Liver SBRT
Toxicity & response Assessment

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

Knowledge of changes is 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

Transplant = cure
Ablation = resection
Embolization = palliation
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
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

\[ PTV = GTV + 6\text{-}10\text{mm Geometric Expansion} \]

Dose gradient outside

(Asymmetric / complex / Non-anatomical)

\[ \rightarrow \text{Compounded with multiple BH} \]

Intermediate & Low Dose Spillage
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 struc}) – 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

<table>
<thead>
<tr>
<th>Fractionation Regimen</th>
<th>Total dose/fractionation</th>
<th>BED$_{10}$</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Noncirrhotic (primarily IHC): 4000-6000 cGy/3-5 fx</td>
<td>7200-18,000 cGy</td>
<td></td>
<td>110</td>
</tr>
<tr>
<td>CP class A: 4000-5000 cGy/3-5 fx</td>
<td>7200-12,500 cGy</td>
<td></td>
<td>24,27,28,30,34,43, 44,61,86,101,113</td>
</tr>
<tr>
<td>Ultrahypofractionation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CP class B7: 3000-4000 cGy/5 fx</td>
<td>4800-7200 cGy</td>
<td></td>
<td>28,36,86,94,101</td>
</tr>
<tr>
<td>4000-5400 cGy/6 fx</td>
<td>6700-10,300 cGy</td>
<td></td>
<td>85,95</td>
</tr>
<tr>
<td>5000-6600 cGy/10 fx</td>
<td>7500-11,000 cGy</td>
<td></td>
<td>57,59,83,90,100,112</td>
</tr>
<tr>
<td>4800 cGy/12 fx</td>
<td>6720 cGy</td>
<td></td>
<td>110</td>
</tr>
<tr>
<td>4500-6750 cGy/15 fx</td>
<td>5900-9800 cGy</td>
<td></td>
<td>42,50,62,90,113,114</td>
</tr>
<tr>
<td>6000 cGy/20 fx</td>
<td>7800 cGy</td>
<td></td>
<td>57</td>
</tr>
<tr>
<td>6600-7200 cGy/22 fx</td>
<td>8600-9600 cGy</td>
<td></td>
<td>57-59,112</td>
</tr>
<tr>
<td>Standard fractionation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5040 cGy/28 fx</td>
<td>5947 cGy</td>
<td></td>
<td>114,115</td>
</tr>
<tr>
<td>6000 cGy/30 fx</td>
<td>7200 cGy</td>
<td></td>
<td>114,115</td>
</tr>
<tr>
<td>7700 cGy/35 fx</td>
<td>9400 cGy</td>
<td></td>
<td>58,59</td>
</tr>
</tbody>
</table>

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 you meet the Nearby Critical organ constraints - Bowel constraints
Liver Radiobiology

**Liver – Parallel** (independent Lobules)
(Volume effects - Small vol. High Dose )

**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

30-40 Gy/5 fxs

40-45 Gy/5 fxs

55 to 84 Gy EQD2 range
70 – 100 Gy BED

Combine modalities
30-40 Gy/5 fxs
SABR Biology – Vascular Effects!!

Single Dose (>8-10gy)

- Tumor cell damage
- Tumor cell death
- Tumor response


ASMase

Ceramide

VEGF

b-FGF

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

Phostidylyserine expressed to Outer Leaflet

Cell Phagocytosed

- Park, Radtn Research, 2013;
- Hillmann, Radiotherapy Oncology, 2013
SABR Biology – Vascular Effects!!

Hepatic irradiation

1. endothelial cell damage
2. stellate cell activation $\rightarrow$ (MF-Stellate Cell)

- High dose Region - perisinusoidal and hepatic fibrosis $\rightarrow$ Atrophy
- Low dose region - modulation of liver regeneration $\rightarrow$ Compensatory Hypertrophy

Radiotherapy of Liver Cancer,
https://doi.org/10.1007/978-981-16-1815-4_2
Immune Effects of Radiation – Negative

Irradiated TME
- ↑ICD
- ↑MHC Class 1
- ↑Type 1 IFN
- ↑TAA Release

MDSC’s
- Translocation of Calreticulin
- Release of HMGB-1
- MHC class 1
- Granzyme B / Perforin
- Tumor asst Antigens

TAA Specific Cyt.T Cell
- IFN-β, TNFα

Tregs

Cytotoxic T Cell

Immature DC

Mature DC

TAM’s (M2)

Tumor Asst. Draining Lymph nodes

Naïve T Cell

Tumor Asst.
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.

Intended Learning Objectives

- Setting the Stage – Basics Revised !

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  - Changes in liver parenchyma
  - Changes in Tumor Tissue

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

**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**
  - PV (75%)
  - HA (25%)
  - BD
  - Hep. Plexus
  - PS - vagus
  - Sym - Celiac
  - Lymphatics

- **Glison Capsule**
  - (Inflamed)
  - IC nerves

- **Sinusoid capillaries**
  - between portal triads

- **Liver Lobules**

- **Lobule**
  - portal triad
  - central vein
  - hepatocyte
  - hepatic artery
  - hepatic vein

- **Liver**

- **CV**

- **hepatic v**

- **Interlobular v**
Kupffer 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

Heme → Globin

Bilirubin → AA

Conjugated in Hepatocyte
Basic Anatomy – Stellate Cells / ITO cells

5% Liver
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
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  - Changes in Tumor Tissue

- **Radiation Induced Liver Disease (RILD)**

- **Image Response Evaluation**
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  - Tumor changes & Parenchymal Changes (FLC)
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

| RILD – Basic Concepts |

<table>
<thead>
<tr>
<th>Chr. Liver Damage</th>
<th>Fatigue</th>
<th>Abdominal Pain</th>
<th>LFTs</th>
<th>Factors of Child Pugh Score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Ascites</td>
</tr>
<tr>
<td>Classical RILD</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Non-Classical RILD</td>
<td>+ (cirrhosis) (hepatitis)</td>
<td>+</td>
<td>-</td>
<td>GOT/GPT (↑↑) (&gt;5UL)</td>
</tr>
</tbody>
</table>

Factors of Child Pugh Score:
- Ascites
- T-Bil
- Alb
- NH3
- Plt

- ↑: Increased
- ↓: Decreased
- (): Normal
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

<table>
<thead>
<tr>
<th>OAR</th>
<th>UF-3#</th>
<th>UF-5#</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uninvolved liver (Non cirrhotic)</td>
<td>Mean &lt;12gy &gt;700 cc &lt;15gy</td>
<td>Mean &lt;15gy &gt;700 cc &lt;21gy</td>
</tr>
<tr>
<td>Uninvolved liver (CP class A)</td>
<td>Mean &lt;12gy &gt;700 cc &lt;15gy</td>
<td>Mean &lt;13-15gy &gt;700ccc &lt;15gy</td>
</tr>
<tr>
<td>Uninvolved liver (CP class B)</td>
<td>--</td>
<td>Mean &lt;10gy &gt;700ccc &lt;10gy &gt;500cc &lt;7gy</td>
</tr>
<tr>
<td>Central Liver</td>
<td>--</td>
<td>V26 &lt;40cm3 V21 &lt;37cm3 Mean &lt; 19gy</td>
</tr>
</tbody>
</table>
Future Remnant Liver Reserve

Test for prediction of FRLF

- Functional (Global fn.)
  - Dynamic
    - Metabolism
      - C-13 Methacetin (LiMax)
    - Elimination capacity
      - Galactose
  - Clearance Test
    - ICG
      - Tc-99m-Mebrofenin
  - Tc-99m GSA

- Morphological (Global + regional)
  - MRI - Gd-EOB-DTPA

Static

Child Pugh
MELD

Passive LFT’s – Nonspecf.
- Transaminases
- Albumin & clott. fac.(PT)
- Bilirubin
- Ser.Hyaluronic Acid
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.
$^{99m}$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
**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.

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

- **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

**Biomarkers**

<table>
<thead>
<tr>
<th>Inflammatory</th>
<th>TNFalpha and IL1β, IL8, sIL2R, VEGF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endothelial</td>
<td>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</td>
</tr>
<tr>
<td>Fibrosis</td>
<td>N-terminal propeptide for type III procollagen (P-III-P), TGF-β</td>
</tr>
<tr>
<td>Coagulation</td>
<td>Protein C, Antithrombin III, plasminogen</td>
</tr>
<tr>
<td>Circulating</td>
<td>Serum hyaluronic acid</td>
</tr>
<tr>
<td>Metabolomics</td>
<td>Plasma metabolites, regulation of amino acid and lipid metabolism, change in energy metabolism, calcium signaling, choline metabolism, pentose and purine metabolism and microbiome</td>
</tr>
</tbody>
</table>

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 fluid 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 Preferred - 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 Transplantation: Intraportal transplantation of LSEC with HGF
→ engraftment and gradual regeneration of the radiation-damaged hepatic sinusoidal endothelium by the donor cells.
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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)
1. **Preferred Tool:** Dynamic Contrast CT except:
   - Post TACE – Lipoidal
     - Beam hardening
     → Difficulty Tumor viable enhancement
   - Post Fudicials artefactcs

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

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

Reduced Enhancement

Reduced FDG Uptake

Gradual Redtn over mo.
Gradual Progress over mo.

Pre-Rx

8 mon.

Minimal Change Post SBRT
Response Evaluation pitfall - Fiducials

CT Scan
Streak Artifacts

PET Scan

Baseline
4 mon.
12 mon.

BASELINE
4Mon.
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
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.

**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)**

**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

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**Subacute phase (3–6 mo, post-SBRT)**

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

**CT PVP** – Hypo enhancement

**CT Delayed** – Hyper Enhancement due to impaired contrast clearance 2° to sublobar veins obstruction

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**Chronic phase (> 6 mo.)**

**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

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

Haddad et al; Abdom Radiol (2016) DOI: 10.1007/s00261-016-0768-x
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
• 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.
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.
Traditional Approach for Future Liver Remnant procurement: Preop. portal vein ligation/embolization (Rt. usually) → redistribution of portal blood flow + shear 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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