STEREOTACTIC RADIOSURGERY IN THE MANAGEMENT OF LIVER AND PANCREATIC TUMORS

C. RONALD KERSH, MD, FACR
LIVER AND PANCREAS CANCER STEREOTACTIC RADIOSURGERY

OBJECTIVES

DEFINE WHAT IS STEREOTACTIC RADIOSURGERY

REVIEW METASTATIC LIVER TUMORS

REVIEW OUR PUBLISHED LITERATURE

REVIEW PRIMARY LIVER TUMORS

REVIEW ROLE OF RADIATION IN PANCREAS
WHAT IS RADIATION ONCOLOGY??

- ONE OF THE THREE SPECIALTIES
  SURGERY
  MEDICAL ONCOLOGY

LINEAR ACCELERATOR

GAMMA KNIFE
WHAT IS RADIATION ONCOLOGY??

• USED AS A PRIMARY TREATMENT
  PROSTATE, LUNG, HEAD AND NECK, HODGKINS DISEASE

• USED AS AN ADJUVANT TO SURGERY
  CHEMOTHERAPY AND IMMUNOTHERAPY
  COLO-RECTAL, LUNG, HEAD AND NECK, BREAST, GYN
  PANCREAS, STOMACH, SARCOMAS

• USED TO IMPROVE SYMPTOMS
  BRAIN, SPINE, LIVER, ADRENAL, BONE
ISN’T RADIATION BAD ??
WHAT IS A RADIATION ONCOLOGIST?

- 4 YEARS OF COLLEGE
- PHYSICS AND MATH
WHAT IS A RADIATION ONCOLOGIST?

- 4 YEARS OF MEDICAL SCHOOL
WHAT IS A RADIATION ONCOLOGIST?

- **INTERNSHIP** ONE YEAR
- **RESIDENCY** FOUR YEARS +/- FELLOWSHIP
- HELPED TRAIN > 100 RESIDENTS IN 37 YEARS
WHAT IS A RADIATION ONCOLOGIST?

- **Top 10%** of medical students
- 4,400 radiation oncologists in USA
  - 400 dedicated radiosurgeons
- Treat 300 – 400 new patients per year
- Odds of cancer in lifetime
  - Males = **39.66%**
  - Females = **37.65%**
WHAT IS A RADIATION ONCOLOGIST?

INVOLVED IN THE TRAINING AND INSTALLATION OF 4 RUSSIAN CENTERS
WHAT IS A RADIATION ONCOLOGIST?

- USE OF EXTERNAL BEAM RADIATION
  WILLIAMSBURG RADIATION – DR. CHISAM

- USE OF INTERNAL OR IMPLANTABLE RADIATION
  BRACHYTHERAPY

- STEREOTACTIC RADIOSURGERY
1951 – STEREOTACTIC RADIOSURGERY

Lars Leksell, MD, PhD
Stereotactic Radiosurgery

Greek
Stereo = solid;
3 – dimensional
(stere’os)

Latin
Tactic = to touch
(tactus)

Radio = beam
(radius)
Modern Stereotactic Systems

- Incorporate all advanced neuroimaging (e.g. SPECT, PET, functional MRI)
- MR compatible
- Accurate and precise
- User friendly
- Concept of “minimally invasive surgery”
Types of Stereotactic Radiosurgery

- Gamma Knife
- Modified LINAC’s
- Proton Beam
- Cyberknife
- X-Knife
- Synergy-S
- Tomotherapy
- Novalis
- Edge
Chesapeake Regional, Riverside & UVA Radiosurgery Center Background

- Joint venture
  - Riverside Health System – Newport News
  - University of Virginia Gamma Knife Center
  - Chesapeake General Hospital (recent)
- June 2006 – Gamma Knife
  - SEPT 2019 - over 1200 SRS cases treated
- May 2007 – Synergy S
  - June 2018- over 2250 SBRT cases treated
  - Varian Edge – 350 9/30/19
Chesapeake Regional, Riverside & UVA Radiosurgery Center

- Intra-cranial SRS (Gamma Knife)
- Intra-cranial SRS/SRT (Varian Edge)
  - Mets, Clivus, Sinus, Parotid, Pituitary
- Extra-cranial SBRT (Varian Edge)
  - Lung (incl. lymph nodes) and Spine – majority of cases
  - Other – liver, pancreas, adrenal, kidney, bladder, lymph nodes and other soft tissue masses, etc.
What is Stereotactic Radiation?

- Non-invasive form of cancer treatment
- Small, highly focused accurate radiation beams
- Delivery in 1–5 fractions
- Represents a major paradigm shift in radiation biology
- Advancement in tumor motion quantification and image guidance was key
Why is SBRT useful?

- **High ablative dose**
  - SRS=Single Fx, SBRT=1-5 Fx
  - Overwhelms repair/repopulation mechanisms
  - Results in a high Biological Equivalent Dose (BED)

- **Short Treatment** (1-5 treatments)

- Tight target and rapid dose fall off
  - Damages tumor in high dose area
  - **Limits toxicity to surrounding normal tissue**
Advantage of SBRT

- Outpatient
- 30-45 Minutes Per Treatment
- Entire course of Rx in 3-5 weeks
- No Sedation or Anesthesia (painless)
- 1 Treatment weekly
- Immediate Return To Activities
Proposed Biological Basis of SBRT

Balagamwala et al.
Multidisciplinary Approach to Stereotactic Radiosurgery Liver

Radiology

Radiotherapy
  Radiation Technicians and Radiation Oncologists

Medical Physics

Gastrointestinal Physicians

Medical Oncology

Pathology
Role of SBRT in Liver Cancer

METASTATIC LIVER TUMORS

HEPATOCELLULAR CARCINOMA
WHAT IS A METASTASIS?

CANCER THAT **HAS SPREAD** FROM PRIMARY SITE TO OVER SITES IN THE BODY.
<table>
<thead>
<tr>
<th>Cancer type</th>
<th>Main sites of metastasis*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bladder</td>
<td>Bone, liver, lung</td>
</tr>
<tr>
<td>Breast</td>
<td>Bone, brain, liver, lung</td>
</tr>
<tr>
<td>Colorectal</td>
<td>Liver, lung, peritoneum</td>
</tr>
<tr>
<td>Kidney</td>
<td>Adrenal gland, bone, brain, liver, lung</td>
</tr>
<tr>
<td>Lung</td>
<td>Adrenal gland, bone, brain, liver, other lung</td>
</tr>
<tr>
<td>Melanoma</td>
<td>Bone, brain, liver, lung, skin/muscle</td>
</tr>
<tr>
<td>Ovary</td>
<td>Liver, lung, peritoneum</td>
</tr>
<tr>
<td>Pancreas</td>
<td>Liver, lung, peritoneum</td>
</tr>
<tr>
<td>Prostate</td>
<td>Adrenal gland, bone, liver, lung</td>
</tr>
<tr>
<td>Stomach</td>
<td>Liver, lung, peritoneum</td>
</tr>
<tr>
<td>Thyroid</td>
<td>Bone, liver, lung</td>
</tr>
<tr>
<td>Uterus</td>
<td>Bone, liver, lung, peritoneum, vagina</td>
</tr>
</tbody>
</table>
WHERE DO CANCERS SPREAD?
WHY DO CANCERS SPREAD TO THE LIVER

**BLOOD FLOW** PER MINUTE LIVER IS SECOND TO ONLY THE LUNG
WHY DO CANCERS SPREAD TO THE LIVER??

- The most common site for blood born metastases
- **Common primaries**: colon, breast, lung, stomach, pancreases, and melanoma
- Mild cholestatic picture (ALP, LDH) with preserved liver function
- Dx imaging or FNA
- Treatment depends on the primary cancer
- Incase of metastasis from intestinal cancer or neuroendocrine cancer. Surgery can offer cure.
INCIDENCE OF LIVER METASTASES WHEN CANCERS SPREAD

COLON CANCER = 65%

PANCREAS = 63%

BREAST = 61%

OVARY = 52%

RECTUM AND STOMACH = 47%

LUNG = 36%
METASTATIC LIVER TUMORS - CURRENT TREATMENTS

- SURGICAL RESECTION = 20-40% SURVIVAL (ONLY 10-20% RESECTABLE)
- CHEMOTHERAPY = 20% RESPONSE RATE
- RADIOfREQUENCY ABLATION = RECURRENCE RATE OF 40% - NEW METS = 50%
- CHEMOEMBOLIZATION = RESPONSE RATES 15 – 40 %

HEPATIC ARTERY CHEMOINFUSION = 20-30% RESPONSE RATE
LIVER METASTASES
RADIOSURGERY

3 OR FEWER TUMORS

< 4.0 CM = 1.57 INCHES

MUST HAVE DEDICATED RADIOSURGERY PROGRAM
47 NURSE, BREAST CANCER, TOLD SHE HAD 6 MONTHS TO LIVE
Stereotactic Body Radiation Therapy for Liver Metastases

David Asher, MD ¹; David Bergman, MD ¹ Akanksha Rajeurs, MD ¹; Zaker Rana, MD ¹ Kelly Spencer, MS, DABMP ¹; Martin K. Richardson, MS, DABR ¹; Ronald Kersh, MD ¹,²
1 Chesapeake Regional, Riverside and University of Virginia Radiosurgery Center, Newport News, VA, 2 University of Virginia, Charlottesville, VA
Background

• Nearly 50% of colon cancer patients will develop liver metastases, which is approximately 50,000 patients per year.¹
• Surgical resection with a negative margin is a standard therapy for liver metastasis.²
• Only approximately 25% of patients are surgical candidates.³
• Local therapy has been utilized to establish local control.
• Radiofrequency ablation is safe and offers good local control but loses efficacy with lesions > 3 cm and is limited based on lesion location within the liver.
• **SBRT** has emerged as alternative approach.

¹Blumgart et al. 1995
²Rusthoven et al. 2009
³Hoyer et al. 2006
UVA-RIVERSIDE RADIOSURGERY

• Retrospective clinical and imaging review.
• All patients that received SBRT to liver metastases were included.
• July 2007 – August 2015
• Pre- and post-SBRT clinical follow ups, hepatic panels, and imaging were analyzed.
• Tumor response evaluated per revised RESIST 1.1
• Primary Outcome:
  • Local Control
• Secondary Outcome:
  • Toxicity

^Eisenhauer et al. 2009
<table>
<thead>
<tr>
<th>Total Patients</th>
<th>80</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Number of Lesions</td>
<td>128</td>
</tr>
<tr>
<td>Females</td>
<td>46</td>
</tr>
<tr>
<td>Males</td>
<td>34</td>
</tr>
<tr>
<td># that received chemotherapy within 6 months</td>
<td>64</td>
</tr>
<tr>
<td>Median/ Mean Age (years)</td>
<td>67.3 / 64.5</td>
</tr>
<tr>
<td>Age Range</td>
<td>32 - 91</td>
</tr>
</tbody>
</table>

- No patients were considered candidates for surgical resection at time of radiation
- All patients had to have either isolated metastasis to liver or controlled non-hepatic disease
Primary Cancer Locations

- Breast: # of Patients, # of Lesions
- Colorectal: # of Patients, # of Lesions
- Lung: # of Patients, # of Lesions
- Gynecologic: # of Patients, # of Lesions
- Skin: # of Patients, # of Lesions
- GI (non-colorectal): # of Patients, # of Lesions
- Genitourinary: # of Patients, # of Lesions
- Other: # of Patients, # of Lesions

Legend:
- Blue: # of Patients
- Red: # of Lesions
Planning and Delivery

• All plans created by 1 of 2 senior physicists.
• All plans utilized:
  • 6 MV X-ray, static beams, often non-coplanar
  • 4D image guidance
  • ITV to account for respiratory motion.
  • Further expansion to PTV included 8 mm cranial, 6 mm caudal, and 3-5 mm in axial plane.
  • Convolution algorithm on 0.2 cm grid for calculation of final isodose display and treatment monitor units.
• All treatment deliveries utilized:
  • Vacuum bag attached to a stereotactic body frame for patient stabilization.
  • Fiducials within frame were used as coordinate system.
## Fractionation Schemes

<table>
<thead>
<tr>
<th></th>
<th>Median / Mean Prescription Dose (Gy)</th>
<th>30.0 / 28.8 Gy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose (Gy) Range</td>
<td></td>
<td>18 – 40 Gy</td>
</tr>
<tr>
<td>Median / Mean # of Fractions</td>
<td></td>
<td>3 / 3</td>
</tr>
<tr>
<td>Median / Mean # of Lesions Treated</td>
<td></td>
<td>1.0 / 1.6</td>
</tr>
<tr>
<td>Range of # of Lesions Treated</td>
<td></td>
<td>1 – 4</td>
</tr>
<tr>
<td>Mean Interval Between Fractions (days)</td>
<td></td>
<td>5 days</td>
</tr>
</tbody>
</table>
Outcomes

• 109 of 128 lesions had post-SBRT imaging follow-up
• 68 of 80 patients had oncology-specific, clinical follow up
• Local Control:
  • 15 lesions failed locally.
  • 86.2% Local control rate
• Overall Survival
  • At 1 year: 41.3%
• Hepatic Progression (outside of PTV)
  • 34 patients (34/68)
• Extra-Hepatic Progression
  • 58 patients (58/68)
• No incidences of Radiation Induced Liver Disease (RILD)
• <5% complication rate (Grade 2+ toxicity)
### Lesion Response

<table>
<thead>
<tr>
<th>Tumor Response</th>
<th>Number of Lesions</th>
<th>% of Lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete or Partial Response</td>
<td>41</td>
<td>37.6%</td>
</tr>
<tr>
<td>Stable</td>
<td>53</td>
<td>48.6%</td>
</tr>
<tr>
<td>Increase</td>
<td>15</td>
<td>13.8%</td>
</tr>
</tbody>
</table>
• Local Control at
  • 6 months: 89.3%
  • 12 months: 81.8%
  • 24 months: 79.5%
• Log-Rank test: $X^2 = 5.78$, $P$-value $= 0.0163$
• Hazard Ratio: $3.23$ (95% CI: $1.09 - 9.57$)
- Log-Rank Test: $X^2 = 14.0$, $P$-value = 0.0073
## Local Control Correlations

<table>
<thead>
<tr>
<th>Category</th>
<th>Log-Rank P-value</th>
<th>Statistically Significant?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Tumor</td>
<td>0.0073</td>
<td>Yes</td>
</tr>
<tr>
<td>Prescription Dose</td>
<td>0.0163</td>
<td>Yes</td>
</tr>
<tr>
<td>Tumor Size (GTV)</td>
<td>0.0991</td>
<td>No</td>
</tr>
<tr>
<td>Number of Lesions</td>
<td>0.3538</td>
<td>No</td>
</tr>
</tbody>
</table>
Gynecologic Metastases to Liver

- 20 lesions; 13 patients.
- Median Follow-up: 15.1 months.
- **Median Overall Survival: 21.0 months.**
- Local Control at 2 years: 100%
- Local failures occurred 26.7 and 45.8 months, both still alive.
## Toxicity

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Number of Patients</th>
<th>CTCAE 4.0 Grade</th>
<th>Resolved?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>5</td>
<td>Grade 1 (4)</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Grade 2 (1)</td>
<td></td>
</tr>
<tr>
<td>Nausea / Vomiting</td>
<td>4</td>
<td>Grade 1</td>
<td>Yes</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3</td>
<td>Grade 1</td>
<td>Yes</td>
</tr>
<tr>
<td>Cholangitis</td>
<td>1</td>
<td>Grade 2</td>
<td>Yes</td>
</tr>
</tbody>
</table>
• **No Radiation Induced Liver Disease**
Conclusions

• SBRT is safe and effective way to establish local control of metastatic liver lesions.

• A dose-response relationship appears to exist and is supported by prior Phase I/II dose escalation trials.

• Our data suggests the number of liver lesions (up to 4) is not correlated with local failure.

• Gynecologic metastases responded well to SBRT with a high rate of local control with potential for long-term survival.

• Gynecologic metastases to liver may represent an underutilized area in SBRT.