Moving Radiation Out of Obsolescence in Melanoma: Is There a Role for Radiation Beyond Palliation in Systemic Disease?

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Location: FHCRC Pelton Auditorium
"Half of what we are going to teach you in medical school is wrong, and half of it is right"

"Our problem is that we don't know which half is which"
‘Truisms’ about melanoma

- “No more hopeless diagnosis than melanoma that has spread to the brain”
  - “No one survives past the six month mark- if they do- you have the wrong diagnosis”
  - Sir Murray F. Brennan, Chair of Surgery MSKCC at a palliative care lecture c. 2004

- “If a patient refuses surgery for melanoma, as a radiation oncologist, it is your duty to carry that patient to the surgical suite. Any other answer will get you a return trip to the boards”
  - Melanoma expert, Radiation oncology board examiner c 2005

- “No role for radiation in melanoma. It’s a radioresistant tumor. Come back with a better idea”
  - L. Schuchter to B. Vonderheide and R. Rengan in response to research proposal to use radiation in combination with immunotherapy in metastatic melanoma. Feb 2010

Table 1: Clinical and pathologic characteristics at initiation of BRAF inhibition

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Sex</th>
<th>TNM stage</th>
<th>Prior systemic therapy</th>
<th>Reason surgically incurable</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>19</td>
<td>Female</td>
<td>T3bN2bM0</td>
<td>None</td>
<td>Rapid recurrence&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>2</td>
<td>58</td>
<td>Female</td>
<td>T3N2bM0</td>
<td>None</td>
<td>Rapid recurrence&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td>51</td>
<td>Male</td>
<td>T2bN3M0</td>
<td>None</td>
<td>In-transit + nodal mets</td>
</tr>
<tr>
<td>4</td>
<td>56</td>
<td>Male</td>
<td>T4aN2cM0</td>
<td>Temodar</td>
<td>In-transit mets</td>
</tr>
<tr>
<td>5</td>
<td>58</td>
<td>Female</td>
<td>T2aN2cM0</td>
<td>None</td>
<td>In-transit mets</td>
</tr>
<tr>
<td>6</td>
<td>70</td>
<td>Male</td>
<td>T4bN0M1</td>
<td>GM-CSF</td>
<td>Mediastinal mets</td>
</tr>
</tbody>
</table>

Table 2: Characteristics of tumors treated with BRAF therapy

<table>
<thead>
<tr>
<th>Patient</th>
<th>BRAF therapy (months)</th>
<th>RT total dose (fractions) (Gy)</th>
<th>Area treated</th>
<th>Overall response after RT</th>
<th>LRC (monthly&lt;sup&gt;+&lt;/sup&gt;)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3.5</td>
<td>60 (30)</td>
<td>Right neck and supraclavicular</td>
<td>CR</td>
<td>28+</td>
</tr>
<tr>
<td>2</td>
<td>0.3</td>
<td>66.6 (37)</td>
<td>Left axilla</td>
<td>CR</td>
<td>30+</td>
</tr>
<tr>
<td>3</td>
<td>6.6</td>
<td>60 (30)</td>
<td>Left axilla</td>
<td>CR</td>
<td>27+</td>
</tr>
<tr>
<td>4</td>
<td>5.9</td>
<td>62 (31)</td>
<td>Left shin</td>
<td>CR</td>
<td>28+</td>
</tr>
<tr>
<td>5</td>
<td>3.7</td>
<td>38 (6)</td>
<td>Left shin</td>
<td>CR</td>
<td>34+</td>
</tr>
<tr>
<td>6</td>
<td>5.8</td>
<td>60 (30)</td>
<td>Mediastinum</td>
<td>CR</td>
<td>29+</td>
</tr>
</tbody>
</table>

Seeley et al Melanoma Res. 2015
“No role for radiotherapy beyond palliation in management of melanoma”
The challenge/myth of radioresistance
Dose Fractionation: Implications for Tumor Control

![Graph showing survival vs. dose for single and multiple 2 Gy fractions.](image)

- **Single Fraction**: A single dose of 8 Gy shows a significant decrease in survival, indicating high sensitivity.
- **Multiple 2 Gy Fractions**: Over multiple fractions, the survival rate is improved compared to a single dose, suggesting a therapeutic benefit.

**Therapeutic Ratio** for Fractionation and Large Fractions are marked on the graph.
Melanoma is a relatively radioresistant tumor
### Radiation Dose for Melanoma: History

<table>
<thead>
<tr>
<th>Dose/ Frac (cGy)</th>
<th>N</th>
<th>Response (%)</th>
<th>Dose/ Frac (cGy)</th>
<th>N</th>
<th>Response (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>200-300</td>
<td>5</td>
<td>1 (20)</td>
<td>200-300</td>
<td>14</td>
<td>3 (21)</td>
</tr>
<tr>
<td>301-400</td>
<td>7</td>
<td>2 (29)</td>
<td>301-400</td>
<td>15</td>
<td>9 (60)</td>
</tr>
<tr>
<td>401-500</td>
<td>2</td>
<td>0</td>
<td>401-500</td>
<td>14</td>
<td>8 (57)</td>
</tr>
<tr>
<td>501-600</td>
<td>17</td>
<td>15 (88)</td>
<td>501-600</td>
<td>13</td>
<td>9 (69)</td>
</tr>
<tr>
<td>601-700</td>
<td>5</td>
<td>5 (100)</td>
<td>601-700</td>
<td>4</td>
<td>4 (100)</td>
</tr>
<tr>
<td>&gt;700</td>
<td>15</td>
<td>15 (100)</td>
<td>&gt;700</td>
<td>7</td>
<td>6 (86)</td>
</tr>
</tbody>
</table>

**Habermalz & Fischer**

- **Fraction Size (cGy)**
  - 195 - 550
  - 28/ 56 (50%)
  - p=0.003
- **600 - 1500**
  - 32/ 40 (80%)

**Konefal et al.**

- Borrowed from Dr. Zagars
## RTOG 83-05 Results

### Skin Toxicity

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>8Gy x 4</td>
<td>3/62</td>
<td>3/62</td>
</tr>
<tr>
<td>2.5 Gy x 20</td>
<td>3/64</td>
<td>0/64</td>
</tr>
</tbody>
</table>

*Length of follow-up not reported

### Table 4. Best response by tumor size and treatment arm

<table>
<thead>
<tr>
<th>Best response</th>
<th>&lt;5 cm 4 × 8.0 Gy</th>
<th>&lt;5 cm 20 × 2.5 Gy</th>
<th>≥5 cm 4 × 8.0 Gy</th>
<th>≥5 cm 20 × 2.5 Gy</th>
<th>All sizes 4 × 8.0 Gy</th>
<th>All sizes 20 × 2.5 Gy</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete</td>
<td>33.3%</td>
<td>28.6%</td>
<td>17.1%</td>
<td>19.4%</td>
<td>24.2%</td>
<td>23.4%</td>
<td>23.8%</td>
</tr>
<tr>
<td>Partial</td>
<td>18.0%</td>
<td>28.6%</td>
<td>48.6%</td>
<td>38.9%</td>
<td>35.5%</td>
<td>34.4%</td>
<td>34.9%</td>
</tr>
<tr>
<td>No change</td>
<td>33.3%</td>
<td>39.3%</td>
<td>34.3%</td>
<td>38.9%</td>
<td>33.9%</td>
<td>39.1%</td>
<td>36.5%</td>
</tr>
<tr>
<td>Progression</td>
<td>14.8%</td>
<td>3.6%</td>
<td>2.8%</td>
<td>6.5%</td>
<td>3.1%</td>
<td>4.8%</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>27</td>
<td>28</td>
<td>35</td>
<td>36</td>
<td>62</td>
<td>64</td>
<td>126</td>
</tr>
<tr>
<td>CR + PR rate</td>
<td><strong>0.52</strong></td>
<td><strong>0.57</strong></td>
<td><strong>0.66</strong></td>
<td><strong>0.58</strong></td>
<td><strong>0.60</strong></td>
<td><strong>0.58</strong></td>
<td></td>
</tr>
</tbody>
</table>
How do we deliver high-dose ‘ablative’ radiation safely?
Stereotactic Body Radiation Therapy

- Control rate with SBRT 95-98%
- These control rates are similar to that observed with surgery
- Why is this treatment so effective?
What is the relevance of SBRT for the management of melanoma?
Gamma Knife: “SBRT” for the brain in Melanoma

- 46 yom with BRAF+ melanoma with new brain metastasis after ipi/nivo
- Gamma knife radiosurgery (20Gy) delivered to metastasis
- Post-treatment MRI at 9 months demonstrates CR
- Expected tumor control in melanoma with GK ~85%
What is the relevance of SBRT for the management of melanoma in the era of immunotherapy?
Clinical design

676 HLA-A2+ pts with met melanoma
Progression despite one prior Rx
Ipi vs. gp100 vaccine vs. both q3wk x 4

Results

Ipi arms extended median survival by 4mo
Improved 1 yr survival by 72%
(from 25% to 43%)
ORR 11% ipi vs. 1.5% with vaccine alone

Hodi et al NEJM 2010
Introduction: Therapeutic Index

Tumor control

Toxicity

The promise of cancer immunotherapy

Normal tissue exposure

Treatment Intensification
Phase III Trial of CTLA-4 Blockade with Ipilimumab

- Overall response rate of 11% for patients receiving ipilimumab
- Why did 80+% of patients fail to respond?

Hodi et al NEJM 2010
Clinical approach to immunomodulation: Cutting off the brakes

CTLA-4 Feedback Pathway

Proliferation

Inhibition
Clinical approach to immunomodulation: Cutting off the brakes

Proliferation

No inhibition
Gamma Knife: “SBRT” for the brain in Melanoma

- Gamma knife radiosurgery (20Gy) delivered to metastasis
- Peri-tumoral inflammation observed on interim scan
- What underlying process does the peri-tumoral inflammation represent?
- Is it helpful to the patient?
Metastatic lung adenocarcinoma

The ‘abscopal’ effect

Siva et al Cancer Letters 2013
Immune Cooperation with RT: Is there relevance for the primary tumor response to radiation?

Lee et al Blood 2009
Using High-Dose RT to prime T-cells against cancer

Tumor antigen presentation has not occurred

Checkpoint inhibition is ineffective

Tumor antigen is released and presentation occurs

Checkpoint inhibition is effective
Use of radiation as a tool to optimize immunogenicity of the tumor
Abscopal effect in melanoma patient after treatment with CP-870,893 and tremelimumab

Treme: 1-13-11
CD40: 1-14-11
Left c.w. XRT to tumor (outlined in red): 1-31-11 to 2-14-11
300cGy x 10
Stratified phase I/II dose escalation trial of stereotactic body radiotherapy followed by ipilimumab in metastatic melanoma

**Hypofractionated RT to single 'index' lesion**
(over 3-7 days)

- **Stratum 1: lung or bone**
  - 8 Gy x 3
  - (DL-1 of 8Gy x 2)

- **Stratum 2: liver or s.c.**
  - 6 Gy x 3
  - (DL-1 of 6Gy x 2)

**ipilimumab**
i.v. q3weeks x 4
1st ipi 5 days after RT

Follow up
Restaging

Biosamples and analysis

Clinicaltrials.gov NCT01970527
PI, Rengar/Maity/Hahn

- Stage IV melanoma (any number of priors)
- Index lesion ≥1 cm
- ECOG PS 1-0
Tumor response to SBRT/ipilimumab

Baseline

4d s/p SBRT

2mo s/p ipi #4

SBRT to index lesion

RECIST: -68% (exclude index)

Twyman-Saint Victor Nature 2015 Apr 16;520(7547):373-7
Clinical Results

- 18% of patients had a partial response as best response.
- Some major regressions were seen (PT-402).
- None of the irradiated tumors had progressive metabolic disease as evaluated by PET.
- Companion mouse studies demonstrated increased efficacy with combination checkpoint inhibition.

Twyman-St. Victor Nature 2015
How do we know if SBRT generated an immune response against the tumor?
Dissecting the cellular basis of response to immune checkpoint blockade

Timeline

- July 2013
  - Radiation to skin metastasis
- July 2013
  - TRB sequencing skin metastasis

UMEXR1 – 68 year-old female, smoker, diagnosed with metastatic lung adenocarcinoma with bone, brain, and skin metastases
TCR deep sequencing to explore abscopal effect

Hodge et al Oncology 2008
The most abundant peripheral blood clone detected (CDR3β sequence CASSLERGLAVSGANVLTF) dramatically increased in frequency following anti-PDL1 therapy and was present within the CD8+ sorted T cell population. The frequency of this clone among productive TCRβ sequences was 0.3% in the pre-treatment skin biopsy, 6.6% in the 1-month blood sample, 9.9% in the 5-month blood sample, and 12.5% in the 9-month blood sample.
IMMUNORAD: Stratified Phase II Trial of Image Guided Hypofractionated Radiotherapy with Concurrent Nelfinavir and Nivolumab in Advanced Melanoma, Lung Cancer, and Renal Cell Carcinoma

Nivolumab 240 mg every 2 weeks Day 7-14 until progression

Enrollment
Baseline studies and staging

Daily Nelfinavir (1250mg PO BID): Day 0 to 4th Cycle of Nivolumab

Hypofractionated RT to single ‘Index’ lesion between 2nd and 3rd dose of Nivolumab (8 Gy per fraction* With 3 fractions over 3-14 days)

Biosamples and analysis

irRECIST 1.1 Response q12 weeks until PD

Stratum 1: Stage IV NSCLC; immune checkpoint naïve
Stratum 2: Stage IV NSCLC; prior immune checkpoint therapy
Stratum 3: Stage IV Melanoma; immune checkpoint naïve
Stratum 4: Stage IV Melanoma; prior immune checkpoint therapy
Stratum 5: Stage IV RCC; immune checkpoint naïve
Stratum 6: Stage IV RCC; prior immune checkpoint therapy

* 6Gy per fraction dose reduction allowable at MD discretion
Conclusions

- Radiation may have a greater role in melanoma management in the era of immunotherapy
  - Much work to be done

- Multiple ongoing trials aimed at optimizing hypofractionated radiation with immune checkpoint inhibition are underway
  - Treatment resistance is still common
  - Important to develop predictors of response

- Need to move melanoma immunotherapy beyond checkpoint inhibition and radiation to address other required components for durable anti-tumor immunity
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