Stereotactic Body Radiotherapy (SBRT) for Liver Metastases

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I have no commercial interests or off label usage to disclose.

Overview

I. Objectives
II. Definition of SBRT
III. Technological Advances
IV. Treatment of Liver Metastases
V. Summary

Objectives

- To understand the definition and technical aspects of SBRT
- To understand the rationale and indications for SBRT for liver metastases
- To review the clinical outcomes of SBRT of the liver, including efficacy and toxicity
- To discuss the Mayo Clinic Florida experience with utilizing SBRT for the liver
Overview

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Stereotactic Body Radiotherapy

- Delivery of a large dose of radiation to an extracranial lesion in a limited number of high-dose treatments
  - 5 or fewer fractions
- Multiple external beams are utilized
  - precise, conformal dose distribution to the target
  - relative sparing of the nearby normal tissues

Stereotactic Body Radiotherapy

- Modeled after intracranial stereotactic radiosurgery (SRS)
  - Treatment of brain metastases with a single high dose fraction
  - Precise targeting and dose delivery using the skull as a reference system
  - Allows for ablative doses to be delivered with acceptable toxicity in appropriately selected pts

Stereotactic Body Radiotherapy

- Stereotactic RadioSurgery
  - Margins can be minimized with the use of a rigid head frame fixed to the skull
Stereotactic Body Radiotherapy

- Extracranial sites are subject to movement from normal physiological processes
  - Respiration
  - Heartbeat
  - Involuntary muscle contraction (e.g. GI tract)

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Technological Advances

- Improved immobilization and targeting techniques
- Compensation for respiratory movement
- Improved imaging and targeting
- Advancements in treatment delivery systems

Technological Advances

- Immobilization and Targeting
  - Custom body cast with radiopaque markers
    - Establishes coordinate system in 3-dimensional space
  - Implantation of markers internally (fiducials)
    - Facilitate tumor targeting
Technological Advances
- Compensation for respiratory movement
  - Direct abdominal compression
    - Reduces normal breathing (tidal volume)
    - Decreases maximum displacement during respiration by 12-13 mm


Question 1: Direct abdominal compression can reduce respiratory motion of liver lesions by how many millimeters?

- 1. 8 mm
- 2. 10 mm
- 3. 12 mm
- 4. 15 mm
- 5. 20 mm

13% 1. 8 mm
36% 3. 12 mm
13% 4. 15 mm
5% 5. 20 mm
Question 1: Direct abdominal compression can reduce respiratory motion of liver lesions by how many millimeters?

- Answer C: 12-13 mm


Technological Advances

- Image guided radiation therapy (IGRT)
  - KV & MV Imaging, Cone Beam CT
    - Allows verification of the target position with the patient in the treatment position
    - Radiographic imaging is performed immediately before a treatment and/or during an individual treatment session

Cine Imaging

- Image guided radiation therapy (IGRT)
  - Electronic Portal Imaging (EPI)
    - Verifies target position during treatment
    - Allows for evaluation of intrafraction movement of the target
  - Cine (MV) imaging
    - Cine images may be taken during treatment to verify that the target remains within the treatment field while the beam is on
4D CT Imaging
- Image guided radiation therapy (IGRT)
- 4D-CT imaging (Cone Beam CT)
  - Allows us to see the amount of liver movement present with the patient’s normal respiratory cycle
  - Enables respiratory gating

Technological Advances
- SBRT may be delivered through a variety of machines:
  - Linac-based SBRT (e.g. Novalis, Varian)
  - Cyberknife

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   1. SBRT at Mayo Clinic Florida
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V. Summary
SBRT at Mayo Clinic Florida

- Immobilization and Targeting
  - Reproducible treatment position with Bodyfix device

(BodyFix, Medical Intelligence, Schwabmuchen, Germany)

SBRT at Mayo Clinic Florida

- Immobilization and Targeting

(BodyFix, Medical Intelligence, Schwabmuchen, Germany)

SBRT at Mayo Clinic Florida

- Infrared camera/detector
- Gating workstation
- Multi-slice CT scanner
- Infrared Reflector
- Control system

(Real-Time Position Management (RPM) respiratory gating system, Varian Medical, Palo Alto, CA)
SBRT at Mayo Clinic Florida
- CT simulation images are fused with MRI images to better delineate the tumor volume.

SBRT at Mayo Clinic Florida
- Develop a highly conformal treatment plan w/ or w/out gating

SBRT at Mayo Clinic Florida
- Fiducial gold seeds (1.2 mm x 3 mm) are placed prior to treatment
- Cine imaging of implanted fiducial markers with respiratory gating to evaluate intrafraction movement during treatment

Cine Imaging
SBRT at Mayo Clinic Florida

- KV images are taken prior to treatment to verify target position based on fiducial markers

Lateral kV-DRR match

AP kV-DRR match

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I. Objectives
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   - MSKCC/Stanford study
   - Multi-institutional Phase I/II trial
   - Mayo Clinic Phase I/II trials
V. Summary

Liver Metastasis

- Local control of oligometastases may yield improved systemic control and prolonged survival
- Researchers began exploring utilizing this stereotactic technique for extracranial sites, including the liver, lungs, spinal cord

Liver Metastasis

- Common site for metastatic disease from a wide variety of malignancies
  - Management is dependent on the location and extent of hepatic disease, as well as the extent of extraneoplastic disease
  - Median survival 8 mos with supportive care alone

Treatment Options for Liver Metastasis

**Surgery**
- Resection of a limited number of intrahepatic metastases has been shown to provide long term benefit.
- 5-yr Relapse Free Survival (RFS) after resection of isolated colorectal or neuroendocrine liver metastases is ~ 30% (20-46%).

**Non-surgical treatment options**
- Chemotherapy
  - Systemic or hepatic arterial chemotherapy
  - Despite aggressive chemotherapy, median survival is ~ 12-14 months.

**Stringent eligibility criteria:**
- Medically fit
- Disease limited to the liver
- Location
- Multifocality
- Adequate reserve of normal liver parenchyma
- Only a small fraction of patients are eligible for metastectomy (~ 10%).

**Non-surgical treatment options**
- Tumor Ablation (e.g. radiofrequency ablation, ethanol injection, cryotherapy)
- Strict selection criteria
- Most patients are not appropriate candidates.
Treatment Options for Liver Metastasis

- Non-surgical treatment options
  - Radiation Therapy

Liver Toxicity

- Normal hepatocytes are highly sensitive to radiation therapy

- Toxicity
  - Fatigue
  - Nausea
  - Gastritis
  - Liver enzyme dysfunction

Liver Toxicity

<table>
<thead>
<tr>
<th>Common Toxicity Criteria (CTC) Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CTCAE v4.0</strong></td>
</tr>
<tr>
<td>Nausea</td>
</tr>
<tr>
<td>Fatigue</td>
</tr>
<tr>
<td>Gastritis</td>
</tr>
<tr>
<td>Liver Dysfunction</td>
</tr>
</tbody>
</table>

Liver Toxicity

- Radiation Induced Liver Dysfunction (RILD) is the dose limiting toxicity
  - Clinical syndrome
    - Anicteric hepatomegaly
    - Ascites
    - Elevated liver enzymes (alkaline phosphatase)
  - 2-8 weeks after completion of radiation
Liver Toxicity

- Emami, et al.
  - Whole liver irradiation of 30 Gy carried a 5% risk of RILD
  - Whole liver irradiation of 40 Gy carried a 50% risk of RILD


Liver Toxicity

- QUANTEC (Quantitative Analysis of Normal Tissue Effects in the Clinic)
  - Whole liver – GTV conventional irradiation of <30-32 Gy carries <5% risk of RILD
  - Doses >30-35 Gy to the whole liver are associated with a higher probability of RILD


Question 2: At what dose of radiation to the whole liver is there a 5% chance of RILD?

- Answer: C - 30 Gy (30-32 Gy)

Liver Dose Escalation

- Prospective trial to test probability model parameters for dose escalation
  - Normal tissue complication probability (NTCP) model calculated from previous data
  - Pts with primary hepatobiliary disease or colorectal cancer metastatic to the liver with normal liver function


- Compared to whole liver ± hepatic artery Fluorodeoxyuridine
  - Median dose: 57 Gy (range 40.5 to 81 Gy)
  - Actual rate of complications (1/21 pts, 4.8%), close to the calculated rate (9%)


Liver Dose Escalation

- Median dose: 60.75 Gy in 1.5-Gy BID (range 40-90 Gy)
- Median F/U: 16 mos (26 mos in pts who were alive)

Ben-Josef E., et al., J Clin Oncol 23:8739-8747, 2005

- Median survival: 15.8 mos
- Actuarial 3-year survival: 17%
- 61% failed within the liver
- Acceptable overall toxicity:
  - grade 3 (21%)
  - grade 4 (9%)
  - grade 5 (<1%)

Ben-Josef E., et al., J Clin Oncol 23:8739-8747, 2005
Liver Dose Escalation

- Overall survival of patients by dose quartile. Patients receiving 75 Gy or more had significantly better survival ($P = 0.01$).

Liver Dose Escalation

<table>
<thead>
<tr>
<th>Organ</th>
<th>2D Dose</th>
<th>3D dose</th>
<th>Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>60-70</td>
<td>102</td>
<td>1%/Gy 2 yr OS</td>
</tr>
<tr>
<td>Prostate</td>
<td>68-70</td>
<td>78-86.4</td>
<td>1-2%/Gy increase in 5 year PFS</td>
</tr>
<tr>
<td>Liver</td>
<td>30</td>
<td>90</td>
<td>24 mos MS for ≥70 Gy vs 6-10 mos MS for less</td>
</tr>
<tr>
<td>Head &amp; Neck</td>
<td>70-76</td>
<td>70-76</td>
<td>Decreased Xerostomia</td>
</tr>
</tbody>
</table>

Biologically Effective Dose

- Biologically effective dose (BED or E/$\alpha$): an approximate quantity by which different radiotherapy fractionation regimens may be intercompared:
  - $BED = E/\alpha = nD \times (1 + (D / (\alpha/\beta)))$
  - $n =$ number of fractions
  - $D =$ dose/fraction
  - $nD =$ total dose
- Difficult to compare with SBRT fractionation

Liver Toxicity

- AAPM TG 101
- Threshold dose
  - Minimum critical volume below 700cc
  - $\geq$ Grade 3 toxicity

<table>
<thead>
<tr>
<th>Fraction</th>
<th>One Fraction</th>
<th>Three Fractions</th>
<th>Five Fractions</th>
</tr>
</thead>
<tbody>
<tr>
<td>9.1 Gy</td>
<td>19.2 (4.8 Gy/fx)</td>
<td>21.0 (4.2 Gy/fx)</td>
<td></td>
</tr>
</tbody>
</table>
Question 3: What is the AAPM TG 101 single fraction threshold dose to the liver?

- Answer: D - 9.1 Gy


Treatment of 1° Liver Tumors and Mets - MSKCC/Stanford

- 26 pts treated for 40 identifiable lesions
  - 19 hepatic metastases
  - 5 IHCC
  - 2 recurrent HCC
- Prescribed RT dose escalated from 18 Gy up to 30 Gy in 4-Gy increments

MSKCC/Stanford
- Phase I dose-escalation study
- Explore the feasibility & safety of treating primary and metastatic liver tumors with single-fraction SBRT

Treatment of 1° Liver Tumors and Mets - MSKCC/Stanford

- Results
  - All pts tolerated the single-fraction SBRT well w/o developing a dose-limiting toxicity
  - 9 acute Grade 1 toxicities
  - 1 acute Grade 2 toxicity
  - 2 late Grade 2 GI toxicities


Treatment of 1° Liver Tumors and Mets - MSKCC/Stanford

- Results
  - Median f/u: 17 mos (range 2-55 mos)
  - Cumulative risk of LF @ 12 mos: 23%
  - 15 pts died:
    - 11 liver mets
    - 4 primary liver tumors
  - Median survival: 28.6 mos
  - 2-year actuarial OS: 50.4%


Treatment of 1° Liver Tumors and Mets - Multi-institutional

- Conclusions
  - Feasible & safe to deliver single-fraction, ↑ dose SBRT to 1° or metastatic liver malignancies measuring ≤ 5cm
  - Single-fraction SBRT for liver lesions show promising local tumor control w/ minimal acute & long-term toxicity
  - Viable nonsurgical option
  - Further studies warranted to evaluate both control rates & impact on QOL


Treatment of Liver Mets - Multi-institutional

Multi-Institutional Phase II/II Trial of Stereotactic Body Radiation Therapy for Liver Metastases

Treatment of Liver Mets - Multi-institutional

- Phase I dose: Total dose safely escalated from 36 Gy to 60 Gy
- Phase II dose: 60 Gy in 3 fractions
- 1° endpoint: local control
  - Lesions w/ at least 6 months of radiographic f/u were considered assessable for local control
- 2° endpoints: toxicity & survival


Results

- Local progression: only 3 lesions progressed at a median of 7.5 mos (range, 7 to 13 mos)
- Actuarial in-field local control rates:
  - 1-year: 95%
  - 2-year: 92%
  - 2-year local control: 100% for lesions with max diameter of \( \leq 3 \) cm


Results

- Toxicity
  - Only 1 pt experienced grade 3 or higher toxicity (2%)
    - Skin breakdown requiring surgical debridement and a trial of hyperbaric oxygen (48 Gy)
    - No grade 4 or 5 toxicity
- Median survival: 20.5 mos


Results

- 63 hepatic lesions in 47 patients
  - 69% had received at least 1 prior systemic therapy regimen for metastatic disease (range, 0 to 5 regimens)
  - 45% had extrahepatic disease
- Median follow-up (assessable lesions): 16 mos (range, 6 to 54 months)

Treatment of Liver Mets - Multi-institutional

- Conclusions
  - Multi-institutional, phase I/II trial demonstrates that high-dose liver SBRT is safe & effective for the treatment of pts with 1-3 hepatic mets.


Question 4: What is the 2-year actuarial local control rate reported by Rusthoven, et al. in their multi-institutional review of SBRT for metastatic liver disease?

- Answer: B – 2 year actuarial local control was 92%


Efficacy of SBRT for Liver Metastasis

<table>
<thead>
<tr>
<th>Author</th>
<th># of targets</th>
<th>Median follow up</th>
<th>Total Dose (Gy)</th>
<th># of fractions</th>
<th>Local Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blomgren, 1995</td>
<td>21</td>
<td>9 mo</td>
<td>20-45</td>
<td>1-5</td>
<td>95%</td>
</tr>
<tr>
<td>Herfarth, 2001</td>
<td>60</td>
<td>6 mo</td>
<td>14-26</td>
<td>1</td>
<td>78%</td>
</tr>
<tr>
<td>Sato, 1998</td>
<td>23</td>
<td>10 mo</td>
<td>50-60</td>
<td>5-10</td>
<td>100%</td>
</tr>
<tr>
<td>Wulf, 2007</td>
<td>56</td>
<td>15 mo</td>
<td>28-37.5</td>
<td>3-4</td>
<td>1 yr: 92% 2 yr: 66%</td>
</tr>
<tr>
<td>Katz, 2007</td>
<td>174</td>
<td>14.5 mo</td>
<td>30-55</td>
<td>7-20</td>
<td>10 mo: 76% 20 mo: 57%</td>
</tr>
<tr>
<td>Lee, 2009</td>
<td>143</td>
<td>11 mo</td>
<td>30-60</td>
<td>6</td>
<td>1 yr: 71%</td>
</tr>
<tr>
<td>Rusthoven, 2009</td>
<td>63</td>
<td>16 mo</td>
<td>60</td>
<td>3</td>
<td>1 yr: 95% 2 yrs: 92%</td>
</tr>
</tbody>
</table>

Small studies with wide variety of fractionation schemes, but local control was excellent at 1 year (71-100%).
Toxicity of SBRT for Liver Metastasis

Comparison of Toxicity Between Different Liver SBRT Regimens

<table>
<thead>
<tr>
<th>Author</th>
<th>No. Patients</th>
<th>No. Fractions</th>
<th>Grade 1-2</th>
<th>Grade 3-4</th>
<th>Grade 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blomgren, 1998</td>
<td>50</td>
<td>2-3</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Sato, 1998</td>
<td>18</td>
<td>2-12</td>
<td>5%</td>
<td>5%</td>
<td>0%</td>
</tr>
<tr>
<td>Herfarth, 2004</td>
<td>37</td>
<td>1</td>
<td>NR</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Wulf, 2001</td>
<td>24</td>
<td>3</td>
<td>29%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Katz, 2007</td>
<td>69</td>
<td>7-20</td>
<td>20%*</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Wulf, 2006</td>
<td>44</td>
<td>3-4</td>
<td>26%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Méndez Romero, 2006</td>
<td>25</td>
<td>3-5</td>
<td>96%</td>
<td>16%</td>
<td>4%</td>
</tr>
<tr>
<td>Rusthoven, 2009</td>
<td>47</td>
<td>3</td>
<td>NR</td>
<td>2%</td>
<td>0%</td>
</tr>
<tr>
<td>Goodman, 2010</td>
<td>26</td>
<td>1</td>
<td>54%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>van der Pool, 2010</td>
<td>20</td>
<td>3</td>
<td>95%</td>
<td>15%</td>
<td>0%</td>
</tr>
<tr>
<td>Tzou, 2011</td>
<td>9</td>
<td>1</td>
<td>33%</td>
<td>22%</td>
<td>0%</td>
</tr>
</tbody>
</table>

*Rate of liver function toxicity only. Percentage of non-hepatic toxicities (fatigue and nausea) was not documented in manuscript.

Well-tolerated treatment with minimal to no grade 3-5 toxicity.

Phase I: Single Fraction SBRT for Liver Mets-Mayo

To determine the MTD of SBRT in pts with liver mets

Metastatic liver lesions ≤ 5 cm enrolled at Mayo Clinic Florida and treated single fraction SBRT and followed prospectively


Phase I: Single Fraction SBRT for Liver Mets-Mayo

Protocol Schema:
- Dose escalation from 15 to 25 Gy in 1 fraction
  - 5 Gy increments
- 3 pts per dose level (15, 20, 25 Gy)
- BED = 87.5 Gy (for 25 Gy/1 fraction)

9 Participants Enrolled

Dose Level 1 (15 Gy) 3 Participants
Dose Level 2 (20 Gy) 3 Participants
Dose Level 3 (25 Gy) 3 Participants

Technical Aspects
- Fiducial markers placed w/in 1 week of SBRT
- Image-guidance (KV imaging)
- Gated treatment
- 6 MV photons using a standard linear accelerator

Tumor Measurements
- Performed via CT or MRI abdomen at 3, 6, and 9 mos post-treatment

Tzou, et al. ASTRO 2010
Phase I: Single Fraction SBRT for Liver Mets-Mayo

- **1st Endpoint:** Maximum Tolerated Dose (MTD)
  - Dose limiting Toxicity:
    - Occurrence of radiation induced liver dysfunction (RILD)
    - Clinical liver dysfunction/failure adverse event of grade ≥ 3 according to CTCAE v3.0
    - Assessment (toxicity, hem labs, coags, & chemistries) performed:
      - prior to SBRT, & at wks 2, 4, 6 & 8 post-treatment
      - at months 3, 6, & 9 post-treatment

- **Results**
  - No dose limiting hepatic toxicities observed in any of the 9 pts

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>15 Gy</th>
<th>20 Gy</th>
<th>25 Gy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>↑ Alk Phos</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>↑ AST</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RUG Pain</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>↑ ALT</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RUG Pain</td>
<td>X</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **Conclusions**
  - Single fraction SBRT administered at 25 Gy is well tolerated and safe for treatment of 1-6 liver mets up to 5 cm
  - No dose-limiting toxicity (DLT) was observed at any level
  - DLT = RILD as defined by clinical liver dysfunction/failure of ≥ Grade 3
Phase II: Single Fraction SBRT for Liver Mets-Mayo

- Phase II Protocol
  - To evaluate:
    - Tumor response
    - Progression-free survival
    - Safety
    - Effect on quality of life
    - SBRT administered at 25 Gy in 1 fraction

Phase II: Single Fraction SBRT for Liver Mets-Mayo

- Results
  - Tumor Response
    - 5/9 pts: PR or SD post treatment at 3 mos

Question 5: Up to what size lesion was treated by SBRT at Mayo Clinic Florida per protocol?

- 68%
- 3%
- 3%
- 26%
- 0%

1. 6.5 cm
2. 6.0 cm
3. 5.8 cm
4. 5.5 cm
5. 5.0 cm

68% ✅ 5.0 cm
Question 5: Up to what size lesion was treated by SBRT at Mayo Clinic Florida per protocol?

- Answer: E - 5 cm


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Summary

- Definition and technical aspects of SBRT
  - Delivery of a large dose of radiation therapy to extracranial lesions in typically 5 or fewer high-dose treatments
  - Multiple technological advances have allowed for SBRT
    - Improved immobilization and targeting techniques
    - Compensation for respiratory movement
    - Improved imaging and targeting
    - Advancements in treatment delivery systems

Rationale and indications for liver SBRT

- One of several non-surgical treatment options
  - Comparable to other local ablative therapy options, non-invasive and less stringent eligibility criteria
  - Numerous liver dose escalation trials attempting to determine dose vs. toxicity
  - Limited intrahepatic lesions with limited and/or stable extrahepatic disease
Summary

- Clinical outcomes, including efficacy and toxicity
  - Small studies with wide variety of fractionation schemes, but excellent 1-year local control (71-100%)
  - Small studies show well-tolerated treatment with minimal to no grade 3-5 toxicity

Summary

- MCF experience
  - SBRT is a safe, well-tolerated, and efficacious treatment alternative for non-surgical candidates with a limited number of small to moderate sized liver metastases.
  - The optimal dose and fractionation scheme has yet to be determined and continues to be under investigation.