Stereotactic Body Radiation Therapy: Updates on Clinical, Biological, and Physics/QA

Part One: Biological and Clinical Updates

AAPM 54th Annual Meeting, Charlotte, NC
7/30/12

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Professor
University of Virginia

Disclosures:

Current Federal Funding:
2012 CMS Innovation Challenge Award to Develop STAT RAD
Discussion Topics

- SBRT Radiobiology and Normal Tissue Constraints
- SBRT Institutional and Cooperative Group Trials
- STAT RAD: Possible future direction for rapid pain palliation of osseous metastases

Radiobiology

- Classical Fractionated Radiobiology
- SBRT Radiobiology: variations of the LQ model
- Normal Tissue Constraints for SBRT

Radiobiology: How does radiation interact and effect living cells and organisms?

Physics to Chemistry to Biology
Curie’s discoveries lead to “Curie Therapy”
(*Beginning of “Radiation Oncology”*)

Radium was shown to be a useful tool for destroying cancer cells and normal tissues.

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Late Radiation Toxicity

Occurs 90 days or longer after completing radiation.
Mainly due to a combination of:
1) Vascular effects (obliteration of the microvasculature and development of telangiectasias leading to bleeding).
2) Chronic stem cell depletion, leading to poor mucosalization, fibrosis, and ulceration.

Late Toxicity is related to: Total Dose, Dose per fraction, Radiation Dose Rate, Volume of Tissue Treated, Type of tissues treated, Patient specific factors.

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Animal Model for fractionated radiation therapy: Ram Sterilization Model

Using sterilization of the Ram as a model system (spermatogonia modeled tumor and the scrotum modeled normal tissues), early radiation researchers realized that they could sterilize the Ram with less scrotal irritation if they delivered multiple smaller radiation doses rather than one large dose.
Conventionally fractionated radiation becomes standard of care to minimize normal tissue toxicity

The Four R’s of Radiobiology:
1. Repair of sublethal damage
2. Reassortment of cells into radiosensitive phases of the cell cycle (G₂/M)
3. Repopulation of cells due to cell doubling / proliferation
4. Reoxygenation of hypoxic cells in a tumor core


Single and Multiple Fractionated Radiation Therapy Survival Curves

Shoulder of curve: sublethal repair
Cells have differential radiation sensitivity depending on their cell cycle status

Cell cycle dependency of radiosensitivity
General age response pattern for x or γ-rays – synchronized cells

Effect of tumor repopulation during fractionated therapy
Dependence of radiosensitivity on oxygen concentration (idealized)

Only a small quantity of oxygen is required for radiosensitization (0.5% oxygen increases R.R to 2.0)

Linear-quadratic model:

\[ S = e^{-\alpha D - \beta D^2} \]

Linear and quadratic components equal at:

\[ D = \frac{\alpha}{\beta} \]

The model provides the mechanistic biological rationale related to single- and double-strand DNA breaks.


Multi-target Model for Cell Kill

Multi-target model assumes an alternative description of clonogenic survival as a function of dose with \( n \) targets that need to be hit to disrupt clonogenicity.

\[ S = e^{-\alpha D_1 - \beta D_2^2} \left(1 - (1 - e^{-\alpha D_1})^n\right) \]

where \( \alpha \) and \( \beta \) are the parameters that determine the initial (first log kill) and final "slopes" of the survival curve. In the high-dose range, when \( D > D_2 \), the multi-target model survival curve approaches an acceptable.

\[ \ln S = \frac{1}{D_2} \ln(1 - (1 - e^{-\alpha D_1})) + \frac{1}{D_2} \ln(1 - (1 - e^{-\alpha D_1}))^n \]

Rationale for a universal survival curve and single fraction equivalent dose

Universal Survival Curve

Other Novel SBRT Radiobiologic Considerations
- Endothelial Apoptosis: mediated via acid sphingomyelinase pathway at high dose per fraction.

- T-cell priming in draining lymphoid tissue resulting in distant tumor reduction/eradication via CD8+ T-cell dependent fashion.
Emami normal tissue dose constraints for fractionated therapy

Emami B et al, IJROBP 1991;21(1):109-122

How do we determine the dose?
Tumor/Normal Tissue Response Curves

Parallel vs. Serial Organ Structure
SBRT: Normal Tissue Dose Constraints

- Constraints are confusing as these have been reported by multiple institutions with little followup toxicity data.

- Parameters used include max point doses, absolute volume constraint, percentage volume constraint, critical volume spared


Summary of Table 2: Mostly Unvalidated Normal Tissue Dose Constraints for SBRT

From Timmerman 2008 "Overview of Hypofractionation" in Seminars in Radiation Oncology (Vol. 18, Num. 4)

<table>
<thead>
<tr>
<th>Patient Name</th>
<th>Smith, John</th>
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<tbody>
<tr>
<td>MRN:</td>
<td></td>
</tr>
<tr>
<td>Rx # and name</td>
<td>1a - liver SBRT</td>
</tr>
<tr>
<td>Total Rx Dose</td>
<td>45 Gy</td>
</tr>
<tr>
<td>Dose / fx</td>
<td>15 Gy / fx</td>
</tr>
<tr>
<td># fractions</td>
<td>3</td>
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</table>

### 3 Fraction Treatment

<table>
<thead>
<tr>
<th>Organ</th>
<th>Critical Vol (cc)</th>
<th>Critical Vol Dose Max (Gy)</th>
<th>Total OAR volume DVH volumes</th>
<th>Met Requirement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>700</td>
<td>17.1</td>
<td>900.00 cc V17.1 Gy 150.00 cc 750.00 cc</td>
<td>Yes</td>
</tr>
<tr>
<td>Kidneys</td>
<td>200</td>
<td>14.4</td>
<td>350.00 cc V14.4 Gy 145.00 cc 205.00 cc</td>
<td>Yes</td>
</tr>
</tbody>
</table>

### Critical Organs | Max Point Dose | Max Dose Limit | Met Requirement | DVH Input Volume Limit (cc) | Met Requirement |
<table>
<thead>
<tr>
<th></th>
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<th></th>
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</thead>
<tbody>
<tr>
<td>Spinal Cord</td>
<td>13.00</td>
<td>22.0</td>
<td>Yes</td>
<td>V18.0 Gy 0.20 cc 0.25 cc</td>
<td>Yes</td>
</tr>
<tr>
<td>Spinal Cord</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>V11.1 Gy 1.10 cc 1.20 cc</td>
<td>Yes</td>
</tr>
<tr>
<td>Skin</td>
<td>na</td>
<td>24.0</td>
<td>-</td>
<td>V22.5 Gy na na cc</td>
<td>-</td>
</tr>
<tr>
<td>Heart</td>
<td>21.00</td>
<td>30.0</td>
<td>Yes</td>
<td>V24.0 Gy 14.00 cc 15.00 cc</td>
<td>Yes</td>
</tr>
<tr>
<td>Esophagus</td>
<td>27.00</td>
<td>27.0</td>
<td>No</td>
<td>V21.0 Gy 6.50 cc 5.00 cc</td>
<td>No</td>
</tr>
<tr>
<td>Stomach</td>
<td>15.00</td>
<td>24.0</td>
<td>Yes</td>
<td>V21.0 Gy 9.00 cc 10.00 cc</td>
<td>Yes</td>
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<tr>
<td>Duodenum</td>
<td>na</td>
<td>24.0</td>
<td>-</td>
<td>V15.0 Gy na 5.00 cc</td>
<td>-</td>
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<tr>
<td>Jejunum / ileum</td>
<td>na</td>
<td>27.0</td>
<td>-</td>
<td>V16.2 Gy na 5.00 cc</td>
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<tr>
<td>Chestwall</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>V30.0 Gy 21.00 cc 30.00 cc</td>
<td>Yes</td>
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</tbody>
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9
Major SBRT Institutional and Cooperative Group Clinical Trials

- Lung
- Liver
- Spine
- Prostate

Key Retrospective Japanese Lung SBRT experience

- Uematsu reported a 94% 3-year local control rate for patients treated with 50-60 Gy in 5-6 fractions.
- Nagata reported a 98% local control rate at 30 months for patients treated with 48 Gy in 4 fractions.
- Onishi reported a retrospective study involving 245 patients treated at 13 institutions with a 92% 2-year median local control rate for patients treated to a biologic effective dose BED of at least 100 Gy.

[References]


Phase I dose escalation trial by Timmerman at University of Indiana

- 47 patients were stratified into 3 groups based on tumor size (<3 cm, 3-5 cm, 5-7 cm).
- Dose escalation in cohorts of 3 patients with all patients receiving 3 fractions of 3D conformal radiation starting at 8 Gy per fraction.
- The maximal tolerated dose was not reached for the 2 smaller tumor subgroups despite treating to 60-66 Gy and was 66 Gy for the largest tumor subgroup.
- 2-year local control rate for patients treated with 18-24 Gy x 3 fractions was 90%. (BED = 100 Gy)


Phase II dose escalation trial by Timmerman at University of Indiana

- 70 patients: patients stratified for tumor size
  - 35 patients with smaller tumors (5 cm or less) treated with 60 Gy/3 fractions
  - 35 patients with larger tumors treated with 66 Gy/3 fractions
- The actuarial 2-year local control rate was 95% with a 56% overall survival with death mostly from co-morbid illness.
- Dose limiting toxicity (grade 3-5) was reported to be 11 times higher for patients treated with central tumors compared to peripheral tumors.


JCOG 0403

- Single arm phase II study for patients with stage 1A lung cancer based on excellent local control rates reported from Kyoto University Hospital
- Study stratifies patients based on medically operable and medically inoperable
- Treatment is 48 Gy/4 fractions prescribed to the isocenter.
- Primary endpoint was 3-year overall survival (OS)
- 64 evaluable patients: the 3-yr OS =76% and local PFS=68.5% with only 6.2% grade 3 toxicity no grade 4 or 5 toxicity
- Concluded that dose escalation is feasible based on toxicity and may improve PFS.
RTOG Lung SBRT Trials

- **RTOG 0236** phase II closed n = 59 3D
- **RTOG 0618** phase II closed n = 33 3D and IMRT
- **RTOG 0813** phase I/II open n = 97 3D and IMRT
- **RTOG 0915** Phase II closed n = 94 3D and IMRT
- **RTOG 1021** Phase III open target n= 420

**RADIATION THERAPY ONCOLOGY GROUP RTOG 0236**

A Phase II Trial of Stereotactic Body Radiation Therapy (SBRT) in the Treatment of Patients with Medically Inoperable Stage I/II Non-Small Cell Lung Cancer

Patients with T1, T2 (≤ 5 cm), T3 (≤ 5 cm), N0, M0 medically inoperable non-small cell lung cancer; patients with T3 tumors chest wall primary tumors only; no patients with tumors of any T-stage in the zone of the proximal bronchial tree. Patients with T3 tumors based on mediastinal invasion or ≤ 2 cm toward carina invasion are not eligible.

**Primary Tumor Control: RTOG 0236**

One patient failed within 2 cm of the primary tumor

- 36 month primary tumor control = 96% (CI: 84-100%)  
- 3-year Kaplan Meier lobar local control = 90.7%

Slide courtesy of Dr. Timmerman
Overall Survival RTOG 0236

Slide courtesy of Dr. Timmerman

RADIATION THERAPY ONCOLOGY GROUP RTOG 0618
A Phase II Trial of Stereotactic Body Radiation Therapy (SBRT) in the Treatment of Patients with Operable Stage I/II Non-Small Cell Lung Cancer

RADIATION THERAPY ONCOLOGY GROUP: RTOG 0813
SEAMLESS PHASE I/II STUDY OF STEREOTACTIC LUNG RADIOTHERAPY (SBRT) FOR EARLY STAGE, CENTRALLY LOCATED, NON-SMALL CELL LUNG CANCER (NSCLC) IN MEDICALLY INOPERABLE PATIENTS

SCHERIA

Exceeding dose levels at all levels, patients will be treated q 2 day fractionation 1.5 fractions over 1.5 weeks.

Dose per Fraction

<table>
<thead>
<tr>
<th>Level</th>
<th>0.5 Gy</th>
<th>0.5 Gy</th>
<th>1.0 Gy</th>
<th>1.5 Gy</th>
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<tr>
<td>Level 1</td>
<td>40 Gy</td>
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<td>45 Gy</td>
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<tr>
<td>Level 2</td>
<td>40 Gy</td>
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<td>45 Gy</td>
<td>45 Gy</td>
<td>45 Gy</td>
</tr>
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</table>

Protocol treatment begins at Level 1. Levels 1-4 will be employed if dose-limiting toxicity is seen with the Level 1 (5 Gy) starting dose.

Patients with stage T1-2, N0, N2, non-small cell lung cancer, tumor size ≤ 5.5 cm, who are not candidates for a complete surgical resection, in the opinion of the thoracic surgeon, only patients with tumors within or touching the zone of the proximal bronchial tree or adjacent to mediastinal or pericardial pleura (see Section 3.1.5 for details).
**RADIATION THERAPY ONCOLOGY GROUP**

**RTOG 0915 (NCTG N0927)**

A RANDOMIZED PHASE II STUDY COMPARING 2 STEREOTACTIC BODY RADIATION THERAPY (SBRT) SCHEDULES FOR MEDICALLY INOPERABLE PATIENTS WITH STAGE I PERIPHERAL NON-SMALL CELL LUNG CANCER

<table>
<thead>
<tr>
<th>SBRT SCHEDULE</th>
<th>External Performance Status (EPS)</th>
<th>Tumor Volume (TV)</th>
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<tbody>
<tr>
<td>A</td>
<td>EPS 1-3 TV ≤ 1 cc</td>
<td>12 Gy in 1 fraction</td>
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<tr>
<td>B</td>
<td>EPS 1-3 TV &gt; 1 cc</td>
<td>12 Gy in 2 fractions</td>
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</table>

Phase III trials randomizing operable candidates with early NSCLC to SBRT vs Surgery

**RTOG 1021**

A Randomized Phase III Study of Sublobar Resection (+/- Brachytherapy) versus Stereotactic Body Radiation Therapy in High Risk Patients with Stage I Non-Small Cell Lung Cancer (NSCLC)

**STARS TRIAL**

A Randomized Phase III study of Cyberknife (60 Gy in 3-4 fractions) versus VATS or Open Thoracotomy in operable patients with T1N0 or T2N0 (<4 cm) NSCLC

**ROSEL Trial**

A Randomized Phase III study of SBRT (60 Gy in 3-5 fractions) vs. Surgical Resection in operable Stage IA patients with NSCLC

**SBRT FOR LUNG METASTASES**

Local control rates of 78-100%

Eligibility
- 1-3 liver metastases
- Solid tumors
- No tumor diameter >6cm
- Liver and kidney function OK
- No systemic therapy within 14 days pre- or post-SBRT

SBRT Dose
- Phase I escalation to 20 Gy x 3
- 20 Gy x 3 fractions for Phase II

Liver and Non-liver Protocol Dose
Volume Constraints
- Non-liver:
  - Total kidney volume > 15 Gy to be < 35%
  - Max spinal cord dose 18 Gy
  - Max dose to stomach or intestine 30 Gy
  - Later, max point to skin <21 Gy
- Modified critical volume method for liver:
  - At least 700 cc had to receive < 15 Gy

Results: (1) no severe liver toxicity
(2) tumor volume effect

1 grade 3 skin toxicity due to inadvertent subcutaneous hotspot


**SBRT FOR LIVER METASTASES**
Local control rates of 71-100%


**SBRT FOR SPINAL METASTASES**
Local control rates of 77-94%

**RADIATION THERAPY ONCOLOGY GROUP: RTOG 0631**
**PHASE II/III STUDY OF IMAGE-GUIDED RADIOSURGERY/SBRT FOR LOCALIZED SPINE METASTASIS**
**Phase II Component:** Determine the feasibility of successfully delivering image-guided radiosurgery/SBRT for spine metastases in a cooperative group setting.

**Phase III Component:** Determine whether image-guided radiosurgery/SBRT (single dose of 16 Gy) improves pain control (as measured by the 11 point NRPS) as compared to conventional external beam radiotherapy (single dose of 8 Gy).

*Patients with localized spine metastases from the G1 to G5 levels (as solitary spine metastases, 2 separate spine levels, or up to 3 separate sites, each of the separate sites must have a minimal involvement of 2 contiguous vertebral bodies).*

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**SBRT for Localized Prostate Cancer**

**Table of SBRT for Localized Prostate Cancer**

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<th>N/A</th>
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<td>N/A</td>
<td>N/A</td>
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<tr>
<td>Clinic 2011</td>
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<td>N/A</td>
<td>N/A</td>
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**Radiation Therapy Oncology Group: RTOG 0938**

**A Randomized Phase II Trial of Hypofractionated Radiotherapy for Favorable Risk Prostate Cancer**

**Schema**

1. All linear accelerator based treatment (excluding CyberKnife)
2. CyberKnife
3. Proton

For proton doses, see Section 8.1.4.

Histologically confirmed diagnosis of adenocarcinoma of the prostate within 180 days of randomization. Gleason scores 2-6. Clinical stage T1-T2a. PSA < 10 ng/ml. PSA should not be obtained within 10 days after prostate biopsy.
A Real Time TomoTherapy-based Scan-Plan-QA-Treat STAT RAD treatment procedure in 30 minutes is possible

TomoTherapy to Introduce StatRT at AAPM

MADISON, Wis., July 8, 2007 - TomoTherapy Incorporated (NASDAQ: TTPY) today announced that it will introduce StatRT™ at the annual American Association of Physicists in Medicine (AAPM) meeting in Minneapolis, July 22-26, 2007.
Lung SBRT Dosimetric Comparison of “beamlet” algorithm and “full scatter” STAT RT algorithm
20 Gy prescribed to cover 95% of the PTV

Liver SBRT Dosimetric Comparison of “beamlet” algorithm and “full scatter” STAT RT algorithm
20 Gy prescribed to cover 95% of the PTV

Spine SBRT Dosimetric Comparison of “beamlet” algorithm and “full scatter” STAT RT algorithm
20 Gy prescribed to cover 85% of the PTV
2007 STAT RT Clinical Problems

- No good contouring tools
- No QA methods

2011 ASTRO Consensus Guidelines on Bone Metastases

ASTRO GUIDELINE

PALLIATIVE RADIOThERAPY FOR BONE Metastases: AN ASTRO EVIDENCE-BASED GUIDELINE

STEVEN LUTZ, M.D.1,2, LAURENCE BRES, M.D., Ph.D.,3,4, I. ERIC CAVOCO, M.D.,1,5, EDWARD CHEN, M.D.,6,7, CONNIE BUERI, M.D.1,5
PETER HOWELL, M.D.1,2, DOUG HOWELL, M.D.1,2, ARMITA KIYASTOK, M.D.1,5, LESLIE KACHUR, M.D.1,5
SHERIE LE, M.D., G.L.R.6,7, ANN TENG, M.D.2,7, LORI KRYLIS, M.D.4,7
CRAIG W. GOSLING, M.D., Ph.D., F.A.C.P.2,7, ETHAN MOLOK, M.D., F.A.C.S.,8

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2012 ACR Appropriateness Criteria Non-spine Bone Metastases

ACR Appropriateness Criteria® Non-Spine Bone Metastases

Radiation Oncology Patient Workflow: Major Barrier to Patient Access

- Physics Quality Assurance
- Treatment Planning
- CT Simulation
- Consultation & Preauthorization
- Request Consultation

10 Fractions of Treatment Delivery (Monday – Friday)

50 mile radius around Charlottesville

1200 miles is approximately the distance from New York to Omaha, Dallas or Miami

New York
Omaha
Dallas
Miami
Adoption of SBRT treatment concepts for spinal irradiation to non-spinal bone metastases.

**Proposed SCAN PLAN QA TREAT WORKFLOW**

- Pre-contour
- Diagnostic Image Set
- Immobilization and MVCT simulation
- Image Co-registration
- Velocity @
- QA: Monte Carlo Second Dose Check
- Dose Delivery with second QA: CT Detector Dose Check
Acknowledgements

Robert Timmerman
Brian Kavanagh
Stanley Benedict
Quan Chen
Ke Sheng
Lydia Handsfield
Neal Dunlap
Alyson McIntosh
James Larner
Josh Evans

Thanks for your attention!!

Questions? Email: pwr3u@virginia.edu
US: prefers 30 Gy/10 fractions

- Case 1: Breast cancer with brain metastases
- Case 2: Breast cancer with liver metastases
- Case 3: MOC with spine metastases
- Case 4: MOC with metastatic pain, spine IM
- Case 5: Breast cancer with spine metastases
- Case 6: Breast cancer with multiple brain metastases
- Case 7: Breast cancer with spine metastases

Fig. 1. Use of single fraction radiotherapy.
At least tumor motion management is not this complex!!!
Wenlock (above), the mascot of the Olympic Games, is named after the English town of Much Wenlock, which inspired Baron Pierre de Coubertin to found the modern Olympic movement.

Mandeville (above), the mascot of the Paralympics, is named after the town of Stoke Mandeville, the birthplace of the Paralympic Games.