Demonstration of differential clinical radiosensitivity based upon mutation profile in metastatic melanoma

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Disclosures

- The authors have no potentially relevant conflicts of interest to disclose
Introduction

- Metastatic melanoma associated with a high risk of brain metastases
  - 3rd most common source\textsuperscript{1,2}
  - 6th most common cancer in United States and incidence is rising\textsuperscript{3-6}

- Radiotherapy is standard in brain metastasis treatment
  - WBRT
  - SRS

- Considered radioresistant, although data is heterogeneous\textsuperscript{7-15}
  - Underlying cause of variability unknown\textsuperscript{16}

- Defining markers of altered radiosensitivity key to optimal outcomes
  - Improved control $\rightarrow$ Longer survival with retained QOL
Introduction

- Key oncogenic mutations in melanoma\textsuperscript{17,18}
  - \textit{B-RAF}
  - \textit{N-RAS}
  - \textit{c-KIT}

- Associated with progression and metastasis\textsuperscript{19-21}

- Important therapeutic targets\textsuperscript{22-25}
  - Vemurafenib, Dabrafenib
  - MEK inhibitors
  - Imatinib

- Impact on response to radiation unknown
Objectives

• Determine impact of $B$-$RAF$, $N$-$RAS$, and $c$-$KIT$ mutation on clinical radiosensitivity

• Compare rates of distant brain failure after SRS based upon mutation profile
Methods

• Metastatic melanoma patients with brain metastases identified within institutional SRS database

• Treatment
  – Leksell Gamma Knife Model 4C, Perfexion
  – 22Gy (<1cm), 20Gy (1-2cm), 18Gy (2-3cm), 16Gy (3-4cm) to 50-60% IDL

• Clinical radiosensitivity model\textsuperscript{26}
  – Standardized follow-up MRI schedule
  – MRIs reviewed for local recurrence
    • Persistent >20% increase in lesion diameter on >2 scans \textit{or} consensus
    • Pathology, brain PET, MRS sufficient but not necessary
  – Modified cox regression to compare local recurrence at lesion level
  – Advantage of model
    • Avoid selection bias of cell lines and retain tumor-microenvironment interaction
    • Increase statistical power by studying response at lesion level
Results – Cohort Characteristics

- 102 patients, 190 SRS treatments, 1028 brain metastases
  - 45 B-RAF mutated patients, 505 metastases
  - 9 N-RAS mutated patients, 68 metastases
  - 4 c-KIT mutated patients, 78 metastases
  - 44 Wild Type patients, 377 metastases

- Median radiographic follow-up of 6 months (range 0-80 months)
- Median age 62 years

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Overall 102 Patients 1028 Metastases</th>
<th>Wild Type 44 Patients 377 Metastases</th>
<th>B-RAF Mutant 45 Patients 505 Metastases</th>
<th>N-RAS Mutant 9 Patients 68 Metastases</th>
<th>c-KIT Mutant 4 Patients 78 Metastases</th>
<th>p - Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Lesions</td>
<td>3 (1 – 37)</td>
<td>3 (1 – 37)</td>
<td>4 (1 – 32)</td>
<td>1 (1 – 14)</td>
<td>7 (3 – 21)</td>
<td>0.04</td>
</tr>
<tr>
<td>Lesion Volume (cm³)</td>
<td>0.20 (0.01 – 36.5)</td>
<td>0.20 (0.02 – 18.6)</td>
<td>0.19 (0.01 – 30.3)</td>
<td>0.39 (0.03 – 36.5)</td>
<td>0.13 (0.021 – 9.7)</td>
<td>0.68</td>
</tr>
<tr>
<td>Dose (Gy)</td>
<td>20 (8 – 25)</td>
<td>20 (8 – 24)</td>
<td>20 (9 – 25)</td>
<td>20 (18 – 22)</td>
<td>18 (16 – 24)</td>
<td>0.03</td>
</tr>
</tbody>
</table>
Results – Overall Recurrence Patterns

- **Local recurrence**
  - 25.5% of patients (26/102)
  - 5.4% of lesions (56/1028)

<table>
<thead>
<tr>
<th>Patient-level Analysis</th>
<th>Wild Type</th>
<th>B-RAF Mutant</th>
<th>N-RAS Mutant</th>
<th>c-KIT Mutant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local</td>
<td>13 / 44 (29.5%)</td>
<td>8 / 45 (17.8%)</td>
<td>2 / 9 (22.2%)</td>
<td>3 / 4 (75%)</td>
</tr>
<tr>
<td>Lesion-level Analysis</td>
<td>22 / 377 (5.8%)</td>
<td>25 / 505 (5.0%)</td>
<td>3 / 68 (4.4%)</td>
<td>6 / 78 (7.7%)</td>
</tr>
</tbody>
</table>

- **Distant brain recurrence**
  - 59.8% of patients (61/102)
  - Recurrence occurred after 60.5% of SRS treatments (115/190)

<table>
<thead>
<tr>
<th>Patient-level Analysis</th>
<th>Wild Type</th>
<th>B-RAF Mutant</th>
<th>N-RAS Mutant</th>
<th>c-KIT Mutant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distant brain</td>
<td>26 / 44 (59.1%)</td>
<td>26 / 45 (57.8%)</td>
<td>6 / 9 (66.7%)</td>
<td>3 / 4 (75%)</td>
</tr>
<tr>
<td>SRS Treatment-level</td>
<td>49 / 79 (62.0%)</td>
<td>45 / 78 (57.7%)</td>
<td>14 / 23 (60.9%)</td>
<td>7 / 10 (70%)</td>
</tr>
</tbody>
</table>
Results – Local Recurrence by Mutation Type

- **B-RAF Mutated**
  - HR 0.89 (95% CI 0.50-1.58), p=0.681
Results – Local Recurrence by Mutation Type

- **N-RAS Mutated**
  - HR 0.17 (95% CI 0.04-0.74), p=0.018
Results – Local Recurrence by Mutation Type

- **c-KIT Mutated**
  - HR 1.75 (95% CI 0.79-3.92), p=0.170
Results – Local Recurrence by Mutation Type

- Four-group comparison
  - LC at 1 year 97% (N-RAS), 89% (B-RAF), 84% (wild type), and 80% (c-KIT)
  - $p=0.046$
### Results – Multivariable Model of Local Recurrence

<table>
<thead>
<tr>
<th>Mutation Profile</th>
<th>HR</th>
<th>95% CI</th>
<th>p – value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wild type</td>
<td>–</td>
<td>–</td>
<td>0.041</td>
</tr>
<tr>
<td>( B-RAF ) Mutated</td>
<td>0.55</td>
<td>0.28 – 1.08</td>
<td></td>
</tr>
<tr>
<td>( N-RAS ) Mutated</td>
<td>0.13</td>
<td>0.03 – 0.64</td>
<td></td>
</tr>
<tr>
<td>( c-KIT ) Mutated</td>
<td>0.92</td>
<td>0.34 – 2.49</td>
<td></td>
</tr>
<tr>
<td>Number of Lesions Treated</td>
<td>1.11</td>
<td>1.06 – 1.15</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age (&gt;55 years)</td>
<td>1.95</td>
<td>0.84 – 4.52</td>
<td>0.119</td>
</tr>
<tr>
<td>Metastasis volume</td>
<td>1.17</td>
<td>1.07 – 1.28</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Margin dose</td>
<td>1.12</td>
<td>0.90 – 1.39</td>
<td>0.299</td>
</tr>
</tbody>
</table>
Results – Distant Brain Recurrence

- Distant control at 1 year 47% (N-RAS), 28% (B-RAF), 24% (wild type), and 17% (c-KIT)
  - $p=0.177$
Results – Multivariable Model of Distant Brain Failure

<table>
<thead>
<tr>
<th></th>
<th>HR</th>
<th>95% CI</th>
<th>p – value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mutation Profile</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wild type</td>
<td>–</td>
<td>–</td>
<td>0.227</td>
</tr>
<tr>
<td>B-RAF Mutated</td>
<td>0.88</td>
<td>0.57 – 1.34</td>
<td></td>
</tr>
<tr>
<td>N-RAS Mutated</td>
<td>0.53</td>
<td>0.29 – 0.97</td>
<td></td>
</tr>
<tr>
<td>c-KIT Mutated</td>
<td>1.02</td>
<td>0.45 – 2.33</td>
<td></td>
</tr>
<tr>
<td><strong>Number of Lesions Treated</strong></td>
<td>1.03</td>
<td>1.00 – 1.06</td>
<td>0.075</td>
</tr>
<tr>
<td>Age (&gt;55 years)</td>
<td>1.38</td>
<td>0.88 – 2.17</td>
<td>0.162</td>
</tr>
</tbody>
</table>
Conclusions

- **N-RAS** mutated melanoma less likely to recur locally after SRS
  - May indicate enhanced radiosensitivity vs. WT, **B-RAF**, or **c-KIT**
  - Requires validation

- If validated, may allow:
  - More accurate prognostication
  - SRS dose reduction in **N-RAS** mutated patients
    - Wider therapeutic window
  - Treatment intensification for other groups
Acknowledgements

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  – Kimberly Johung
  – James Yu
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  – Lucia Jilaveanu
  – Harriet Kluger

• Yale Departments of Therapeutic Radiology & Neurosurgery

Questions?

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References

References


Supplementary Slides
Recurrence Definition

• 11 post-SRS craniotomies for enlarging enhancing lesion in 9 patients
  – 6 viable tumors
  – 5 radionecroses

• Recurrence supported by Brain PET used in 6 cases, MRS in 2 cases
Possible Mechanisms

- Altered balance of MAPK activity
  - \textit{RAS} upstream from \textit{RAF}, affects more targets
  - Perhaps balance of activity favors radiosensitivity

- \textit{PTEN} mutation in 10-30% of melanoma
  - Loss leads to enhanced radiosensitivity (as in glioma)
  - Mutually exclusive with \textit{RAS} mutation (hence preserved sensitivity)
  - Commonly occurs along w/ \textit{RAF} mutation (hence radioresistant)