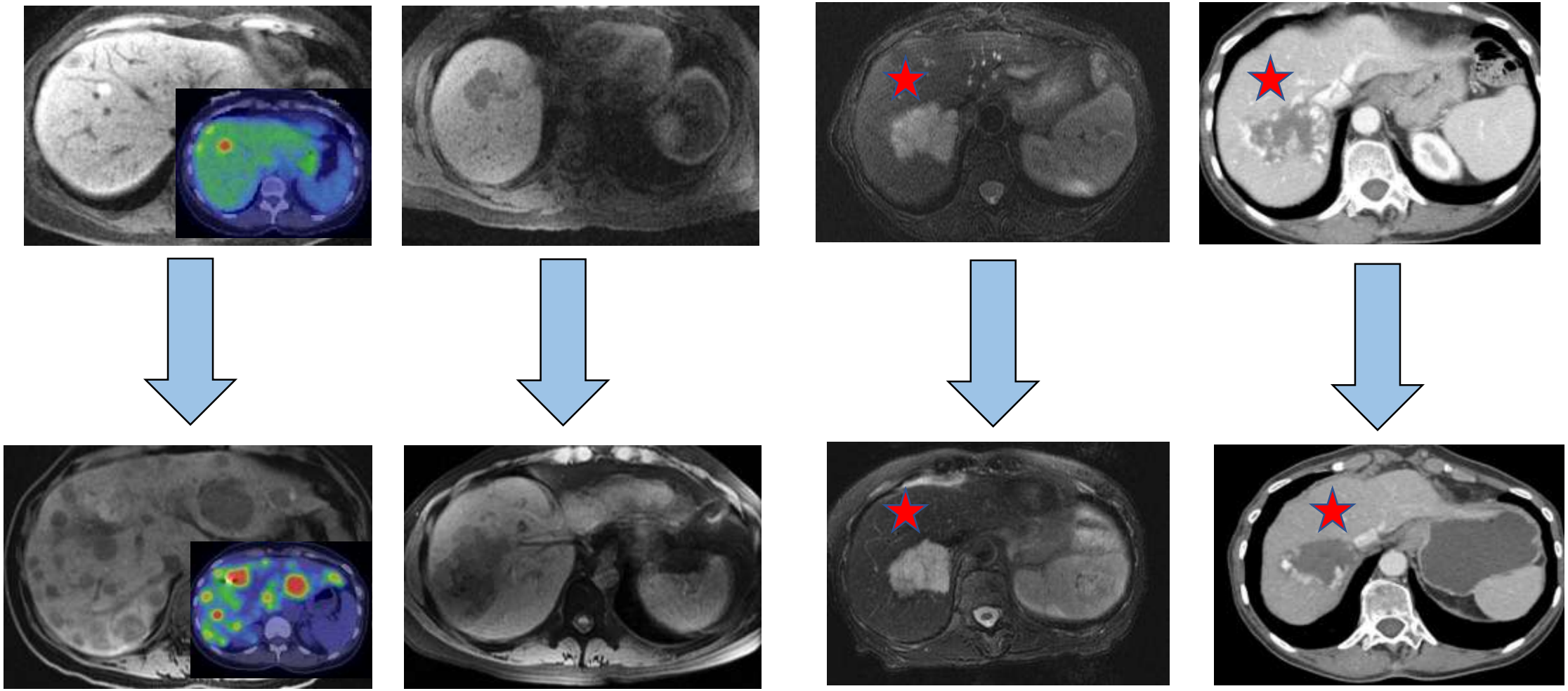















Gradual Progress over mo.

Minimal Change Post SBRT

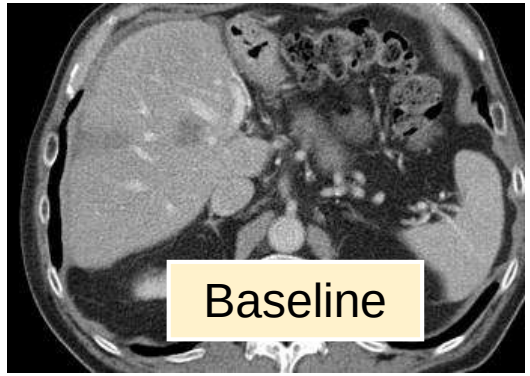
Pre-Rx

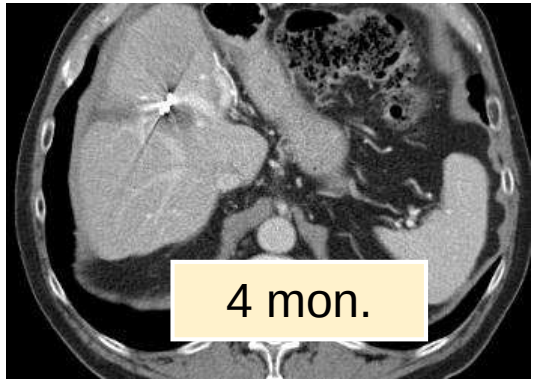
8 mon.

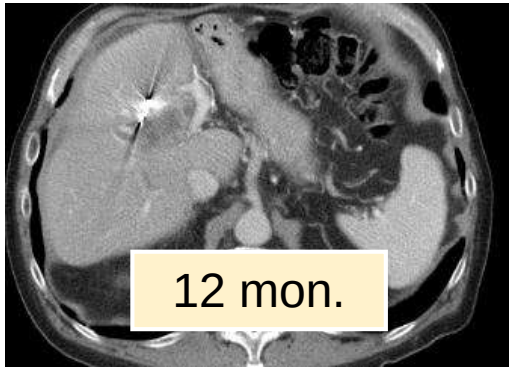


Response Evaluation pitfall - Fiducials

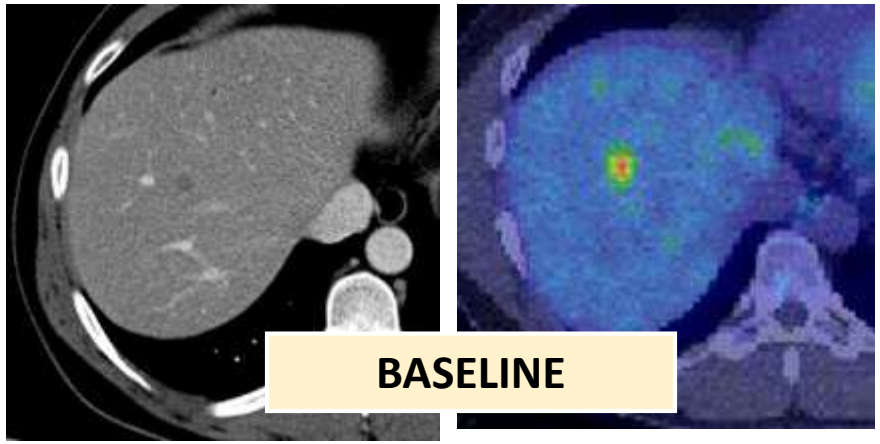
CT Scan
Streak Artifacts

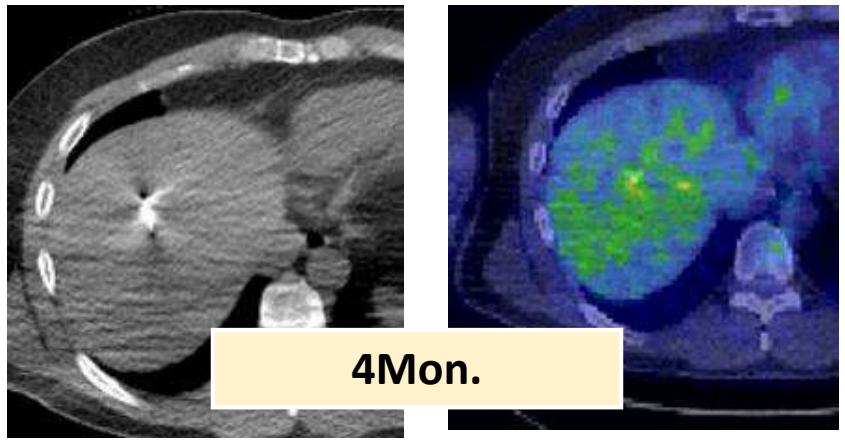






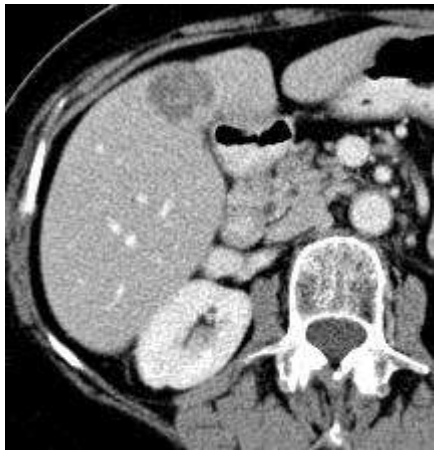
PET Scan



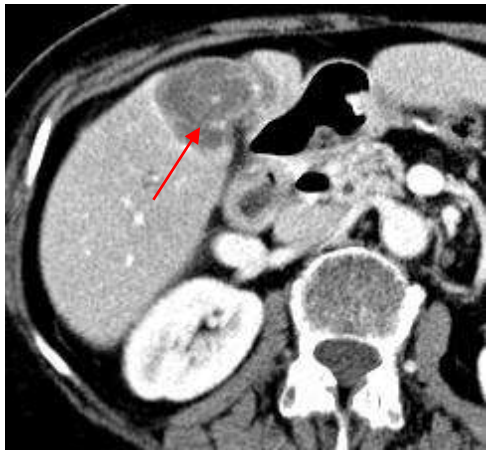


Response Evaluation pitfall

Baseline



4 mon.



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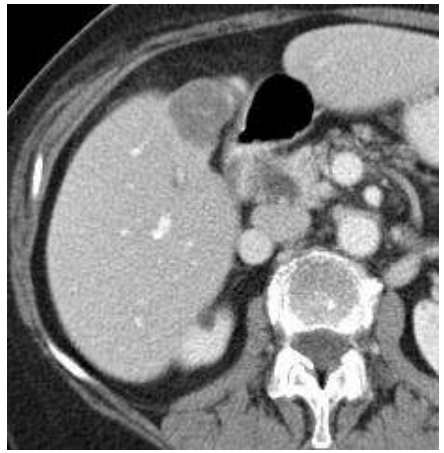
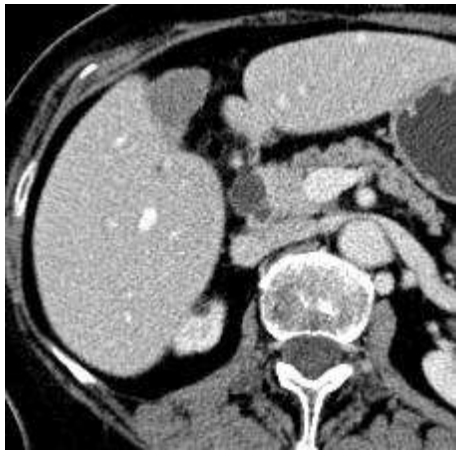
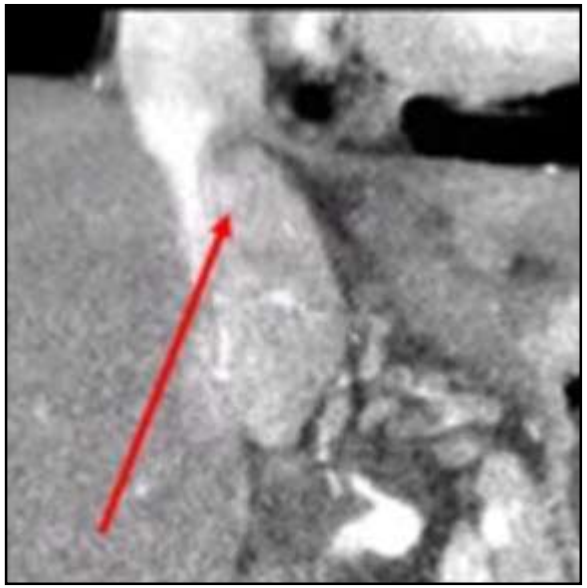


24 mon.

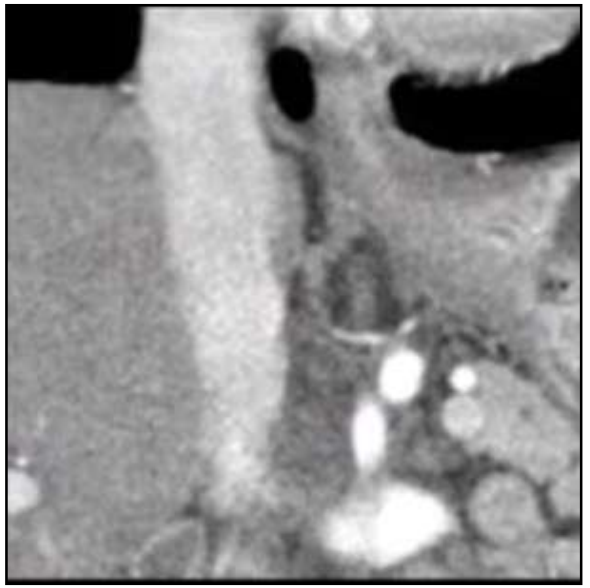


Hypodense FLR around tumor should not be interpreted as increase in size of treated lesion as reduction in size usually occurs after 3-6 months post SBRT

Response Evaluation – Portal Venous Thrombus



Portal Vien tumor thrombus



6mo. Post SBRT

Focal Liver Reactions – Liver Parenchymal Changes

FLR represents two simultaneous processes in the liver:

(1) atrophy and death of hepatocytes with congestive changes in sinusoids and

(2) physiologic repair by the liver

Normal liver tissue → decrease in density - time-dependent fashion and

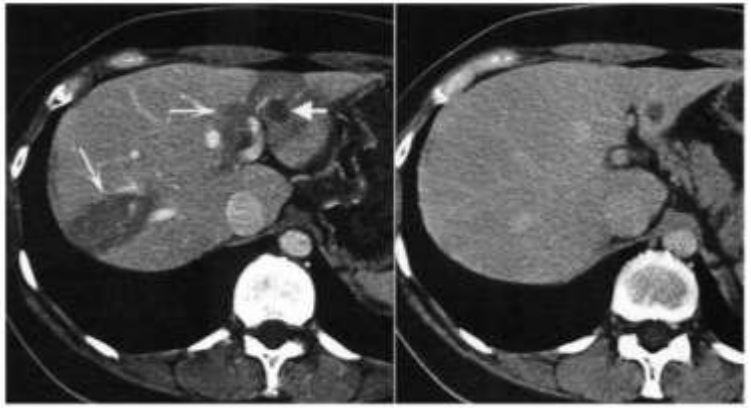
1. Radiation dose & fractionation
2. Concurrent therapies → Chemoembolisation

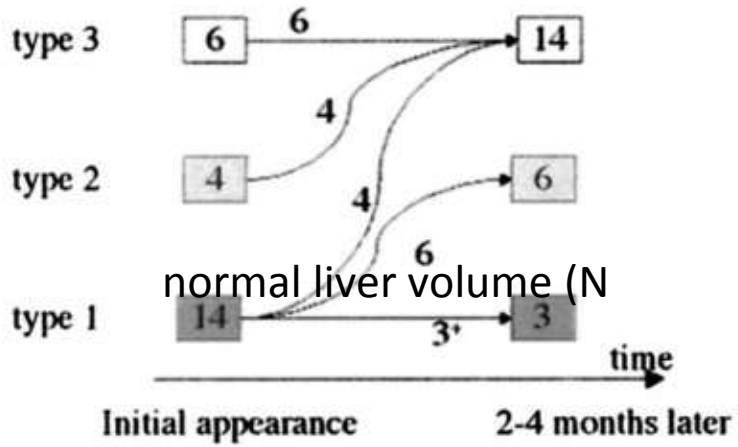
within 3 – 6mo. postRx best for FLR assessment

Herfarth Liver Reactions – Mets.- Post SBRT

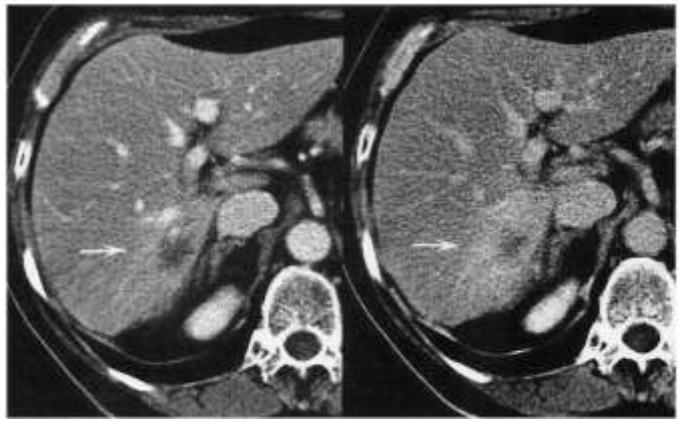
normal liver volume → decreased transiently at 2–3 months → regenerate at 3–8 months after SBRT

Basis of the density of the irradiated areas in the portal-venous or late phase after contrast agent administration.





normal liver volume (N



Herfarth type 1

PVP: Hypodense

Late Ph: Isodense

Herfarth type 2

PVP: Hypodense

Late Ph: Hyperdense

Herfarth type 3

PVP: Hypodense / Isodense

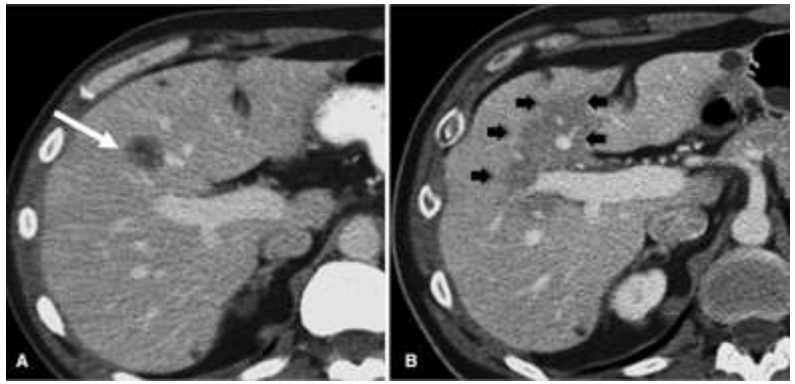
Late Ph: Hyperdense

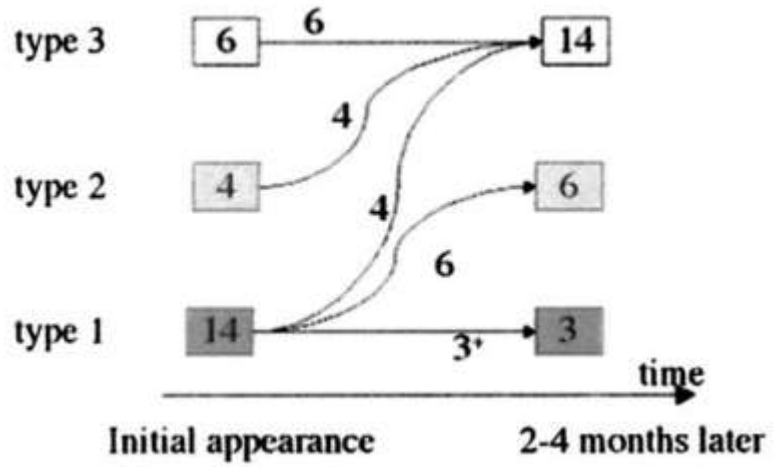
(mean density difference to nonirradiated liver given)

K. K. HERFARTH et al, IJROBP, 57, 2, 2003

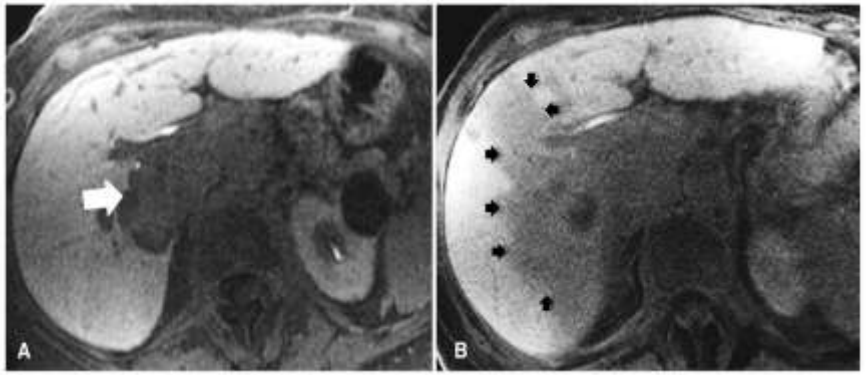
Herfarth (focal) Liver Reactions – Mets - Post SBRT

Acute phase (<3mo)





chronic phase (> 6 mo.)



Histology: severe sinusoidal congestion, hyperemia, and hemorrhage

CT PVP - reduced enhancement

CT Delayed – Enhancement similar to the non-irradiated liver as the irradiated liver will still be able to clear contrast

Histology: sub-lobular veins are obstructed fine collagen fibers (2º endothelial damage)

CT PVP – Hypo enhancement

CT Delayed – Hyper Enhancement due to impaired contrast clearance 2º to sublobar viens obstruction

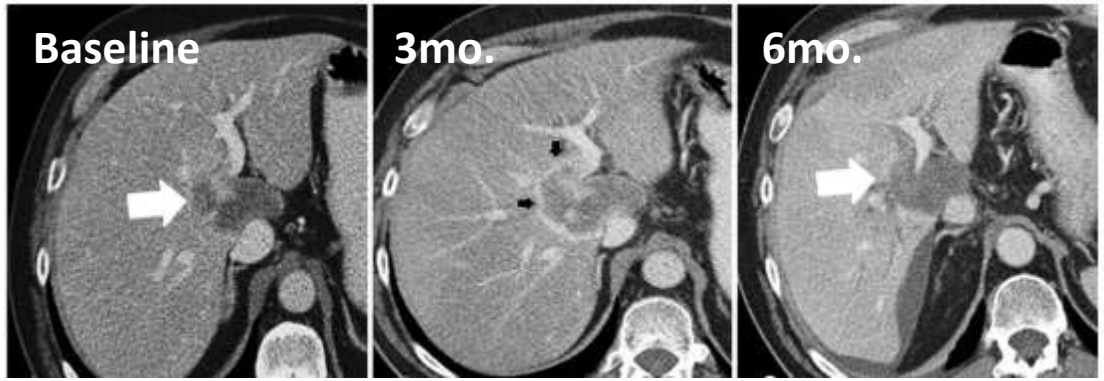
Histology: CV fibrosis with Lobules collapse. lobular architecture changes and volume loss

CT PVP – Hypo enhancement

CT Delayed – Diffuse Hypo Enhancement due to permanently non-functioning hepatocytes- → Parenchymal atrophy

focal Liver Reactions - Variations

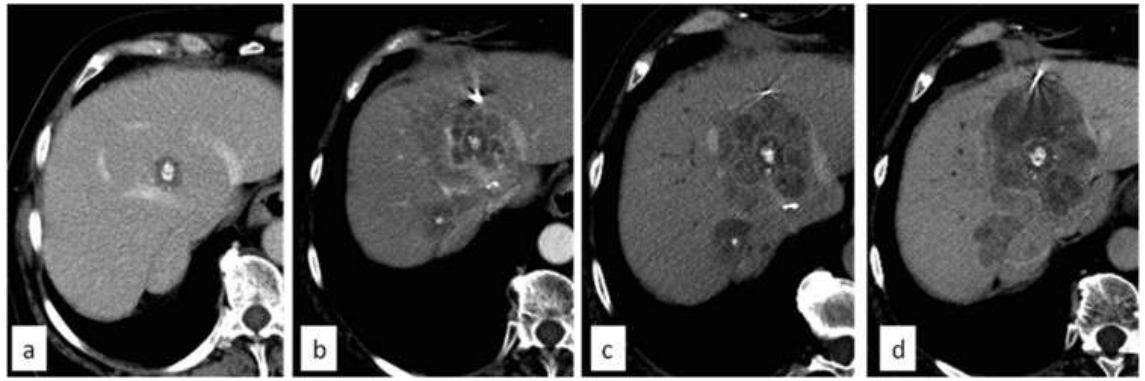
Ring Enhancement



PVP : Ring Enhancement - Early phase of Rx

Resolves at 6mo. → Persists - Recurrence

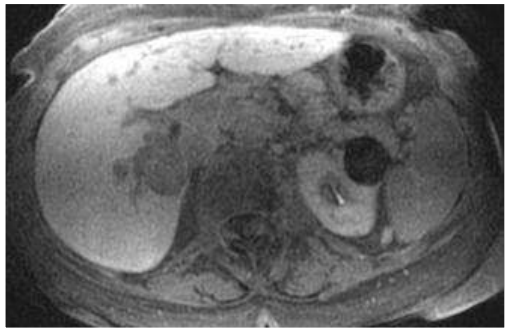
Lobulated Ring Enhancement



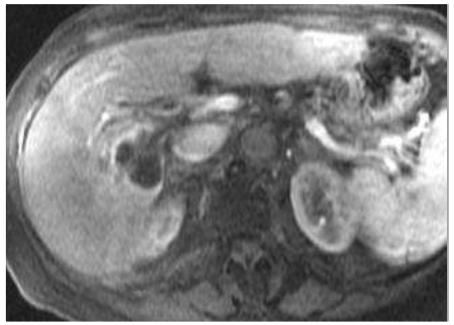
nodular rim enhancement or a tumor that had rim enhancement before treatment that persists after treatment is suspicious for residual or recurrent tumor

IJROBP,2015,92, 2, 292-298,

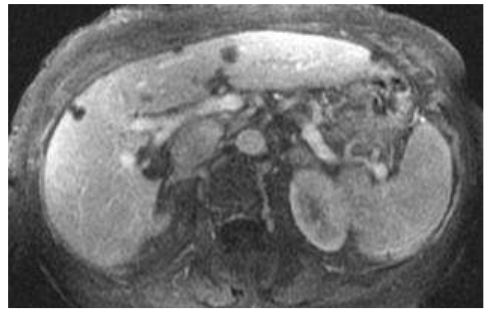
Response Evaluation – Thin Rim Enhancement



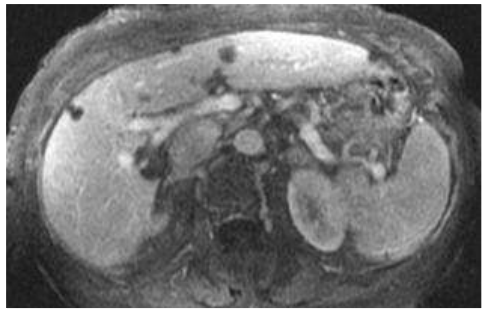
Baseline



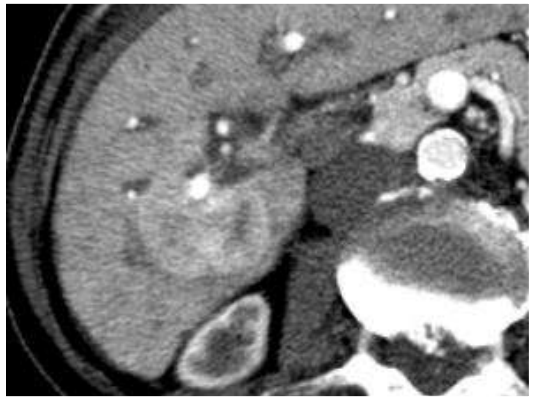
4 mon.

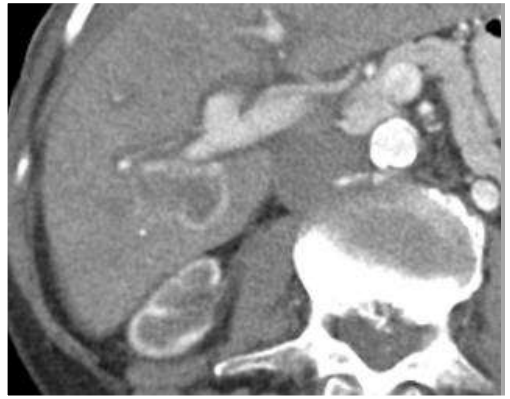


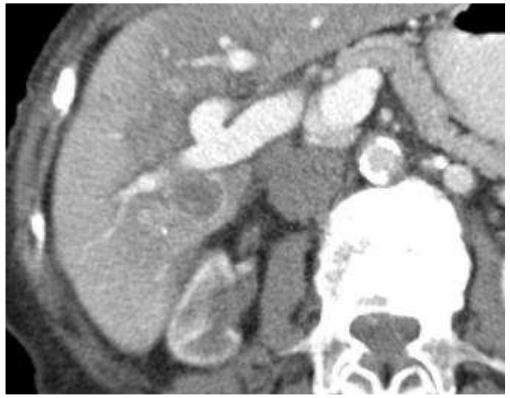
8 mon.

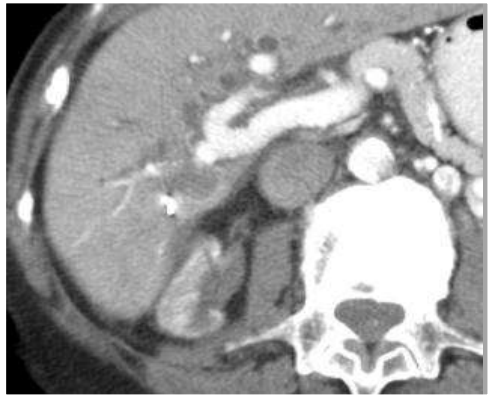


12 mon.





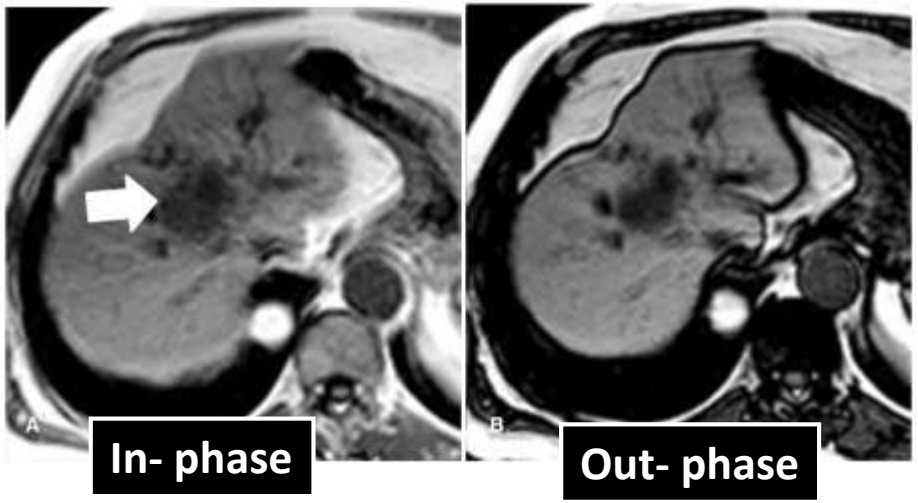




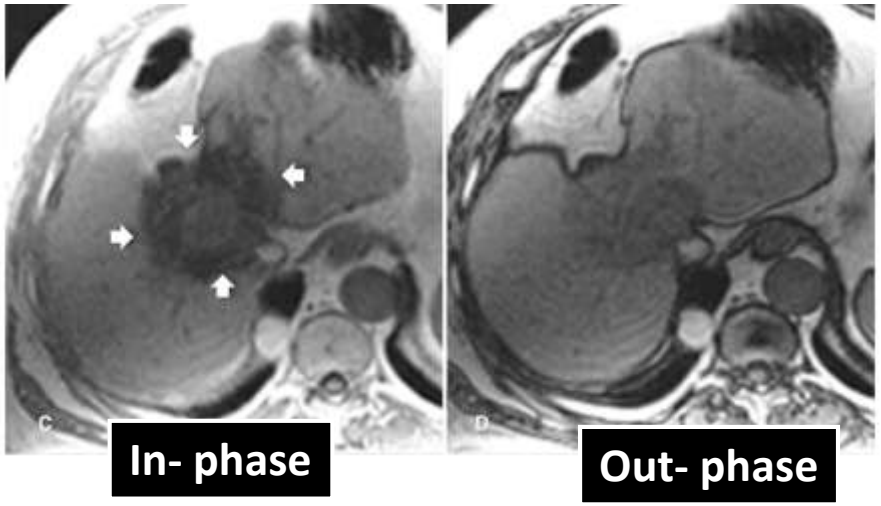
Representing FLR/inflammatory response → Not Residual Tumor // Nodular Rim suspicious

Focal Liver Reactions - Variations

Cholangioca - Baseline



Cholangioca – 6mo. Post SBRT



Inplane - hypointense rim // Outplane – Signal Loss

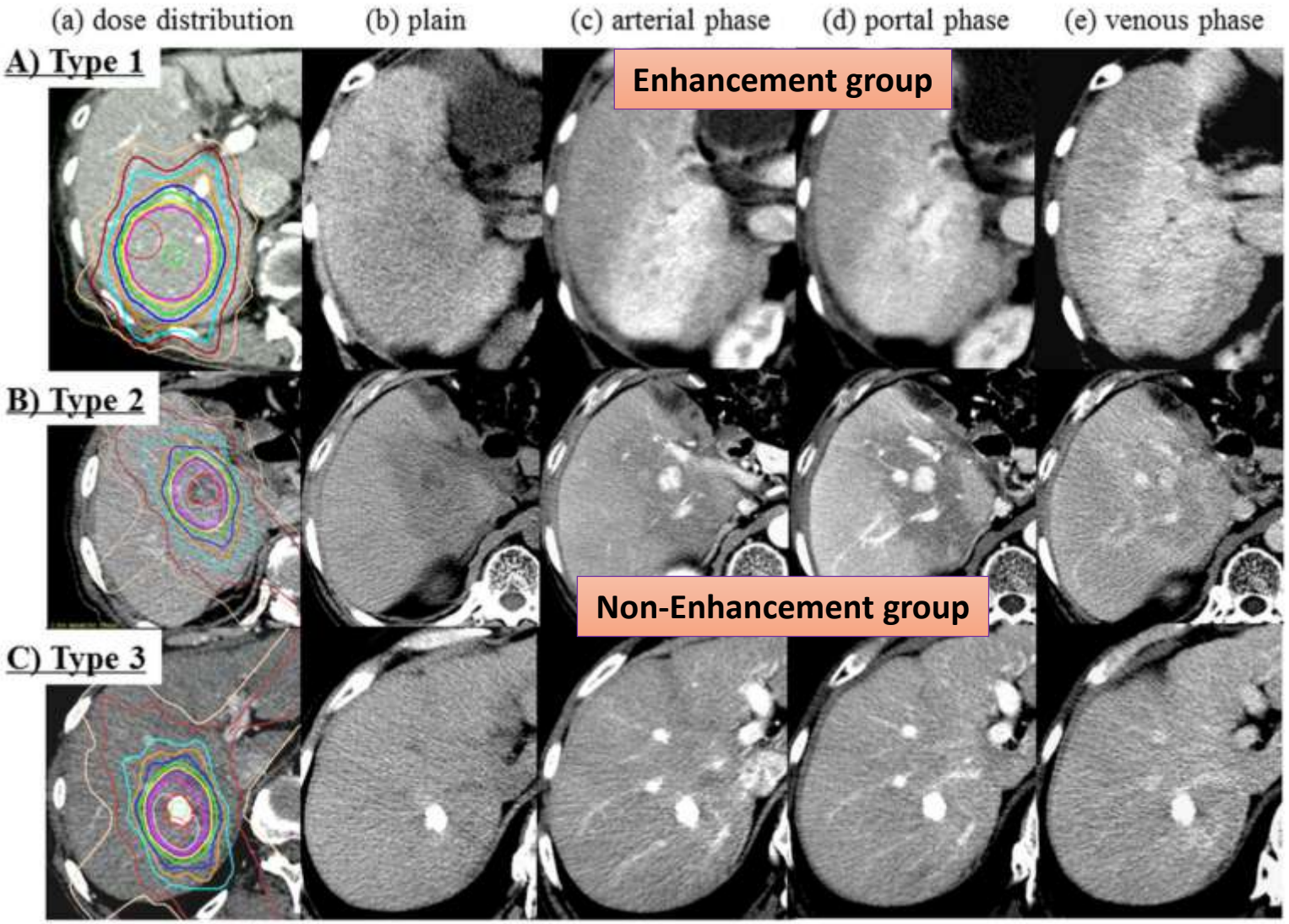
hemosiderin deposition and hemorrhage in the surrounding liver secondary to SBRT

Temporal Changes in Surrounding Parenchyma

Phase	Pathology	Imaging Findings (Herfarth Reactions)
Acute (1-3mo) **Herfarth ty.1**	Sinusoidal Congestion Hyperemia, Haemorrhage	PVP: Hypodense Late Ph: Isodense Ring Enhancement (-/+)
Subacute (3-6mo.) **Herfarth Ty.2**	Acute phase findings + Sublobar viens obstruction	PVP: Hypodense Late Ph: Hyperdense
Chronic (>6mo.) **Herfarth Ty.3**	Fibrotic Occlusion of central Viens Collapse of Lobules Accumulation of Kuppfer cells - Hemosiderin	PVP: Hypodense / Isodense Late Ph: Hyperdense Ring Enhancement resolves Hypointensity on gradient sequences - Hemosiderin Volume Loss

Haddad et al; Abdom Radiol (2016) DOI: 10.1007/s00261-016-0768-x

Focal Liver Reactions – HCC Cirrhotic Liver



hyperdensity in all enhanced phases

↓

Ty.3 reported by Herfarth

Child Pugh class A

hypodensity in arterial and portal phases

↓

Ty.1 & 2 reported by Herfarth

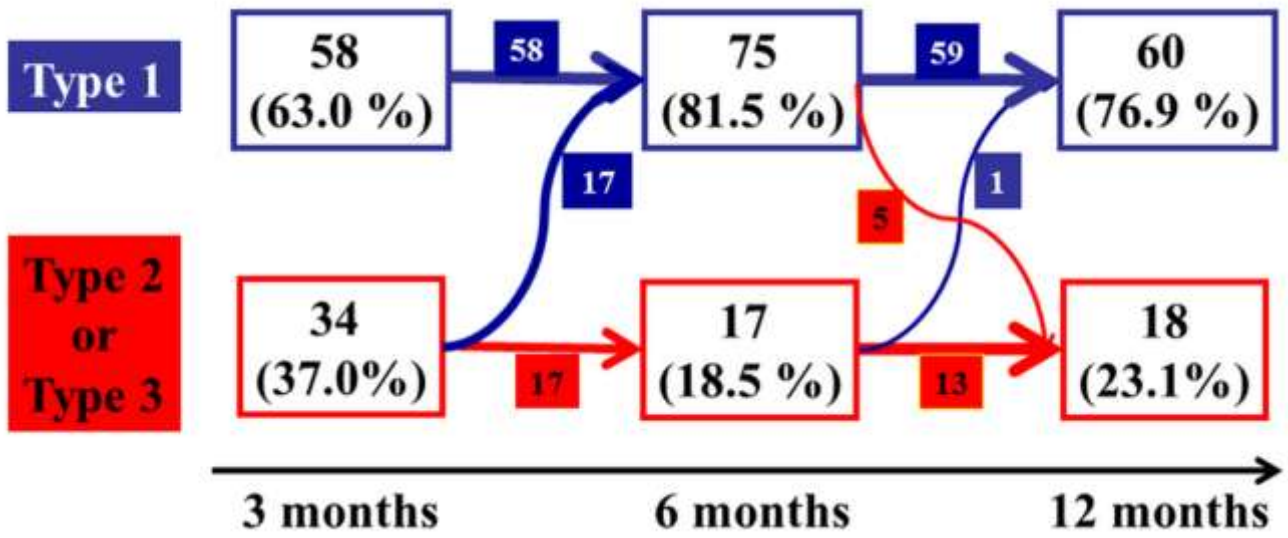
Child Pugh class B

↑

Isodensity in all enhanced phases

Kimura Et al, PLOS ONE DOI:10.1371/journal.pone.0125231 June 11, 2015

FLR Time Course Cirrhotic HCC– Dyn CT Tracking



		3 months	3-6 months	p-value (vs 3 months)	6-12 months	p-value (vs 3 months)
Child A	1	49	66	0.0013	54	0.0209
	2 or 3	27	10		12	
Child B	1	9	9	1	6	0.7428
	2 or 3	7	7		6	
total	1	58	75	0.0051	60	0.0503
	2 or 3	34	17		18	

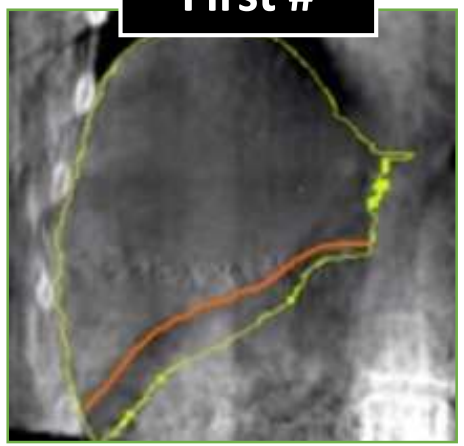
- Half of the type 2 or 3 appearances → changed to type 1, particularly in patients belonging to Child–Pugh class A.
- After 3–6 months, Child–Pugh class B was a significant factor in type 3 patients

Kimura Et al, PLOS ONE
DOI:10.1371/journal.pone.0125231 June 11, 2015

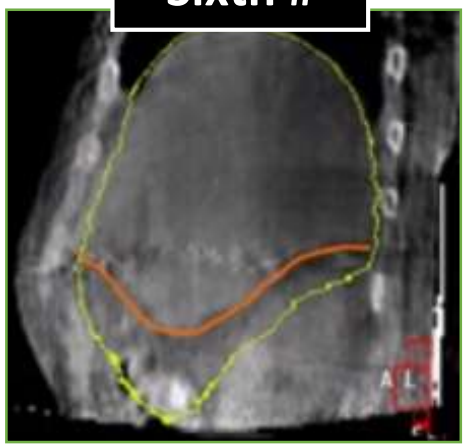
Dynamic Volume Liver Deformations

Interfractional Deformations

First #

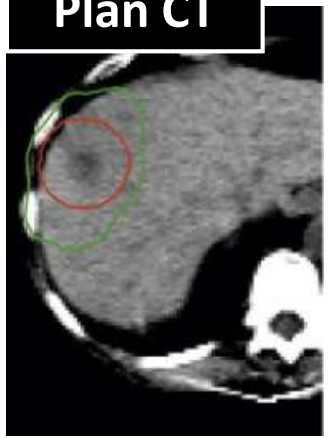


Sixth #

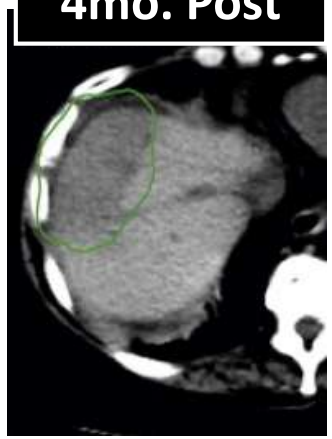


Post SBRT Dynamic Changes

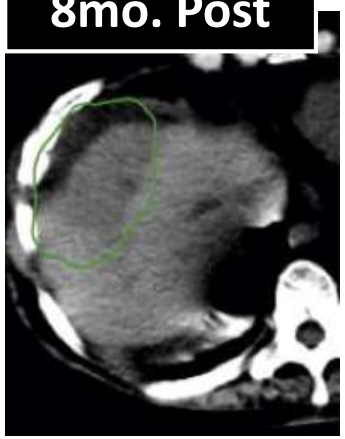
Plan CT



4mo. Post



8mo. Post



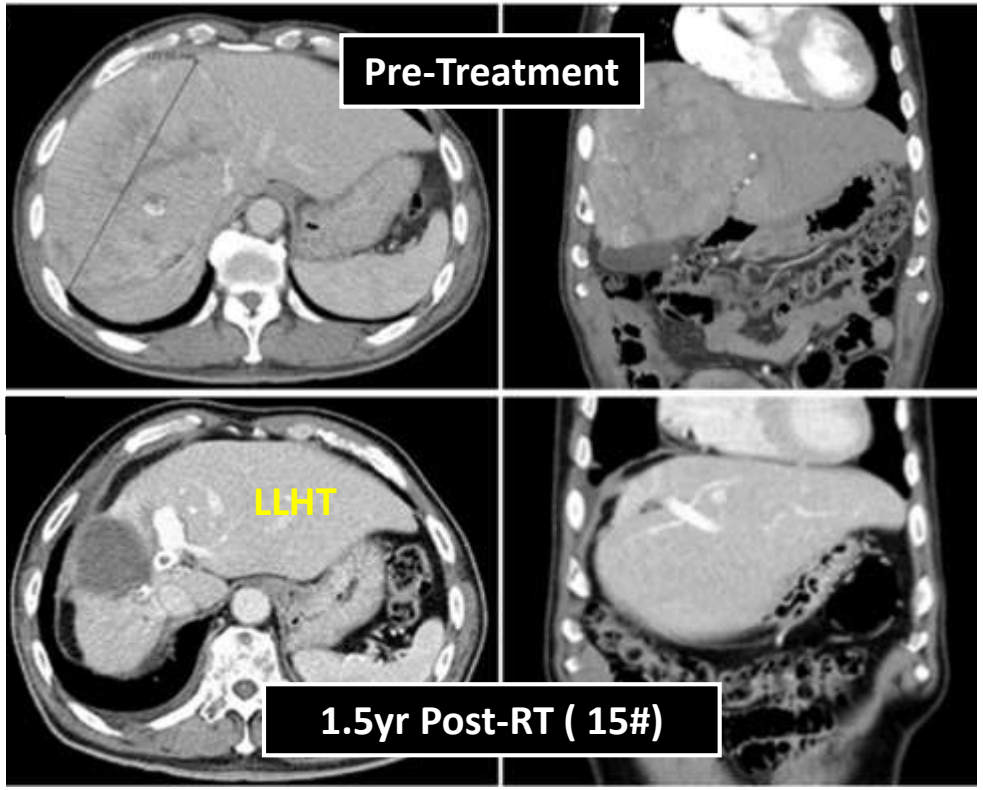
Median change in liver volume was -8.9%/year post-SBRT and was significantly associated with either:

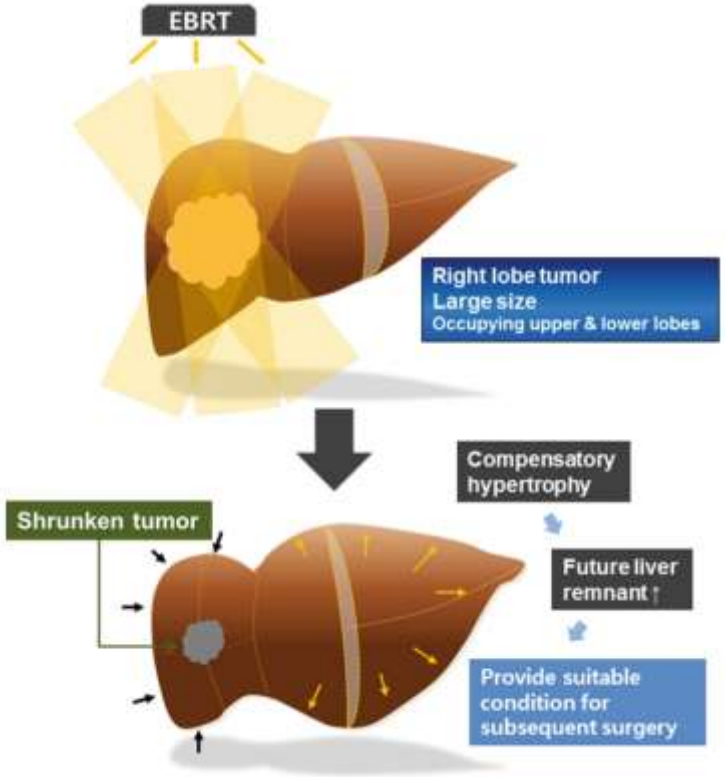
mean liver dose (11.4% larger volume reduction per 10 Gy) or volume of liver spared from receiving > 20 Gy

Alkaline phosphatase levels at the start of RT inversely correlate with the amount of liver hypertrophy.

EBRT-induced liver hypertrophy

Traditional Approach for Future Liver Remnant procurement: Preop.portal vein ligation/embolization (Rt.usually) → redistribution of portal blood fow + shrear Stress → Mitogenic factors release (HGF, EGF, TGF-β, Interleukin-6, TNF-α)





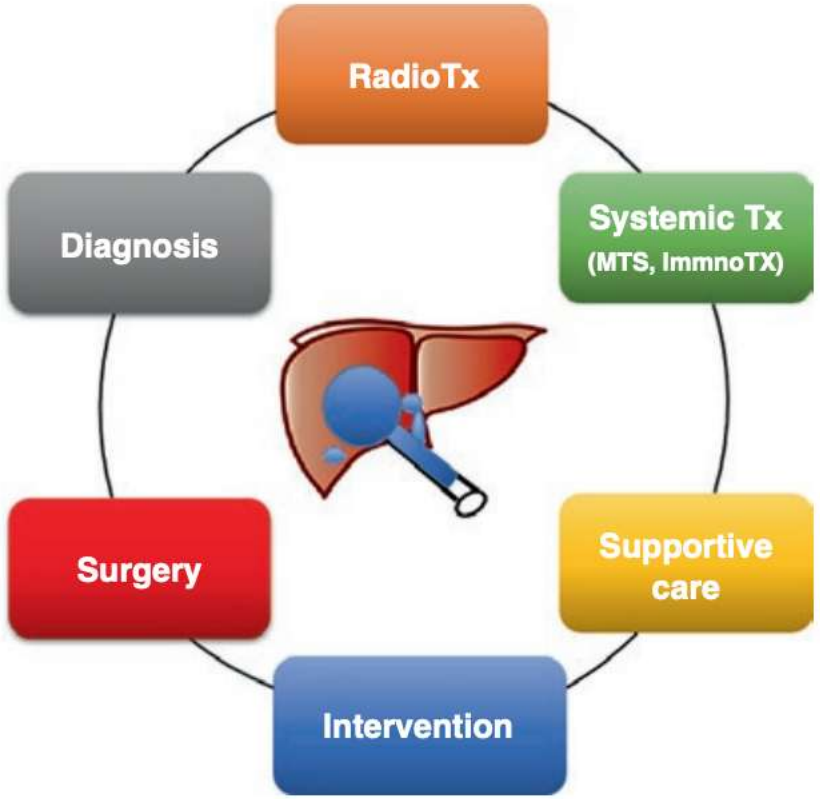
Which Tumors Comp.HT

- Locally advanced tumors with a tumor extent across the upper and lower right lobe hypertrophy after EBRT.
- Lesser 30gy vol > compensatory HT
- Usually After 1 year

Conclusion

- SBRT is an emerging alternative for treatment of liver tumors that are not suitable for other treatment methods.
- Knowledge of the SBRT induced changes in
  - liver tumors and
  - surrounding liver parenchyma

  is important for post-treatment evaluation

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