Stereotactic Radiation Therapy for Metastatic Melanoma

John Armstrong
Some factors of importance in the radiation treatment of malignant melanoma

J. Overgaard¹, M. Overgaard², P. Vejby Hansen³ and H. von der Maase⁴

Response as a function of dose per fraction.

<table>
<thead>
<tr>
<th>Dose fraction (Gy)</th>
<th>No. of tumours</th>
<th>Response</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>None</td>
<td>Partial</td>
<td>Complete</td>
</tr>
<tr>
<td>&lt; 3.0</td>
<td>41</td>
<td>28(68%)</td>
<td>7(17%)</td>
<td>6(15%)</td>
</tr>
<tr>
<td>3.0–3.9</td>
<td>18</td>
<td>6(33%)</td>
<td>4(22%)</td>
<td>8(44%)</td>
</tr>
<tr>
<td>4.0–4.9</td>
<td>12</td>
<td>3(25%)</td>
<td>3(25%)</td>
<td>6(50%)</td>
</tr>
<tr>
<td>5.0–7.9</td>
<td>82</td>
<td>13(16%)</td>
<td>23(34%)</td>
<td>46(56%)</td>
</tr>
<tr>
<td>≥ 8.0</td>
<td>51</td>
<td>5(10%)</td>
<td>15(29%)</td>
<td>31(61%)</td>
</tr>
</tbody>
</table>

* Significant less response at doses per fraction < 4 Gy (p < 0.001).

97 tumours with complete response after radiation treatment.
RTOG randomised trial of fractionation

<table>
<thead>
<tr>
<th></th>
<th>All sizes</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=62</td>
<td>N=64</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 × 8.0 Gy</td>
<td>24.2%</td>
<td>23.4%</td>
<td>23.8%</td>
<td></td>
</tr>
<tr>
<td>20 × 2.5 Gy</td>
<td>35.5%</td>
<td>34.4%</td>
<td>34.9%</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>33.9%</td>
<td>39.1%</td>
<td>36.5%</td>
<td></td>
</tr>
<tr>
<td>POD</td>
<td>6.5%</td>
<td>3.1%</td>
<td>4.8%</td>
<td></td>
</tr>
</tbody>
</table>

Approximately 60% response rate

Melanoma Brain Metastases

• Sources of brain metastases: lung, breast, CUP, melanoma
• 30% at presentation of metastatic disease and may rise to 60% over the next two years in survivors
• 75% at autopsy
• SWOG S0008 adjuvant Stage IIIb and IIIc 16% isolated CNS failure rate @2y
• Symptomatic presentation large or numerous: palliative. Argument for MRI surveillance
Resection of melanoma brain mets
MSKCC

• Median time from diagnosis to brain lesion was 14.1 months.

• Overall median survival was 6.7 months. 1 year survival 36%

• 15 patients with multiple 5.4 months median survival

• 76 patients with single 7.8 months, p = 0.12

• Brain metastasis recurrences in WBRT-treated and untreated patients was similar (56% and 45.7%). Selection bias
60 patients 118 melanoma metastases,
Mean volume of 2.95 ml (0.1–25.5 ml) mean dose 16.4 Gy (10 to 20 Gy).
Median survival was 7 months
Solitary met and no extracranial 15 months median survival (twice the MSKCC surgery series)
Local control was 90% (disappearance = 11%, shrinkage = 44%, and stable = 35%).
New brain metastases in 23% if WBRT vs. 44% without
3 delayed intratumoral hemorrhage at the radiosurgery site, 2 of whom had new symptoms.
Prognostic factors after radiosurgery

Survival

Multivariate analysis of overall survival

<table>
<thead>
<tr>
<th>Variable</th>
<th>Test for favorable status</th>
<th>Relative risk</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total tumor volume</td>
<td>≤3 mL vs &gt;3 mL</td>
<td>1.89</td>
<td>0.0030</td>
</tr>
<tr>
<td>Systemic disease</td>
<td>Active vs. inactive</td>
<td>1.98</td>
<td>0.0065</td>
</tr>
<tr>
<td>Location</td>
<td>Posterior fossa vs. supratentorial</td>
<td>0.60</td>
<td>0.056</td>
</tr>
<tr>
<td>KPS</td>
<td>≤80 vs. &gt;80</td>
<td>0.68</td>
<td>0.086</td>
</tr>
<tr>
<td>Gender</td>
<td>Female vs male</td>
<td>1.44</td>
<td>0.153</td>
</tr>
<tr>
<td>Number of lesions</td>
<td>1 vs. &gt;1</td>
<td>1.15</td>
<td>0.510</td>
</tr>
<tr>
<td>WBI</td>
<td>no vs. yes</td>
<td>1.10</td>
<td>0.661</td>
</tr>
<tr>
<td>Age</td>
<td>≤70 vs. &gt;70</td>
<td>0.96</td>
<td>0.893</td>
</tr>
</tbody>
</table>

250 individual lesions
Median 20 Gy (14-24)
84% local control at 1 year

Yu et al. John Wayne IJROBP
Volume 52, Issue 5, Pages 1277-1287 (April 2002)
Ipilimumab with Stereotactic Radiosurgery  
Kiess et al. MSKCC ASTRO 2012

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th># Mets</th>
<th>Increase size &gt;140%</th>
<th>Local Failure</th>
<th>Neurologic death @1 year</th>
<th>1 year Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>During</td>
<td>14</td>
<td>25</td>
<td>40%</td>
<td>0%</td>
<td>0%</td>
<td>68%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>p=.028</td>
<td>p=0.001</td>
</tr>
<tr>
<td>Before</td>
<td>19</td>
<td>44</td>
<td>40%</td>
<td>14%</td>
<td>15%</td>
<td>60%</td>
</tr>
<tr>
<td>After</td>
<td>12</td>
<td>40</td>
<td>10%</td>
<td>14%</td>
<td>29%</td>
<td>30%</td>
</tr>
</tbody>
</table>

Before 19 vs After 12:
- Increase size >140%: 44% vs 10%
- Local Failure: 14% vs 14%
- Neurologic death @1 year: 15% vs 29%
- 1 year Survival: 60% vs 30%

**p**-values for comparisons:
- Increase size >140%: 0.14
- Local Failure: 0.028
- Neurologic death @1 year: 0.001

**Survival Rates**
- Before: 60%
- During: 68%
- After: 30%
• 63 patients median dose of 20 Gy (Range 15-20 Gy).
• CTLA-4 inhibitors were given to 27 patients.
• The median LC, diffuse PFS and OS for the entire group were 8.7, 4.3 and 5.7 months
• No difference +/- Ipilimumab
• Intracranial hemorrhage unaltered (+7, -10)
Abscopal effect

- Ipilimumab no effect
- Local RT
- Progression axilla
- RT hypofractionated
- CR in field
- Then CR out of field
Abscopal effect

- Ipilimumab no effect
- Local RT
- Progression axilla
- RT hypofractionated
- CR in field
- Then CR out of field

Intact cancer cell
“Ags cloaked”
RT fragments and
Exposes antigens
Stereotactic body radiotherapy

Exhalation

1st couch position

2nd couch position

3rd couch position
Surgery for liver metastases
John Wayne Cancer Institute and the Sydney Melanoma Unit

- 1750 patients with hepatic metastases
- 34 (2%) exploration to resect the metastases
- 24 (71%) underwent resection and 10 (29%) underwent exploration only
- Eighteen patients (75%) underwent complete surgical resection, while the remaining 6 underwent palliative or debulking procedures with incomplete resection.
- The median number of resected lesions was 1, and median lesion size was 5 cm (range, 0.7-22 cm).
- The median disease-free interval between initial diagnosis and hepatic metastases was 58 months.
- Median DFS and OS in the 24 patients resected were 12 months and 28 months.
- Five-year DFS and OS in this group were 12% and 29%.
- Median OS 4 months for patients who underwent exploration only.

1.3% of all patients with liver mets had resection
1% radical resection

Surgical for melanoma lung metastasis
Melanoma Institute Sydney

- November 1984 and April 2010 (26 years)
- 292 patients
- Four patients (1%) died within 30 days of surgery
- The median progression-free survival time was 10 months.
- The median overall survival 23 months and 5-year survival 34%,
- Metastasis size >2 cm [hazard ratio HR 1.4, PFS
- Positive surgical margin HR 1.5 PFS
- More than one metastasis HR 1.4, PFS

Melanoma lung metastases

- Failed Braf inhibitor and Ipilimumab
- Brain metastasis SRS - CR
- Progressed in lung 4 metastases
- Deep inspiration breath - hold
- 60Gy/3 to all four
- 3 month CT scan
Stereotactic body radiotherapy
Stinauer University of Colorado

- Metastatic melanoma (n = 17 patients, 28 lesions) or RCC (n = 13 patients, 25 lesions)
- 40-50 Gy/5 fractions (n = 23) or 42-60 Gy/3 fractions (n = 30)
- Lung (n = 39), liver (n = 11) and bone (n = 3)
- LC for all patients was 88% at 18 months

Radiation Oncology 2011, 6:34
Thirty-seven patients with 52 lesions: lung (N = 19), bone (N = 12), liver (N = 11), abdominal lymph node (N = 6), lower extremity (N = 1), adrenal gland (N = 1), and parotid gland (N = 1).

Median soft tissue dose 54 Gy in 3 fractions (28 to 60 Gy).

For bone median 21 Gy/1, range 18 to 50 Gy

Median follow-up 9 months.

PET: 27% CR, 31% PR, 29% SD

3 patients progression within the SBRT field (6%),

Survival 63% @12- months

Two patients (5%) Grade 3 toxicities: uropathy, gastric ulcer.

No Grade 4 or 5.

B.M. Barney ASTRO 2011
SABR for Melanoma
Kang et al Harvard ASTRO 2012

- 20 pts. 34 tumours
- Chest 16, spine 9, pelvis/abd 6, H+N 2, liver 1
- Most commonly 8Gy x3
- Median 20 month FU, 8 alive, 12 dead
- Median survival 22 months, local control 80%
- All local failures in lung
Spine SBRT MSKCC
Thiagaragan ASCO 2010

- RCC (n = 50) or melanoma (n = 30)
- 18-24 Gy in a single fraction (median 24 Gy)
- Serial MRI or CT spine imaging, VAS pain scale, narcotic use, and American Spine Injury Association scores
- Local Control 18-22Gy cohort 77% vs. 96% if 24Gy
- All melanomas <24 Gy failed
- Only grade 1 or 2 complications, no spinal cord injury
Neck Node Metastasis

- 45 Year old female
- Node positive arm melanoma
- Adjuvant interferon
- 2 years later Spine SBRT
- 1 year isolated node
- 40Gy /5 fractions in 1.5 weeks

- Larynx
- Submandibular
- Target
- Gross tumour
Conclusions

• **BRAIN**: stereotactic appears to be at least as good as surgery!

• Case for routine surveillance with MRI in follow up

• New biologicals don’t appear to be interacting adversely (haemorrhage + ipi)

• **SPINE**: Caution dose of $\geq 24$Gy single fraction

• **OTHER SITES**: No evidence of superiority of surgery
END
Following slides for attendees
information only
Melanoma: Is WBRT necessary with SRS?

- 74 patients (46 male and 28 female) with brain metastases
- All treated with SRS, 29 got WBRT prior to SRS
- Twenty-nine patients were treated with WBRT followed by SRS.
- Of these patients, 24 (83%) had 1 metastasis, 3 (10%) had 2 metastases, and 2 (7%) had 3 metastases.
- 45 patients were treated with SRS alone. Of these patients, 35 (78%) had 1 metastasis, 6 (13%) had 2 metastases, 3 (7%) had 3 metastases, and 1 (2%) had 4 metastases.
- Ten of the 45 patients (22%) treated with SRS alone later received WBRT as salvage therapy. Patients were classified as RTOG recursive partitioning analysis (RPA) class I (13), class 2 (52), and class 3 (6).

Results
- The median OS for all patients was 6.3 months (95% CI 4.60-7.63), and the median intracranial PFS was 2.7 months (95% CI 2.07-3.45). Median OS for WBRT + SRS was 6.5 months vs. 6.0 months for patients undergoing SRS alone ($p = 0.956$). There was no significant difference in median intracranial PFS for patients treated with SRS alone (2.1 months) vs. WBRT + SRS (3.0 months), ($p = 0.815$). On univariate analysis, RPA class ($p = 0.002$) and the absence of systemic disease ($p = 0.004$) were associated with survival. Using a Cox proportional hazards model that adjusted for gender, RPA class, age at treatment, systemic disease, and number of lesions, patients receiving WBRT plus SRS had a hazard of progression or death 1.12 times greater than an otherwise identical patient who received SRS alone, however this was not statistically significant.
- WBRT followed by SRS did not improve either intracranial PFS or OS when compared to SRS alone. Prospective studies are needed to determine the best approach for patients with 1-4 brain metastases from malignant melanoma.
BRAF inhibitor Dabrafenib in melanoma brain metastases: Phase 1 trial.

- 184 patients, of whom 156 had metastatic melanoma
- Patients with melanoma and untreated brain metastases, nine of ten patients had reductions in size of brain lesions

*Lancet.* 2012 May 19;379(9829):1893-901
Safety and Efficacy of Vemurafenib Combined With Stereotactic Radiosurgery for Brain Metastases in BRAF+ Melanoma

- Vemurafenib (VEM) prolongs survival in B-raf mutation-positive (BRAF+) metastatic melanoma
- Sensitivity to ultraviolet radiation is a major side effect.
- VEM crosses the blood-brain barrier in clinically meaningful concentration,
- Clinical trial of VEM alone for brain metastases is underway.
- 11 patients concurrent VEM + SRS
- Median interval from start of VEM to SRS was 7 months (range, 1 to 18).
- Total of 30 SRS treatments were given to a total of 170 measurable discrete lesions evaluable on follow-up a median of 6 mos (range, 1-32) post-SRS.
- The median dose was 22 Gy (range, 15-24), typically prescribed to the 40-50% isodose line.
- No local skin reactions on the scalp were observed after SRS.
- The lesion LC at 6 and 12 months was 100% and 93%, respectively.
- Presumed radionecrosis manifested as self-limited, asymptomatic hemorrhage was observed in 3.5% (6/170) of lesions at a median 12 mos post-SRS.
- Actuarial OS at 1 year was 91% (10/11), and median OS has not been reached.
- Encouraging LC and OS results in this patient cohort

University of Colorado Kavanagh et al. Proc. ASTRO 2012
Table 5. Actuarial 1-year local tumor control, distant brain metastasis–free survival, and overall survival in three treatment groups.

<table>
<thead>
<tr>
<th>Treatment groups</th>
<th>n</th>
<th>1-year LTC, % (median in months)</th>
<th>1-year DBMFS, % (median in months)</th>
<th>1-year OS, % (median in months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial SRS alone</td>
<td>6</td>
<td>160.4 (14.7)</td>
<td>17.6 (5.5)</td>
<td>30.5 (7.5)</td>
</tr>
<tr>
<td>SRS and WBRT</td>
<td>1</td>
<td>0 (2.2)</td>
<td>0 (3.7)</td>
<td>8.3 (3.7)</td>
</tr>
<tr>
<td>Salvage SRS after WBRT</td>
<td>3</td>
<td>36.6 (5.1)</td>
<td>51.1 (13.3)</td>
<td>20 (5.4)</td>
</tr>
<tr>
<td>Total</td>
<td>10</td>
<td>48.5 (10.3)</td>
<td>23.9 (4.7)</td>
<td>24.7 (6.7)</td>
</tr>
<tr>
<td>p value</td>
<td></td>
<td>0.001</td>
<td>0.25</td>
<td>0.19</td>
</tr>
</tbody>
</table>

MDAH: Stereotactic radiosurgical treatment in 103 patients for 153 cerebral melanoma metastases

Gamma Knife Radiosurgery for Renal Cell Carcinoma and Melanoma Brain Metastases-Higher Doses to Treat Melanoma <4 mL to Improve Local Control
H. Lin
University of Minnesota, Minneapolis, MN
ASTRO 2013

- Medical records of 50 melanoma patients with 143 tumors
- Median follow-up 5.4 months
- Median survivals 9.6 months
- The overall LC at 6 months for melanoma 79.2%,
- Melanoma tumors <4 mL exhibited LC dose dependence. The LC was higher for RCC when compared to melanoma at ≤18 Gy ($p < 0.0001$) and 20 Gy ($p = 0.02$). The LC were similar between the two histology at 22 Gy ($p = 0.19$). At 24 Gy, melanoma had better LC than RCC ($p = 0.02$). Toxicity was not significantly different between the two histology and prescription doses.
- Higher margin doses could be used for melanoma tumors <4 mL to improve melanoma LC.
Local Control of Melanoma Brain Metastases
H.P. Bagshaw et al
Univ of Utah

• 185 patients with a total of 435 brain metastases.
• 35 of the 435 surgical cavity
• The mean tumor volume treated was 2.41 cc
• Mean prescription dose 1979.02 cGy (Range 1200-2927 cGy) to the isocenter. (unusable info)
• Median follow-up of 41.07 months, 76.55% of all brain metastases were controlled locally,
• 69.19% of patients failed in other areas of the brain, and 85.41% of patients had died.
• (no local control dose response data)
• OS for all patients was 7.8 months

Proceedings ASTRO 2014
N=57
Cone-based SRS n=24 and mMLCs n=13
6 patients WBRT prior to SRS.
Median SRS dose was 18 Gy (range 15-20 Gy) prescribed to a median isodose line of 85% (range 56-99%).
Median number of lesions treated was 2 (range 1-4), median diameter was 13.4 mm (range 4.7-48.9 mm), and median lesion volume was 0.94 cm³ (range 0.01-12.4 cm³). Median age was 62.0 years with median ECOG = 1.
Extracranial metastases were present in n=32 and the primary tumor was controlled in n=29. Actuarial
OS at 6 months and 1 year was 69.9% and 30.8%, respectively. For patients, the actuarial FFLF and FFDICF at 1-year was 66.2% and 57.9%, respectively. On univariate analysis melanoma trended towards a worse FFDICF (p=0.08). Analysis of individual lesions demonstrated a 1-year FFLF of 65.0% for melanoma and 59.5% for RCC. Single-lesion univariate analysis showed a trend towards improved FFLF for conformity index (CI) >2 (p=0.10) and mMLCs (p=0.07). On multivariable analysis CI >2 was significantly associated with improved FFLF (hazard ratio = 0.16, p = 0.02), while mMLCs trended towards improved FFLF (HR = 0.16, p = 0.09). Salvage therapy included WBRT (n = 6), SRS (n = 5), surgery (n = 2), and surgery + SRS (n = n=3 developing biopsy proven radionecrosis).
### Lentigo Maligna – Princess Margaret Experience

<table>
<thead>
<tr>
<th>Size</th>
<th>Total Gy</th>
<th># Fractions</th>
<th>Fraction size</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2cm</td>
<td>32.50Gy</td>
<td>5</td>
<td>6.5Gy</td>
</tr>
<tr>
<td>2-5cm</td>
<td>45Gy</td>
<td>10</td>
<td>4.5Gy</td>
</tr>
<tr>
<td>&gt;5</td>
<td>50Gy</td>
<td>15</td>
<td>3.33Gy</td>
</tr>
</tbody>
</table>

**TABLE 26-4. Results of Radiation Therapy in the First 40 Cases of Lentigo Maligna and Lentigo Maligna Melanoma**

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Patients</th>
<th>Controlled (Follow-Up)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lentigo maligna</td>
<td>17</td>
<td>15 (6 mo–13 y)</td>
<td>Two local failures controlled by further irradiation and surgery</td>
</tr>
<tr>
<td>Lentigo maligna melanoma</td>
<td>23</td>
<td>21 (6 mo–7 y)</td>
<td>Two local failures both controlled by further surgery; one regional failure controlled by surgery and adjuvant irradiation</td>
</tr>
</tbody>
</table>