Stereotactic Body Radiotherapy (SBRT) for Liver Metastases

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Disclosures

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

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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

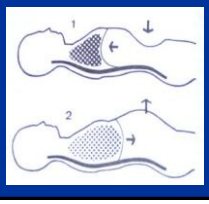
- Modeled after intracranial stereotactic radiosurgery (SRS)
  - Treatment of brain metastases with a single high dose fraction
  - Precise targeting and dose delivery using the skull as a reference system
  - Allows for ablative doses to be delivered with acceptable toxicity in appropriately selected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

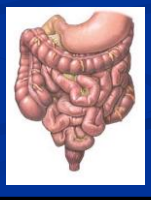
Stereotactic Body Radiotherapy

- 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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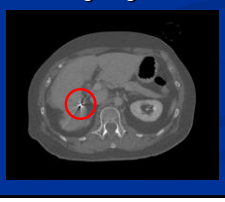
Technological Advances

- 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

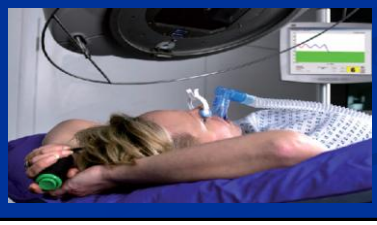


Technological Advances

- Compensation for respiratory movement
  - Direct abdominal compression
    - Reduces normal breathing (tidal volume)
    - Decreases maximum displacement during respiration by 12-13 mm

Technological Advances

- Compensation for respiratory movement
  - Breathe holding technique
    - Treatment machine is only on while the patient is holding their breath (voluntary or active)
    - Diaphragmatic motion is limited



Technological Advances

- Compensation for respiratory movement
  - Respiratory Gating
    - Turning the beam on & off in conjunction w/ the normal respiratory cycle
    - Account for organ movement with respiration by incorporating tumor positional variation into the target volume
    - Determine which phases of the patient's respiratory cycle allow for the least amount of tumor movement

Berbeco, et al. Int J Radiot Oncol Biol Phys 2007;69:258-266.

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

13%	1.	8 mm
10%	2.	10 mm
58%	3.	12 mm
13%	4.	15 mm
6%	5.	20 mm

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

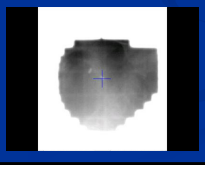
- Answer C: 12-13 mm
- Ref: Berbeco, et al. Clinical Feasibility of Using an EPID in cine Mode for Image-Guided Verification of Stereotactic Body Radiotherapy. Int J Radiot Oncol Biol Phys 2007;69:258-266

Technological Advances

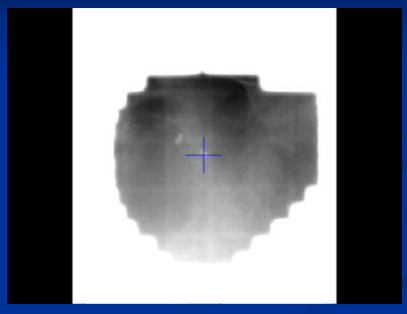
- Image guided radiation therapy (IGRT)
  - KV & MV Imaging, Cone Beam CT
    - Allows verification of the target position with the patient in the treatment position
    - Radiographic imaging is performed immediately before a treatment and/or during an individual treatment session

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

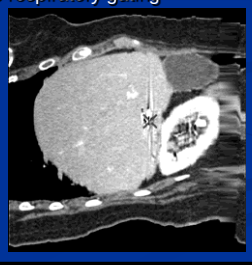


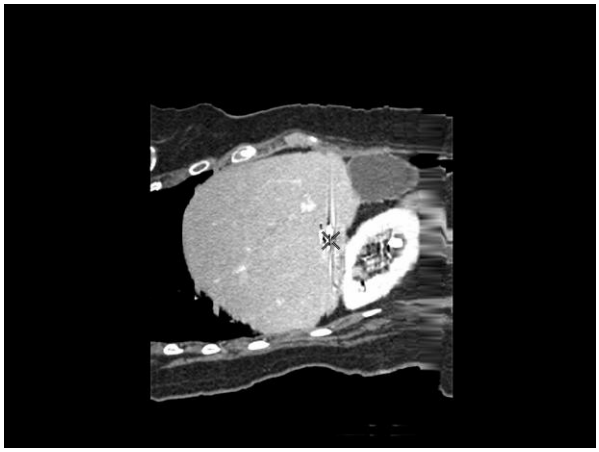
Cine Imaging



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

Overview

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   I. SBRT at Mayo Clinic Florida
IV. Treatment of Liver Metastases
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SBRT at Mayo Clinic Florida

- Immobilization and Targeting
  - Reproducible treatment position with bodyfix device

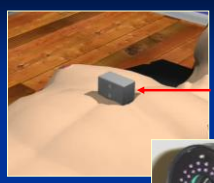
(BodyFix, Medical Intelligence, Schwabmuchen, Germany)

SBRT at Mayo Clinic Florida

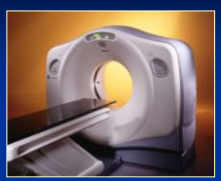
- Immobilization and Targeting

(BodyFix, Medical Intelligence, Schwabmuchen, Germany)

SBRT at Mayo Clinic Florida

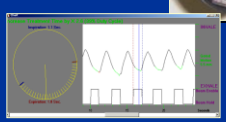


Infrared Reflector



Multi-slice CT scanner

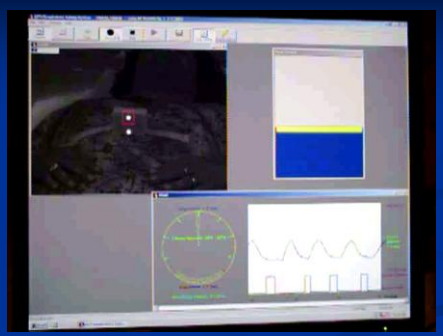
Infrared camera/detector



Control system

Gating workstation

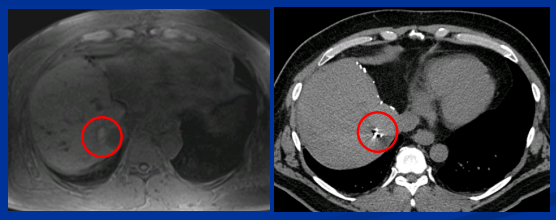
SBRT at Mayo Clinic Florida



(Real-Time Position Management (RPM) respiratory gating system, Varian Medical, Palo Alto, CA)

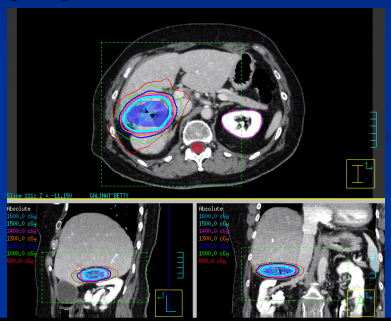
SBRT at Mayo Clinic Florida

- CT simulation images are fused with MRI images to better delineate the tumor volume.



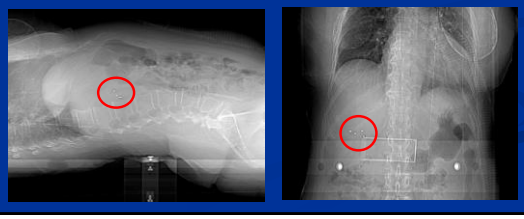
SBRT at Mayo Clinic Florida

- Develop a highly conformal treatment plan w/ or w/out gating

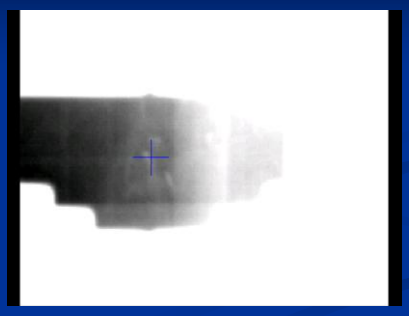


SBRT at Mayo Clinic Florida

- 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

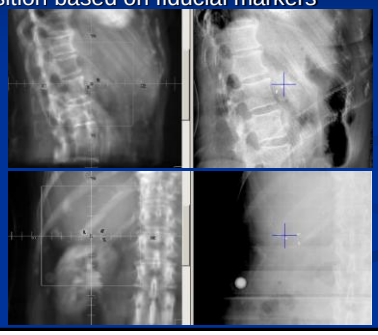


SBRT at Mayo Clinic Florida

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

Lateral
kV-DRR match

AP
kV-DRR match



Overview

I. Objectives
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IV. Treatment of Liver Metastases
  - MSKCC/Stanford study
  - Multi-institutional Phase I/II trial
  - Mayo Clinic Phase I/II trials
V. Summary

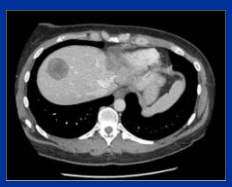
Liver Metastasis

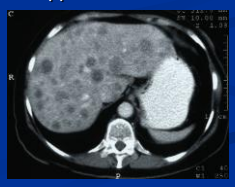
- Local control of oligometastases may yield improved systemic control and prolonged survival
- Researchers began exploring utilizing this stereotactic technique for extracranial sites, including the liver, lungs, spinal cord

Hellman S, Weichselbaum RR. Oligometastases. J Clin Oncol 1995; 13:8-10

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 extrahepatic 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%)

Treatment Options for Liver Metastasis

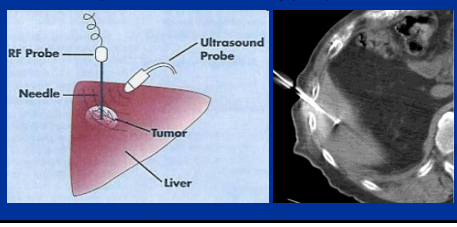
- Stringent eligibility criteria:
  - Medically fit
  - Disease limited to the liver
  - Location
  - Multifocality
  - Adequate reserve of normal liver parenchyma
  - Only a small fraction of patients are eligible for metastectomy (~ 10%)

Treatment Options for Liver Metastasis

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

Treatment Options for Liver Metastasis

- 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

- Common Toxicity Criteria (CTC) Adverse Events

CTCAE v4.0	1	2	3	4	5
Nausea	Loss of appetite	Decreased oral intake w/o weight change	Inadequate oral intake; tube feedings or TPN	Life threatening consequences	Death
Fatigue	Mild	Moderate; causing difficulty with some ADLs	Severe; interfering with ADL	Disabling	Death
Gastritis	Asymptomatic; Radiographic, endoscopic	Symptomatic	Symptomatic; tube feedings or TPN	Life-threatening; surgical intervention	Death
Liver Dysfunction	Mild	Moderate	Severe	Life Threatening; disabling	Death

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

Emami, et al. Int J Radiot Oncol Biol Phys 1991.

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

Marks, et al. Int J Radiat Oncol Biol Phys., Vol. 76, No. 3, Supp., pp. S10–S19, 2010

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

0%	1.	20 Gy
3%	2.	25 Gy
94%	3.	30 Gy
3%	4.	35 Gy
0%	5.	40 Gy

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)
  - Ref: Emami, et al. Tolerance of normal tissue to therapeutic irradiation. Int J Radiot Oncol Biol Phys 1991.
  - Ref: Marks, et al. Use of Normal Tissue Complication Probability Models in the Clinic. Int. J. Radiation Oncology Biol. Phys., Vol. 76, No. 3, Supplement, pp. S10–S19, 2010

Liver Dose Escalation

Treatment of Intrahepatic Cancers With Radiation Doses Based on a Normal Tissue Complication Probability Model

By Cornelius J. McGinn, Randall K. Ten Haken, William D. Ensminger, Suzette Walker, Songbai Wang, and Theodore S. Lawrence

- 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 w/ normal liver function

McGinn CJ, et al., J Clin Oncol, 16:2246-2252, 1998

Liver Dose Escalation

Treatment of Intrahepatic Cancers With Radiation Doses Based on a Normal Tissue Complication Probability Model

By Cornelius J. McGinn, Randall K. Ten Haken, William D. Ensminger, Suzette Walker, Songbai Wang, and Theodore S. Lawrence

- 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%)

McGinn CJ, et al., J Clin Oncol, 16:2246-2252, 1998

Liver Dose Escalation

Phase II Trial of High-Dose Conformal Radiation Therapy With Concurrent Hepatic Artery Floxuridine for Unresectable Intrahepatic Malignancies

Edgar Ben-Josef, Daniel Normolle, William D. Ensminger, Suzette Walker, Daniel Tatro, Randall K. Ten Haken, James Knol, Laura A. Dawson, Charlie Pan, and Theodore S. Lawrence

- 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

Liver Dose Escalation

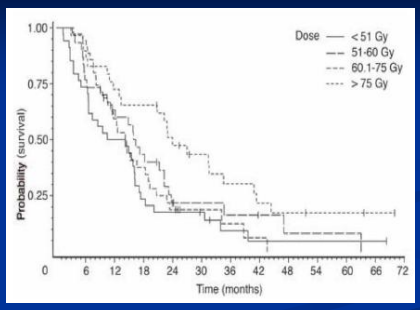
Phase II Trial of High-Dose Conformal Radiation Therapy With Concurrent Hepatic Artery Floxuridine for Unresectable Intrahepatic Malignancies

Edgar Ben-Josef, Daniel Normolle, William D. Ensminger, Suzette Walker, Daniel Tatro, Randall K. Ten Haken, James Knol, Laura A. Dawson, Charlie Pan, and Theodore S. Lawrence

- Results
  - 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*).

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

Liver Dose Escalation

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

Lawrence T, University of Michigan, 2006

Biologically Effective Dose

- Biologically effective dose (BED or E/α): an approximate quantity by which different radiotherapy fractionation regimens may be intercompared:
  - BED = E/α = nD (1 + (D / (α/β)))

    n = number of fractions
    D = dose/fraction
    nD = total dose
- Difficult to compare with SBRT fractionation

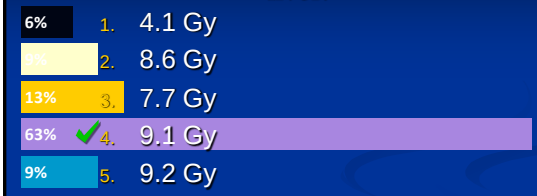
Liver Toxicity

- AAPM TG 101
- Threshold dose
  - Minimum critical volume below 700cc
  - ≥ Grade 3 toxicity

One Fraction	Three Fractions	Five Fractions
9.1 Gy	19.2 (4.8 Gy/fx)	21.0 (4.2 Gy/fx)

Benedict, et al. Medical Physics, Vol. 37, No. 8, August 2010

Question 3: What is the AAPM TG 101 single fraction threshold dose to the liver?



Question 3: What is the AAPM TG 101 single fraction threshold dose to the liver?

- Answer: D - 9.1 Gy
- Ref: Benedict, et al. Stereotactic body radiation therapy: The report of AAPM Task Group 101. Medical Physics, Vol. 37, No. 8, August 2010

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

DOSE-ESCALATION STUDY OF SINGLE-FRACTION STEREOTACTIC BODY RADIOTHERAPY FOR LIVER MALIGNANCIES

KARYN A. GOODMAN, M.D.,* ELLEN A. WIEGNER, M.D.,† KATHERINE E. MATUREN, M.D.,‡ ZHIGANG ZHANG, PH.D.,§ QIANXING MO, PH.D.,§ GEORGE YANG, M.D.,¶ IRIS C. GIBBS, M.D.,† GEORGE A. FISHER, M.D., PH.D.,‖ AND ALBERT C. KOONG, M.D., PH.D.†

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

Goodman, K, et al. *IJROBP*, Vol. 78, No. 2, pp. 486–493, 2010

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

Goodman, K, et al. *IJROBP* , Vol. 78, No. 2, pp. 486–493, 2010

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

Goodman, K, et al. *IJROBP* , Vol. 78, No. 2, pp. 486–493, 2010

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%

Goodman, K, et al. *IJROBP* , Vol. 78, No. 2, pp. 486–493, 2010

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

- 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

Goodman, K, et al. *IJROBP* , Vol. 78, No. 2, pp. 486–493, 2010

Treatment of Liver Mets - Multi-institutional

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

Kyle E. Rusthoven, Brian D. Kavanagh, Higinia Cardenes, Volker W. Stieber, Stuart H. Burri, Steven J. Feigenberg, Mark A. Chidel, Thomas J. Pugh, Wilbur Franklin, Madeleine Kane, Laurie E. Gaspar, and Tracey E. Schefter

- Multi-institutional, phase I/II clinical trial
  - U of Colorado, Wake Forest, Fox Chase
- 1 to 3 hepatic lesions w/ max tumor size < 6 cm
  - Median tumor diameter: 2.7 cm (range, 0.4 to 5.8 cm)
- SBRT delivered in 3 fractions

Rusthoven, et al. *J Clin Oncol.* 2009; 27: 1572-1578

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

Rusthoven, et al. *J Clin Oncol.* 2009; 27: 1572-1578

Treatment of Liver Mets - Multi-institutional

- 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)

Rusthoven, et al. *J Clin Oncol.* 2009; 27: 1572-1578

Treatment of Liver Mets - Multi-institutional

- 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 ≤ 3 cm

Rusthoven, et al. *J Clin Oncol.* 2009; 27: 1572-1578

Treatment of Liver Mets - Multi-institutional

- 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

Rusthoven, et al. *J Clin Oncol.* 2009; 27: 1572-1578

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

Rusthoven, et al. *J Clin Oncol.* 2009; 27: 1572-1578

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?

25%	1.	88%
44%	✔ 2.	92%
28%	3.	95%
3%	4.	97%
0%	5.	100%

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%
- Ref: Rusthoven K, et al. Multi-institutional Phase I/II Trial of Stereotactic Body Radiation Therapy for Liver Metastases. J Clin Oncol. 2009 Apr 1;27(10):1572-8.

Efficacy of SBRT for Liver Metastasis

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

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

Author	No. Patients	No. Fractions	Grade 1-2	Grade 3-4	Grade 5
Blomgren, 1998	50	2-3		0%	0%
Sato, 1998	18	2-12	5%	5%	0%
Herfarth, 2004	37	1	NR	0%	0%
Wulf, 2001	24	3	29%	0%	0%
Katz, 2007	69	7-20	28%*	0%	0%
Wulf, 2006	44	3-4	26%	0%	0%
Méndez Romero, 2006	25	3-5	96%	16%	4%
Rusthoven, 2009	47	3	NR	2%	0%
Goodman, 2010	26	1	54%	0%	0%
van der Pool, 2010	20	3	95%	15%	0%
Tzou, 2011	9	1	33%	22%	0%

NR = Not recorded
*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.

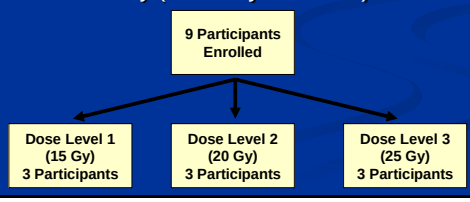
Phase I: Single Fraction SBRT for Liver Mets-Mayo

- 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
  - 9 pts with 1-6 lesions enrolled at MCF between 4/2007 – 2/2009

Tzou, et al. ASTRO 2010

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)



Phase I: Single Fraction SBRT for Liver Mets-Mayo

- 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

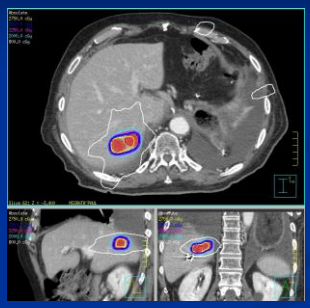
Tzou, et al. ASTRO 2010

Phase I: Single Fraction SBRT for Liver Mets-Mayo

- 1º 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

Tzou, et al. ASTRO 2010

Phase I: Single Fraction SBRT for Liver Mets-Mayo



Tzou, et al. ASTRO 2010

Phase I: Single Fraction SBRT for Liver Mets-Mayo

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

Toxicity	15 Gy	20 Gy	25 Gy
Grade 1			
nausea			X
↑ Alk Phos	X		
Grade 2			
↑ AST	X		
Fatigue	X		
RUQ Pain	X		
Grade 3			
↑ ALT	X		
RUQ Pain	X		

Tzou, et al. ASTRO 2010

Phase I: Single Fraction SBRT for Liver Mets-Mayo

- 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

Tzou, et al. ASTRO 2010

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

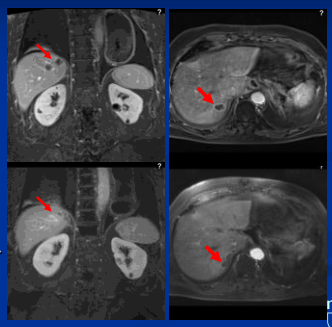
- Results
  - Tumor Response
    - 5/9 pts: PR or SD post treatment at 3 mos

Phase II: Single Fraction SBRT for Liver Mets-Mayo

- Radiographic Partial Response

Pre-SBRT

3 Months Post-SBRT



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

0%	1.	6.5 cm
26%	2.	6.0 cm
3%	3.	5.8 cm
3%	4.	5.5 cm
68% ✓	5.	5.0 cm

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

- Answer: E - 5 cm
- Ref: Vallow L, et al. "A Phase I Dose Finding Pilot Study of Stereotactic Body Radiotherapy for the Treatment of Liver Metastasis." Mayo Clinic Cancer Center protocol MC0642. Activation date: April 2, 2007.

Overview

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

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

Summary

- 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.