Immunotherapy Killed the IGRT Star: Integrating Radiotherapy Into Systemic Therapy for Metastatic Disease

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Director of Clinical and Translational Research
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Disclaimer

• Spouse: Medical Oncologist & Medical Director for Oncology Products at Astellas Pharmaceutical

• RefleXion Medical Systems

40 Minute Outline

• Expanding the role of radiotherapy for:
  – Local therapy for Limited (Oligometastatic) Disease

• What is immunotherapy? A Primer

• Can Radiotherapy Enhance Immunotherapy?
  – Local Therapy for Widespread Disease (polymetastatic) with Immunotherapy be a new paradigm?
Radiotherapy for metastatic Disease

The Clinical Problem of Metastasis

- Metastasis accounts for 85-90% of cancer mortality
- Regarded as widely disseminated and incurable in adult solid tumors
- Treated with systemic therapies: usually not curative
Overarching Clinical Question:

How can we cure more patients with metastatic disease?

Oligometastasis Hypotheses and Characteristics

- Metastasis represents a spectrum of disease: number of metastases/organisms involved/pace of progression
- Subsets of patients with limited (oligometastatic) disease are potentially curable with metastasis-directed therapies (SBRT)
- Cytoreduction with could synergize with systemic agents to improve outcomes

Spectrum of Metastatic Disease

Limited Spread (Oligometastasis) 1-5 Metastases

Widely Disseminated (Polymetastases)
Oligometastases exist and are common

Many claim to see them...

### Oligometastatic Patients Exist...

**Breast Cancer**

<table>
<thead>
<tr>
<th>First Author</th>
<th>Phase</th>
<th>ER/PR (%)</th>
<th>HER2</th>
<th>&lt; 2 Met sites (%)</th>
<th>&lt; 4 Met Sites (%)</th>
<th>Notes</th>
<th>PFS (%)</th>
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<tbody>
<tr>
<td>Elmore 2008†</td>
<td>8</td>
<td>699</td>
<td>32</td>
<td>88</td>
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<td>Rosenberg 2007‡</td>
<td>88</td>
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<td>Steller 2005⊥</td>
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<td>175</td>
<td>45</td>
<td>98</td>
<td>97</td>
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</table>

*See text for notes.*

50% have <4 sites of metastases at diagnosis

Patients with oligometastases have **indolent disease:**

*Metastatic Breast Cancer Patients*

**Multivariate Analysis of Prognostic Factors in Metastatic Breast Cancer**

- 1.7% of 1,581 patients remained alive/complete remission >10 year
- 619 patients treated with anthracycline chemo
- Minimum f/u 4 years

| Table 7: **Regression Model: Making Initial vs. Remission Characteristics** |
|---|---|---|---|---|---|---|
| Characteristics | Regression Initial | Remission | T-stat | p-value | Odds | 95% CI |
| Number sites | 0.513 | -1.82 | -3.06 | 0.002 | 0.51 | 0.31-0.84 |
| Prognostic score | 0.60 | -1.29 | -1.34 | 0.176 | 1.84 | 0.92-3.69 |

Note: Parameters 0.1 < p < 0.25; rough estimate p < 0.1.
Patients with oligometastases have **indolent disease**: Metastatic Breast Cancer Patients

**Multivariate Analysis of Prognostic Factors in Metastatic Breast Cancer**

By N. Hortobagyi, T. J. Smith, S. S. Leather, J. D. Lembersky, D. J. Kaski, K. F. Yap, M. B. Buzdar, and G. A. Western

**Table 7. Regression Model Relating Survival to Prognostic Characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Regression Coefficient</th>
<th>Significant Level of Entry</th>
<th>Favorable</th>
<th>Unfavorable</th>
<th>Relative Risk</th>
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<tbody>
<tr>
<td>IDH</td>
<td>0.360</td>
<td>&lt;0.01</td>
<td>0.89</td>
<td>1.70</td>
<td>2.0</td>
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<tr>
<td>Performance status</td>
<td>0.291</td>
<td>&lt;0.01</td>
<td>0.87</td>
<td>1.41</td>
<td>1.7</td>
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<tr>
<td>ER status</td>
<td>0.470</td>
<td>&lt;0.01</td>
<td>0.88</td>
<td>1.42</td>
<td>1.6</td>
</tr>
<tr>
<td>Prior anthracycline chemotherapy</td>
<td>0.320</td>
<td>&lt;0.01</td>
<td>0.76</td>
<td>1.60</td>
<td>1.8</td>
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<tr>
<td>Alkaline phosphatase</td>
<td>0.198</td>
<td>&lt;0.01</td>
<td>0.80</td>
<td>1.43</td>
<td>1.7</td>
</tr>
<tr>
<td>Extent of disease</td>
<td>0.198</td>
<td>&lt;0.01</td>
<td>0.80</td>
<td>1.43</td>
<td>1.7</td>
</tr>
</tbody>
</table>

**NOTE.** Favorable risk was IDH < 0.25; performance status 0-1; long not treated; no prior anthracycline chemotherapy; < 80 performance status; < 24; prior anthracycline chemotherapy < 4; long interval treated; prior chemotherapy > 4; alkaline phosphatase < 250; and extent of disease > 20.

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A Biologic Basis exists:

**Metastatic disease evolves**

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**Intravasation, Survival, Extravasation**

1. Circulating tumor cell
2. Adhesion to blood vessel wall
3. Extravasation
4. Growth of secondary tumor

**Caveat:** known to be an inefficient process; not “everywhere, always”
Clonal heterogeneity of primary tumors and selection of secondary tumors -> types of metastases

Tumor heterogeneity leads to different clinical presentations

Darwinian Evolution: (Human) Metastasis-to-Metastasis

Intensified Treatments and integration with systemic therapy leads to improved outcomes
**SPINE SBRT: Dose Matters (Single Fraction)**

- **23-24Gy (Ablative)**
- **18-20Gy (Homeopathic)**

**SBRT: Dose Matters (Lung mets)**

**NRG-BR001: A Phase 1 Study of Stereotactic Body Radiotherapy (SBRT) for the Treatment of Multiple Metastases**

Steven J Chmura, MD, PhD; Kathryn A Winter, MS; Joseph K Salama, MD; Clifford Robinson, MD; Thomas M. Pisansky, MD; Virginia Borges, MD; Ram Parikh, PhD; Martha Makarjian, PhD; Swati S. Park, MD; Victor Gonzalez, MD; Yameen Hasan, MD; Jose Bazan, MD; Philip Wong, MD; Harold A Yoon, MD; Janet K. Horton, MD; Gregory N Gao, MD, PhD; Michael T Minas, MD, PhD; Erin Ruth Signorason, MD; Jennifer Maughan, MS; Julia White, MD

1 University of Chicago Comprehensive Cancer Center; 2 NRG Oncology Statistics and Data Management Center/ACR; 3 Duke University Medical Center; 4 Washington University in St. Louis; 5 Mayo Clinic; 6 University of Colorado – Anschutz Medical Campus; 7 University of Michigan; 8 University of Rochester Medical Center – University Campus; 9 Ohio State University Comprehensive Cancer Center; 10 Centre Hospitalier de l’Université de Montréal; 11 Heartland Cancer Research NCORP; 12 University of New Mexico Comprehensive Cancer Center; 13 University of Rochester; 14 Fox Chase Cancer Center

ASTRO Annual Meeting: 10/24/2018
Hypothesis: 3-4 or 2 anatomically close metastases can be safely treated with established SBRT doses.

Primary Objective: To determine the recommended SBRT dose for each of the metastatic locations.

Inclusion: Metastatic NSCLC, Breast, and Prostate patients.

Sample size: 42-84 patients.

NRG BR001: Treat Multiple Sites in the NCI BED > 100

<table>
<thead>
<tr>
<th>Metastatic Location</th>
<th>#Enrolled for DLT Assessment</th>
<th>#Evaluable for DLT Assessment</th>
<th>#DLTs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone/Osseous Starting Dose</td>
<td>8</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Spinal/Paraspinal Starting Dose</td>
<td>7</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Peripheral Lung Starting Dose</td>
<td>7</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Abdominal pelvic Starting Dose</td>
<td>9</td>
<td>7†</td>
<td>0</td>
</tr>
<tr>
<td>Central lung Starting Dose</td>
<td>8</td>
<td>7†</td>
<td>0</td>
</tr>
<tr>
<td>Liver Starting Dose</td>
<td>9</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Mediastinal/Cervical Starting Dose</td>
<td>7</td>
<td>6</td>
<td>0</td>
</tr>
</tbody>
</table>

The DLT analysis was based on the first 6 of these 7 patients.

Protocol Specified DLTs - None

...But Do These Treatments Help?
Metachronous 5yr OS: 47.8%
Overall 5yr OS: 29.4%

Synchronous N1,N2 5yr OS: 13.8%

Metastasis-directed treatment and Survival
Radiation for (limited) metastatic disease

- Clinical presentation of Oligometastases is common, Biologic evidence exists that drives the clinical phenotype

- **SBRT Dose Matters:** BED >100 for control of oligometastases

- Randomized data ➔ with ablative techniques improves PFS and OS

- Ongoing trials will answer whether local ablative therapy with surgery or (real) SBRT improves OS in specific disease types

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**Beyond Oligo**
The Good Fights infection  
Kills Cancer  
Causes Autoimmunity  
Asthma  
Heart Attacks  

- Turns off Fire after infection gone  
- Hijacked by Cancer

**Innate and Adaptive Immunity**

<table>
<thead>
<tr>
<th>Innate Immunity</th>
<th>Adaptive Immunity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Granulocytes (or polymorphonuclear leukocytes)</td>
<td>TYPE I INTERFERONS</td>
</tr>
<tr>
<td>neutrophil, eosinophil, basophil, monocyte</td>
<td>B cell, T cell</td>
</tr>
</tbody>
</table>

Not specific  
No memory  
Specific  
Immunologic memory

**Function of Adaptive Immunity**

**B cells**  
Function  
Recognize circulating antigens  
Make antibodies

**T cells**  
Function  
Recognize processed antigen  
Make cytokines  
CD4+ T cells: Make cytokines  
CD8+ T cells: Kill abnormal cells
Tumor Immunology: Overview

MHC, major histocompatibility complex; TCR, T-cell receptor.

Courtesy of Scott Gettinger, MD; Yale.

TYPE 1 INTERFERONS

The Immunoediting Hypothesis: Shaping Tumor Development


Elimination
Equilibrium
Escape

Genetic instability/tumor heterogeneity
Immune selection

CTL
NK
T reg
T cyto
NKT
T reg
T reg
CTL
NK

T-Cell Exhaustion During Chronic Antigen Exposure

Wherry, 2011.
Science names “Cancer Immunotherapy” the “Breakthrough of the Year” for 2013.

This year marks a turning point in cancer, as long-sought efforts to unleash the immune system against tumors are paying off—even if the future remains a question mark.

© 2013, The American Association for the Advancement of Science.

Couzin-Frankel J. Cancer Immunotherapy. Science 342(6165) 2013; reprinted with permission from AAAS.

CTLA-4, cytotoxic T-lymphocyte–associated antigen 4, HVEM, herpesvirus entry mediator; PD-1, programmed cell death protein 1; PD-L1, programmed cell death protein ligand 1.


Targeting The ICE: Immune Checkpoints in the Tumor Microenvironment

How Does Immunotherapy Work?

Tumor cells bind to T-cells to deactivate them

Immunotherapy drugs can block tumor cells from deactivating T-cells

PD-L1
Targeting PD-L1: Our best target so far

- Opdivo (pembrolizumab)
- Keytruda (nivo)
- Duravelamab

Immunotherapy (PD-L1) works

- Metastatic Melanoma
- Advanced NSCLC
- Advanced Urothelial Carcinoma
  - Balmus N Engl J Med 2017
- Advanced Renal Cell Carcinoma
  - Motzer N Engl J Med 2018

15%-20% responders

Immune System Background Summary

- Immune system balancing attack (Fire/Hot) with Suppression (Cold)
- Immune system has innate (nonspecific) and adaptive (specific) elements
- The persistence of cancer leads to immune dysfunction and Exhausting T-Cells that mount the response!
- Immune checkpoints and features of tumor microenvironment are targets for drug development
Does the Immune System Augment Stereotactic Body RadioTherapy (SBRT)?

Radiation-induced Equilibrium is a balance between tumor cell proliferation and T cell-mediated killing.

Radiation-induced dormancy can relapse years later.
Radiation-induced tumor equilibrium (RITE) is a balance between cell birth (Ki67 positive), and cell death (TUNEL positive), mediated principally by CD8+ T cells.

Depleting CD8 cells reduces SBRT Tumor Killing

SBRT Doses require CD8 activity!!!!!
Immune System augments SBRT

- Tumor cells and immune system evolve and escape
- CD8+ T cells contribute to SBRT tumor cell killing and can lead to lasting immunity

Opportunity: Immunotherapy to Improve Radiotherapy and local control

Can Radiotherapy Augment the immune response?

ABSCOPAL:
IN SITU VACCINATION HYPOTHESIS
Why is ABscopal so rare?

Given so many potential options, is there a way to rationally guide immunotherapy and radiation development?
Working model: immunobiology of T cell-inflamed and non-inflamed tumor microenvironment

- T cell-inflamed
  - CD8+ T cells, Type I IFN signature, high mutational burden, PD-1 positive, Chemotaxis
  - Most immunotherapy responders have this phenotype

- Non-T cell-inflamed
  - Low inflammatory signature, absent intratumoral CD8+ T cells
  - Immune escape, T cell exclusion

Most patients are this type

Radiation Converts tumors to Inflamed Phenotype: Therapeutic Potential?

- T cell-inflamed
  - Chemokines, CD8+ T cells, Type I IFN signature
  - Immune escape, inhibitory pathways

- Non-T cell-inflamed
  - Radiation
  - T cell infiltration

The Truth is Out There

If we can see it, we can Study it...
Abscopal Clinical Data and Design

Treat **one** site hope for Vaccine effect

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Abscopal: SBRT overcomes resistance to Immunotherapy

Melanoma *progressing* on IPI

Single Site Progress

SBRT

Systemic Clearing

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Randomized phase II study of anti-PD-1 alone vs. anti-PD-1+SBRT in patients with advanced NSCLC (n=64)

- Median PFS was 1.8 months in the PD-1 alone arm vs 6.4 months in the PD-1+SBRT arm

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**ASCO 2018 abstract**

Theelen WC, et al. (Netherlands)
Barriers to a Better Response? … Opportunities

Heterogenous Tumor-Immune Microenvironments among Differentially growing metastases

Large Tumor Burden -> Poor αPD1 response
Who responds **BEST** to immunotherapy?

Immunologically **“Hot”** or **“Inflamed”** tumors

- Patients with small volume disease
- Tumors that are PDL-1 positive
- Tumor with high mutational burden

Hypothesis: **Potentiation** of Immunotherapy and combination w/RT

- **Potentiation** of immunotherapy and combination with XRT **produce T-cell inflamed phenotype “HOT”**
- **Cytoreduction** → **relieve** immune suppression and overcome heterogeneity

MOSART Clinical Data and Design
Treat **MANY** sites hope for Vaccine effect

**iMOSART (SBRT+PEMBRO)**

<table>
<thead>
<tr>
<th>Anatomic Cohort</th>
<th>Lung - Peripheral</th>
<th>Lung - Central</th>
<th>Med/Thoracic</th>
<th>Liver</th>
<th>Spinal</th>
<th>Osseous</th>
<th>Abd/Pelvic</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sites with DLTs</td>
<td>1/12 (8.3%)</td>
<td>2/10 (20.0%)</td>
<td>1/10 (10.0%)</td>
<td>0/8</td>
<td>1/8</td>
<td>0/5</td>
<td>1/9</td>
<td>6/62 (9.7%)</td>
</tr>
</tbody>
</table>

- Median follow-up for toxicities: 5.5 months (IQR 3.3 - 8.1)
- 62 patients with at least 3 months of follow-up
- All 6 patients who experienced DLT had 2 lesions treated with RT
- 3/6 had both lesions in the same anatomic locations and 3/6 pts had lesions treated in separate anatomic locations
- No SBRT dose reductions

**Treatment Related Severe Dose-Limiting Toxicity (DLTs) by Anatomic Cohort**
Systemic Therapy Augments Radiotherapy?

IGRT not needed: Partial Tumor Radiation

- 17/68 patients (21 lesions) had at least one lesion larger than 65cc and least one imaging follow-up
- Median initial gross tumor volume (GTV)
  - Partially irradiated: 116.6cc (IQR 90.7-219.7cc)
  - Completely irradiated: 7.2cc (IQR 2.6-14.8cc)

Median coverage: 20% isodose line IQR 7%-51%
### Results

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Complete-Rx (118 Mets)</th>
<th>Partial-Rx (21 Mets)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treated Metastasis Location</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdomen/Pelvis</td>
<td>17 (14.4%)</td>
<td>9 (42.9%)</td>
</tr>
<tr>
<td>Liver</td>
<td>12 (10.2%)</td>
<td>8 (38.1%)</td>
</tr>
<tr>
<td>Lung-Central</td>
<td>21 (17.4%)</td>
<td>2 (9.5%)</td>
</tr>
<tr>
<td>Lung-Peripheral</td>
<td>10 (25.6%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Mediastinum/Cervical</td>
<td>14 (11.9%)</td>
<td>1 (4.8%)</td>
</tr>
<tr>
<td>Osseous</td>
<td>10 (10.2%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Spinal</td>
<td>12 (10.2%)</td>
<td>3 (14.8%)</td>
</tr>
<tr>
<td>Largest Treated Tumor Volume (cubic cm³), Mean (SD)</td>
<td>12.8 (14.8)</td>
<td>157.6 (95.7)</td>
</tr>
<tr>
<td>Dose to OARs (Minimum BED$_{3}$), Mean (SD)</td>
<td>222.8 (93)</td>
<td>42.4 (59.3)</td>
</tr>
<tr>
<td>Dose to Tumor (Minimum BED$_{10}$), Mean (SD)</td>
<td>55.0 (35.3)</td>
<td>23.8 (25.8)</td>
</tr>
</tbody>
</table>

### Results: Treated Metastasis Control (TMC)

- 1-yr TMC – 89.5%

- No difference between Complete-Rx vs Partial-Rx Despite:
  - V95% of 67.2% (Partial-Rx) vs 100% (Complete-Rx)
  - Minimum BED$_{10}$ of 23.8 Gy (Partial-Rx) vs 95.0 Gy (Complete-Rx)
Systemic Therapy Augmented by Radiotherapy?

ABscopal (non-irradiated) RECIST response

Clinical Benefit

ABscopal (distant) Response

ORR = 13.5%

No difference for Partial vs Complete Tumors

SBRT Response

OS = 18mo

SBRT Fail

OS = 3.5mo

Mixed

OS = 9mo
post-SBRT biopsies: Unsupervised 2-way hierarchical clustering ->
Innate + Adaptive Immunity, ACROSS histologies

• Type-1 Interferon
• Immune function
• DNA repair

Radio-immunotherapy Platform to test for specific Hypotheses

The RIT™ Pipeline
Conclusions

- SBRT may improve survival in Oligometastases with High Doses (BED >100)
- Best responders to immunotherapy (minority) have low disease low tumor burden, Type 1 INF PDL-1 positive (checkpoints), and high Tumor Mutational Burden
- SBRT modulates immune pathways through Type-1 Interferon, Innate and Adaptive immune function, and DNA repair
- SBRT may turn patients from "cold" to "hot" and respond to immunotherapy -> Immunotherapy may improve local control assuming some portion receives high BED (NRG BR003/BRO02/Lu002)
Acknowledgments

Dr. Weichselbaum
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University of Chicago Radiation Oncology Residents

END TRANSMISION