Clinical Targets and Treatment Planning III
GI - Pancreas and Liver

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Memorial Sloan-Kettering Cancer Center
Learning Objectives

1. Achieve a basic understanding of abdominal anatomy
2. Appreciate the clinical outcomes of SBRT for liver and pancreas tumors
3. Evaluate the use of imaging, treatment planning, and treatment delivery techniques to account for respiratory motion
4. Review the normal tissue constraints for SBRT for abdominal tumors
Outline of Presentation

• Anatomy
  – Basic abdominal anatomy

• Rationale for SBRT for abdominal tumors
  – Emerging clinical data

• Simulation and Motion Management Techniques
  – Compression Belt
  – Respiratory Gating

• Treatment Planning
  – Dose constraints
Abdominal Anatomy

- Highly radiosensitive organs
  - Small bowel
  - Stomach
  - Colon
  - Liver
  - Kidneys
  - Adrenals
  - Pancreas
  - Spleen

- Rich lymphatic supply
  - Para-aortic
  - Celiac
  - Superior mesenteric
  - Peri-gastric

Jabbour, et. al., PRO, 2014
Hepatic Anatomy

• 2 Liver lobes
  – Right and left

• 8 Liver segments
  – Divided by hepatic vasculature
  – Determines extent of surgical resections

• Unique regenerative capacity

• Normal liver volume
  – Approx. 2100 cc
  – Need to maintain 1/3 of liver after resection (700cc)

Jabbour, et. al., PRO, 2014
Pancreatic Anatomy

Classic Arterial Anatomy

Which of the following is not an important vascular landmark in the abdomen?

1. Subclavian vein
2. Celiac artery
3. Portovenous confluence
4. Superior mesenteric vein
5. Inferior vena cava
Which of the following is not an important vascular landmark in the abdomen?

<table>
<thead>
<tr>
<th>Percentage</th>
<th>Option</th>
</tr>
</thead>
<tbody>
<tr>
<td>61%</td>
<td>1. Subclavian vein</td>
</tr>
<tr>
<td>3%</td>
<td>2. Celiac artery</td>
</tr>
<tr>
<td>2%</td>
<td>3. Portovenous confluence</td>
</tr>
<tr>
<td>2%</td>
<td>4. Superior mesenteric vein</td>
</tr>
<tr>
<td>32%</td>
<td>5. Inferior vena cava</td>
</tr>
</tbody>
</table>
Subclavian Vein

- The subclavian vein is in the thorax, it is not in the abdomen
- All of the other vessels are located in the abdomen
Outline of Presentation

• Anatomy
  – Basic abdominal anatomy

• Rationale for SBRT for abdominal tumors
  – Emerging clinical data

• Simulation and Motion Management Techniques
  – Compression Belt
  – Respiratory Gating

• Treatment Planning
  – Dose constraints
Radiotherapy for Liver Tumors

• Limited by low tolerance of liver to radiation
• Whole liver irradiation associated with risk of radiation-induced liver disease (RILD)

<table>
<thead>
<tr>
<th>Clinical Syndrome</th>
<th>Pathologic Changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>– Fatigue</td>
<td>– Hyperemia acutely</td>
</tr>
<tr>
<td>– Elevated liver enzymes (Alk phos)</td>
<td>– Veno-occlusive disease</td>
</tr>
<tr>
<td>– Tender anicteric hepatomegaly</td>
<td>– Central venous congestion, sparing large veins</td>
</tr>
<tr>
<td>– Ascites</td>
<td>– Atrophy of adjacent hepatocytes</td>
</tr>
</tbody>
</table>
Excessive dose of radiation to the liver can cause radiation-induced liver disease (RILD) which is characterized by all of the following except:

1. Fatigue
2. Ascites
3. Neuropathy
4. Elevated Liver Enzymes
5. Hepatomegaly
Excessive dose of radiation to the liver can cause radiation-induced liver disease (RILD) which is characterized by all of the following except:

1. Fatigue (2%)
2. Ascites (7%)
3. Neuropathy (82%)
4. Elevated Liver Enzymes (3%)
5. Hepatomegaly (7%)
Neuropathy

RILD Clinical Syndrome

– Fatigue
– Elevated liver enzymes (Alk phos)
– Tender anicteric hepatomegaly
– Ascites

– Neuropathy is not a classic finding of RILD
Radiotherapy for Liver Tumors

- Improved imaging and localizing techniques allow accurate targeting of focal hepatic lesions
- Deliver tumoricidal doses while sparing normal liver parenchyma
- Options to deliver RT more focally
  - 3DCRT
  - Intensity Modulated Radiotherapy
  - Stereotactic Body Radiotherapy
Unresectable Liver Metastases

• 150,000 cases of colorectal cancer diagnosed annually

• 50% of CRC patients will develop liver metastasis

• Surgery is gold standard for CRC liver metastases
  – 5-year survival approximately 50%

• Only 15% of CRC liver metastases are resectable

• Chemotherapy
  – 15 - 40 % Response Rate
  – First Line Chemo: 15-22 months survival
  – Historical 5-year survival <5%
First Liver SBRT Experience

- 50 patients treated to 75 lesions with SBRT for primary and metastatic liver tumors
- 15 to 45 Gy, 1-5 fractions
- Mean follow-up of 12 months
- 30% of tumors demonstrated growth arrest, 40% were reduced in size, and 32% disappeared by imaging studies
- 4 local failures (5.3%)
- Mean survival time was 13.4 months

Blomgren, et. al., J Radiosurgery, 1998
Single Fraction SBRT

- N = 60 unresectable liver tumors (37 pts)
- Dose escalation: 14-26 Gy, 80% isodose line surrounding PTV
- No RILD

<table>
<thead>
<tr>
<th># Patients</th>
<th>Dose</th>
<th>18 month LC</th>
</tr>
</thead>
<tbody>
<tr>
<td>60</td>
<td>14-26 Gy</td>
<td>67%</td>
</tr>
<tr>
<td>5</td>
<td>14-16 Gy</td>
<td>0%</td>
</tr>
<tr>
<td>55</td>
<td>20-26 Gy</td>
<td>81%</td>
</tr>
</tbody>
</table>

Herfarth, et. al., JCO, 2001
Single Fraction SBRT

- Stanford Phase I Dose Escalation Study
- 2/04 – 2/08, 26 patients treated to 32 targets
- 40 identifiable lesions treated within targets
- 4 dose levels (18Gy, 22Gy, 26Gy, 30Gy)
- Mean treatment volume: 32.6cc (range 7.5 – 146.6 cc)
- 19 with hepatic metastases, 5 with IHCC, 2 with recurrent HCC

Goodman KA, et al., IJROBP, 2010
## Single Fraction SBRT Toxicity

<table>
<thead>
<tr>
<th>Dose Group (Gy)</th>
<th>No. Patients</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Nausea</td>
<td>Ab Pain</td>
<td>Fatigue</td>
</tr>
<tr>
<td>18</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>22</td>
<td>6</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>26</td>
<td>9</td>
<td>3</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>30</td>
<td>8</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>22</td>
<td>5</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

* All three of the patients who developed duodenal ulcers had been treated to sites in the porta hepatis
** This patient developed a duodenal ulcer after additional external beam irradiation to the porta hepatis for local failure

*Goodman KA, et al., IJROBP, 2010*
Single Fraction SBRT Outcomes

Median Follow-up = 14 mos

Median Survival: 22.4 months

1 year LF = 23%

Overall Survival

Cumulative Incidence of LF

Goodman KA, et al., IJROBP, 2010
Hypofractionated SBRT

• Phase I/II Study
  – Dose escalation: 36 – 60 Gy in 3 fractions
• 47 patients with 56 lesions (1-3 lesions)
  – 13 pts received <60Gy, 36 received 60Gy
  – Median lesion volume: 15 cc
  – Respiratory gating
  – At least 700 cc had to receive < 15Gy
• Median follow-up: 16 mos
• 2 yr LC: 92% (100% for lesions ≤3cm)
• Grade 3+ toxicity: <2%

Rusthoven K, et. al., J Clin Oncol, 2009
Hypofractionated SBRT

- Phase I study of individualized 6 fraction SBRT for liver metastases in 68 pts
- Median SBRT dose: 41.8 Gy (27.7 to 60 Gy)
- Median tumor vol: 75 cc
- 1-year LC: 71%
- Minimal Toxicity
  - 2 grade 3 LFT changes
  - 6 acute grade 3 toxicities
  - No RILD

Lee M, et. al., J Clin Oncol, 2009
Hypofractionated SBRT

• Phase I/II Study UT Southwestern
  • 28 patients/136 tumors – 27 patients evaluable
  • Dose escalation to 60 Gy (5 fractions)
  • No Grade 3+ treatment-related toxicities

<table>
<thead>
<tr>
<th>Dose</th>
<th>Response rate</th>
<th>2 yr LC</th>
</tr>
</thead>
<tbody>
<tr>
<td>30Gy (n=9)</td>
<td>30%</td>
<td>56%</td>
</tr>
<tr>
<td>50Gy (n=9)</td>
<td>50%</td>
<td>90%</td>
</tr>
<tr>
<td>60Gy (n=9)</td>
<td>90%</td>
<td>100%</td>
</tr>
</tbody>
</table>

Hypofractionated SBRT

- 61 patients with 76 liver metastases treated on Phase II trial of SBRT
- Objective: In-field local control, assess toxicity
- 75 Gy in 3 fractions to CTV
  - PTV covered by 67% - 50Gy in 3 fractions
  - Dose reduction of up to 30% in 14 patients
- No RILD, 1 Grade 3 chest wall pain
- 1 yr median f/u, 1 yr LC – 94%, 1 yr OS – 84%

Scorsetti M, Int J Rad Oncol Biol Phys, 2013
Pooled Analyses

• Chang, *et al.* *Cancer*, 2011
  – 65 patients with 102 colorectal metastases
  – Multiple regimens pooled to estimate optimal local control
  – 46 – 52 Gy (3 fractions)
  – 90% 1 yr local control

• Berber, *et al.* *HPB*, 2013
  – 153 patients with 363 metastatic liver lesions
  – Mean RT dose of 37.5 Gy in 5 fractions
  – 62% 1 yr local control, 51% 1 yr overall survival
MSKCC Experience

• 46 patients, 50 tumors (10 primary, 40 metastases) treated with SBRT from 3/04-3/11

Local Failure

Overall Survival

2 yr Cumulative Incidence of Local Failure = 25%

Median Survival – 15.4 mos

Katsoulakis, Am J Clin Oncol, 2013
Predictors of Local Control

• 3 Late Grade 3-4 GI toxicities, all in 24Gy single fraction and central lesions

Katsoulakis E, Am J Clin Oncol, 2013
<table>
<thead>
<tr>
<th>Author/yr</th>
<th>Lesions</th>
<th>Dose-fractionation</th>
<th>Median follow-up (m)</th>
<th>Local control (%)</th>
<th>Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blomgren/’98</td>
<td>20</td>
<td>2-4x10-20Gy</td>
<td>Mean 9.6</td>
<td>95</td>
<td>Mean 17.8m</td>
</tr>
<tr>
<td>Herfarth/’01</td>
<td>102</td>
<td>1x20-26Gy</td>
<td>Mean 14.9</td>
<td>66, 60</td>
<td>76, 55</td>
</tr>
<tr>
<td>Fuss/’04</td>
<td>17</td>
<td>6x6Gy or 3x12Gy</td>
<td>6.5</td>
<td>94, NRC</td>
<td>80, NRC</td>
</tr>
<tr>
<td>Wulf/’01</td>
<td>51</td>
<td>3x12-12.5Gy or 1x26Gy or 3x10Gy or 4x7Gy</td>
<td>15</td>
<td>100, 82 (high)</td>
<td>72, 34</td>
</tr>
<tr>
<td>MéndezRomero/’06</td>
<td>34</td>
<td>3x10-12.5Gy</td>
<td>12.9</td>
<td>100, 86</td>
<td>85, 62</td>
</tr>
<tr>
<td>Hoyer/’06</td>
<td>141</td>
<td>3x10 Gy</td>
<td>52</td>
<td>NRP, 86</td>
<td>67, 38</td>
</tr>
<tr>
<td>Katz/’07</td>
<td>182</td>
<td>17.5 – 56 Gy in 2-10 fx</td>
<td>88%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rusthoven/’09</td>
<td>47</td>
<td>3 x 12-20Gy Dose escalation</td>
<td>16</td>
<td>95, 92</td>
<td>Median 17.6m</td>
</tr>
<tr>
<td>Lee/’09</td>
<td>68</td>
<td>Individualized dose 27.7-60Gy/ 6 fx</td>
<td>10.8</td>
<td>71, NRP</td>
<td>47% @18mo</td>
</tr>
<tr>
<td>Goodman/’10</td>
<td>19</td>
<td>18-30Gy single fx</td>
<td>17.3</td>
<td>77, NRP</td>
<td>62, 49</td>
</tr>
<tr>
<td>Rule/’11</td>
<td>136</td>
<td>5 x 6-10Gy Dose escalation</td>
<td>20</td>
<td>56/56</td>
<td>56 @ 2yr</td>
</tr>
</tbody>
</table>

Note: NRP stands for not reported.
Unresectable Hepatocellular Carcinoma

• Until recently, minimal role for RT
  – Perceived radioresistance of HCC
  – Underlying liver dysfunction increased risk of liver toxicity

• CT-based planning allowed more targeted RT

• Studies of 3DCRT in Asia and Univ. of Michigan demonstrated feasibility of dose escalated RT

• 1-year local control ranged from 50-80%
SBRT for Primary Liver Tumors

- 102 patients with locally advanced HCC enrolled on 2 prospective studies of SBRT
  - Childs A liver function
  - Tumor vascular thrombosis in 55%
- Prescribed a variable dose (24 – 54 Gy) over 6 fractions
- Median gross tumor volume was 117.0 cc (1.3 to 1,913.4 cc)
- Median follow-up was 31.4 months

Bujold A, et. al., J Clin Oncol, 2013
SBRT for Primary Liver Tumors

- 1 year LC was 87%
- Median OS was 17 mos
- Grade 3+ toxicity in 30%
- Possible Grade 5 in 7 patients (2 with TVT PD)
- Dose >30 Gy improves LC rates
- Even in this high-risk HCC population, SBRT associated with good LC
Phase I-II Trial of SBRT in Patients with HCC, Child-Pugh Class A and B

- Interim analysis of variables affecting toxicity and outcome

<table>
<thead>
<tr>
<th></th>
<th>CPC A</th>
<th>CPC B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Dose/# Fractions</td>
<td>4800cGy/3</td>
<td>4000cGy/5</td>
</tr>
<tr>
<td>2 yr LC</td>
<td>87%</td>
<td>85%</td>
</tr>
<tr>
<td>2 yr PFS</td>
<td>55%</td>
<td>28%</td>
</tr>
<tr>
<td>2 yr OS</td>
<td>81%</td>
<td>28%</td>
</tr>
<tr>
<td>Grade 3-4 Liver Toxicity</td>
<td>14%</td>
<td>33%</td>
</tr>
</tbody>
</table>

- Mean Tumor Volume = 33 cc
- For CPC B pts, volume effect on Grade III/IV liver toxicity
- SBRT for CPC A patients is feasible and safe
- SBRT for CPC B patients is still associated with significant toxicity in uncompensated liver and while SBRT results in LC, the overall outcome of this disease may not be addressed by local therapy

Lasley FD, ASTRO 2012
<table>
<thead>
<tr>
<th>Author/yr</th>
<th>Lesions</th>
<th>Dose-fractionation</th>
<th>Median follow-up (m)</th>
<th>Local control (%)</th>
<th>Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mendez-Romero/’06</td>
<td>5 CPC A, 2 CPC B, 1 w/o cirrhosis 11 lesions</td>
<td>5 Gy x 5 or 10-12.5 Gy x 3</td>
<td>12.9</td>
<td>75% at 22 mo</td>
<td>75%, 40%</td>
</tr>
<tr>
<td>Tse/’08</td>
<td>21 CPC A</td>
<td>36 Gy (24-54 Gy) in 6 fx</td>
<td>17.6</td>
<td>65% @ 1yr</td>
<td>48% @ 1yr</td>
</tr>
<tr>
<td>Cardenes/’10</td>
<td>6 CPC A, 11 CPC B</td>
<td>12-16 Gy x 3, 8 Gy x 3</td>
<td>24</td>
<td>100%</td>
<td>75%, 60%</td>
</tr>
<tr>
<td>Lasley/’12</td>
<td>36 CPC A/ 21 CPC B</td>
<td>48Gy in 3 or 40Gy in 5 fx</td>
<td></td>
<td>87%/85% @ 2yr</td>
<td>81%/35% @ 2 yrs</td>
</tr>
<tr>
<td>Dawson/’13</td>
<td>102 CPC A</td>
<td>24Gy - 54Gy in 6</td>
<td>31</td>
<td>87% @ 1yr</td>
<td>Median Survival = 17 mo</td>
</tr>
</tbody>
</table>
SBRT for Unresectable Intrahepatic and Hilar Cholangiocarcinoma

• Brachytherapy has been used as a boost to improve focal delivery of RT dose
• Availability of and expertise in biliary brachytherapy is limited
• SBRT is another option to deliver high, focal doses to the liver hilum and intrahepatic tumors
# SBRT for Unresectable Intrahepatic and Hilar Cholangiocarcinoma

<table>
<thead>
<tr>
<th>Author/yr</th>
<th>Lesions</th>
<th>Dose-fractionation</th>
<th>Median follow-up (m)</th>
<th>1 Year Local control (%)</th>
<th>Median Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tse/'08</td>
<td>10 IHCC</td>
<td>32.5 in 6 fx</td>
<td>17.6</td>
<td>65%</td>
<td>15 mo</td>
</tr>
<tr>
<td>Kopek/'10</td>
<td>27 (26 hilar CC, 1 IHCC)</td>
<td>45 Gy in 3 fx</td>
<td>60 mo</td>
<td>84%</td>
<td>10.4 mo</td>
</tr>
<tr>
<td>Goodman/'10</td>
<td>5 IHCC</td>
<td>18-30Gy in 1 fx</td>
<td>17</td>
<td>77%</td>
<td>29 mo</td>
</tr>
<tr>
<td>Barney/’12</td>
<td>10 pts, 12 lesions</td>
<td>55 Gy in 3-5 fx</td>
<td>14</td>
<td>100%</td>
<td>14 mo</td>
</tr>
<tr>
<td>Mahadevan/'12</td>
<td>20 pts/25 lesion</td>
<td>30 Gy in 3 fx</td>
<td>93%</td>
<td>17 mo</td>
<td></td>
</tr>
</tbody>
</table>
Unresectable Pancreatic Cancer
Pancreatic Cancer Epidemiology

- 45,000 pancreatic cancers diagnosed
- 38,500 deaths
- 4th leading cause of mortality from malignant disease

Median Survival Times
- Resectable, 18-22 months
- Locally advanced, 12-15 months
- Metastatic, 6-10 months

## SBRT: Trials for Pancreas Cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Prior EBRT</th>
<th>Regimen</th>
<th>Median OS Months</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Koong, Phase I</td>
<td>15</td>
<td>2</td>
<td>15-25Gy /1 fx</td>
<td>11</td>
<td>33% G1-2 acute/NR</td>
</tr>
<tr>
<td>Koong, Phase II</td>
<td>16</td>
<td>16</td>
<td>45Gy/25 fx + 25Gy/1 fx</td>
<td>8.3</td>
<td>12% G3 acute/G2 late ulcers</td>
</tr>
<tr>
<td>Schellenburg,</td>
<td>16</td>
<td>0</td>
<td>25 Gy/1 fx</td>
<td>11.4</td>
<td>6% acute G3/ 13% late G3</td>
</tr>
<tr>
<td>Hoyer,</td>
<td></td>
<td>0</td>
<td>45 Gy/3 fx</td>
<td>5.7</td>
<td>18% severe GI toxicity</td>
</tr>
<tr>
<td>Mahadevan, 2010</td>
<td>36</td>
<td>0</td>
<td>24-36 Gy/3 fx</td>
<td>20.0</td>
<td>5% G3</td>
</tr>
<tr>
<td>Polistina, 2010</td>
<td>23</td>
<td>0</td>
<td>30 Gy/3 fx</td>
<td>10.6</td>
<td>No acute /late G2/3</td>
</tr>
<tr>
<td>Tozzi, 2013</td>
<td>30</td>
<td>0</td>
<td>45 Gy/6 fx</td>
<td>11.0</td>
<td>No acute /late G2/3</td>
</tr>
<tr>
<td>Gurka, 2013</td>
<td>11</td>
<td>0</td>
<td>25 Gy/5 fx</td>
<td>12.2</td>
<td>No acute /late G2/3</td>
</tr>
<tr>
<td>Herman, 2013</td>
<td>49</td>
<td>0</td>
<td>33 Gy/5 fx</td>
<td>13.9</td>
<td>8% late G3</td>
</tr>
</tbody>
</table>
Duodenal Doses

• Median time to duodenal toxicity: 6.2 mos
• 6- and 12-mo actuarial rates of toxicity: 11% and 29%

<table>
<thead>
<tr>
<th>Variable*</th>
<th>Cutoff†</th>
<th>Incidence of Grade 2–4 duodenal toxicity (%)‡</th>
<th>Log-rank p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>V5</td>
<td>&lt;25 cm³</td>
<td>28</td>
<td>0.39</td>
</tr>
<tr>
<td></td>
<td>≥25 cm³</td>
<td>31</td>
<td></td>
</tr>
<tr>
<td>V10</td>
<td>&lt;16 cm³</td>
<td>15</td>
<td>0.015</td>
</tr>
<tr>
<td></td>
<td>≥16 cm³</td>
<td>46</td>
<td></td>
</tr>
<tr>
<td>V15</td>
<td>&lt;9.1 cm³</td>
<td>11</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>≥9.1 cm³</td>
<td>52</td>
<td></td>
</tr>
<tr>
<td>V20</td>
<td>&lt;3.3 cm³</td>
<td>11</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>≥3.3 cm³</td>
<td>52</td>
<td></td>
</tr>
<tr>
<td>V25</td>
<td>&lt;0.21 cm³</td>
<td>12</td>
<td>0.010</td>
</tr>
<tr>
<td></td>
<td>≥0.21 cm³</td>
<td>45</td>
<td></td>
</tr>
</tbody>
</table>

* V5 refers to the volume of duodenum receiving 5 Gy.
† Cutoff refers to the median value.
‡ Actuarial incidence at 12 months.

Murphy J, et al., IJROBP, 2012
Phase II Multi-Institutional Study of Stereotactic Body Radiation Therapy for Unresectable Pancreatic Cancer

(Herman, Chang, Goodman, Koong PI’s)

(GEM, up to 1 Cycle allowed)*
1 week break

F-SBRT 6.6 Gy x 5 Mon-Fri
1 week break

GEM Chemotherapy (3 wks on, 1 wk off)
Until toxicity or progression

Primary endpoint: Late GI Toxicity > 4 months

Secondary: Tumor Progression Free Survival, pre-tx biopsy, PET/CT QOL, biomarkers.
Outcomes

Overall Survival

Median: 13.9 mos

Progression Free Survival

Median: 7.6 mos

Local Progression–Free Survival

Median: 12.1 mos

Herman et al. J Clin Oncol, 2014 submitted
Toxicity and QOL

• Toxicity
  – Acute GI
    • Grade 1-2: 10%
    • Grade ≥3: 0%
  – Late GI
    • Grade ≥3: 8%
    -GI bleed (2)

• Quality of Life (EORTC)
  – Mean global QOL
    • scores unchanged
      pre/post SBRT
  – Pancreas specific QOL
    • Improved (p<0.05)
      – pancreatic pain
      – body image

Herman et al. J Clin Oncol, 2014 submitted
For a 2 cm locally advanced tumor of the pancreatic head, the most severe dose limiting factor for 5 fraction SBRT would be:

1. Risk of radiation induced liver toxicity
2. Proximity to the right kidney
3. Proximity to the duodenum
4. Proximity to the chest wall
5. Proximity to the common bile duct
For a 2 cm locally advanced tumor of the pancreatic head, the most severe dose limiting factor for 5 fraction SBRT would be:

- 1. Risk of radiation induced liver toxicity (7%)
- 2. Proximity to the right kidney (3%)
- 3. Proximity to the duodenum (84%)
- 4. Proximity to the chest wall (2%)
- 5. Proximity to the common bile duct (4%)
Proximity to the Duodenum

• The head of the pancreas is surrounded on 3 sides by the C-loop of the duodenum, thus, irradiating the pancreatic head mass would lead to partial irradiation of the duodenum.
Outline of Presentation

• Anatomy
  – Basic abdominal anatomy

• Rationale for SBRT for abdominal tumors
  – Emerging clinical data

• Simulation and Motion Management Techniques
  – Compression Belt
  – Respiratory Gating

• Treatment Planning
  – Dose constraints
Challenges in Targeting Abdominal Tumors

• Limited visualization of the target
• Organ deformation with respiration
• Changes in GI organ luminal filling
  – Critical structures (stomach) may change in shape and position between planning and treatment
• Interfraction target displacement with respect to bony anatomy
Fiducial Markers
Fiducial Markers

EUS-guided placement
Fiducial Markers: Daily Set-Up

DRR

KV

Cone-beam CT scan
### Treatment Paradigm at MSKCC

#### Induction chemotherapy for 3 months

| FOLFIRINOX for good KPS patients | Gemcitabine-based for elderly, lower KPS |

#### Re-staging CT scan to evaluate for distant metastases

| Distant Mets: 2nd line chemotherapy | No Distant Mets: Chemoradiation |

#### Chemoradiation or SBRT

| 5040cGy/5600cGy | 6.6 Gy x 5 |
Simulation

- Supine, arms up immobilized in alpha cradle
- IV and PO contrast
- NPO 4 hours prior to simulation
  - Empty stomach for simulation and for daily treatment
- For respiratory gating patients
  - Scan during end-exhalation breath hold
  - 2.5 mm slice thickness
  - 4DCT with voice coaching
- For compression belt patients
  - Fluoro to determine pressure needed
  - PET/CT with compression applied
4-D PET/CT Simulation
GE Discovery ST\textsuperscript{8} PET/CT and Varian RPM

Infrared reflective markers

Infrared camera
Respiratory Cycle Tracing

Increase Treatment Time by X 2.0 (49% Duty Cycle)

Inspiration: 2.1 Sec.
Expiration: 2.1 Sec.
Breathing Period: 4.2 Sec.
Target Delineation

Nodal Regions
- Celiac nodes
- SMA nodes
- Peripancreatic
- Porta Hepatis
- PA/RP Lymph Nodes
- Splenic hilum (tail lesions)

Normal Tissues
- Spinal Cord
- Stomach
- Duodenum
- Kidneys
- Liver
- Bowel
- Heart
Daily KV Imaging

- Match on fiducials or stent
- KV’s taken at beginning of gating interval
Intrafraction Imaging

- IMRLite on Truebeam Linear Accelerator
Abdominal Compression

- Abdominal belt with inflatable bladder
- Inflation: 15-40 mmHg

Courtesy of Michael Lovelock, P
Abdominal Compression

- 44 patients treated with SBRT between 2004-2012 using abdominal compression belt
  - Liver (30), adrenal glands (6), pancreas (3) and lymph nodes (30)
- 2-3 radiopaque fiducial markers or clips
- Craniocaudal (CC) motion measured fluoroscopically with and without pneumatic pressure
- Objective: reduce CC motion ≤ 5 mm peak to peak

Lovelock, TCRT, 2014
Abdominal Compression

- Mean CC motion with no air pressure: 11.6 mm (range 5-20 mm)
- Mean CC motion with pressure applied: 4.4 mm (range 1-8 mm) (P-value < 0.001)

Lovelock, TCRT, 2014
Abdominal Compression

- Impact of Lorazepam use
  - Benzodiazepine anti-anxiety medication
  - Average motion reduction and % reduction of CC motion was 7.4 mm (61%) and 5.8 mm (55%) with and without Lorazepam
Motion Management Techniques

**Respiratory Gating**
- Cyclical delivery of RT
- Patient compliance with breathing instructions
- Requires fiducial marker and daily OBI
- Does not take into account non-respiratory motion
- Poor quality CBCT
- Standard fractionation RT

**Abdominal Compression**
- Continuous delivery of RT
- Patient tolerance of the compression belt
- Requires fiducial marker and daily OBI
- Does not take into account non-respiratory motion
- Less motion artifact in CBCT
- SBRT
Abdominal compression for motion management:

1. Requires a metal plate for compression
2. Causes artifact on daily CBCT
3. Is better tolerated with pre-tx Lorazepam
4. Is not a good option for diabetics
5. Does not reduce cranio-caudal motion <5mm
Abdominal compression for motion management:

1. Requires a metal plate for compression
2. Causes artifact on daily CBCT
3. Is better tolerated with pre-treatment Ativan
4. Is not a good option for diabetics
5. Does not reduce cranio-caudal motion to <5mm
Abdominal Compression for Motion Management

• Is better tolerated with Lorazepam
  – Approximately a 1 mm decrease in CC respiratory motion was observed for each 10 mmHg increase in pneumatic pressure in both groups. Use of Lorazepam resulted in a small additional improvement in motion reduction of approximately 1 mm per 10 mmHg increase in pressure
Permanent Spacers

• Biological mesh spacer (Alloderm)
  – Cadaveric human skin treated to remove cells and preserve extracellular matrix

• 6 IHCC, 3 HCC, 5 liver metastases

• Mean Displacement:
  – Stomach 23 mm, duodenum 23 mm, small bowel 20 mm, colon 24 mm

Yoon S, et al. PRO, 2014
Permanent Spacer

Median Dose: 54 Gy, 5-15 fractions (Protons/SBRT/IMRT)
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  – Dose constraints
Challenge for Treatment Planning
<table>
<thead>
<tr>
<th>Organ at Risk (OAR)</th>
<th>Constraints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>V12 &lt; 50%</td>
</tr>
<tr>
<td>Kidney</td>
<td>V12 &lt; 25% (both kidneys combined)</td>
</tr>
<tr>
<td>Cord</td>
<td>V8 &lt; 1cc</td>
</tr>
<tr>
<td>Stomach</td>
<td>V33 &lt; 1cc, V20 &lt; 3cc, V15 &lt;9cc, V12 &lt;50%</td>
</tr>
<tr>
<td>Duodenum</td>
<td>V33 &lt; 1cc, V20 &lt; 3cc, V15 &lt;9cc, V12 &lt;50%</td>
</tr>
<tr>
<td>Bowel (not duodenum)</td>
<td>V20 &lt; 5cc (bowel is contoured 2cm superior and inferior to PTV)</td>
</tr>
</tbody>
</table>
SBRT Dosimetry

- Able to meet protocol dose constraints
RT Plan: DVH

Dose Volume Histogram

Dose (cGy)

Duodenum
Liver Tolerance

• 204 pts treated with liver RT (hyperfrac) for primary or metastatic liver lesions at U. Michigan analyzed

• Lyman NTCP model applied to predict RILD
  – Large volume effect
  – Strong correlation of RILD and mean liver dose

• Mean liver doses associated with a 5% risk of classic RILD in 2 Gy per fraction:
  – Primary liver cancer: 28 Gy
  – Metastatic liver disease: 32 Gy

Dawson LA, IJROBP, 2002
Liver Tolerance to Hypofractionation

• U. Colorado SBRT Phase I trial
  – Used 700cc < 15Gy in 3 fractions
  – No reported RILD
  – None had underlying liver dysfunction

• PMH Phase 1/2 Trials of SBRT for primary liver tumors
  – Used Veff <80% (median 44%)
  – Median mean liver dose:
  – No RILD
  – Included Child-Pugh A patients
Liver Tolerance to Hypofractionation

- TD5/5 for RILD with hypofraction (4-8 Gy/fraction, median dose 54 Gy):
  - 23 Gy for hepatocellular carcinoma with Child-Pugh A cirrhosis

Jiang GL, IJROBP, 2006; Son SH, IJROBP, 2010
Liver Dose Constraints

Palliative whole-liver doses

Liver metastases
≤ 30 Gy, in 2 Gy per fraction
21 Gy in seven fractions (39)

Primary liver cancers
≤ 28 Gy, in 2 Gy per fraction
21 Gy in seven fractions (40)

Nonuniform liver recommendations (SBRT, three to six fractions)

Mean normal liver dose (liver minus gross tumor volume)
< 13 Gy for primary liver cancer, in three fractions
< 18 Gy for primary liver cancer, in six fractions
< 15 Gy for liver metastases, in three fractions
< 20 Gy for liver metastases, in six fractions
< 6 Gy for primary liver cancer, Child-Pugh B, in 4–6 Gy per fraction (for classic or nonclassic RILD)
Critical volume model-based
≥ 700 mL of normal liver receives ≤ 15 Gy in three to five fractions

Therapeutic partial liver RT (standard fractionation)

Mean normal liver dose (liver minus gross tumor volume)
< 28 Gy in 2-Gy fractions for primary liver cancer
< 32 Gy in 2-Gy fractions for liver metastases

Pan CC, IJROBP, 2010
The risk of Radiation Induced Liver Disease (RILD) at 3 months is highest following SBRT in:

1. HCC, 700 cc liver receives 15 Gy/3 fx
2. Liver metastasis, 700 cc receives 15 Gy/3 fx
3. HCC, mean liver dose 13 Gy/6 fractions
4. Biliary tumor, mean liver dose 18 Gy/6 fx
5. Liver metastasis, mean liver dose 18 Gy/6 fx
The risk of Radiation Induced Liver Disease (RILD) at 3 months is highest following SBRT in:

1. HCC, 700 cc liver receives 15 Gy/3 fx (38%)
2. Liver metastasis, 700 cc receives 15 Gy/3 fx (18%)
3. HCC, mean liver dose 13 Gy/6 fractions (15%)
4. Biliary tumor, mean liver dose 18 Gy/6 fx (5%)
5. Liver metastasis, mean liver dose 18 Gy/6 fx (23%)
HCC, 700 cc liver receives 15 Gy/3 fx

- Poor underlying liver function increases risk of RILD
- 700cc limited to 15 Gy is based on SBRT for liver metastases
Conclusions: SBRT for Pancreas Tumors

- Pancreatic SBRT with 3-5 fractions results in favorable OS compared to conventional regimens
- Minimal grade ≥2 acute/late toxicity and improved quality of life
- Combining SBRT with more aggressive systemic therapy (FOLFIRINOX) may improve survival by controlling distant disease
- Need biomarkers to select which patients will benefit from SBRT
Conclusions: SBRT for Liver Tumors

• **Safe:** high doses well tolerated in patients with normal underlying liver function

• **Effective:** Recent prospective studies of more focal RT for liver tumors suggest that higher doses associated with good local control

• **Caution:** SBRT may not be appropriate in patients with underlying liver dysfunction
Conclusions

• Newer techniques using functional imaging may help to identify functional regions that can be better spared to minimize normal tissue injury

• Prospective trials are necessary:
  – To define dose/fractionation schemes of SBRT
  – To evaluate SBRT in combination with radiosensitizers, VEGF inhibitors, hypoxic cell sensitizers
Thank you