External and Internal Radiation Therapy for Liver Cancer

Laura A. Dawson
Radiation Oncology, PMH
University of Toronto, Canada

Outline

• Rationale
• External Beam Radiation Therapy
  – Liver metastases
  – Hepatocellular carcinoma
  – Most suitable patients
• Internal Radiation Therapy
  – Liver metastases
  – Hepatocellular carcinoma
  – Most suitable patients

Rationale: Liver metastases

• Liver metastases from colorectal ca (CRC) and other solid cancers a large source of morbidity and mortality
• Rationale for more liver directed therapies with improved systemic therapies
• Surgery CRC mets: 5 year survival 25 – 50%
  – Long term survival not possible in absence of surgery
• Most patients not suitable for surgery or radiofrequency ablation (RFA)

Rationale: Hepatocellular Carcinoma

• Sixth most common cancer globally
  – 626,000 cases worldwide annually
  – Increasing globally
• Third cause of global cancer death
  – 598,000 deaths worldwide annually
• ≈ 7% 5 year survival
• Transplant, resection, RFA can cure: 5 year survival 20 – 80%
  – Most patients not eligible for these local therapies

Disclosures

• Research Grants: Elekta, Bayer
Hypothesis

- Radiation therapy should improve outcomes in patients with primary and metastatic liver cancer, unsuitable for standard local therapies

RT Strategies

- External beam radiotherapy
  - 2D low dose palliative radiotherapy
  - 3D conformal radiotherapy
  - Intensity modulated radiotherapy
  - Stereotactic radiotherapy
  - Protons, Carbon ions

- Brachytherapy
  - Interstitial
  - Interluminal

- Intra-operative RT (IORT)
  - Mobile electron unit

Radioisotopes
- Iodine 131 Lipiodol
- Yttrium 92 microspheres

Roles of Radiation Therapy

- Palliative (low dose focal / whole liver RT)
  - To delay recurrence
  - To improve symptoms and quality of life

- Radical (tumorcidal / high focal dose RT)
  - Definitive therapy to improve survival
  - To downstage borderline resectable tumors
  - In conjunction with other liver treatment

TROG Palliative RT for Liver Metastases

- N=28
- 10 Gy in 2 # over 2 days
- Symptoms:
  - Pain (27)
  - Distension (19)
  - Night sweats (12)
  - Nausea (18)
  - Vomiting (8)
- Premedication: steroid and anti-emetic
- Med survival 10 weeks

TROG Palliative RT for Liver Metastases

- N=28
- 10 Gy in 2 # over 2 days
- Symptoms scored by MDs (+/- telephone assessment): Symptom scale 0 – 4
  - Symptom response rates: 53-66% at 2 weeks
  - Partial/ complete global symptom responses 54%
- Patient assessment:
  - 12 / 17 “better” on at least 1 occasion

Palliative RT for liver cancer

- Few studies with QOL and symptom scales
- ~80% pain relief in palliative RT studies for bone or soft tissue metastases
- Ongoing palliative RT study at PMH for symptomatic CRC liver metastases or HCC
  - 40 patients
  - 8 Gy x 1, ‘simple’ RT
  - Child A or B
  - Endpoints
    - Symptom improvement
    - QOL

Symptom Improvement with RT

- At 1 month, 3/11 patients had a complete response (CR)
- 7/11 patients - improvement in worst symptom by at least 1 point
- 4/11 patients - no improvement or symptom worsening
- Reduction in 1 mo. symptom score by 1.2 (95% -0.4, 1.5)

Palliative RT for HCC portal vein thrombosis

- 47 y. o. man with locally advanced HCC
- Progression post ++ tx (including targeted therapies)
- Symptomatic portal vein, IVC and atrium thrombosis
- RT ant-post pair: 25 Gy in 5#

Potential RT Toxicities

- Radiation induced liver disease (RILD)
  - Anicteric ascites
  - Elevated liver enzymes (ALP > AST/ALT)
- Non-RILD hepatic toxicity
  - Elevation of transaminases
  - Reactivation of viral hepatitis
  - Liver decompensation
  - Thrombocytopenia
  - Biliary obstruction
  - Elevated bilirubin
- Non-hepatic
  - Vascular
  - Capsular pain, rib fracture
  - Stomach, bowel bleeding, obstruction, fistula
**Hepatitis B reactivation**

- Reported after RT for HCC
- Antiviral therapy reduces risk
- Figure
  - Group I antiviral therapy
  - Group II none

**Liver Tolerance – U Michigan**

- Series of phase I/II trials since 1987
  - Individualized RT 1.5 Gy twice daily (max 90 Gy)
  - Hepatic arterial FUdR or BUdR
- 203 patients (98 mets, 105 primary); 13 RILD
- Significant multivariate analysis risk factors
  - Male > female
  - BUdR > FUdR chemotherapy
  - HCC > liver metastases
- Dose and volume of RT delivered

**Liver Tolerance – U Michigan**

- Radiation Induced Liver Disease
- Liver Volume
- Dose (Gy), 1.5 Gy bid
- Liver Metavolume
- 3/3
- 2/3
- 1/3
- 0.0
- 0.2
- 0.4
- 0.6
- 0.8
- 1.0
- 0 2 0 4 0 6 0 8 0 1 0 0 1 2 0

**Tolerance: Stereotactic Body RT (SBRT)**

- SBRT= highly conformal potent dose RT delivered in few fractions (30-60Gy in 1-10#)
  - Liver toxicity uncommon following SBRT
  - Most SBRT series: <30% effective liver volume irradiated
- ’Safe’ liver dose-volume constraints
  - 6 fractions: mean liver dose < 20 Gy
  - 3 fractions: >700 cc < 15 Gy
  - 1 fraction: D30% < 12 Gy, D50% < 7 Gy

**How to deliver RT safely**

- Appropriate patient selection
  - Child-Pugh A > B >>> C
- Technological advances
  - Imaging (tumor and vascular)
  - RT breathing motion management
  - RT planning
  - RT image guidance
  - Interventional radiology technical advances
- Ensure enough residual liver and other critical tissues spared from RT

**Outline**

- Rationale
- External Beam Radiation Therapy
  - Metastases
  - Hepatocellular carcinoma
  - Most suitable patients
- Internal Radiation Therapy
  - Metastases
  - Hepatocellular carcinoma
  - Most suitable patients
**Imaging**
- Multi-modal imaging: CT, MR, US
- Improved spatial and temporal resolution
- Image registration and fusion

**RT Dose Planning**
- CT based dose planning with geometric conformation of dose
- Intensity modulated radiation therapy
- Automated computer optimization

**RT Treatment Volumes - HCC**
- GTV
- CTV 5 mm in liver (PMH, Toronto)
- PTV (5-30 mm)
  - Individualized
- Portal vein thrombus, PVT
- PVT CTV 0 mm
- PVT PTV

**Breathing Motion Management**
- Liver breathing motion measurement tools
  - Fluoroscopy, cine MR, respiratory sorted CT
- Motion management strategies
  - Increase volume irradiated
  - Breath hold
  - Gating beam
  - Track beam

**Image Guided Radiation Therapy, IGRT**
- IGRT: Daily imaging immediately before or during RT delivery to position patient more accurately and precisely
- Changes in liver position relative to bones day-to-day
  - Free breathing
  - Breath hold
- IGRT increases likelihood of dose being delivered as planned

**Image Guided Radiotherapy (IGRT)**
- MV EPID
- MV CT
- MV cone beam CT
- kV Fluoroscopy + markers
- Ultrasound
- kV Cone-beam CT
- Integrated systems, MR-linac, ...

Dawson, Jaffray, JCO, 2007
3D (Volume) and 4D (Temporal) IGRT

**kV Cone Beam CT**

- Breath hold

**Contrast (IV)**

**Contrast (oral)**

**Outline**

- **Rationale**
  - External Beam Radiation Therapy
    - Metastases
    - Hepatocellular carcinoma
    - Most suitable patients
  - Internal Radiation Therapy
    - Metastases
    - Hepatocellular carcinoma
    - Most suitable patients

**University of Michigan**

- **Week 1**
  - 1.5 Gy bid
  - HA FUdR 0.2 mg/kg/d

- **Week 2**
  - **Week 5**
  - **Week 6**
  - **Week 7**

**HA FUdR**

- Phase I study, n = 128
- Concurrent hepatic arterial FUdR radiosensitizer
- Individualized prescription dose - based on volume of liver irradiated/ risk of RILD
- Maximum dose 90 Gy, 1.5 Gy/# bid

**University of Michigan: Phase I/II**

128 unresectable colorectal ca (CRC) liver metastases, HCC or cholangiocarcinoma

- Med diameter 10 cm
- RT dose:
  - median 61 Gy
- 1.5 Gy fractions twice daily
- 47 CRC mets:
  - med survival 17 mo

**Toxicity: Michigan, n=123**

- Grade 1/2 - 30% (fatigue common)
- Grade 3/4 - 30% (primarily biochemical)
- Grade 5 - 0.8%

- Most common severe complications:
  - Upper GI ulcer and bleeding 5%
  - Radiation induced liver disease 4%
  - Hepatic catheter-related 3%

**Trials of Liver Metastases SBRT**

<table>
<thead>
<tr>
<th>Institution</th>
<th>No. lesions</th>
<th>Fractions</th>
<th>Dose/#, Gy</th>
<th>Med followup, mos</th>
<th>Time</th>
<th>Actuarial LC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prospective</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wurzburg</td>
<td>55</td>
<td>1</td>
<td>14-28</td>
<td>6</td>
<td>18m</td>
<td>67</td>
</tr>
<tr>
<td>Aarhus</td>
<td>141*</td>
<td>3</td>
<td>15</td>
<td>4.3</td>
<td>2yr</td>
<td>79</td>
</tr>
<tr>
<td>Rotterdam</td>
<td>40</td>
<td>3</td>
<td>12.5</td>
<td>13</td>
<td>2yr</td>
<td>62</td>
</tr>
<tr>
<td>Colorado</td>
<td>49</td>
<td>3</td>
<td>20</td>
<td>16</td>
<td>2yr</td>
<td>52</td>
</tr>
<tr>
<td>Toronto</td>
<td>140+^</td>
<td>6</td>
<td>6-10</td>
<td>11</td>
<td>1yr</td>
<td>70</td>
</tr>
<tr>
<td><strong>Retrospective</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rochester</td>
<td>292**</td>
<td>10</td>
<td>5</td>
<td>41</td>
<td>2yr</td>
<td>67</td>
</tr>
</tbody>
</table>

*Total number of colorectal cancer metastases: 44 liver metastases.
**Total number of lesions treated: 49% of patients were treated for hepatic metastases.
†In surviving patients.
‡Different fractionation (3 10 Gy or 5 5 Gy) used for patients with hepatocellular carcinoma or with lesions 4 cm.
* 18 patients.

Ben Josef E et al, JCO, 2005
PMH Phase I/II Study - Metastases

- Conformal RT for unresectable liver cancer
  - Individualized 'iso-toxic' dose (6 fractions)
  - Breath hold for liver immobilization
- Daily IGRT and repositioning
- 68 patients with metastases (1-8/patient)
  - 40 CRC
  - 12 breast ca
  - 4 gall bladder ca
  - 12 other (lung ca, melanoma..)
  - Median volume 75 cc (2 – 3000 cc)
  - Median dose 41 Gy (28 – 60 Gy), in 6 fractions

PMH Phase I/II Study - Survival

Median survival 17.6 months (10.4, 38.1)

PMH Phase I/II Study - Metastases

PMH Phase I - Tumor control

Tumor response at last follow-up
- PD
- CR, PR, SD

Responses

RR 57%, SD 32%, PD 11%
79 y.o. man - rectal cancer liver metastases, bad COPD
Chemo-refractory, 45 Gy/6 #, 'NED' 27 months
Baseline 1 month 3 months 27 months

Lee., Dawson, JCO, April 2009

PMH Phase I/II Study - Survival

Lee., Dawson, JCO, April 2009
PMH Phase I/II Study - Survival

- Colorectal (n=40)
- Breast (n=12)
- Other (n=16)

Median survival CRC mets 14.6 months (10.3, 30.1)

Lee., Dawson. JCO, April 2009

Outline

- Rationale
- External Beam Radiation Therapy
  - Metastases
  - Hepatocellular carcinoma
    - Most suitable patients
- Internal Radiation Therapy
  - Metastases
  - Hepatocellular carcinoma
    - Most suitable patients

Results: Michigan

- 82 unresectable HCC or intrahepatic cholangioca
  - Child-Pugh A
  - Median tumor volume 276 cc
  - No portal vein thrombosis
  - Tx with individualized RT 1.5 Gy bid to 90 Gy max, with hepatic arterial 5FU dR

<table>
<thead>
<tr>
<th></th>
<th>HCC</th>
<th>Cholangioca</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>36</td>
<td>46</td>
</tr>
<tr>
<td>Response rate</td>
<td>58%</td>
<td>36%</td>
</tr>
<tr>
<td>Median survival</td>
<td>15.2 months</td>
<td>13.3 months</td>
</tr>
</tbody>
</table>

Ben Josef E, JCO, 2005

RT & TACE vs TACE - HCC: Korea

- 73/105 HCC incomplete response to TACE
  - 35 TACE repeated
  - 38 received radiotherapy
- Multivariate analysis sign. factors (survival)
  - Tumor size
  - Treatment

- 2 yr survival RT no RT
  - All 37% 14%
  - 5-7 cm 63% 42%
  - 8-10 cm 50% 0%

Shin, Seong et al. Liver International, 2005

China, TACE and RT – Dose Effect (5-10#)

- RT dose 60 Gy
- RT dose 55 Gy
- RT dose 48 Gy

Wu et al. World J Gastroenterol, 2004
HCC with Portal Vein Thrombosis, Korea

- 40 patients
- RT 45 Gy in 25#, conformal RT
- Concurrent hepatic arterial 5FU wk 1 and 5
- Post RT hepatic arterial 5FU+ Cisplatin
- Median survival 13.1 months

Protons for HCC: Japan n=162

- Fractionations: 55 – 96.8 GyE / 10-30 fractions
- N=162
  - 5 yr LOCAL CONTROL 87%
  - 5 yr SURVIVAL 24%
  - 5 late toxicities
    - Biliary stenosis 13 months post RT
    - Biloma (2) 29 and 38 months post RT
    - Gastric ulcer 4 months post RT
    - Colon ulcer 6 months post RT

Protons for HCC: Japan n=51

- Confirmatory prospective studies
- > 2cm from portal hepatis
- 66 GyE in 10#
  - 5 yr local control 88%

PMH Phase I Study, n=31 HCC pts, 27-54 Gy in 6#

- Med. Age (range): 66 (41-85)
- HBV: HCV: EtOH: other 13: 12: 4: 2
- Med. AFP (range): 1047 (< 5, 714000)
- Child A5: A6 28:3
- Portal vein/ IVC involvement n=16 (52%)
- Prior treatment: 61 %
  - Resection/ transplant + other 6 (19%)
  - RFA or EtOH ablation only 7 (23%)
  - TACE only 2 (6%)
  - Discontinue only 1 (3%)
  - Other combinations 3 (9%)

Tokuuye, Akine Clin Cancer Res 2005
Tokuuye, Akine Clin Cancer Res 2005
Fukumitsu, IJROBP, July 1, 2009
Han, Seong, et al, Cancer 103, Sept 2008
Tse et al, JCO, 2008
Phase I Study, HCC Toxicity, n=31

- Grade 3 nausea/vomiting: 1
- Grade 1 / 2 / 3 platelets: 21 / 2 / 1
- Radiation Liver Disease, RILD: 0
- Grade 3 liver enzymes: 8 (6 preexisting)
- Decline in Child score (3 mo): 5
  - Large tumors treated to doses < 36 Gy, 6#
  - 3 with rapid extensive hepatic progressive HCC
  - 2 with Child A6 function at baseline

Tse et al, JCO, 2008

Late Toxicity

- 1 tumor-duodenal connection: 15 mo post RT (30 Gy in 6#)
  - Detected on imaging, with persistent HCC
  - Ultimate infection and GI bleed leading to death at 18 mo

Pre RT

15 mo post RT

Responses

Hepatocellular carcinoma, 33 Gy/6#

Baseline 12 months

12 mo in-field local control 65% (95% CI: 44, 79%)
SD > PR > CR

Patterns of Recurrence

- Majority recur outside irradiated volume

Survival by Portal Vein Thrombosis, PVT

- PVT: med survival 11.6 mo (3.3 - 21.6)
- no PVT: med survival 17.2 mo (9.0 - 22.5)

Outline

- Rationale
- External Beam Radiation Therapy
  - Metastases
  - Hepatocellular carcinoma
  - Most suitable patients
- Internal Radiation Therapy
  - Metastases
  - Hepatocellular carcinoma
  - Most suitable patients
Most Suitable Patients

- Liver confined disease
- Not appropriate for other standard local therapies
- > 700 cc uninvolved liver
- No cirrhosis or active hepatitis
- Non-diffuse, focal, < 5 tumors
- < 8 cm diameter metastases
- Breathing motion < 10 mm
- Tumors not adjacent to stomach or small bowel

More Challenging Patients

- Underlying cirrhosis or Hepatitis
  - Treat viral Hepatitis pre-RT
- < 700 cc uninvolved liver
- > 5 non focal tumors
- > 8 cm diameter tumors
- Breathing motion > 10mm
- Tumors close to stomach or small bowel

Location: Lowest Risk to Higher Risk

- Lowest risk: Away from stomach, bowel, caudate lobe, capsule, gall bladder
- Low risk: Away from stomach, bowel
- Risk of stomach and bowel toxicity: Near stomach and small bowel
Ongoing External RT Studies

- RTOG phase I mets: 40-50 Gy in 10# (PI: Katz)
- Ph II: RT in CRC metastases (PI: Dawson)
- Ph II: RT in HCC (PI: Dawson)
- Ph I: RT + sorafenib in HCC (PI: Dawson)
- Randomized Ph II: sorafenib +/- RT for HCC (PI: Dawson, RTOG)
- Ph III: SBRT (12 – 16Gy x 3) vs RFA for unresectable CRC liver mets < 4cm (PI: Hoyer- Denmark, Mendez- Netherlands)

Outline

- Rationale
- External Beam Radiation Therapy
  - Metastases
  - Hepatocellular carcinoma
  - Most suitable patients
- Internal Radiation Therapy
  - Metastases
  - Hepatocellular carcinoma
  - Most suitable patients

**Radioembolization Devices**

- **TheraSphere®**
  - MDS Nordion, Canada
  - Glass
  - Yttrium-90
  - Size = 25 microns
  - # spheres/t = 1.2-8 million
  - FDA approved for HCC
  - European approval for liver cancer

- **SIR-Spheres®**
  - Sirtex Medical, Australia
  - Resin
  - Yttrium-90
  - Size = 35 microns
  - # spheres/t = 0-30 million
  - FDA approved for colon liver metastases
  - European approval for liver cancer

Physical half life 64 hr
Penetration range: Ave = 2.5 mm, max 10 mm

Workup algorithm

- Review of case-cirrhosis, portal HTN, tumour burden
- Angiographic evaluation-shunting
  - Tc99m-MAA
  - Coil embolization of vessels
- Dose calculation based on target liver volume (lobe/segment)
  - 80-150 Gy, wide range allows for flexibility in treatment
  - Typical treatment range is 100–120 Gy
  - 2 treatments using lobar/segmental approach

Potential Complications and Solutions

1) Gastrointestinal
   - Gastritis ===> Proton pump inhibitors
   - Ulceration ===> lobar approach (distal to collaterals)

2) Abdominal Pain Prevention
   - Burning ===> prophylactic embolization/identification of collaterals

3) Fatigue ===> 5-7 day steroid dose pack

4) Dose Selection
   - Wide range ===> segmental infusion
**Hepatic Arterial Yttrium-90 Microspheres**

- Liver sparing via
  - Hepatic arterial delivery
  - Subsegmental delivery versus whole liver
  - Rapid fall off in dose (ave range ≈ 2.5 mm)

![Histology](image1.png)  ![Monte Carlo dosimetry](image2.png)

Kennedy, et al. IJROBP 60(5), 2004

- 35 patients with a total of 38 lesions who underwent liver explantation after Y-90
- 90% of lesions < 3cm complete necrosis
- Less chance of complete necrosis with increasing tumor size
  - Increased chance of 'cold spot' with larger tumors

Riaz et al. Hepatology 2009

**Outline**

- Rationale
- External Beam Radiation Therapy
  - Metastases
  - Hepatocellular carcinoma
  - Most suitable patients
- Internal Radiation Therapy
  - Metastases
  - Hepatocellular carcinoma
  - Most suitable patients

**Randomised trial of SIR-Spheres plus hepatic arterial FUDR vs. FUDR alone for patients with CRC liver metastases**

- 74 CRC patients randomised to Y90 + FUDR vs FUDR
- Response: 50% vs 24%
- TTP: 12 vs 7.6 months

Gray et al, Ann Oncol 2001

**Van Hazel Randomized Phase II**

- 1st line liver metastases from CRC
- 5FU/leucovorin (n=10) +/- SIRT (n=11)
- Best response: 8 PR 3 SD vs 0 PR 6 SD 4 PD
- Time to progression: 18.6 mo vs 3.6 mo p<0.0005
- Med survival: 29.4 mo vs 12.8 mo p=0.02

Van Hazel et al (Australia), J Surg Oncol 88:78-85,2004
Belgium Randomized Phase III

- Chemo-refractory CRC
- 5FU infusion +/- Y90
- 44 eligible patients randomized
- Med fu 24.9 mo
- Med TTP improved: 2.1 mos to 4.6 mos (p=0.03)
- Med TTLP improved: 2.1 mos to 5.1 mos (p=0.003)
- Increased toxicity in 5FU alone arm

137 patients with chemorefractory liver metastases

- WHO response rate: 42.8% (2.1% CR, 40.7 PR)
- Biologic tumor response rate: 87% (any decrease in tumor size)
- Median survival:
  - colorectal: 15.2 mo
  - neuroendocrine: 25.9 mo
  - non-colorectal, non-neuroendocrine: 6.9 mo

Survival Analysis (Cont..)

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Median in days</th>
<th>1-Yr Survival (%)</th>
<th>2-Yr Survival (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angiographic Vascularity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyper</td>
<td>106</td>
<td>300</td>
<td>48.5</td>
<td>25.9</td>
<td>0.0046</td>
</tr>
<tr>
<td>Hypo</td>
<td>107</td>
<td>301</td>
<td>47.0</td>
<td>23.8</td>
<td></td>
</tr>
<tr>
<td>CT Vascularity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyper</td>
<td>24</td>
<td>236</td>
<td>47.6</td>
<td>25.1</td>
<td>0.0012</td>
</tr>
<tr>
<td>Hypo</td>
<td>113</td>
<td>286</td>
<td>46.3</td>
<td>20.1</td>
<td></td>
</tr>
<tr>
<td>&gt;4 Lesions</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>91</td>
<td>234</td>
<td>37.4</td>
<td>21.4</td>
<td>0.0126</td>
</tr>
<tr>
<td>No</td>
<td>46</td>
<td>632</td>
<td>68.6</td>
<td>38.1</td>
<td></td>
</tr>
<tr>
<td>Tumor Burden</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-25%</td>
<td>100</td>
<td>506</td>
<td>54.6</td>
<td>35.8</td>
<td>0.0005</td>
</tr>
<tr>
<td>25-50%</td>
<td>21</td>
<td>181</td>
<td>33.2</td>
<td>22.1</td>
<td></td>
</tr>
<tr>
<td>&gt;75%</td>
<td>7</td>
<td>105</td>
<td>6</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Hepatic Arterial Iodine-131 Lipiodol

- RCT in resected HCC
  - N=74
  - Hepatic arterial I-131 Lipiodol versus no further therapy
    - 3 yr DFS improved from 36% to 74%, p=0.04
    - 3 yr survival improved from 46% to 86%, p=0.04
- Underpowered

Underpowered* Lau, Lancet 353, p797, 1999

Outline

- Rationale
- External Beam Radiation Therapy
  - Metastases
  - Hepatocellular carcinoma
  - Most suitable patients
- Internal Radiation Therapy
  - Metastases
  - Hepatocellular carcinoma
  - Most suitable patients

Change from baseline in cross product of lesions following therapy
**Hepatic Arterial Yttrium-90 - HCC**

<table>
<thead>
<tr>
<th>Study</th>
<th>No of HCC Patients</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dancey et al 2000</td>
<td>20</td>
<td>Median = 54 weeks</td>
</tr>
</tbody>
</table>
| Carr 2004              | 65                 | Okuda I (n=42) Median = 649 d  
                           |                    | Okuda II (n=23) Median = 302 d |
| Geschwind et al 2004   | 80                 | Okuda I (n=54) Median = 628 d  
                           |                    | Okuda II (n=26) Median = 384 d  
                           |                    | CLIP 3 (n=26) Median = 812 d  
                           |                    | CLIP 1-2 (n=31) Median = 452 d  
                           |                    | CLIP > 2 (n=13) Median = 216 d |
| Liu et al 2004         | 11                 | Okuda II (n=7) Median = 11 mo  
                           |                    | Okuda III (n=4) Median = 7 mo   |
| Salem et al 2004       | 43 (86 tumors)     | Okuda I (n=21) Median = 617 d  
                           |                    | Okuda II (n=22) Median = 315 d  |

**Survival of Patients in Low and High Risk Groups**

![Survival Plot](SurvivalPlot.png)

*Goin et al, Risk Stratification Analysis, JVIR, 2005

**University of Pittsburgh: Patient Survival for High and Low Risk Groups (65 patients)**

![Survival Plot](SurvivalPlot_Pittsburgh.png)

*Goin et al, Risk Stratification Analysis, JVIR, 2005

**Pre treatment**

- **AFP → 2200**

**1 month post treatment**

- **AFP → 130**

**Pre treatment**

- **AFP → 2200**

**6 months post treatment**

- **AFP → 4.5**

*Courtesy of Riad Salem, Chicago
PORTAL VEIN THROMBOSIS

108 HCC patients
- 37 with PVT
- 71 without PVT
- Analyzed toxicities based on:
  - Child Pugh in cirrhosis
  - Dose
  - Location of PVT
- Assessed overall survival

Patient Selection Criteria
- Non-Infiltrative disease
- AST/ALT < 5 x ULN
- Tumor Volume < 50%
- Albumin > 3 g/dL
- Bilirubin < 2 mg/dL
- Good performance status
- Appropriate vascular anatomy
  - <20-30% hepatopulmonary shunting
  - Able to embolize aberrant vessels

Outline
- Rationale
- External Beam Radiation Therapy
  - Metastases
  - Hepatocellular carcinoma
  - Most suitable patients
- Internal Radiation Therapy
  - Metastases
  - Hepatocellular carcinoma
  - Most suitable patients

Pre Tx: AFP
1368
36 months
post Tx: AFP
9.5

Kulik et al Hepatology Jan 2008
Goin et al, Factors Associated with Liver Toxicities, JVIR, 2005
Conclusions

- High dose conformal RT and internal RT can be delivered safely to unresectable liver metastases and hepatocellular carcinoma
- Sustained local control is possible
- Optimal integration of RT with other therapies unknown
- Quality assurance and education important for both external and internal RT
- Multi-disciplinary team required
- Strong rationale and need for randomized trials

Acknowledgements

PMH
Charles Cho
Mark Lee
Regina Toe
Maria Hawkins
John Kim
Jolie Ringash
Rob Dinell
Rebecca Wong
Bernard Cummings
Tom Inouye
Tim Craig
Kristy Brock
Cynthia Eccles
Andrea Marshall
Kawalpreet Singh
Gina Lockwood

Jennifer Knox
Morris Sherman
PMH HCC and GI tumor boards
All patients and referring MDs
International
Riad Salem, Chicago
Jim Walsh, Wisconsin
Harpreet Wason, UK
B Kavanagh, Colorado
J Wulf, Germany

Funding
Canadian Cancer Society
Radiation Medicine Program, PMH