Radiation Therapy for Advanced HCC with Portal Vein Invasion

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The 11th Annual Symposium of Korean Liver Cancer Study Group
Pubmed Search;
Publication on radiotherapy of liver cancer

- RT result for intrahepatic tumor
- RT toxicity
- RT technique
- Particle therapy
- RT for extrahepatic tumor
- Others
HCC with Portal Vein Invasion

- Poor prognosis (median survival time < 4-6 months)
- Rapid development of intrahepatic metastasis.
- Available therapeutic modality is severely limited.
Radiotherapy for HCC with portal vein invasion; *Is it beneficial?*
Radiotherapy 45 Gy concurrently with intra-arterial 5-Fu

AFP; preTx 12800 IU/ml

AFP; postTx 6 mo. 298
30-54 Gy (2-3 Gy/fr)

Kim DY et al., Cancer, 2005
• What is the optimum radiotherapy?
  – *Radiation field; PVTT only vs. PVTT + primary tumor*
  – *The best dose/fractionation scheme*
Clinical results after radiotherapy on portal vein thrombosis only

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Treatment</th>
<th>RT dose</th>
<th>Response rate</th>
<th>Median survival time (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zeng et al, 2005</td>
<td>44</td>
<td>RT+TACE</td>
<td>50 Gy (36–60 Gy)</td>
<td>CR 34.1%, PR 11.4%</td>
<td>RT: 8 non-RT: 4</td>
</tr>
<tr>
<td>Nakagawa, 2005</td>
<td>52</td>
<td>3D RT</td>
<td>57 Gy (39–60 Gy)</td>
<td>50%</td>
<td>3 year: 15.2%</td>
</tr>
<tr>
<td>Yamada et al, 2003</td>
<td>19</td>
<td>3D RT+ TACE For Liver tumor</td>
<td>60 Gy</td>
<td>57.9%</td>
<td>7</td>
</tr>
<tr>
<td>Tazawa et al, 2001</td>
<td>24</td>
<td>RT+TACE</td>
<td>50 Gy</td>
<td>50.0%</td>
<td>CR, PR: 9.7 NR, PD: 3.8</td>
</tr>
</tbody>
</table>
Clinical results after radiotherapy on portal vein thrombosis+primary liver tumor

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Treatment</th>
<th>RT dose</th>
<th>Response rate</th>
<th>Median survival time (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>You et al, 2007</td>
<td>49</td>
<td>3D RT + TACE</td>
<td>40–45 Gy</td>
<td>48%</td>
<td>TACE: 13</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>TACE+RT: 13.5</td>
</tr>
<tr>
<td>Kim T et al, 2006</td>
<td>41</td>
<td>3D RT</td>
<td>44–54 Gy in 2–3 Gy</td>
<td>CR 9.7%, PR 29.3%</td>
<td>Responder: 20.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Nonresponder: 7.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Nonresponder: 5.3</td>
</tr>
<tr>
<td>Kim J et al, 2002</td>
<td>54</td>
<td>RT + ia-5-Fu</td>
<td>45 Gy</td>
<td>42.1%</td>
<td>11.6</td>
</tr>
<tr>
<td>Ishikura et al, 2002</td>
<td>20</td>
<td>RT+TACE</td>
<td>50 Gy</td>
<td>50%</td>
<td>5.3</td>
</tr>
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</table>
• What is the optimum radiotherapy?
  – Radiation field;
    PVTT only vs. PVTT + primary tumor
  – The best dose/fractionation scheme
## Radiation dose

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Treatment</th>
<th>RT dose (mean)</th>
<th>Response rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sugiyama et al, 2007</td>
<td>15</td>
<td>3D RT+TACE, TACI, systemic Ctx</td>
<td>38.5 Gy</td>
<td>20%</td>
</tr>
<tr>
<td>Lin et al, 2006</td>
<td>43</td>
<td>Stereotic RT (SRT): 22</td>
<td>45 Gy in 3 Gy</td>
<td>SRT 75%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3D RT: 21</td>
<td>45 Gy in 1.8 Gy</td>
<td>3D RT 83%</td>
</tr>
<tr>
<td>Zeng et al, 2005</td>
<td>44</td>
<td>RT+TACE</td>
<td>50 Gy</td>
<td>45.5%</td>
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<td>Tazawa et al, 2001</td>
<td>24</td>
<td>RT+TACE</td>
<td>50 Gy</td>
<td>50%</td>
</tr>
<tr>
<td>Huang et al, 2001</td>
<td>41</td>
<td>RT+TACE</td>
<td>51.4 Gy</td>
<td>80%</td>
</tr>
<tr>
<td>Nakagawa, 2005</td>
<td>52</td>
<td>3D RT</td>
<td>57 Gy</td>
<td>50%</td>
</tr>
<tr>
<td>Yamada et al, 2003</td>
<td>19</td>
<td>3D RT+TACE for liver tumor</td>
<td>60 Gy</td>
<td>57.9%</td>
</tr>
</tbody>
</table>
## Radiation fractionation schedule

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Treatment</th>
<th>RT dose</th>
<th>Fraction (Gy)</th>
<th>Response rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hsu et al, 2006</td>
<td>53</td>
<td>3D RT + thalidomide</td>
<td>45–70 Gy</td>
<td>1.5 x2/d</td>
<td>50%</td>
</tr>
<tr>
<td>Lin et al, 2006</td>
<td>21</td>
<td>3D RT</td>
<td>45 Gy</td>
<td>1.8</td>
<td>83%</td>
</tr>
<tr>
<td>You et al, 2007</td>
<td>49</td>
<td>3D RT+TACE</td>
<td>40–45 Gy</td>
<td>1.8</td>
<td>48%</td>
</tr>
<tr>
<td>Kim T et al, 2006</td>
<td>41</td>
<td>3D RT</td>
<td>44–54 Gy</td>
<td>2–3</td>
<td>39%</td>
</tr>
<tr>
<td>Lin et al, 2006</td>
<td>22</td>
<td>Stereotactic RT</td>
<td>45 Gy</td>
<td>3</td>
<td>75%</td>
</tr>
<tr>
<td>Wu, 2004</td>
<td>35</td>
<td>3D RT+TACE</td>
<td>48–60 Gy</td>
<td>4–8</td>
<td>71.4%</td>
</tr>
</tbody>
</table>
Is concurrent treatment working?  
Then what is the best one?
### Radiation & concurrent treatment

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Concurrent Treatment</th>
<th>RT dose</th>
<th>Response rate</th>
<th>Median survival time (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hsu et al, 2006</td>
<td>53</td>
<td>Thalidomide</td>
<td>45-70 Gy (1.5 x2/d)</td>
<td>50%</td>
<td>-</td>
</tr>
<tr>
<td>Sugiyama et al, 2007</td>
<td>3</td>
<td>TACI (2), Systemic Ctx (1)</td>
<td>38.5 Gy</td>
<td>20%</td>
<td>10</td>
</tr>
<tr>
<td>Kim J et al, 2002</td>
<td>54</td>
<td>Intraarterial 5 Fu</td>
<td>45 Gy</td>
<td>42.1%</td>
<td>11.6</td>
</tr>
<tr>
<td>Han et al, 2008</td>
<td>101</td>
<td>Intraarterial 5 Fu</td>
<td>45 Gy</td>
<td>43%</td>
<td>16.7</td>
</tr>
</tbody>
</table>
Increased lethality after concurrent chemoradiotherapy in rat liver cirrhosis model

Rat cirrhosis model
Thioacetamide 0.3 g/L for 30 wks

Partial hepatectomy
Partial liver RT
Partial liver RT+5-Fu

Isn’t tumor metastasis enhanced by radiotherapy?
Radiation enhances the growth of a dormant metastasis.

Increased metastatic burden after local radiotherapy to a Lewis lung ca

Camphausen et al., Cancer research 2001
51/Male, B-viral HCC with PVTT (T4N0M0)


AFP: >83000 42089 28328
PIVKA-II: >2000 168 75
Incomplete TACE induces angiogenesis by increasing VEGF and bFGF.

Sergio et al., Am J Gastroenterol 2007
M/52, B-viral HCC

PIVKA-II (mAU/mL):
Survival prolongation in Radiotherapy with intraarterial chemotherapy

1998-2007, n=101

Median survival; 16.7 months

*Reported median survival time < 4-6 months (Llovet et al. AASLD 2007)

Han & Seong et al. 2008, Cancer, in press
Tumor response brings survival benefit

Median survival time (months);
Responder: 18.0
Nonresponder: 6.8
p<0.001

Kim T et al., Am J Clin Oncol 2006
Conclusions

• In advanced HCC with portal vein invasion, radiotherapy might result in tumor metastasis.

• However, clinical benefit seems much greater through tumor regression/survival prolongation.

• Antimetastatic strategy is strongly recommended.

Thank you Dr. Roentgen!
Acknowledgement

Yonsei Liver Cancer Clinic

Radiation Oncology
Increased metastatic burden after local radiotherapy to a LLC-LM tumor. Twenty-four mice whose tumors were 750 mm$^3$ were separated into two groups, one of which received radiation to the primary tumor. Within 18–21 days, the number of surface metastases (A) and the lung weights (B) had increased significantly in the irradiated mice compared with the nonirradiated mice.

Exogenous Angiostatin Suppresses the Growth of Metastases in LLC-LM. Sixteen mice were injected with LLC-LM on the right thigh. When the tumors were 500 mm$^3$, the mice were randomized into two groups. Both groups were irradiated with 10-Gy fractions for five doses. One group was treated with mFc-mAS at a dose of 20

Fig. 1. Representative gelatin zymograms of urinary MMPs. Increased production of MMP-2 in the urine of mice implanted with LLC-LM as measured by substrate gel electrophoresis. An increasing level of enzymatic activity was detected in the urine of mice from day 1 to day 4 and again from day 4 to day 8. However, urine collected on day 15, 6 days post radiotherapy, contained significantly lower levels of MMP-2 concomitant with the tumor regression observed at this same time point.
## Radiotherapy for Portal Vein Tumor Thrombosis

<table>
<thead>
<tr>
<th>Study</th>
<th>No. pts</th>
<th>Radiation Dose (Gy)</th>
<th>Response rate (%)</th>
<th>MST (month)</th>
<th>OS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zeng et al., 2005</td>
<td>44</td>
<td>36-60 (2 /fr)</td>
<td>CR, 34 PR, 11 SD, 52</td>
<td>8.0</td>
<td>1 y, 35</td>
</tr>
<tr>
<td>Tazawa et al., 2001</td>
<td>24</td>
<td>50 (2 /fr)</td>
<td>CR, 8 PR, 25 SD, 25</td>
<td>9.7</td>
<td>1 y, 61 3 y, 10</td>
</tr>
<tr>
<td>Yamada et al., 2003</td>
<td>19</td>
<td>46-60 (2 /fr)</td>
<td>CR, 0 PR, 57 SD, 42</td>
<td>7.0</td>
<td>1 y, 40 2 y, 10</td>
</tr>
<tr>
<td>Ishikura et al., 2002</td>
<td>20</td>
<td>50 (2 /fr)</td>
<td>CR, NA PR, 50 SD, NA</td>
<td>5.3</td>
<td>1 y, 25</td>
</tr>
</tbody>
</table>

*Hawkins MA et al., Cancer, 2006*
### Liver; Radiation Tolerance

<table>
<thead>
<tr>
<th>Fr. Normal liver (%)</th>
<th>Total dose (Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 33</td>
<td>66-72.6</td>
</tr>
<tr>
<td>33 - 66</td>
<td>48-52.8</td>
</tr>
<tr>
<td>&gt; 66</td>
<td>36</td>
</tr>
<tr>
<td></td>
<td>(whole)</td>
</tr>
</tbody>
</table>

*Burman et al., 1991  Lawrence et al, 1992; 1993, Dawson et al, 2000*
Conclusion

• By integrating radiotherapy, better clinical outcome can be achieved in hepatocellular carcinoma.

Thank you Dr. Roentgen!
Portal Vein Tumor Thrombosis
Portal Vein Tumor Thrombosis
Lovett et al, 2008

- **Very early stage**: single HCC mass <2 cm carcinoma in situ
  - 1 HCC
    - Portal pressure/bilirubin
      - Normal: Resection
      - Possibly contraindication to transplant
        - NO: Potentially curative treatments
        - YES: OLT, PEI/RFA

- **Early stage**: 1 HCC or 3 nodules <3 cm, PS 0
  - 3 nodules ≤3 cm
    - Possible contraindication to transplant
      - NO: Potentially curative treatments
      - YES: OLT, PEI/RFA

- **Intermediate stage**: No portal vein thrombosis
  - Multinodular, PS 0
    - Chemoembolization
    - Potential treatments

- **Advanced stage**: Portal invasion, Metastases, PS 0-2
  - Sorafenib
  - Potential treatments

- **Terminal stage**
  - Symptomatic therapy
Growth factors

? hematogenous
Radiation enhances HCC cell invasion with MMP-9 expression

Increased invasiveness in HCC cells but not in normal cell after radiation

Increased expression of MMP-9 in HCC cells (HepG2)

Cheng et al., Oncogene 2006
Radiation Therapy for Advanced HCC with Portal Vein Invasion

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Acknowledgement

Dept. of Radiation Oncology

Yonsei Liver Cancer Clinic
Irradiation of tumor suppresses angiogenesis at a distal site

Tumor growth suppresses angiogenesis. Resection enhances angiogenesis. Radiation suppresses angiogenesis

Hartford et al., Cancer Research, 2000