RADIOTHERAPY FOR PORTAL VEIN THROMBOSIS IN PATIENTS WITH UNRESECTABLE HEPATOCELLULAR CARCINOMA
ANATOMY AND BLOOD SUPPLY:

8 Segments

2 Separate blood supply:
- Hepatic artery
- Portal vein
PORTAL VEIN TUMOR THROMBUS (PVTT):

• Several factors contribute to the poor prognosis associated with HCC, Portal vein thrombosis being one of the most important ones.

• Median survival is 2.7–4.0 months if left untreated.
When the tumor thrombus extends to involve the main portal vein, prognosis is extremely poor because:

- Tumor cells may spread along the portal vein, resulting in extensive intrahepatic metastases.
- Portal vein obstruction causes further deterioration in liver function, resulting in liver failure.
- Portal hypertension is aggravated, leading to intractable ascites and esophageal variceal bleeding.
Diagnosis: Multiphase CT

Arterial phase

Portal venous phase
The optimal treatment for HCC with PVTT remains controversial.

**Treatment:**
- **Curative therapy**
  - Liver resection
- **Palliative therapy:**
  - TAC/TACE
  - External Beam Radiotherapy
  - Chemoimmunotherapy
  - Combination therapy
    - TACE plus external radiotherapy
    - Systemic chemotherapy
Curative Therapy:

- PVTT remains a contraindication to liver transplantation because of early tumor recurrence.
- Surgical resection with complete resection of tumor and thrombus gives the best chance of cure.

The potential benefits of surgical resection of HCC with PVTT include:
- Portal venous pressure may decrease
- Liver function may improve
- Survival may be prolonged
- Quality of life may improve
• A patient is selected for liver resection when the tumor thrombus is located in the first or second branch of the main portal vein. The tumor can be completely removed by liver resection with resection of the ipsilateral portal venous branch containing the tumor thrombus.

• It is still unclear whether there is any difference in outcome between thrombectomy and partial portal vein resection, as there is no comparative study on this.

• The long-term survival and postoperative morbidity/mortality after surgery for HCC with PVTT have not been well documented.
<table>
<thead>
<tr>
<th>Study</th>
<th>No. of patients</th>
<th>Extent of PVTT</th>
<th>Median survival (months)</th>
<th>1-year survival (%)</th>
<th>3-year survival (%)</th>
<th>5-year survival (%)</th>
<th>Operative mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chen et al.(^{18}) (2006)</td>
<td>286/152</td>
<td>First branch of PV vs. main PV</td>
<td>18.8/10.1</td>
<td>58.7/39.5</td>
<td>22.7/5.7</td>
<td>18.1/0</td>
<td>0/2.6</td>
</tr>
<tr>
<td>Ikai et al.(^{21}) (2006)</td>
<td>78</td>
<td>First branch of PV</td>
<td>8.9</td>
<td>45.7</td>
<td>21.7</td>
<td>10.9</td>
<td>3.8</td>
</tr>
<tr>
<td>Le Treut et al.(^{22}) (2006)</td>
<td>20</td>
<td>First branch of PV/Main PV</td>
<td>12</td>
<td>50</td>
<td>26</td>
<td>17</td>
<td>—</td>
</tr>
<tr>
<td>Pawlik et al.(^{23}) (2005)</td>
<td>102</td>
<td>First branch of PV/Main trunk of hepatic vein</td>
<td>11</td>
<td>45</td>
<td>17</td>
<td>10</td>
<td>5.9</td>
</tr>
<tr>
<td>Konishi et al.(^{19}) (2001)</td>
<td>18</td>
<td>Main PV</td>
<td>—</td>
<td>48</td>
<td>—</td>
<td>—</td>
<td>0</td>
</tr>
<tr>
<td>Wu et al.(^{20}) (2000)</td>
<td>15/97</td>
<td>Main PV vs. branch of PV</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>26.4/28.5</td>
<td>0/3</td>
</tr>
<tr>
<td>Ohkubo et al.(^{24}) (2000)</td>
<td>47</td>
<td>Segmental branch of PV/First branch of PV/Main PV</td>
<td>33</td>
<td>53.9</td>
<td>33.2</td>
<td>23.9</td>
<td>2.1</td>
</tr>
</tbody>
</table>
The survival benefit of TACE for unresectable HCC has been shown in two RCTs from Europe and Hong Kong. As HCCs derive their blood supply mainly from the hepatic artery, infusion of chemotherapeutic agents into the hepatic artery has the theoretical advantage of increasing total drug exposure to the tumor.

However, portal vein thrombosis is generally considered as a contraindication. The theoretical concern is that as the blood supply to the liver has already been compromised by portal vein thrombosis, embolization of the hepatic artery may result in hepatic infarct or acute hepatic failure.
• TACE may be a safe treatment for HCC with PVTT, provided that the patients have good hepatic function and collateral circulation. RCTs are necessary to show this conclusively.

• Adjustments to the TACE protocol is necessary through superselective catheterization of the hepatic artery and through the degree of embolization.
External Beam Radiotherapy:

- External radiotherapy has been regarded as ineffective for HCC because the radiation dose that can be delivered to the tumor is limited by the tolerance of the non-tumorous liver.
- With technological advances in radiotherapy, these methods increase the likelihood of killing cancer cells by delivering a higher dose of radiation to the tumor, while at the same time sparing healthy tissue from excessive irradiation.
- Three-dimensional radiotherapy had encouraging and comparable results in the recanalization of the thrombosed portal vein.
• **Advanced Radiotherapy techniques:**

  - Three-Dimensional Conformal Radiation Therapy (3D-CRT)
  - Intensity-Modulated Radiotherapy (IMRT)
  - Stereotactic Body Radiotherapy (SBRT)
  - Image-Guided Radiation Therapy (IGRT)
  - Proton Beam Radiation Therapy
RADIOTHERAPY TARGET AND DOSE:

• The clinical target volume (CTV) includes the PVTT which is defined by the hypodense filling defect in the portal vein.

• The planning target volume (PTV) includes a 1.5–2 cm CTV margin to allow for daily set-up variations and respiratory motion of the liver.

• A daily dose of 1.8 to 3 Gy can be used at five fractions per week to deliver a goal dose of 30 - 60 Gy.

• The patients should be evaluated every week during radiation therapy for early detection of Radiation-Induced Liver Disease (RILD) if developed.
The 3DCRT plan must fulfill the following criteria to be acceptance:

- PTV must receive at least 95% of the prescribed dose.
- Liver volume receiving dose more than 30 Gy (V30) must not exceed 30%.
- The dose to the spinal cord must not exceed 45 Gy.
- The total dose received by 70% of each Kidney must not exceed 20 Gy (V20).
Patient selection for radiotherapy treatment:

- Liver function of Child-Pugh class A or B.
- Good performance status.
- The patient should have no history of radiotherapy for the liver.
- Tumor thrombus in the main trunk and/or first branches of the portal vein.
• Many retrospective and several phase 2 studies have demonstrated responses of HCC PVT to RT.

• Median survival time was reported as long as 6 to 13 months.

• Outcomes are best in patients with preserved liver function, less extensive PVT, and lower levels of tumor markers.

• Guidelines for assessing response of PVT and other vascular invasion from HCC are needed.
### Radiation therapy for hepatocellular carcinoma with portal venous thrombosis

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Patients</th>
<th>Design</th>
<th>CP-B (%)</th>
<th>CP-C (%)</th>
<th>RT only</th>
<th>Dose (Gy)</th>
<th>Fractionation</th>
<th>Median survival (mo)</th>
<th>Toxicity grade ≥3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rim, 2012</td>
<td>45</td>
<td>Ret</td>
<td>38</td>
<td>0</td>
<td>7%</td>
<td>38-65</td>
<td>1.8-2.5 Gy/fx</td>
<td>11.2</td>
<td>2%</td>
</tr>
<tr>
<td>Yoon, 2012</td>
<td>412</td>
<td>Ret</td>
<td>36</td>
<td>0</td>
<td>30%</td>
<td>21-60</td>
<td>2-5 Gy/fx</td>
<td>10.6</td>
<td>10%</td>
</tr>
<tr>
<td>Chuma, 2011</td>
<td>20</td>
<td>Ret</td>
<td>25</td>
<td>0</td>
<td>0</td>
<td>30-48</td>
<td>7-16 fx</td>
<td>12</td>
<td>15%</td>
</tr>
<tr>
<td>Katamura, 2009</td>
<td>16</td>
<td>Ret</td>
<td>25</td>
<td>0</td>
<td>0</td>
<td>30-45</td>
<td>3 Gy/fx</td>
<td>7.5</td>
<td>2 gr. 4, 7 gr. 3 leuk</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6 gr. 3 thromb, 1 gr. 3 anorexia</td>
</tr>
<tr>
<td>Zhang, 2009</td>
<td>16</td>
<td>Ret</td>
<td>19</td>
<td>6</td>
<td>0</td>
<td>30-60</td>
<td>2 Gy/fx</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Huang, 2009</td>
<td>326</td>
<td>Ret</td>
<td>NA</td>
<td>0</td>
<td>100%</td>
<td>60</td>
<td>2-3 Gy/fx</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Han, 2008</td>
<td>40</td>
<td>Pro</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>45</td>
<td>25 fx</td>
<td>13.1</td>
<td>1 gr. 5 liver dysfunction, 9 gr. 4, 33 gr. 3 toxicities RT or chemo caused toxicity</td>
</tr>
<tr>
<td>Toya, 2007</td>
<td>38</td>
<td>Ret</td>
<td>24</td>
<td>0</td>
<td>100%</td>
<td>17.5-50.4</td>
<td>1.8-4 Gy/fx</td>
<td>9.6</td>
<td>0</td>
</tr>
<tr>
<td>Lin, 2006</td>
<td>22</td>
<td>SBRT</td>
<td>Pro</td>
<td>50</td>
<td>18</td>
<td>45</td>
<td>3 Gy/fx, 3 fx/week</td>
<td>6</td>
<td>0 gr. ≥3</td>
</tr>
<tr>
<td></td>
<td>21</td>
<td>CRT</td>
<td></td>
<td>33</td>
<td>43</td>
<td>45</td>
<td>1.8 Gy/fx</td>
<td>6.7</td>
<td>14/43 pts finished RT</td>
</tr>
<tr>
<td>Kim, 2005</td>
<td>59</td>
<td>Ret</td>
<td>12</td>
<td>0</td>
<td>100%</td>
<td>30-54</td>
<td>2-3 Gy/fx</td>
<td>7.8</td>
<td>0</td>
</tr>
<tr>
<td>Zeng, 2005</td>
<td>44</td>
<td>Ret</td>
<td>NA</td>
<td>NA</td>
<td>23%</td>
<td>36-60</td>
<td>2 Gy/fx</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Yamada, 2003</td>
<td>19</td>
<td>Pro</td>
<td>32</td>
<td>5</td>
<td>0</td>
<td>60</td>
<td>2 Gy/fx</td>
<td>7</td>
<td>5 gr. 3 thromb, 2 gr. 3 leuk</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2 gr. 3 GI ulcers</td>
</tr>
<tr>
<td>Ishikura, 2002</td>
<td>20</td>
<td>Pro</td>
<td>50</td>
<td>5</td>
<td>0</td>
<td>50</td>
<td>25 fx</td>
<td>5.3</td>
<td>5%</td>
</tr>
<tr>
<td>Tazawa, 2001</td>
<td>24</td>
<td>Ret</td>
<td>33</td>
<td>17</td>
<td>0</td>
<td>50</td>
<td>25 fx</td>
<td>CP-A: 12.7</td>
<td>CP-B: 2.6</td>
</tr>
</tbody>
</table>

**Abbreviations:** chemo = chemotherapy; CP = Child-Pugh; CRT = conformal radiation therapy; fx = fraction(s); gr. = grade; Gy = Gray; HCC = hepatocellular carcinoma; leuk = leukopenia; mo = months; NA = not available; Pro = prospective; pts = patients; Ret = retrospective; RT = radiation therapy; SBRT = stereotactic body radiation therapy; thromb = thrombocytopenia.
COMBINATION THERAPY:

• TACE, when used on advanced HCC, has limited effects on PVTT.

• Local radiotherapy together with TACE has been investigated. The strategy is to use radiation to treat PVTT and to use TACE to treat liver tumors. The median survival rates ranged from 5.3 months to 9.7 months.

• Large HCCs, when treated by TACE alone, rarely achieve complete remission. A combination of systemic chemotherapy and TACE was investigated, systemic chemotherapy with TACE for large HCC (>10 cm) with PVTT was found to be more beneficial than conservative treatment alone (median survival, 8.7 months vs. 3.5 months, respectively).
### Results of combined therapy for HCC with PVTT.

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of patients</th>
<th>Treatment combination</th>
<th>Complete response (%)</th>
<th>Partial response (%)</th>
<th>Median survival (months)</th>
<th>1-year survival (%)</th>
<th>2-year survival (%)</th>
<th>3-year survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jang et al. (2007)</td>
<td>80</td>
<td>TACE &amp; systemic 5-FU</td>
<td>21.3</td>
<td>-</td>
<td>8.7</td>
<td>29.8</td>
<td>13.4</td>
<td>-</td>
</tr>
<tr>
<td>Yamada et al. (2003)</td>
<td>19</td>
<td>TACE &amp; 3D conformal radiotherapy targeting the PVTT</td>
<td>-</td>
<td>-</td>
<td>7</td>
<td>40.6</td>
<td>10.2</td>
<td>-</td>
</tr>
<tr>
<td>Ishikura et al. (2002)</td>
<td>20</td>
<td>TACE &amp; external radiotherapy targeting the PVTT</td>
<td>0</td>
<td>50</td>
<td>5.3</td>
<td>25</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Tazawa et al. (2001)</td>
<td>24</td>
<td>TACE &amp; external radiotherapy targeting the PVTT</td>
<td>16.7</td>
<td>33.3</td>
<td>9.7/3.8 (responder/nonresponder)</td>
<td>61/19 (responder/nonresponder)</td>
<td>21/9 (responder/nonresponder)</td>
<td>10/0 (responder/nonresponder)</td>
</tr>
</tbody>
</table>
CONCLUSION AND RECOMMENDATIONS

• The prognosis of HCC patients with portal vein tumor thrombosis (PVTT)) is poor; without treatment, their survival is less than 3 months.

• Recently, few studies have shown that three-dimensional conformal radiation therapy 3DCRT is effective for survival in HCC patients with PVTT. Median survival time on those patients was reported as long as 6 to 13 months.

• The most promising results were obtained with combined treatments that included hepatic resection.
• The combination of TACE and CRT is more effective in the control of PVTT associated with HCC and improves patient’s survival compared with TACE alone.

• This disease does not have a homogenous prognosis, and therefore it is important to select patients who have a good prognosis and to treat these patients with combined treatments.

• The combination therapy seems feasible and efficacious in patients with good hepatic functional reserve. More controlled studies are necessary to clarify the survival advantage with the combination therapy.

• Guidelines for assessing response of PVT and other vascular invasion from HCC are needed.
THANK YOU