Emerging role of precision Radiotherapy SBRT in liver tumors

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Liver: Anatomy

Human Liver Anatomy
- inferior vena cava
- aorta
- hepatic artery
- gall bladder
- portal vein
- common bile duct

Liver: Anatomy
- hepatic artery branch
- portal vein branch
- bile duct
- hepatocyte

Ligamentum Teres
- Right Posterior
- Left Portal

Antegrade flow in portal vein
LEFT PORTAL VEIN BRANCHES MAY SHOW ENHANCEMENT DURING ARTERIAL PHASE

Tumoral venous
Cortical invasion into portal vein
Fortis with early FTC
HCC: Treatment principle

HCC: 3rd M/c cancer

**Surgery**

**Transplant**

Popcorn effect: background of Cirrhosis

Gold standard
5 yr OS – 70%

MELD / Milan criteria

Only 20% fit for surgery
HCC: Treatment

- HCC: 3rd M/c cancer

- **Surgery**
  - Resection: 85% recurrence

- **Limited availability of donor organs → up to 20-40% dropouts**
  - Need for alternative non surgical management
  - advanced HCC → progressive disease while on a waitlist

- Solution: **local therapy as “bridge” → until a donor organ is available**

- Traditionally: RFA and TACE → neoadjuvant/ downstaging

- However - RFA usable < 40% of cases – not for >5 cm/ close to vessels
  - TACE better, although → only results in a 65% LC @ 1 yr

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### Operable

<table>
<thead>
<tr>
<th>Treatment</th>
<th>In-Operable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver Transplant Gold standard 5 yr OS – 70%</td>
<td>Radiofrequency Ablation</td>
</tr>
<tr>
<td>MELD / Milan criteria</td>
<td>Percutaneous Ethanol Ablation</td>
</tr>
<tr>
<td>Only 20% fit for surgery</td>
<td>Transarterial Chemoembolization</td>
</tr>
<tr>
<td>Resection/Partial Hepatectomy</td>
<td>Cryo-ablation</td>
</tr>
<tr>
<td>Radiofrequency Ablation</td>
<td>Systemic Chemotherapy</td>
</tr>
<tr>
<td>Radiation Therapy</td>
<td>Radio-embolization</td>
</tr>
<tr>
<td>Resection/Partial Hepatectomy</td>
<td></td>
</tr>
</tbody>
</table>
BCLC staging: Treatment decision

AASLD:

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

Criteria

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

The concept of salvage LT is only a minor topic in the guidelines. AASLD, APASL, and EASL all agree that it is not the first-line treatment. AASLD, American Association for the Study of Liver Diseases; APASL, Asian Pacific Association for the Study of the Liver; BCLC, Barcelona Clinic Liver Cancer; BSC, best supportive care; CPA & B, Child-Pugh class A and B; EASL, European Association for the Study of the Liver; LRT, locoregional therapy; LT, liver transplantation; SIRT, selective internal radiation therapy; TACE, transarterial chemoembolisation.
HCC - proposed modern management – systemic approach
<table>
<thead>
<tr>
<th></th>
<th>AASLD</th>
<th>APASL</th>
<th>EASL</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Surveillance</strong></td>
<td>US every 6 months, AFP optional</td>
<td>US + AFP every 6 months</td>
<td>US every 6 months</td>
</tr>
<tr>
<td><strong>CEUS</strong></td>
<td>Not recommended</td>
<td>As sensitive as CT/MRI</td>
<td>Suitable for nodules ≥1 cm in cirrhosis</td>
</tr>
<tr>
<td><strong>Biopsy</strong></td>
<td>No routine use</td>
<td>For indeterminate nodules ≥1 cm</td>
<td>Required in non-cirrhotic HCC</td>
</tr>
<tr>
<td><strong>Bridging</strong></td>
<td>Recommended for T2</td>
<td>No recommendation</td>
<td>Recommended if feasible</td>
</tr>
<tr>
<td><strong>LT after</strong></td>
<td>Recommended</td>
<td>No recommendation</td>
<td>Possible</td>
</tr>
<tr>
<td><strong>downstaging</strong></td>
<td>LRT - Recommended in cirrhotic non-surgical patients (T2 or T3, no vascular involvement) - No preference regarding modality</td>
<td>LRT - Ablation: For HCCs ≤2 cm in CP-A/B - TACE: For unresectable, large/multifocal HCCs - SIRT: Alternative to TACE</td>
<td>LRT - Ablation: or unresectable BCLC 0 and A + selected surgical patients - TACE: For BCLC B - SIRT: Good safety profile, efficacy not yet proven</td>
</tr>
<tr>
<td><strong>Radiotherapy</strong></td>
<td>No recommendation</td>
<td>Option when other LRTs have failed</td>
<td>Insufficient evidence</td>
</tr>
<tr>
<td><strong>Systemic</strong></td>
<td>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</td>
<td>Systemic therapy - Sorafenib for advanced HCC with CP-A liver function (possible with caution in CP-B)</td>
<td>Systemic therapy - Sorafenib &amp; lenvatinib: 1st line for BCLC-C - Treatment stage migration - Regorafenib: 2nd line - Cabozantinib: Benefit as 2nd line - Nivolumab: No recommendation yet</td>
</tr>
</tbody>
</table>

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

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

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

Whole liver radiation

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

**Radiation hepatitis of past**

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

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

Rx: diuretics, paracentesis, and vitamin K

**Literature support for Radiation safety**

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

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

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

**Safety of partial liver RT safely studies in multiple centres** – careful dose selection by CP score and normal liver sparing
Modern Radiotherapy: Overcoming challenges of past
## HCC - RT

<table>
<thead>
<tr>
<th>Pitfalls of past</th>
<th>Solutions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiation Induced Liver disease (RILD)</td>
<td>Data on partial liver tolerances</td>
</tr>
<tr>
<td></td>
<td>Image Guided Radiotherapy (IGRT) and Stereotactic Body Radiotherapy (SBRT)</td>
</tr>
<tr>
<td>Target Delineation</td>
<td>Volumetric &amp; Triple phase CECT, PET-CT, MRI</td>
</tr>
<tr>
<td></td>
<td>Image fusion tools</td>
</tr>
<tr>
<td>Respiratory motion induced / Set-up uncertainties</td>
<td>ABC, Respiratory Gating (RPM), tracking (Cyberknife)</td>
</tr>
<tr>
<td></td>
<td>Newer Immobilization devices/ 4D imaging</td>
</tr>
<tr>
<td>Uncertainties in dose distribution</td>
<td>Advanced Treatment machines/ Equipments</td>
</tr>
<tr>
<td></td>
<td>Better planning software / dose engines</td>
</tr>
</tbody>
</table>
Exploring into depth of Liver RT: partial volume & functional liver
Redefined role of RT in HCC
Partial liver tolerance: effective & safe

- Austin – Seymour:
  - 1st quantitative analysis of RILD as a function of dose – volume
  - Dose > 35 Gy limited to 30% liver

- Emami et al
  - TD 5/5 – 50 Gy, 35 Gy, 30 Gy (1/3, 2/3 or whole)
  - TD 50/5 – 55, 45 or 40 Gy

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

Figure 1. The Lyman-Kutcher-Butman NTCP model displaying 5% iso-NTCP curves, with 80% confidence limits, for patients with primary liver cancer. Effective volume (the organ volume that if irradiated to the prescribed dose uniformly would be associated with the same NTCP as the nonuniform dose distribution) versus normalized dose (prescribed dose normalized to 1.5 Gy bid).
Indocyanine Green - ICG: assessing liver function for dose selection in RT-HCC

<table>
<thead>
<tr>
<th>ICG retention (dose- Gy)</th>
<th>Nontumour part of liver</th>
<th>&lt;10%</th>
<th>10.1%- 20%</th>
<th>20.1%- 30%</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1/3</td>
<td>40</td>
<td>No RT</td>
<td>No RT</td>
<td></td>
</tr>
<tr>
<td>1/3 – ½</td>
<td>50</td>
<td>40</td>
<td>No RT</td>
<td></td>
</tr>
<tr>
<td>&gt;1/2</td>
<td>60</td>
<td>50</td>
<td>40</td>
<td></td>
</tr>
</tbody>
</table>

SBRT – local ablative therapies
Learning from surgical experience

➢ Rusthoven et al, JCO. [2009]
Functioning normal liver sparing

FDG galactose based functional liver
Key to modern Liver RT success:
Adequate normal liver / minimize irradiated liver - RILD

- Base line normal liver > 700 cc
  - Liver volumetry from triple phase
  - Fibroscan – assess cirrhotic component
  - FDG galactose scan (research)
  - ICG studies

- Case selection
  - safe anatomy / safe functions

- Technical improvement
  - SBRT
  - Motion management
  - Targeting – surrogate fiducials
# HCC Treatment in guidelines

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

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

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

**West: Europe & Americas Vs East**

- Follow BCLC
- Hep C more common
- BCLC C → sorafenib alone

**East → Hep B common**

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

**DISCUSSION**

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

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

Allowing for
  - Steep dose gradients
  - Hypofractionation
SBRT in HCC

Advantages

- High possibility of local control
- Minimally invasive treatment modality, no requirements for anesthesia or injections
- High possibility to overcome anatomical limitations, including poorly defined tumors on ultrasound and tumors which are difficult to puncture
- No concern regarding the location close to major vessels, including the portal vein, inferior vein cava, and bile duct
- Possible to treat complicated forms of tumors, particularly using IMRT
- Short treatment term (usually within 2 weeks), possibility of benefit to the patient’s quality of life and reduced medical cost
- Possibility to enhance the immune reaction to tumors

Current issues

- Poor outcomes and high possibility of toxicity with large tumors
- Challenges involved in the treatment of tumors close to critical organs such as the gastrointestinal tract
- Effects of re-irradiation are unclear
- Inaccuracy due to respiration and the presence of ascites

Abbreviations: SBRT = stereotactic body radiation therapy; IMRT = intensity modulated radiation therapy.

Table 1. Features of SBRT for liver tumors.
Sub-classification of Locally advanced HCC

- Nodular
- Massive with intrahepatic metastasis
- Diffuse
- Vascular invasion

HCC

PVTT

Park et al. Oncology 2011
## Eligibility Criteria for Different Radiation Techniques

<table>
<thead>
<tr>
<th></th>
<th>CRT</th>
<th>SBRT</th>
<th>Proton</th>
<th>Brachy</th>
<th>Yttrium-90</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;3 cm</td>
<td>++++</td>
<td>++++</td>
<td>++++</td>
<td>++++</td>
<td>+++</td>
</tr>
<tr>
<td>3-6 cm</td>
<td>++++</td>
<td>++++</td>
<td>++++</td>
<td>++++</td>
<td>++</td>
</tr>
<tr>
<td>6-10 cm</td>
<td>++++</td>
<td>+++</td>
<td>+++</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>&gt;10 cm</td>
<td>++</td>
<td>++</td>
<td>+++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Diffuse</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>++</td>
</tr>
<tr>
<td>High bleeding risk</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Child-Pugh B</td>
<td>++</td>
<td>+</td>
<td>+++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Vascular invasion</td>
<td>++++</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Caudate lobe</td>
<td>++++</td>
<td>++</td>
<td>+++</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Target &lt;1 cm from GI tissues #</td>
<td>++</td>
<td>+</td>
<td>+++</td>
<td>++</td>
<td>++</td>
</tr>
</tbody>
</table>
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)

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

**HCC-PVTT irradiation: A neo-adjuvant route to transplant**
SBRT selection: Suitable Vs more challenging

**Suitable**

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

**More challenging**

1. Underlying hepatitis/ cirrhosis (CP B +/- C)
2. Post viral hepatitis/ deranged liver f/n
3. < 700 cc uninvolved liver
4. > 1 lesions – same lobe/ segment
5. > 8 cm lesion
6. 5-30 mm breathing motion
7. Proximity to OARs
8. PVTT – scheduling combinations
Problems with respiratory movement: Organ Hit & Tumor miss

“If you can’t see it, you can’t hit it.
If you can’t hit it, you can’t cure it”
H.E. Johns or W. Powers

“If it’s moving, you can’t hit it.
If you can’t hit it, you can’t cure it”
J. Battista
Modern age Radiotherapy

Paradigm shift from conventional to conformal Radiotherapy

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

Role of newer modalities
Motion management

- **Five main strategies** are currently used:
  - integration of motion: (geometrical or dosimetric)
    - 4DCT acquisition of anatomical data specific to a respiratory phase
  - Motion dampening:
    - forced shallow breathing with abdominal compression: Karolinska hospital → good for motion > 5 mm
    - breath-hold techniques (active or voluntary): ABC (active breathing control, Elekta, proposed by MSKCC)
  - Motion tracking:
    - respiratory gating techniques: RPM [real time position management, Varian, 2000]
    - tracking techniques: involves real time localization + beam adaptation
Respiratory motion management: Breath dampening/Holding

Change breathing pattern and not hold breathing
Respiratory motion management: Breath Holding

Free Breathing

Breath-Hold
Respiratory motion management: Gating
Synchrony® Respiratory Tracking System
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.
Role of stereotactic body radiation therapy for hepatocellular carcinoma

Naoko Sanuki, Atsuya Takeda, Ebsuo Kunieda

Table 1: Eligibility criteria for different treatment modalities

<table>
<thead>
<tr>
<th>Modality</th>
<th>Tumor size</th>
<th>Number of tumors</th>
<th>Location or characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery</td>
<td>&lt; 5 cm (or more)</td>
<td>&lt; 3</td>
<td>Depends on location</td>
</tr>
<tr>
<td>Percutaneous ablative therapy</td>
<td>&lt; 3 cm</td>
<td>Depends on liver function</td>
<td></td>
</tr>
<tr>
<td>TACE</td>
<td>&gt; 3-5 cm</td>
<td>1-multiple (&gt; 4)</td>
<td>Hypervascular lesions</td>
</tr>
<tr>
<td>SBRT</td>
<td>4 (or 5) cm</td>
<td>&lt; 1-3</td>
<td>Away from bowels</td>
</tr>
</tbody>
</table>

Local control (2 yr): > 90% for all modalities

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

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Country</th>
<th>Patient number</th>
<th>Median volume, ml</th>
<th>Median size, cm</th>
<th>Median dose (range)/fraction, Gy</th>
<th>Median follow-up (range), mo</th>
<th>Local control</th>
<th>Overall survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cárdenes <em>et al.</em></td>
<td>United States (Indiana)</td>
<td>17</td>
<td>(8-95)</td>
<td>-</td>
<td>Variable</td>
<td>CP-A: 36-48 Gy/3 fr; CP-B: 40 Gy/5 fr</td>
<td>24</td>
<td>100%</td>
</tr>
<tr>
<td>Andolino <em>et al.</em></td>
<td>United States (Indiana)</td>
<td>60</td>
<td>(2-112)</td>
<td>3.2</td>
<td>Fixed</td>
<td>CP-A: 44 Gy/3 fr; CP-B: 40 Gy/5 fr</td>
<td>27</td>
<td>90% (2 yr)</td>
</tr>
<tr>
<td>Bujold <em>et al.</em></td>
<td>Canada</td>
<td>102</td>
<td>(1-1913)</td>
<td>7.2</td>
<td>Variable</td>
<td>36 (24-54) Gy/6 fr</td>
<td>36</td>
<td>87% (1 yr)</td>
</tr>
<tr>
<td>Kang <em>et al.</em></td>
<td>South Korea (Korea Inst. of Radiological and Medical Sciences)</td>
<td>47</td>
<td>(2-213)</td>
<td>2.9</td>
<td>Variable</td>
<td>57 (42-60) Gy/3 fr</td>
<td>17</td>
<td>95% (2 yr)</td>
</tr>
</tbody>
</table>

*CT: Computed tomography; MRI: Magnetic resonance imaging; US: Ultrasound; CT-angiogram: Computerized tomography-angiogram.*
SBRT in HCC

HCC SBRT

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

nodular
intrahepatic metastasis
diffuse
vascular invasion
Liver SBRT Role

Clinical Investigation

Stereotactic Body Radiotherapy for Primary Hepatocellular Carcinoma

David L. Andolino, M.D.,* Cynthia S. Johnson, M.S.,† Mary Maluccio, M.D.,† Paul Kwo, M.D.,‡ A. Joseph Tector, M.D.† Jennifer Zook, M.D.,§ Peter A. S. Johnston, M.D.†

Conclusions: SBRT is a safe, effective, noninvasive option for patients with HCC ≤6 cm. As such, SBRT should be considered when bridging to transplant or as definitive therapy for those ineligible for transplant. © 2011 Elsevier Inc.

Table 2

Tumor response, RECIST.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>≤4 cm (N = 52)</th>
<th>&gt;4—&lt;10 cm (N = 55)</th>
<th>≥10 cm (N = 34)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
<td>%</td>
<td>No</td>
<td></td>
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<tr>
<td>Complete response</td>
<td>40</td>
<td>76.92</td>
<td>25</td>
<td>45.45</td>
</tr>
<tr>
<td>Partial response</td>
<td>10</td>
<td>19.23</td>
<td>25</td>
<td>45.45</td>
</tr>
<tr>
<td>Stable</td>
<td>1</td>
<td>1.82</td>
<td>3</td>
<td>3.64</td>
</tr>
<tr>
<td>Tumor progression</td>
<td>1</td>
<td>1.82</td>
<td>2</td>
<td>3.64</td>
</tr>
</tbody>
</table>

RECIST = response evaluation criteria in solid tumors; log-rank test.
Stereotactic Body Radiation Therapy for Hepatocellular Carcinoma: Prognostic Factors of Local Control, Overall Survival, and Toxicity

Jean-Emmanuel Bibault, Sylvain Dewas, Claire Vautravers-Dewas, Antoine Hollebecque, Hajer Jarraya, Thomas Lacornerie, Eric Lartigau, Xavier Mirabel

Abstract

Purpose: Stereotactic body radiation therapy (SBRT) has been used as a treatment option for several recent studies. This study aimed to evaluate the prognostic factors associated with the success of SBRT in the treatment of hepatocellular carcinoma.

Patients and Methods: A total of 75 patients with hepatocellular carcinoma were treated with SBRT at the Department of Radiation Oncology, University of Lille II, France. Prognostic factors were evaluated using a univariate analysis.

Results: Univariate analysis revealed that tumor size, tumor location, and the presence of any comorbidities were significantly associated with the success of SBRT. A multivariate analysis was performed to identify independent prognostic factors.

Conclusion: SBRT is an effective treatment for hepatocellular carcinoma, and the success of this treatment is influenced by several prognostic factors. Further research is needed to identify additional factors that may influence the success of SBRT.


2013

SpinView Software
Scarce data in past → thought to induce local fibrosis/vascular damages → (i) theoretical dissection difficulties (ii) anastomosis-related complications (iii) increased perioperative morbidity

**PMH series: Sandroussi C, Dawson LA, et al 2010**
- 10 patients - refractory to or ineligible for other therapies → 3D-CRT as a bridge to OLT
- Median dose- 33 Gy (range:8.5–54 Gy)/ 1–6 fractions → 100% local control & 10%-50% volume regression
- 5 OLT → treatment effect with 40%–90% necrosis and fibrosis / All without recurrence @ 14 months

**Mount Sinai University : Facciuto ME et at 2012**
- 27 patients → treated with SBRT (26–36 Gy in 2–4 fr) → CR in 14%, PR in 23%, and SD in 63%

**Baylor Medical Center: O’Connor et al. 2012 → 27% pathologic CR**

3D-CRT and SBRT: safe and effective to bridge selected patients with advanced HCC
SBRT as bridge – Pittsburgh group

- 27 HCC with cirrhosis → SBRT with intent for OLT [since 2010 @ Allegheny Health Network
- 19 - within Milan → bridge to transplantation & 8 - outside of Milan → downsized to Milan criteria and listed for liver transplant
- Child's B cirrhosis - 18, while Child's A – 9. No Child's C: No serious complications post SBRT / no hepatic decompensation

Bridge-to-transplant:
- 18/19 (95%) pts - successfully controlled with SBRT
- 1 - HCC progression in the non-treated portion of liver at 9 months
- 13/19 (68%) underwent liver transplant at 1-23 mth post SBRT
- 5 are still listed – without evidence of recurrence
- No recurrence post-transplant in 13 pts @ 3 mth - 4.5 yrs
- Pathology: 13/13 reduction of tumor & 7/13 with no residual

Down-sized group:
- 8/8 were successfully down-sized to within Milan Criteria
- 3 - HCC recurrence outside of treatment area
- 3- liver transplantation / 2 awaiting

Overall success in bridge-to-transplant was 95% and down-sizing was 63%.
Tumor response to SBRT was 100% and local tumor control was 100%.
Clinical Investigation: Gastrointestinal Cancer

Stereotactic Hypofractionated Radiation Therapy as a Bridge to Transplantation for Hepatocellular Carcinoma: Clinical Outcome and Pathologic Correlation

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

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

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

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

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

Keywords: Hepatocellular carcinoma, Stereotactic hypofractionated radiation therapy, Transplant

SHORT: SBRT bridge to transplant

50 Gy in 10 fr
RT as Bridge: safety & selection

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

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

3DCRT as bridge →
• large HCC (>4 cm)
• HCC located close to great vessels or main bile ducts, which were deemed unsuitable for RFA or TACE alone
SBRT Vs TACE or RFA : 2017

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

Sapiochin Q1, Barry A2, Doherty M3, Fischer S4, Goldaracena N5, Rosales R6, Russo M2, Beecroft R7, Chanekar A5, Bhat M6, Brierley J2, Greig PD5, Knox J3, Dawson LA2, Grant DR5.

Abstract

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

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

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

LAY SUMMARY: Patients with liver cancer included in the waiting list for liver transplantation are at risk of tumor progression and death. Stereotactic body radiotherapy may be a good alternative to conventional therapies to reduce this risk.
Comparison: SBRT vs others
### Table 5. (continued)

<table>
<thead>
<tr>
<th>Study, Year</th>
<th>Study Type</th>
<th>n</th>
<th>Modalities Compared</th>
<th>Inclusion Criteria</th>
<th>SBRT Details</th>
<th>Tumor Control</th>
<th>OS</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sapiochin, 2017&lt;sup&gt;81&lt;/sup&gt;</td>
<td>Single-center retrospective</td>
<td>379</td>
<td>SBRT vs TACE or RFA</td>
<td>Received bridging therapy of SBRT, TACE, or RFA prior to transplant</td>
<td>36 Gy/6</td>
<td>Partial and complete necrosis in explanted livers No significant difference</td>
<td>No significant difference</td>
<td>No significant difference in risk of recurrence after liver transplant between SBRT, TACE, or RFA</td>
</tr>
<tr>
<td>Shiozawa, 2015&lt;sup&gt;82&lt;/sup&gt;</td>
<td>Single-center pilot</td>
<td>73</td>
<td>SBRT vs RFA</td>
<td>Solitary tumor ≤ 3 cm (RFA) or ≤ SBRT; CP-A/B; Who PS 0-2; N0 M0</td>
<td>60 Gy/3-5 (adapted based on size)</td>
<td>Local control</td>
<td>1-year 95 vs 100%</td>
<td>SBRT patients were deemed unable to receive RFA based on comorbidities, location, or size</td>
</tr>
<tr>
<td>Yoon, 2018&lt;sup&gt;17&lt;/sup&gt;</td>
<td>Single-center phase 3</td>
<td>90</td>
<td>TACE-hypofractionated RT vs sorafenib</td>
<td>First line for CP-A patients with PVT</td>
<td>45 Gy in 2-3 Gy-fractions (3DCRT)</td>
<td>1-yr 97 vs 97%</td>
<td>MST 55 vs 43 weeks&lt;sup&gt;a&lt;/sup&gt;</td>
<td>In TACE-RT arm, no patient discontinued treatment due to hepatic decompensation, 11.1% in the TACE-RT arm were able to undergo curative surgical resection due to downstaging</td>
</tr>
</tbody>
</table>

**Abbreviations:** BED, biological equivalent dose; CP, Child-Pugh; cTACE, complete TACE; curative, includes surgery, RFA, and percutaneous ethanol injection; DMFS, distant metastasis-free survival; EQU2, equivalent dose in 2 Gy fractions; GI, gastrointestinal; HCC, hepatocellular carcinoma; iTACE, incomplete TACE; LDT, liver-directed therapy; LRFS, local recurrence-free survival; MST, median survival time; n, patient number; NCDB, National Cancer Database; non-curious, includes TACE, sorafenib, or chemotherapy; NR, not reported; OS, overall survival; PFS, progression-free survival; PVT, portal vein thrombosis; RFA, radiofrequency ablation; SBRT, stereotactic body radiation therapy; TACE, transarterial chemoembolization; TAE, transarterial embolization; Tx, treatment; WHO, World Health Organization.

<sup>a</sup>Statistically significant.
Prospective Study of Stereotactic Body Radiation Therapy for Hepatocellular Carcinoma on Waitlist for Liver Transplant

Tiffany Choe-Lam Wong,1,2 Vivien Ho-Fan Lee,1,3 Ada Lai Yin Low,1,4 Herbert H. Pang,1 Ke-Os Lam,1,4 YvonneLow,1 Tracy Yuhl Col,5 Adrienne Sue Yip Fong,2 South Wik Man Leong,3 Edna Chu-Choon Wong,4 Jeff Wing-Cheong Dai,5 Albert Chi-Yan Chau,6 Tin-To Cheng,2 James Yan-Yiu Fung,2 Rebecca Mei-Wen Yeung,2 Mei Yee Lok,2 To-Wai Leung,8,9 and Chung-Man Le2

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).

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

SBRT scores:
✓ LC @ 1 yr
✓ Dropouts @ 1 & 3 yrs
✓ Pathological response
Stereotactic Body Radiation Therapy vs. Transarterial Chemoembolization in Inoperable Barcelona Clinic Liver Cancer Stage a Hepatocellular Carcinoma: A Retrospective, Propensity-Matched Analysis

**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; \( P = 0.04 \)) and OS (HR = 1.61; 95% CI: 1.13–2.29; \( P = 0.009 \)).
HCC with PVTT

HCC with early PVTT

- Tumour vessels
- Left lobe segmental enhancement in arterial phase
- Early invasion into portal vein
- Antegrade flow in portal vein

Left portal vein branches may show enhancement during arterial phase.
HCC & PVTT

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

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

Bland Vs Malignant Thrombus

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

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

Bland

Malignant

arterial

venous
PVTT: Diagnosis

Liver Imaging Reporting and Data System (LiRADs v14)

- Enhancement similar to primary HCC
- Not diagnostic but features to alert:
  - Occluded vein with **expanded lumen, or ill-defined walls**, or restricted diffusion on diffusion-weighted MRI sequences, or contiguous with typical HCC lesion
  - Obscured, **partially visualized vein**
  - Heterogeneous enhancement of vein
- **Non-tumoral thrombus does not enhance or expand the lumen**
- If standard imaging is controversial → Contrast-enhanced Ultrasound or PET-CT contrast or Biopsy
PET + CT

HCC: arterial enhancement

PVTT: Filling defect
PVTT:

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

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

Liver Cancer Study Group of Japan:
- PVTT into 4 classes
  - **Vp1** is 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)
Guidelines for HCC-PVTT

- **BCLC – Stage C:**
  - Recommends - Sorafenib
    

- **AASLD and EASL:**
  - TARE – recognized as effective by AASLD but not specifically recommended
  - EASL – discourage TACE and state safety of TARE – but not recommended
    

- **NCCN – 2015:**
  - Sorafenib / locoregional therapies – indicated
  - Arterially directed therapies – relatively contraindicated
PVTT: significance

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

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

<table>
<thead>
<tr>
<th>Survival data (mo)</th>
<th>Adverse effects</th>
<th>Key references</th>
<th>Additional comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall survival</td>
<td>Main PVTT</td>
<td>Branch PVTT</td>
<td>CP-A</td>
</tr>
<tr>
<td>Supportive care</td>
<td>2-4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgical resection</td>
<td>9-33</td>
<td>9-10</td>
<td></td>
</tr>
<tr>
<td>Sorafenib</td>
<td>6-8</td>
<td>8.1</td>
<td></td>
</tr>
<tr>
<td>XRT</td>
<td>9.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TACE</td>
<td>7-10</td>
<td>5.3</td>
<td>10.2</td>
</tr>
<tr>
<td>Y-90 SIRT</td>
<td>5-17</td>
<td>9</td>
<td>17</td>
</tr>
</tbody>
</table>

- **Supportive care**
  - Overall survival: 2-4 months
  - Main PVTT: 9-10 months
  - Branch PVTT: 8.1 months

- **Surgical resection**
  - Overall survival: 9-33 months

- **Sorafenib**
  - Overall survival: 6-8 months
  - Adverse effects: skin reaction, diarrhea, fatigue
  - Key references: Schoniger et al., Minagawa et al., Llovet et al.
  - Additional comments: Employed in select centers

- **XRT**
  - Overall survival: 9.6 months
  - Adverse effects: radiation induced liver disease

- **TACE**
  - Overall survival: 7-10 months
  - Adverse effects: liver failure, postembolization syndrome
  - Key references: Pinter et al., Chung et al., Luo et al., Xue et al.
  - Additional comments: Lowest risk with nonocclusive thrombus, cavernous transformation, superselective TACE

- **Y-90 SIRT**
  - Overall survival: 5-17 months
  - Adverse effects: fatigue, hyperbilirubinemia, GI ulceration
  - Key references: Salem et al., Hilgard et al., Sangro et al.
  - Additional comments: Employed in select centers

**Flowchart**

- **HCC with PVTT without extrahepatic metastasis**
  - Vp1 or 2
    - Good prognosis (Small, solitary, good biology, etc.)
      - Surgical resection
      - If not indicated
  - Vp3 or 4
    - Worse prognosis (other than good prognosis)
      - RT or TACE
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

<table>
<thead>
<tr>
<th>Survival data (months)</th>
<th>Adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Overall survival</td>
</tr>
<tr>
<td>Supportive care⁵</td>
<td>2-4</td>
</tr>
<tr>
<td>Surgical resection⁶</td>
<td>9-33</td>
</tr>
<tr>
<td>TACE³³</td>
<td>7-10</td>
</tr>
<tr>
<td>External radiation therapy⁷⁶</td>
<td>9.2</td>
</tr>
<tr>
<td>HAIC⁴²,⁴³</td>
<td>6-7</td>
</tr>
<tr>
<td>Radioembolization³³,³⁵</td>
<td>10</td>
</tr>
<tr>
<td>Sorafenib⁴⁴,⁴⁶</td>
<td>6-8</td>
</tr>
</tbody>
</table>

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

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

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

- **Reduction in intrahepatic metastasis** through portal vein

- **Decrease in portal pressure & related complications**

- **Possibility of re-canalization** with feasibility of transplant/ TACE
Radiation in HCC – PVTT:

Literature review
PVTT-RT: evidence

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

- As early as 1994: Chen at al
- Later major reports only after 2000

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

<table>
<thead>
<tr>
<th>First author</th>
<th>Year</th>
<th>No.</th>
<th>Classification of PVTT</th>
<th>Treatment</th>
<th>Survival rate</th>
<th>Median survival time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hata [37]</td>
<td>2005</td>
<td>12</td>
<td>Vp 3–4</td>
<td>Proton beam therapy (50–72 Gy)</td>
<td>24 % (5-year)</td>
<td>11 mo (CR + PR)</td>
</tr>
<tr>
<td>Nakagawa [38]</td>
<td>2005</td>
<td>52</td>
<td>Vp 2–4</td>
<td>3D-CRT (39–60 Gy)</td>
<td>5.1 % (5-year)</td>
<td>NA</td>
</tr>
<tr>
<td>Zeng [39]</td>
<td>2005</td>
<td>44</td>
<td>Vp 1–4, Vv3</td>
<td>External beam radiation (36–60 Gy)</td>
<td>34.8 % (1-year)</td>
<td>8.0 mo</td>
</tr>
<tr>
<td>Kim [40]</td>
<td>2005</td>
<td>59</td>
<td>Vp 3–4</td>
<td>3D-CRT (39–70.2 Gy)</td>
<td>20.7 % (2-year)</td>
<td>10.7 mo (CR + P)</td>
</tr>
<tr>
<td>Lin [41] [RCT]</td>
<td>2006</td>
<td>43</td>
<td>Vp 3–4</td>
<td>Stereotactic radiotherapy (22)</td>
<td>NA</td>
<td>6.0 mo</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3D-CRT (21)</td>
<td>NA</td>
<td>6.7 mo</td>
</tr>
<tr>
<td>Zhang [42]</td>
<td>2008</td>
<td>10</td>
<td>Vp 3</td>
<td>125-iodine seed implantation for PVTT</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Shirai [42]</td>
<td>2009</td>
<td>26</td>
<td>Vp 3–4</td>
<td>3D-CRT using SPECT</td>
<td>30 % (2-year)</td>
<td>10.3 mo</td>
</tr>
<tr>
<td>Giorgio [44]</td>
<td>2009</td>
<td>13</td>
<td>Vp 4</td>
<td>Percutaneous RFA</td>
<td>77 % (3-year)</td>
<td>NA</td>
</tr>
</tbody>
</table>
### Table 1. Stereotactic body radiotherapy outcomes for hepatocellular carcinoma 2006 - 2013

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

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

RT = radiation therapy; NR = no response; PD = progressive disease; IA = intra-arterial; IFN = interferon.
RT in PVTT as neo-adjuvant: possible candidates for Sx

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

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

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

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JCO 2019

Background. Median survival in patients with hepatocellular carcinoma (HCC) and portal vein tumor thrombosis (PVTT) is 3–6 months; conventional liver transplantation is contraindicated. Methods. We studied outcomes following donor liver transplantation (LDLT) post-PVTT downstaging with chemoembolization (SBRT) and tumor ablation with transarterial chemo- or radioembolization. Results. Of 248 consecutive LDLTs, 43 were for HCC, including 25 with PVTT downstaging (DS) after successful DS and 20 with PVTT/SBRT with SBRT/PVTT downstaging (DS + Vp1+2). DS was attempted in 43, was successful in 27 (63%), and 25 underwent LDLT. Median alpha fetoprotein (AFP) at diagnosis and pre-LDLT was 78 (IQR 32–203) and 59 (IQR 2–280), respectively. Median OS to LDLT time was 3.2 months. Excluding 2 postoperative deaths, 1- and 5-year overall survival (OS) and recurrence-free survival (RFS) were 62%, 57%, and 54%, respectively, comparable to survival in 398 HCC patients without PVTT undergoing LDLT (5-year OS: 70%, P = 0.09; 5-year RFS: 63%, P = 0.03, respectively). There was a trend toward better OS in DS than in SVs (RFS: 40% vs. 30%; P = 0.03). Results were better in SVs in DS than in DS+Vp1+2 (OS: 40% vs. 30%, P = 0.03). Conclusion. LDLT patients with PVTT can achieve acceptable survival with LDLT after successful DS. Low initial AFP levels, a significant drop in AFP with DS and low tumor grade, favorably influence survival in those patients.

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

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Overall survival (mo)</th>
<th>Extent of PVTT (mo)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Main PVTT</td>
<td>Branch PVTT</td>
</tr>
<tr>
<td>BSC</td>
<td>2-4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sorafenib</td>
<td>6.5-8.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TACE</td>
<td>7-10</td>
<td>5.3</td>
<td>10</td>
</tr>
<tr>
<td>HAIC</td>
<td>6.5-14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RT</td>
<td>9.6-10.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TARE</td>
<td>6-16.9</td>
<td>7.7</td>
<td>16.9</td>
</tr>
<tr>
<td>TACE plus sorafenib</td>
<td>11-13</td>
<td>3</td>
<td>13-15</td>
</tr>
<tr>
<td>Sorafenib plus RT</td>
<td>8.6-10.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TACE plus RT</td>
<td>10.6-12</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>HAIC plus RT</td>
<td>12.1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

- **TACE alone** when used in advanced HCC, has **limited effects on PVTT**.

- **Local radiotherapy + TACE more beneficial**: RT for PVTT & TACE/ TARE for liver

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

TACE + RT: strategies

- **Sequential**: RT (PVTT) + TACE (HCC)
  - TACE less effective for PVTT

- Planned consolidation - RT for TACE residual
  - Targets peripheral residual cells - due to collateral supply or recanalization

- **Salvage**: RT or TACE upfront – other as salvage for recurrence
Stereotactic body radiotherapy combined with transarterial chemoembolization for hepatocellular carcinoma with portal vein tumor thrombosis

MOLECULAR AND CLINICAL ONCOLOGY 2: 43-50, 2014

JINGBO KANG, QING NIE, RUI DU, LIPING ZHANG, JUN ZHANG, QILIANG LI, JINGGUO LI
Department of Radiotherapy, Navy General Hospital, Beijing 100048, P.R. China
Received March 30, 2013; Accepted July 26, 2013
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Treatment response

101 cases

<table>
<thead>
<tr>
<th>Group</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A</td>
<td>SBRT f/b TACE</td>
</tr>
<tr>
<td>Group B</td>
<td>TACE f/b SBRT</td>
</tr>
<tr>
<td>Group C</td>
<td>SBRT alone</td>
</tr>
</tbody>
</table>

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

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

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

Table IV. Improvement of life quality following radiotherapy.

<table>
<thead>
<tr>
<th>Relief of abdominal discomfort and distension</th>
<th>Jaundice resolution</th>
<th>Ascites release</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A</td>
<td>72.2% (13/18)</td>
<td>66.6% (6/9)</td>
</tr>
<tr>
<td>Group B</td>
<td>71.4% (15/21)</td>
<td>60.0% (6/10)</td>
</tr>
<tr>
<td>Group C</td>
<td>62.5% (10/16)</td>
<td>50.0% (3/6)</td>
</tr>
</tbody>
</table>
Stereotactic body radiotherapy combined with transarterial chemoembolization for hepatocellular carcinoma with portal vein tumor thrombosis

JINGBO KANG, QING NIE, RUI DU, LIPING ZHANG, JUN ZHANG, QILIANG LI, JIANGUO LI and WENJIE QI

Department of Radiotherapy, Navy General Hospital, Beijing 100048, P.R. China

Received March 30, 2013; Accepted July 26, 2013

The combination of γ-SBRT and TACE was shown to be a relatively effective local treatment for primary HCC patients with PVTT. Compared to γ-SBRT followed by TACE and γ-SBRT alone, TACE followed by γ-SBRT may exert a negative effect on liver function. These results suggested that the combination of TACE and γ-SBRT may be considered a relatively effective, safe and feasible treatment method for primary HCC patients with PVTT, although TACE followed by γ-SBRT may negatively affect liver function.
An Emerging Role for Radiation Therapy in the Treatment of Hepatocellular Carcinoma and Intrahepatic Cholangiocarcinoma.

Wu J³, Dawson LA³, Zhu AX³, Hong TS³.

COMBINATION THERAPY: Sorafenib and Radiation Therapy

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

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

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>RT</th>
<th>Added therapy</th>
<th>Objective response rate</th>
<th>Grade ≥3 toxicity rate</th>
<th>In situ recurrence rate</th>
<th>Multifocal recurrence rate</th>
<th>Median survival (mo)</th>
<th>Survival rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Robertson et al., 1993&lt;sup&gt;9&lt;/sup&gt;</td>
<td>11</td>
<td>48–72 Gy</td>
<td>HAI FUDR</td>
<td>100%</td>
<td>16%</td>
<td>–</td>
<td>–</td>
<td>81% (3 y)</td>
<td>–</td>
</tr>
<tr>
<td>Yasuda et al., 1999&lt;sup&gt;10&lt;/sup&gt;</td>
<td>44</td>
<td>36–70 Gy</td>
<td>TAE/PEI</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>11</td>
<td>–</td>
</tr>
<tr>
<td>Dawson et al., 2000&lt;sup&gt;11&lt;/sup&gt;</td>
<td>27</td>
<td>30–90 Gy</td>
<td>HAI FUDR</td>
<td>45%</td>
<td>10%</td>
<td>–</td>
<td>–</td>
<td>10</td>
<td>42% (1 y) 20% (2 y)</td>
</tr>
<tr>
<td>Park et al., 2002&lt;sup&gt;12&lt;/sup&gt;; Seong et al., 2003&lt;sup&gt;13&lt;/sup&gt;</td>
<td>158</td>
<td>40–60 Gy</td>
<td>TACE (107)</td>
<td>67%</td>
<td>–</td>
<td>7%</td>
<td>34%</td>
<td>19</td>
<td>64% (1 y) 19% (5 y)</td>
</tr>
<tr>
<td>Chia-Hsien Cheng et al., 2001&lt;sup&gt;14&lt;/sup&gt;</td>
<td>26</td>
<td>41–53 Gy</td>
<td>TACE (17)</td>
<td>–</td>
<td>–</td>
<td>11%, 12%</td>
<td>33%, 59%</td>
<td>24</td>
<td>69% (1 y) 23% (3 y)</td>
</tr>
<tr>
<td>Guo et al., 2003&lt;sup&gt;15&lt;/sup&gt;</td>
<td>76</td>
<td>30–50 Gy</td>
<td>TACE</td>
<td>48%</td>
<td>–</td>
<td>13%</td>
<td>–</td>
<td>25</td>
<td>57% (2 y)</td>
</tr>
<tr>
<td>Li et al., 2003&lt;sup&gt;16&lt;/sup&gt;</td>
<td>45</td>
<td>50.4 Gy</td>
<td>TACE</td>
<td>91%</td>
<td>27%</td>
<td>27%</td>
<td>–</td>
<td>19</td>
<td>64% (1 y) 19% (5 y)</td>
</tr>
<tr>
<td>Cheng et al., 2004&lt;sup&gt;17&lt;/sup&gt;</td>
<td>89</td>
<td>36–66 Gy</td>
<td>TACE (74)</td>
<td>–</td>
<td>61%</td>
<td>0%</td>
<td>0%</td>
<td>66%</td>
<td>–</td>
</tr>
<tr>
<td>Liu et al., 2004&lt;sup&gt;18&lt;/sup&gt;</td>
<td>44</td>
<td>40–60 Gy</td>
<td>–</td>
<td>61%</td>
<td>0%</td>
<td>0%</td>
<td>43%</td>
<td>15</td>
<td>61% (1 y) 40% (2 y)</td>
</tr>
<tr>
<td>Zeng et al., 2004&lt;sup&gt;19&lt;/sup&gt;</td>
<td>54</td>
<td>40–60 Gy*</td>
<td>TACE</td>
<td>76%</td>
<td>–</td>
<td>0%</td>
<td>65%</td>
<td>20</td>
<td>72% (1 y) 6% (5 y)</td>
</tr>
<tr>
<td>Wu et al., 2004&lt;sup&gt;20&lt;/sup&gt;</td>
<td>94</td>
<td>48–60 Gy</td>
<td>TACE</td>
<td>91%</td>
<td>–</td>
<td>3%</td>
<td>–</td>
<td>25</td>
<td>94% (1 y) 26% (3 y)</td>
</tr>
<tr>
<td>Ben-Josef et al., 2005&lt;sup&gt;21&lt;/sup&gt;</td>
<td>35</td>
<td>40–90 Gy</td>
<td>HAI FUDR</td>
<td>56%</td>
<td>30%</td>
<td>0%</td>
<td>64%</td>
<td>15</td>
<td>–</td>
</tr>
<tr>
<td>Park et al., 2005&lt;sup&gt;22&lt;/sup&gt;</td>
<td>59</td>
<td>30–55 Gy</td>
<td>HAI FUDR</td>
<td>66%</td>
<td>0%</td>
<td>0%</td>
<td>10%</td>
<td>27% (2 y)</td>
<td>–</td>
</tr>
<tr>
<td>Zhou et al., 2006&lt;sup&gt;23&lt;/sup&gt;</td>
<td>50</td>
<td>30–54 Gy*</td>
<td>TACE</td>
<td>18%</td>
<td>6%</td>
<td>62%</td>
<td>60%</td>
<td>17</td>
<td>60% (1 y) 28% (3 y)</td>
</tr>
<tr>
<td>Mornex et al., 2006&lt;sup&gt;24&lt;/sup&gt;</td>
<td>27</td>
<td>66 Gy</td>
<td>–</td>
<td>92%</td>
<td>41%</td>
<td>22%</td>
<td>41%</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

RT, radiotherapy; HAI, hepatic arterial infusion; FUDR, 5-fluorouracil; TAE, transarterial embolization; PEI, percutaneous ethanol injection; TACE, transarterial chemoembolization.

* Hypofractionated regimens used.
SBRT Practice patterns

TABLE 2: Comparisons between common fractionation schedules

<table>
<thead>
<tr>
<th>Fractionation (BED in Gy)</th>
<th>n</th>
<th>BED (Gy)</th>
<th>Median age (y)</th>
<th>Stage 1/2/3</th>
<th>AFP elevated</th>
<th>Size median (cm)</th>
<th>Size groups (2/2.4/4 cm)</th>
<th>Facility volume Low/mod/high</th>
<th>Academic facility</th>
<th>Charlson 0/1/2</th>
<th>Received Chemno</th>
<th>Time to SBRT (&lt;2/2.4/4 m)</th>
<th>2 y OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 in 3 (100)</td>
<td>92</td>
<td>100</td>
<td>60.2</td>
<td>60/29/16</td>
<td>50%</td>
<td>2.8</td>
<td>26/56/18</td>
<td>26/40/94</td>
<td>59%</td>
<td>53/27/20</td>
<td>61%</td>
<td>13/39/48</td>
<td>43.4%</td>
</tr>
<tr>
<td>40 in 5 (72)</td>
<td>64</td>
<td>72</td>
<td>63.7</td>
<td>50/29/16</td>
<td>49%</td>
<td>3.1</td>
<td>22/58/40</td>
<td>27/56/49</td>
<td>87%</td>
<td>59/23/18</td>
<td>15%</td>
<td>41/38/21</td>
<td>44.8%</td>
</tr>
<tr>
<td>46 in 3 (125)</td>
<td>46</td>
<td>125</td>
<td>63.2</td>
<td>76/13/7</td>
<td>46%</td>
<td>2.4</td>
<td>37/70/13</td>
<td>15/28/38</td>
<td>94%</td>
<td>57/29/24</td>
<td>2%</td>
<td>50/30/20</td>
<td>79.0%</td>
</tr>
<tr>
<td>45 in 3 (113)</td>
<td>27</td>
<td>113</td>
<td>65.0</td>
<td>54/17/11</td>
<td>52%</td>
<td>3.5</td>
<td>44/44/32</td>
<td>59/15/26</td>
<td>63%</td>
<td>74/3/19</td>
<td>4%</td>
<td>26/44/30</td>
<td>52.4%</td>
</tr>
<tr>
<td>34 in 3 (151)</td>
<td>17</td>
<td>151</td>
<td>60.2</td>
<td>77/24/0</td>
<td>47%</td>
<td>2.1</td>
<td>30/36/12</td>
<td>47/44/33</td>
<td>77%</td>
<td>55/10/47</td>
<td>6%</td>
<td>24/40/29</td>
<td>70.1%</td>
</tr>
<tr>
<td>P-value</td>
<td>&lt;0.001</td>
<td>0.411</td>
<td>0.156</td>
<td>0.599</td>
<td>0.006</td>
<td>0.014</td>
<td>&lt;0.001</td>
<td>0.003</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&gt;-fractions</td>
<td>158</td>
<td>114</td>
<td>62.5</td>
<td>56/24/14</td>
<td>53%</td>
<td>3.27</td>
<td>29/42/33</td>
<td>20/39/51</td>
<td>78%</td>
<td>65/19/22</td>
<td>2%</td>
<td>39/40/24</td>
<td>59.8%</td>
</tr>
<tr>
<td>-fractions</td>
<td>220</td>
<td>98.9</td>
<td>62.9</td>
<td>54/32/14</td>
<td>51%</td>
<td>3.10</td>
<td>21/44/36</td>
<td>30/40/24</td>
<td>85%</td>
<td>57/22/19</td>
<td>3%</td>
<td>25/36/26</td>
<td>42.3%</td>
</tr>
</tbody>
</table>
Response evaluation

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

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

April 2011 to June 2016
60 HCC+ PVTT cases referred for SBRT

Baseline/ Metastatic work-up
Normal liver > 700 cc / Sr Bilirubin < 3 mg/dl / No Extra hepatic disease

Yes
Curative Intent [42 cases]
\( \leq \) ECOG 2 / Child Pugh A or B
> 5 mm away from luminal structures (duodenum/ stomach/ bowel)

No
Palliative Intent [18 cases]
Multicentric / Bulky HCC unfit for surgery/ alternative therapies
What dose and how much toxicity is expected??
SBRT case selection: risk based on segment & function

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

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

Overall Survival (%) vs Time (Months)

- Child-Pugh Score
  - B7
  - B8-C10

Log-rank test $P = 0.01$
Dose selection & outcomes

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

- Lausch et al. → LC dose dependent – sigmoidal → TD90 @ 6 mths 84 Gy EQD2 (HCC) Vs 95 EQD2 (Mets)
- Rule et al. → LC - 56% (30 Gy in 3 fr – BED 1060) → 100% (60 Gy in 5 fr - BED 132)
  - heavily chemo pre-treated → resistant → higher dosages {London regional cancer program suggestion}
  - Smaller lesions/ Good KPS → Rule et al. - higher dose & higher control rate achievable
  - Larger lesion / proximity to OAR – poor tolerance to high dose 
  - Choose best therapeutic window → threshold dose limit
- 2009, McCammon et al. → > 36 Gy - 3-year LC 59 – 89% → but < 36 Gy LC dropped to 8% [minimal threshold 65.3 Gy EUD {BED 80}]
- Another method to select dose → radiobiologically guided dose selection algorithm → used to individually select the maximum dose possible for each patient with specific toxicity risk levels
  - Cárdenes et al. → 48 Gy in 3 fractions at a maximum of two treatments per week
  - > CP-B7 - reduced dose of 40 Gy in 5 fractions → safer as no benefit from dose escalation in them

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

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

### Table 1: Summary of dose constraints

<table>
<thead>
<tr>
<th>Organ at risk</th>
<th>SBRT constraints (22,23)</th>
<th>Quantec (1.8-2 Gy per fraction) (24)</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver excluding CTV</td>
<td>V10 &lt;70%</td>
<td>Dmean &lt;30 Gy</td>
<td>RILD</td>
</tr>
<tr>
<td>Esophagus</td>
<td>D0.5 mL &lt;32 Gy</td>
<td>V35 &lt;50%</td>
<td>Esophagitis</td>
</tr>
<tr>
<td>Stomach</td>
<td>D0.5 mL &lt;30 Gy</td>
<td>D100 &lt;35 Gy</td>
<td>Ulceration</td>
</tr>
<tr>
<td>Kidney</td>
<td>Dmean &lt;10 Gy</td>
<td>Dmean &lt;28 Gy (1.8-2 Gy per fraction)</td>
<td>Renal Insufficiency</td>
</tr>
<tr>
<td>Ribs</td>
<td>D30&lt;0.5 cc, D27.3&lt;2 cc</td>
<td>Fracture</td>
<td></td>
</tr>
<tr>
<td>Bowel and duodenum</td>
<td>D0.5 ml &lt;30 Gy, Dmax &lt;35 Gy</td>
<td>D45 &lt;195 cc</td>
<td>Enteritis/fistula, bleeding/perforation</td>
</tr>
<tr>
<td>Spinal cord</td>
<td>D0.5 mL &lt;25 Gy</td>
<td>Dmax =45</td>
<td>Myelopathy</td>
</tr>
<tr>
<td>Chest wall</td>
<td>D30 &lt;30 cc</td>
<td></td>
<td>Necrosis/pain</td>
</tr>
<tr>
<td>Heart</td>
<td>D30 mL &lt;30 Gy</td>
<td>V25 &lt;10%</td>
<td>Pericarditis</td>
</tr>
</tbody>
</table>

SBRT, stereotactic body radiotherapy; RILD, radiation induced liver disease; CTV, clinical target volume.
<table>
<thead>
<tr>
<th>Sample</th>
<th>Dose</th>
<th>Prescription</th>
<th>Local control</th>
<th>Toxicity &gt; = grade 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blomgren et al. (1995)</td>
<td>7 Gy–45 Gy</td>
<td>ICRU point</td>
<td>50% response rate</td>
<td>1 hemorrhagic gastritis</td>
</tr>
<tr>
<td>Herfarth et al. (2004)</td>
<td>1x(14–26 Gy)</td>
<td>Isocenter</td>
<td>71% 1 year</td>
<td>None</td>
</tr>
<tr>
<td>Scheffer et al. (2005)</td>
<td>3 x 12 Gy</td>
<td>Isodose</td>
<td>92% at 2 years</td>
<td>DLT not reached</td>
</tr>
<tr>
<td>Rusthoven et al. (2005)</td>
<td>3 x 20 Gy</td>
<td>surrounding PTV</td>
<td>100% for tumors &lt; 3 cm</td>
<td></td>
</tr>
<tr>
<td>Wulf et al. (2006)</td>
<td>3 x 10 Gy</td>
<td>Isodose</td>
<td>65% isodose line</td>
<td>1 classic RILD (liver failure and fat infection, pt Child B initial)</td>
</tr>
<tr>
<td>Mendez-Romero et al. (2006)</td>
<td>5 with HCC</td>
<td>Isocenter</td>
<td>100% HCC last follow up</td>
<td>1 portal hypertension with melena</td>
</tr>
<tr>
<td>Hoyer et al. (2006)</td>
<td>3 x 15 Gy</td>
<td>Isocenter</td>
<td>66% 2 years</td>
<td>2 elevation GCT Grade 3</td>
</tr>
<tr>
<td>McCammon et al. (2009)</td>
<td>3 x 10 Gy</td>
<td>Isodose</td>
<td>89%</td>
<td>One lethal hepatic failure</td>
</tr>
<tr>
<td>Lee et al. (2009)</td>
<td>3 x 20 Gy</td>
<td>surrounding PTV</td>
<td>(31.1–53.9 Gy)</td>
<td>1 colic perforation (surgery) 2</td>
</tr>
<tr>
<td>Rusthoven et al. (2009)</td>
<td>68 pts with mets</td>
<td>Median 41.8 Gy</td>
<td>71% 1 year</td>
<td>1 grade 5 SBO + grade 4 bleed (progression)</td>
</tr>
<tr>
<td>Goodman et al. (2010)</td>
<td>3 x 12–20 Gy</td>
<td>Isodose</td>
<td>92% 2 years</td>
<td>Grade 3 gastritis/oesophagitis 2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>surrounding PTV</td>
<td>77% 1 year</td>
<td>1 grade 3 soft tissue toxicity</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No limiting toxicity</td>
<td></td>
</tr>
</tbody>
</table>
Centrifugal effect of SBRT on liver

- Occluded veins/congestion
- Area of repopulation
- Necrosis/fibrosis
Tips to evaluate 700 cc normal liver
SBRT Liver – our Experience
Planning a new case

HCC: arterial enhancement

PVTT: Filling defect
Planning triple phase MRI
ImageFusion

Planning CT and MRI

CT-MRI fusion

CT portovenous fusion
Dose prescription

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

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

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

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

Rusthoven et al, JCO
Planned for
48 Gy in 3 fractions
BED: 124 Gy
Assessment

Post treatment:

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

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

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, suspicious area are submitted.

Call 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 : Suspicious 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.
Post Transplant CECT
Present status: Summary

PVTT and recurrence in 2015

TARE 2014

HCC 2012

RFA in 2012

Transplant – LDLT - Feb 2016

Post transplant – 5 year – alive & healthy

SBRT PVTT – Dec 2015

5 year – alive & healthy
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.
Alive for 1 year 7 months post surgery – developed lung mets - expired
<table>
<thead>
<tr>
<th>Survival (months) in specific groups</th>
<th>Post Diagnosis</th>
<th>Post RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Cases [n=60] (mean)</td>
<td>15 [1-55]</td>
<td>7 [0-42]</td>
</tr>
<tr>
<td>Curative cases [n=42] (mean)</td>
<td>15 [1-55]</td>
<td>8 [0-42]</td>
</tr>
<tr>
<td>Non Transplant [n=29] mean</td>
<td>9 [1-41]</td>
<td>3 [0-12]</td>
</tr>
<tr>
<td>Palliative [n=18] mean</td>
<td>13 [2-38]</td>
<td>4 [0-14]</td>
</tr>
</tbody>
</table>

**PVTT recanalization**

**Post Transplant**
Role of SBRT in HCC – PVTT: Medanta Experience

PORTAL VEIN THROMBUS IRRADIATION—AN ALTERNATIVE IN INOPERABLE HEPATOCELLULAR CARCINOMA

A Abhishek, T Katara, K Sharma, KP Karr thick, K Madan, T Pipilasi
Cancer Institute, Medanta–The Medicity, Gurugram, India; Institute of Liver and Biliary Sciences (ILBS), New Delhi, India

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

Aims: To review and establish the role of RT in advanced HCC with portal vein thrombosis

Materials and Methods: 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 34-80% incidence, PVTT cannot be overlooked and demands alternative approaches. Results of surgery in such cases are dismal and palliative chemotherapy (TACT) 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-vascularization may be achieved in 60–75% cases and re-considered for TACE/partial management with acceptable outcomes. Therefore, RT is a promising salvage alter-
### Successful Transplant post neo-adjuvant PVTT-RT: limited available world literature

#### Korea 2016

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

Abhishek et al 2016

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

Korea 2016

Abhishek et al 2016

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

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

Medanta-The Medicity, Gurgaon, India

**Courtesy: Medanta –The Medicity**
HCC – PVTT : SBRT + TARE → Transplant

Post successful transplant
HCC – PVTT – unfit for TARE (multiple collaterals)

56 Gy / 7 fr alt days
HCC – PVTT – unfit for TARE (multiple collaterals)

Four pathogenic mechanisms have been described:

- directly by a siphoning effect (lobar multisegmental shape)
- portal hypoperfusion (sectorial shape) due to portal branch compression or infiltration
- thrombosis resulting in a portal branch blockade
- flow diversion caused by an arterioportal shunt
Preliminary data: 20 cases

HCC with PVTT

Multi modality approach – TARE + SBRT combination
New in PVTT- RT: endovascular brachytherapy

**World Journal of Gastroenterology**

**Retrospective Study**

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

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

**CONCLUSION**

EVBT combined with stent placement, TACE, and sorafenib might be a safe and effective palliative treatment option for MPVTT.
New in PVTT- RT: endovascular brachytherapy
HCC – RT

HCC - PVT

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

Inoperable multicentric HCC – median survival 6-9 months

Gains…

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

Median survival - > 13 months
    longest > 20 months
<table>
<thead>
<tr>
<th>Guidelines</th>
<th>Mention of RT as a treatment option</th>
</tr>
</thead>
<tbody>
<tr>
<td>APASL (2009)</td>
<td>No</td>
</tr>
<tr>
<td>AASLD (2005/2010)</td>
<td>2005/one of non-curative treatment</td>
</tr>
<tr>
<td></td>
<td>2010/alleviate pain in bone metastasis</td>
</tr>
<tr>
<td>NCCN (2012)</td>
<td>Unresectable (unable to transplant), Inoperable local disease</td>
</tr>
<tr>
<td>EASL-EORTC (2012)</td>
<td>No evidence/under investigation</td>
</tr>
<tr>
<td>Chinese Society of Liver Disease</td>
<td>Vascular invasion/Extrahepatic spread</td>
</tr>
</tbody>
</table>
NCCN Recommendations for Locoregional Therapies

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

All tumors considered for ablation should be amenable to complete treatment with a margin of normal tissue around the tumor. Tumors should
**Figure 1** Comparisons of staging and treatment algorithms of HCC among 2018 EASL, 2018 AASLD, and 2019 Chinese guidelines.

BCLC, Barcelona Clinic Liver Cancer; EASL, European Association for the Study of the Liver; AASLD, American Association for the Study of Liver Diseases; CNLC, China liver cancer staging; OLT, orthotopic liver transplantation; TACE, transarterial chemoembolization; TARE, transarterial radioembolization; TKIs, tyrosine kinase inhibitors; PD-1, programmed cell death-1; SBRT, stereotactic body...
# 2018 Korean Liver Cancer Study Group

<table>
<thead>
<tr>
<th>mHCC stage</th>
<th>Best option</th>
<th>Alternative option</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ia/Single ≤ 2 cm</td>
<td>REA</td>
<td>TACE, Transarterial chemoembolization (TACE-TEC)</td>
</tr>
<tr>
<td>Ia/Single ≤ 2 cm</td>
<td>REA</td>
<td>Other (RT)</td>
</tr>
<tr>
<td>Ia/Single ≤ 2 cm</td>
<td>REA</td>
<td>EBRT</td>
</tr>
<tr>
<td>Ib/Single ≤ 2 cm</td>
<td>REA, LT</td>
<td>TACE, Transarterial chemoembolization (TACE-TEC)</td>
</tr>
<tr>
<td>Ib/Single ≤ 2 cm</td>
<td>REA, LT</td>
<td>Other (RT)</td>
</tr>
<tr>
<td>Ib/Single ≤ 2 cm</td>
<td>REA, LT</td>
<td>EBRT</td>
</tr>
<tr>
<td>II &lt; 5 cm</td>
<td>REA, LT</td>
<td>TACE, Transarterial chemoembolization (TACE-TEC)</td>
</tr>
<tr>
<td>II &lt; 5 cm</td>
<td>REA, LT</td>
<td>Other (RT)</td>
</tr>
<tr>
<td>II &lt; 5 cm</td>
<td>REA, LT</td>
<td>EBRT</td>
</tr>
<tr>
<td>II ≥ 5 cm</td>
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<tr>
<td>II ≥ 5 cm</td>
<td>REA, LT</td>
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<tr>
<td>II ≥ 5 cm</td>
<td>REA, LT</td>
<td>EBRT</td>
</tr>
<tr>
<td>IIIa &gt; 5 cm</td>
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<td>TACE, Transarterial chemoembolization (TACE-TEC)</td>
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<tr>
<td>IIIa &gt; 5 cm</td>
<td>REA, LT</td>
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<tr>
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<tr>
<td>IIIb &gt; 5 cm</td>
<td>REA, LT</td>
<td>EBRT</td>
</tr>
</tbody>
</table>

**Fig. 5.** First-line treatment recommendations from 2018 Korean Liver Cancer Association-National Cancer Center, Korea Practice Guidelines for Patients with mHCC. Child-Pugh class A, no portal hypertension, and Eastern Cooperative Oncology Group 0-1. EBRT = external beam radiation therapy, LT = liver transplantation, mHCC = modified Union for International Cancer Control, Child-Pugh class A, no portal hypertension, and Eastern Cooperative Oncology Group 0-1.
"With great power, comes great responsibility."

Thank You....