Management of Oligometastatic Breast Cancer

Dr Suman Mallik
Evolution of Breast Cancer Management

SYSTEMIC DISEASE
Hippocrates (400BC)

Barrier Function of Lymph Nodes
Virchow (1863)

Local disease
Valsalva (1704)
LeDran (1757)
Morgagni (1769)

Lymphatic Dissemination
Sylvius, Gendron (1730)

Adjuvant therapies
Bernard Fisher (1976)

Criteria of Operability
Haagensen & Stout (1943)

Radical Mastectomy
Halstead (1882)
Jerome Urban (1949)

Galen (200 A.D)

Jerome Urban (1949)
Oligometastasis

- Metastases limited in number and extent and potentially amenable to definitive directed treatment.

S Hellman

R Weichselbaum

JCO, 1995
Stage IV Breast Cancer: Epidemiology

- 10% Breast cancer present at stage IV at diagnosis. (Howlander SEER).
- “Potentially curable” stage IV estimated to be 1-10% of newly diagnosed metastatic BC. (Pagani, JNCI 2010)
Are metastatic breast cancer curable?

• For select patient with limited metastases receive systemic therapy to sterilize occult metastatic disease and local ablative therapy/Sx to overt sites could be potentially curable.

Oligometastatic Breast Cancer

- Local Therapy
- Ablative/Sx treatment of metastatic disease
Evidence of radical irradiation

Impact of local therapy in metastatic breast cancer

581 Breast Cancer patients
Local RT 320 (55%)
No RT 261 (45%)

Lescodan, JCO 2009
Stereosein Trial: Impact of ablative RT on Mets (primary breast cancer)

1st line treatment
Max 5 lesions <=10cm or <500ml
Positive hormone receptors (IHC), Her2neu negative.
Target accrual: 280

Randomisation

SABR+ Systemic therapy

Systemic therapy

Primary End Point PFS

C Bougier, S Rivera
Experience from Lung

A

ALL PATIENTS
(T: n = 365, V: n = 168)
1yr OS: T: 71.9% (V: 68.3%)
2yr OS: T: 53.8% (V: 47.5%)
3yr OS: T: 41.4% (V: 36.1%)
4yr OS: T: 35.1% (V: 33.6%)
5yr OS: T: 30.5% (V: 27.5%)

Metachronous
(T: n = 101, V: n = 45)

Synchronous
(T: n = 262, V: n = 123)

LOW RISK
1yr OS: T: 88.4% (V: 87.7%)
2yr OS: T: 86.3% (V: 86.3%)
3yr OS: T: 82.5% (V: 59.9%)
4yr OS: T: 50.4% (V: 56.4%)
5yr OS: T: 47.8% (V: 51.7%)

N Stage: N0
(T: n = 140, V: n = 61)

N Stage: N1 or N2
(T: n = 122, V: n = 62)

INTERMEDIATE RISK
1yr OS: T: 75.2% (V: 74.6%)
2yr OS: T: 57.4% (V: 50.6%)
3yr OS: T: 42.9% (V: 36.8%)
4yr OS: T: 40.9% (V: 34.5%)
5yr OS: T: 36.2% (V: 29.2%)

HIGH RISK
1yr OS: T: 53.6% (V: 48.3%)
2yr OS: T: 34.1% (V: 32.1%)
3yr OS: T: 28.6% (V: 20.0%)
4yr OS: T: 18.3% (V: 16.2%)
5yr OS: T: 13.8% (V: 12.1%)

B

Overall Survival by RPA Risk Group

Overall Survival (%)

Lung Cancer 2014

Ashworth, Clin Lung Cancer 2014
SABR-COMET

Patients with up to 5 metastatic lesions from any primary tumor site, meeting inclusion criteria

RANDOMIZATION

(1:2 ratio of randomization to Arm 1 vs. Arm 2)

ARM 1: STANDARD OF CARE
Palliative RT to any symptomatic sites
Further chemotherapy at discretion of medical oncologist

FOLLOW-UP

ARM 2: STANDARD OF CARE + SABR
SABR to all sites of known disease
Further chemotherapy at discretion of medical oncologist

FOLLOW-UP
Endpoints

Primary Endpoint
• Overall Survival

Secondary endpoints:
• Progression-free survival
• Toxicity (CTC-AE 4.0)
• Quality of life (FACT-G)
• Lesional control rate
• Number of cycles of further systemic therapy
  – Changed to binary variable “Receipt of systemic therapy” (Y/N)
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Patients (n=99)</th>
<th>Control Arm (n=33)</th>
<th>SABR Arm (n=66)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age – median, (min, max)</td>
<td>68 (43, 89)</td>
<td>69 (44, 87)</td>
<td>67 (43, 89)</td>
<td>0.494</td>
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<tr>
<td>Sex – n(%)</td>
<td></td>
<td></td>
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<td>0.772</td>
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<tr>
<td>Male</td>
<td>59 (59.6)</td>
<td>19 (57.6)</td>
<td>40 (60.6)</td>
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<tr>
<td>Female</td>
<td>40 (40.4)</td>
<td>14 (42.4)</td>
<td>26 (39.4)</td>
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<tr>
<td>Site of Original Primary</td>
<td></td>
<td></td>
<td></td>
<td>0.204</td>
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<tr>
<td>Tumor – n(%)</td>
<td>18 (18.2)</td>
<td>5 (15.2)</td>
<td>13 (19.7)</td>
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<tr>
<td>Breast</td>
<td>18 (18.2)</td>
<td>9 (27.3)</td>
<td>9 (13.6)</td>
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<tr>
<td>Colorectal</td>
<td>18 (18.2)</td>
<td>6 (18.2)</td>
<td>12 (18.2)</td>
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<tr>
<td>Lung</td>
<td>16 (16.2)</td>
<td>2 (6.1)</td>
<td>14 (21.2)</td>
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<tr>
<td>Prostate</td>
<td>29 (29.3)</td>
<td>11 (33.3)</td>
<td>18 (27.3)</td>
<td></td>
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<tr>
<td>Other</td>
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<td></td>
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<tr>
<td>Characteristic</td>
<td>All Patients (n=99)</td>
<td>Control Arm (n=33)</td>
<td>SABR Arm (n=66)</td>
<td>p-value</td>
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<td>-----------------------------</td>
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<td>---------</td>
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<tr>
<td>Number of Metastases –</td>
<td></td>
<td></td>
<td></td>
<td>0.591</td>
</tr>
<tr>
<td>n(%)</td>
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<tr>
<td>1</td>
<td>42 (42.4)</td>
<td>12 (36.4)</td>
<td>30 (45.5)</td>
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<td>2</td>
<td>32 (32.3)</td>
<td>13 (39.4)</td>
<td>19 (28.8)</td>
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<tr>
<td>3</td>
<td>18 (18.2)</td>
<td>6 (18.2)</td>
<td>12 (18.2)</td>
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<td>4</td>
<td>4 (4.0)</td>
<td>2 (6.1)</td>
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<tr>
<td>5</td>
<td>3 (3.0)</td>
<td>0 (0.0)</td>
<td>3 (4.6)</td>
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<tr>
<td>Location of Metastases –</td>
<td></td>
<td></td>
<td></td>
<td>0.181</td>
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<tr>
<td>n(%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Adrenal</td>
<td>9 (4.7)</td>
<td>2 (3.1)</td>
<td>7 (5.5)</td>
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<tr>
<td>Bone</td>
<td>65 (34.0)</td>
<td>20 (31.3)</td>
<td>45 (35.4)</td>
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<tr>
<td>Liver</td>
<td>19 (10.0)</td>
<td>3 (4.7)</td>
<td>16 (12.6)</td>
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<tr>
<td>Lung</td>
<td>89 (46.6)</td>
<td>34 (53.1)</td>
<td>55 (43.3)</td>
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<tr>
<td>Other</td>
<td>9 (4.7)</td>
<td>5 (7.8)</td>
<td>4 (3.2)</td>
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</tbody>
</table>
Overall survival

Median OS

Control Arm: 28 months (95% CI: 19-33 months)

SABR Arm: 41 months (95% CI: 26 months to ‘not reached’)

Number at risk:

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>SABR</th>
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<tbody>
<tr>
<td>at risk</td>
<td>33</td>
<td>66</td>
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<tr>
<td>28</td>
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<tr>
<td>12</td>
<td>29</td>
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</tr>
<tr>
<td>2</td>
<td>15</td>
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<tr>
<td>2</td>
<td>7</td>
<td></td>
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<tr>
<td>2</td>
<td>1</td>
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</tbody>
</table>
Progression free survival

**Median PFS**

Control Arm: 6 months (95% CI: 3.4-7.1 months)

SABR Arm: 12 months (95% CI: 6.9-30 months)
SABR-COMET 10

Controlled Primary Tumor with 4-10 Oligometastatic Lesions $\rightarrow$ Pre-plan SABR $\rightarrow$ Pre-specify Standard of Care Treatment $\rightarrow$ R 1:2 $\rightarrow$ Arm 1 Standard of Care $\rightarrow$ Follow-up

Arm 2 SABR to all lesions + Standard of Care $\rightarrow$ Follow-up
Abscopal effect of radiation
Ablative Radiotherapy + Immunomodulator

Fig. 2. Before and after PET imaging in a patient with widely metastatic melanoma. Two liver lesions were treated with SBRT.

Postow, NEJM2012, Hinicker, NEJM2012
Randomized evidence of ablative therapy

<table>
<thead>
<tr>
<th>Study</th>
<th>Primary</th>
<th>Number</th>
<th>Protocol</th>
<th>Results</th>
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<tbody>
<tr>
<td>MDACC/Colorado Trial: Phase 2 (Gomez, Lancet Oncology 2016)</td>
<td>NSCLC</td>
<td>49</td>
<td>Local consolidation Vs maintenance therapy or observation</td>
<td>PFS better in SABR + mChemo arm. (p=0.0054)</td>
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<tr>
<td>UT Southwestern Trial, Phase 2 (Iyenger et al JAMA Oncol 2018)</td>
<td>NSCLC</td>
<td>29</td>
<td>mChemo Vs SABR+ mChemo</td>
<td>PFS better in SABR+ mChemo (p=0.01)</td>
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<tr>
<td>STOMP Trial Phase 2 (Ost et al J Clin Oncology 2018)</td>
<td>Prostate</td>
<td>62</td>
<td>Surveillance vs metastatic directed therapy</td>
<td>PFS better in LCT arm (p=0.0054)</td>
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<tr>
<td>ORIOLE (Radwan et al BMC Cancer 2017)</td>
<td>Prostate</td>
<td>54</td>
<td>Observation Vs SABR</td>
<td>PFS better in SABR arm (p=0.03)</td>
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</table>
Selection of favourable candidates

• Tumour Biology and growth kinetics.
• Clinical scenario.

I. Oligometastasis at presentation.
II. Residual oligometastasis after systemic therapy.
III. Relapsed oligometastases after curative locoregional therapy.
Brain Metastasis

• Most common intracranial neoplasm.
• Most common intracranial metastatic site is brain parenchyma.
• Advances in systemic cancer management has lead to higher incidence of brain metastasis.
• Advanced imaging techniques and early suspicion has made it possible to detect oligo brain metastasis.
Primaries

- Lung 39-56%
- **Breast 13-30%**
- Melanoma 6-11%
- Renal 2-6%
- Colorectal 3-4%
Definitions

• Single Brain Metastasis

• Solitary Brain Metastasis

• Oligo Brain Metastasis.
Conventional Management of Brain Metastases

• Medical decompression → Steroids, Mannitol, Glycerol

• 1-3 lesions, resectable → Surgical resection + Whole Brain Radiotherapy

• Multiple/unresectable lesions → Whole Brain Radiotherapy
Decision of Management

• Performance status
• Nature of metastasis
• Primary site
• Extracranial disease status
• Expected survival
RTOG- Classes

- **Class I**
  - < 65 years, KPS ≥ 70,
  - controlled primary
  - no extracranial mets
- **Class II-Rest**
- **Class III-KPS <70**

---

MST: 3.4-25.3 months

Breast cancer

Diagnosis-specific GPA

Sperduto et al.

<table>
<thead>
<tr>
<th>KPS</th>
<th>Age</th>
<th>Number of mets</th>
<th>Extra-cranial mets</th>
<th>Tumour subtype</th>
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<tr>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>Lung</td>
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<tr>
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<td>✓</td>
<td>-</td>
<td>✓</td>
<td>Breast</td>
</tr>
<tr>
<td>✓</td>
<td>-</td>
<td>✓</td>
<td>-</td>
<td>Melanoma</td>
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<td>-</td>
<td>✓</td>
<td>-</td>
<td>Renal</td>
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<tr>
<td>✓</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>GI</td>
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</table>
What is New?

• Expanding definition of oligometastases [from 1-3 lesions with controlled primary to .....?]

• WBRT increasingly being replaced by focal RT (SRS/SRT)

• Surgical resection increasingly being replaced by focal RT (SRS/SRT)

• Emerging role of post-operative focal RT (SRS/SRT)

• Emergence of drugs which can cross the BBB

• Lack of efficacy of WBRT in patients with poor PS
Evolving end points

- Survival
- Brain tumour control
- Quality of life
- Cognitive function
WBRT

**Pros:**
- Most chemotherapy drugs do not cross BBB
- Metastases to CNS can be multifocal
- Reduced steroid-dependence

**Cons:**
- Cognitive decline
- Lack of survival benefit
For single brain metastases, 2 out of 3 trials have shown surgical resection + RT has OS & LC advantage over RT alone.

<table>
<thead>
<tr>
<th>Trial</th>
<th>N</th>
<th>Endpoint</th>
<th>Surgery +RT</th>
<th>RT</th>
<th>p value</th>
<th>Ref</th>
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<tr>
<td></td>
<td></td>
<td>Local failure</td>
<td>20%</td>
<td>52%</td>
<td>&lt;0.02</td>
<td></td>
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<tr>
<td>Noordjik et al (Dutch)</td>
<td>63</td>
<td>OS*</td>
<td>10 months</td>
<td>6 months</td>
<td>0.04</td>
<td>Int J Radiat Oncol Biol Phys 1994;29:711-17.</td>
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<tr>
<td></td>
<td></td>
<td>FIS*</td>
<td>7.5 months</td>
<td>3.5 months</td>
<td>0.06</td>
<td></td>
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<tr>
<td>Mintz et al (Canadian)</td>
<td>84</td>
<td>OS*</td>
<td>5.6 months</td>
<td>6.3 months</td>
<td>NS</td>
<td>Cancer 1996;78:1470-76.</td>
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<tr>
<td></td>
<td></td>
<td>FIS %</td>
<td>32%</td>
<td>32%</td>
<td>NS</td>
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</table>
Post-operative stereotactic radiosurgery versus observation for completely resected brain metastases: a single-centre, randomised, controlled, phase 3 trial

Anita Mahajan, Salmaan Ahmed, Mary Frances McAleer, Jeffrey S Weinberg, Jing Li, Paul Brown, Stephen Settle, Sujit S Prabhu, Frederick F Lang, Nicholas Levine, Susan McGovern, Erik Sulman, Ian E McCutcheon, Syed Azeem, Daniel Cahill, Claudio Tatsui, Amy B Heimberger, Sherise Ferguson, Amol Ghia, Franco Demonte, Shaan Roza, Nandita Guha-Thakurta, James Yang, Raymond Sawaya, Kenneth R Hess, Ganesh Rao

Lancet Oncol 2017

- Phase III RCT
- N=132
- 1-3 metastases; resection cavity <4cm
- Post-op SRS (N=64) vs observation (N=68)
- SRS done within 30 days of resection; dose=12-16Gy
- Median FU = 11.1 months
- Median 12-month freedom from local recurrence was significantly better for SRS (72%) vs observation (43%)
Phase III RCT

- N=194
- One resected brain metastases
- Resection cavity $\leq$5cm diameter
- **SRS** (12-20Gy) [N=98] vs **WBRT**[N=96](30Gy/10#/2weeks OR 37.5Gy/15#/3 weeks)

Significantly longer cognitive deterioration free survival with **SRS** (median 3.7 vs 3 months)

- Significantly poorer surgical bed control at 6 months with **SRS** (80.4%) vs **WBRT** (87.1%)
- Median OS similar :12.2 months (SRS) vs 11.6 months (WBRT)
S vs SRS

• No randomized trials

• Similar LC rates 80-90% (when either one is combined with WBRT)
Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: phase III results of the RTOG 9508 randomised trial

• 3 randomised trials (2 small/non-standard).
• **RTOG 9508 → N=333**: OS benefit for **single** unresectable brain met (no breast cancer patients analysed in this subgroup), LC benefit for 2-3 brain mets, steroid-usage lowered with SRS.
• Subset analysis shows **OS** benefit for single brain met, NSCLC, RPA class I, tumor <2cm.
• For breast cancer patients with 1-3 brain metastases, presence of extracranial disease, TNBC & having >1 brain metastasis predicts for worse OS.

*Int J Radiation Oncol Biol Phys, 2014;90:526-31*
*Lancet 2004; 363: 1665–72*
Phase 3 Trials of Stereotactic Radiosurgery With or Without Whole-Brain Radiation Therapy for 1 to 4 Brain Metastases: Individual Patient Data Meta-Analysis

For patients <50 years age with 1-4 brain metastases, SRS has OS advantage over SRS+WBRT.

- Meta-analysis of 3 randomised trials
- N=364
- SRS alone 51%; SRS+WBRT 49%

- Patients with single metastases had significantly better OS than with 2-4 metastases.
- Local control significantly better with WBRT in all age groups.
Immediate vs delayed RT for asymptomatic oligo brain metastases

• Korean trial
• Metastatic NSCLC; 1-4 asymptomatic brain metastases
• N=105
• SRS (N=49) followed by chemotherapy vs upfront chemotherapy (N=49)
• No difference in OS / time to CNS progression
Neurocognitive decline

• Patients with brain metastases tend to have reduced neurocognition at the time of presentation, which is frequently not evaluated;
• Disease-progression, both intra- and extra-cranially, will negatively skew population distributions of neurocognitive scores;
• The effects of therapeutic interventions, such as chemotherapy, anticonvulsants, steroids, opiates, etc., remain inadequately documented.
Review

Why avoid the hippocampus? A comprehensive review

Vinai Gondi a,*, Wolfgang A. Tomé a,b, Minesh P. Mehta a

a Department of Human Oncology and b Department of Medical Physics, University of Wisconsin Comprehensive Cancer Center, Madison, WI, USA
RTOG 0933

- Single-arm phase II trial of HA-WBRT (30 Gy in 10 fractions
- Credentialing and central review of hippocampal contouring and IMRT planning

![Graph showing HVLT Score over months from start of treatment](image)

- Mean decline in HVLT-Delayed Recall from baseline to 4 months: 7.0%
  (95% CI: -4.7 - 18.7%)
- Significant compared to historical control: 30%
  ($p=0.0003$)

Need phase III data for level I evidence

Gondi et al. JCO 2014
RTOG 0614

- Phase III trial of WBRT with or without memantine

Memantine during WBRT became standard of care

Brown et al. Neuro-Oncol 2013
NRG-CC001: Phase III Trial Memantine and WBRT with or without Hippocampal Avoidance in Patients with Brain Metastases

Basic Eligibility: Brain metastases 5mm outside hippocampus; KPS ≥70; 3D MRI scan; hydrocephalus/ventricular distortion excluded; baseline NCF testing

Brain Metastasis → Stratify → RPA Prior Therapy → Randomize

- WBRT 30Gy + Memantine
- HA-WBRT 30Gy + Memantine
Primary Endpoint

- Hippocampal avoidance prolongs time to cognitive function failure
  - 6 months:
    - HA-WBRT+memantine 59.5%
    - WBRT+memantine: 68.2%
    - Hazard ratio = 0.76 \( p=0.03 \)
  - Separation of the curves starting at 3 months and maintained through the follow-up period
  - Median follow-up for alive patients: 7.90 months
Dose protocols - Brain Metastases

- **SRS: (RTOG 90-05)**
  - <2cm: 24Gy
  - 2.1-3cm: 18Gy
  - 3.1-4cm: 15 Gy

- **FSRT:**
  - 30Gy/5#
  - 40Gy/10#

- Target = tumour + small margin (1-2 mm)
- Unlike conventional RT, dose distribution is deliberately made inhomogeneous, by covering periphery of tumor by 50-80%, rather than 95%. This ensures high dose at the centre of the tumour as well as rapid fall off of dose beyond the periphery of the tumour.
Frame based stereotaxy

- Gamma knife
- Modified Linacs
- Proton beam

Firm immobilisation (stereotactic frames)
Treatment planning (dedicated workstations)
Precise treatment delivery (high QA)
Frameless stereotaxy in a solitary met
Frameless stereotaxy in oligomestatic disease
Is radiation dose escalation clinically relevant in patients with multiple BM?

Toxicity? Efficacy?

EORTC 22111-26111

Whole brain radiotherapy with or without synchronous integrated boost in patients with 2 to 5 brain metastases. A randomized Phase III Study of the EORTC ROG and BTG

PI: B. Baumert, S. Erridge, F. Lagerwaard
Specific dosimetry for WBRT

Integrated WBRT + boost (VMAT)

New delivery techniques allow for more complex tailored planning, including Simultaneous Integrated Boost (SIB) on oligomet.

20 Gy/5 fr WBRT; 40 Gy/5 fr SIB

- Dosimetric advantages (steeper dose gradients)
- Logistic advantages (no separate procedures)
- Patient tolerance advantages (outpatient, frameless, delivery ~5 minutes)
Our Multidisciplinary Team
## Summary of trials

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<tr>
<th></th>
<th>Outcome</th>
<th>Level of evidence</th>
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<tr>
<td>SRS+WBRT Vs WBRT alone</td>
<td>Improve survival in single metastatic disease with KPS&gt;=70</td>
<td>Level I</td>
</tr>
<tr>
<td></td>
<td>Improve local control</td>
<td>Level II</td>
</tr>
<tr>
<td></td>
<td>Improve survival in multiple metastatic disease</td>
<td>Level III</td>
</tr>
<tr>
<td>SRS Vs WBRT+SRS</td>
<td>Equivalent survival</td>
<td>Level II</td>
</tr>
<tr>
<td></td>
<td>improves cognitive function</td>
<td>Level II</td>
</tr>
<tr>
<td></td>
<td>Higher out of field metastatic potential</td>
<td>Level II</td>
</tr>
<tr>
<td>Surgery+WBRT Vs SRS+/-WBRT</td>
<td>Equivalent survival in &lt;3cm</td>
<td>Level II</td>
</tr>
<tr>
<td>SRS Vs WBRT</td>
<td>Better than WBRT up to 3 mets in survival</td>
<td>Level III</td>
</tr>
<tr>
<td>WBRT with hippocampal sparing +memantine</td>
<td>Delayed cognitive decline</td>
<td>Level II+</td>
</tr>
</tbody>
</table>
Bone Metastasis

- **Most common** site of metastasis after lung & liver
- **Most common** malignancy affecting bone
- Prostate, Breast, Lung Most Common (50-70%)
- Thyroid, Bladder, Kidney (15-30%)
- 20% of **workload** in RT center
- 60-65% of all palliative cases
Symptoms/Complications Related to Bone Metastases

- Pain
- Pathological fracture
- Spinal cord compression
- Hypercalcaemia  
  ↓

  poor QOL
Bones Affected

- Spine (Dorsal > Lumbar > Cervical)
- Pelvis
- Ribs
- Proximal Femur
- Humerus
- Skull

Therapeutic Goals

• Improvement in the QOL
• Pain relief
• Maintenance and restoration of function
• Close surveillance for the development complications
• Treatment should be tailored to the patient's prognosis and life expectancy
Treatment Modalities

• Radiotherapy
• Surgery
• Vertebroplasty/kyphoplasty
• Radiopharmaceuticals
• Radiofrequency ablation/Cryotherapy
• Bone modifying agent
• Systemic therapy
Effects of RT on bone metastasis

• **Healing and ossification** – 65-85% of lesions show signs in about 6 mths

• Ionizing radiation diminishes **osteoclast activation and kill tumour cells.**

• Reduction in inflammatory cells and chemical pain mediators.
Dose Fractionation (conventional rt)

- 8 Gy in a single fraction
- 20 Gy in 5 fractions
- 24 Gy in 6 fractions
- 30 Gy in 10 fractions

OPTIMAL DOSE FRACTIONATION SCHEDULE?

- 12 trials, 3621 sites
- **Overall pain-response rates**
  - SF- 60% (1080/1814) vs MF- 59% (1060/1807).

- **Complete pain response rates**
  - SF-34% (508/1476) vs MF- 32% (475/1473)

- **Re-treatment rate**
  - SF- 21.5% vs MF 7.4%
Update on the Systematic Review of Palliative Radiotherapy Trials for Bone Metastases
E. Chow, L. Zeng, N. Salvo, K. Dennis, M. Tsao, S. Lutz
JCO:2012

25 RCTs, For intention-to-treat patients,

**Overall response (OR):**
SF =60% (1,468 of 2,513 patients) Vs MF = 61% (1,466 of 2,487 patients).
ODD’s Ratio = 0.98 (CI- 0.95-1.02)

**Complete response (CR):**
SF = 23% (620 of 2641) Vs MF = 24% (634 of 2622).
ODD’s Ratio = 0.97 (0.88-1.06)

**Increased risk in SF RT arm:**
Pathological fractures 3.3% in SF VS 3% in MF. ODD’s Ratio = 1.10 (0.65-1.86)
Spinal cord compressions, 2.8% in SF Vs 1.9% in MF. ODD’s Ratio = 1.44 (0.90-2.30)

**Re-radiation Rates:**
20% in SF Vs 8% in MF (P .00001), --- “this trend may have been influenced by the fact that physicians were more prepared to retreat those who received an initial single treatment”
Palliative radiation therapy for bone metastases: Update of an ASTRO Evidence-Based Guideline

Stephen Lutz MD,*, Tracy Balboni MD MPH, Joshua Jones MD, Simon Lo MB ChB, Joshua Petit MD, Shayna E. Rich MD PhD, Rebecca Wong MB ChB, Carol Hahn MD

Table 2 New prospective studies comparing SF vs MF RT regimens (KQs 1-3)

<table>
<thead>
<tr>
<th>Investigator, y</th>
<th>Patients (n)</th>
<th>Fractionation</th>
<th>Complete or partial response (%)</th>
<th>Complete response (%)</th>
<th>Acute and late toxicity (%)</th>
<th>Repeat treatment rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chow, 2012</td>
<td>5617 in 25 RCTs</td>
<td>SF</td>
<td>60</td>
<td>23</td>
<td>NR</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MF</td>
<td>61</td>
<td>24</td>
<td></td>
<td>8^a</td>
</tr>
<tr>
<td>Gutierrez Bayard, 2014</td>
<td>90</td>
<td>8 Gy in 1 fx</td>
<td>79</td>
<td>-</td>
<td>NR</td>
<td>13.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>30 Gy in 10 fx</td>
<td>88</td>
<td>17</td>
<td>NR</td>
<td>8.8^a</td>
</tr>
<tr>
<td>Howell, 2013</td>
<td>235</td>
<td>8 Gy in 1 fx</td>
<td>70</td>
<td>19</td>
<td>10</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td></td>
<td>30 Gy in 10 fx</td>
<td>62</td>
<td>17%</td>
<td>20^a</td>
<td>5^a</td>
</tr>
<tr>
<td>Majumder, 2012</td>
<td>64</td>
<td>8 Gy in 1 fx</td>
<td>85</td>
<td>0</td>
<td>No statistically significant difference</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>30 Gy in 10 fx</td>
<td>77</td>
<td>0</td>
<td>(acute grade 2-4)</td>
<td></td>
</tr>
<tr>
<td>Meeuse, 2010</td>
<td>1157</td>
<td>8 Gy in 1 fx</td>
<td>53</td>
<td>NR</td>
<td>NR</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>24 Gy in 6 fx</td>
<td>56</td>
<td>NR</td>
<td>NR</td>
<td>2</td>
</tr>
</tbody>
</table>

fx, fraction; MF, multiple fractions; NR, not reported; RCT, randomized controlled trial; SF, single fraction.

^a Statistically significant comparison.
Paradigm shift

• More utilization of single fraction RT in clinical practice

• SRS/SBRT (stereotactic radiosurgery/radiotherapy) - focusing more towards local control

• Newer radioipharmaceuticals
Why Newer Paradigm Needed?

• Patients with metastatic disease represents a **heterogenous group**.

• Effective systemic and supportive therapies has **increased life expectancy** of metastatic patient- durable pain relief needed

• Oligometastatic patients and bone only metastasis patient have longer median survival- LC important

• What about metastasis from **radioresistant** tumour?

• Re-irradiation cases
SRS/SBRT for spinal Mets

- Image guided **highly conformal** technique of EBRT that delivers large radiation dose in one or few fractions to target volume with **precision** (<1mm) and **steep dose gradients**.

- Provides higher **BED** to the tumour with relative **sparing** of the closely abutting sensitive critical normal tissue (spinal cord)

- Affects tumour vasculature and micro-enviroment and stimulates antitumour immunity- indirect action

- Increase in **local control** and more **durable pain response**.
# International Stereotactic Radiosurgery Society practice guidelines

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inclusion</strong></td>
<td></td>
</tr>
<tr>
<td>Oligometastasis involving the spine</td>
<td>These pts generally have a long expected survival &amp; thus are most likely to benefit from radiosurgery/ SBRT</td>
</tr>
<tr>
<td>Pts w/ radioresistant histology (RCC, melanoma, sarcoma)</td>
<td>Higher doses of radiation might be associated w/ improved local tumor control</td>
</tr>
<tr>
<td>Patients with paraspinal extension contiguous to the spine</td>
<td>Pts w/ extraosseous extension might experience improved soft-tissue tumor control</td>
</tr>
<tr>
<td><strong>Exclusion</strong></td>
<td></td>
</tr>
<tr>
<td>Pts w/ an expected survival time of &lt;3 mos</td>
<td>Pts w/ a shorter expected survival time are less likely to benefit from SBRT</td>
</tr>
<tr>
<td>Mechanically unstable based on the SINS score</td>
<td>Pts w/ mechanical instability should be treated w/ surgical stabilization before radiotherapy</td>
</tr>
<tr>
<td>&gt;3 sites to be treated in a single session</td>
<td>For logistical reasons, it is difficult to keep a pt adequately immobilized for long enough to accurately treat more than 3 lesions in a single session</td>
</tr>
<tr>
<td>Spinal cord compression or cauda equina syndrome</td>
<td>These pts should be preferentially treated w/ up-front decompressive surgery†</td>
</tr>
</tbody>
</table>

*SINS = spinal instability neoplastic score.
2. Spinal Instability Neoplastic Score (SINS Score)

<table>
<thead>
<tr>
<th>SINS Component</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Location</td>
<td></td>
</tr>
<tr>
<td>Junctional (occiput-C2, C7-T2, T11-L1, L5-S1)</td>
<td>3</td>
</tr>
<tr>
<td>Mobile spine (C3-C6, L2-L4)</td>
<td>2</td>
</tr>
<tr>
<td>Semirigid (T3-T10)</td>
<td>1</td>
</tr>
<tr>
<td>Rigid (S2-S5)</td>
<td>0</td>
</tr>
<tr>
<td>Pain*</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>3</td>
</tr>
<tr>
<td>Occasional pain but not mechanical</td>
<td>1</td>
</tr>
<tr>
<td>Pain-free lesion</td>
<td>0</td>
</tr>
<tr>
<td>Bone lesion</td>
<td></td>
</tr>
<tr>
<td>Lytic</td>
<td>2</td>
</tr>
<tr>
<td>Mixed (lytic/blastic)</td>
<td>1</td>
</tr>
<tr>
<td>Blastic</td>
<td>0</td>
</tr>
<tr>
<td>Radiographic spinal alignment</td>
<td></td>
</tr>
<tr>
<td>Subluxation/translation present</td>
<td>4</td>
</tr>
<tr>
<td>De novo deformity (kyphosis/scoliosis)</td>
<td>2</td>
</tr>
</tbody>
</table>

**Score 8**

- **0 to 6** → stability
- **7 to 12** → indeterminate instability
- **13 to 18** → instability

SINS 7-18 warrants surgical consultation before RT
A six-point grading system was designed and validated by the Spine Oncology Study Group (SOSG) to describe the degree of ESCC.
## Literature Review - Local Control

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Tumors/ Pts Treated (n/n)</th>
<th>Cancer Type</th>
<th>Follow-Up Duration Median (mos)</th>
<th>Local Control Rate (%)</th>
<th>Complete Pain Response (%)</th>
<th>Overall Survival</th>
<th>Tumor Dose (Gy)/No. of Fx (range)</th>
<th>BED (α/β = 10) (Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chang et al., 2007</td>
<td>22/17</td>
<td>Mixed</td>
<td>NR</td>
<td>68.1 (7/22 failures)</td>
<td>NR</td>
<td>NR</td>
<td>27–30/3–5</td>
<td>48–51.3 (range)</td>
</tr>
<tr>
<td>Yamada et al., 2008</td>
<td>103/93</td>
<td>Mixed</td>
<td>15 (all pts)</td>
<td>93 (96/103, crude, 2 yrs)</td>
<td>NR</td>
<td>15 mos (all pts, median)</td>
<td>18–24/1</td>
<td>50.4–81.6 (range)</td>
</tr>
<tr>
<td>Sahgal et al., 2009</td>
<td>18/14</td>
<td>Mixed</td>
<td>9</td>
<td>77.8 (14/18, crude)</td>
<td>NR</td>
<td>NR</td>
<td>24/3 (median)</td>
<td>43.2 (median)</td>
</tr>
<tr>
<td>Chang et al., 2012</td>
<td>131/93</td>
<td>Mixed</td>
<td>23.7</td>
<td>89.2 (1-yr crude)</td>
<td>NR; 89.2 (at 1 yr, “pain control”)</td>
<td>19 mos</td>
<td>19.9/1 (mean equivalent)</td>
<td>59.5 (mean)</td>
</tr>
<tr>
<td>Gill et al., 2012</td>
<td>14/14</td>
<td>Mixed</td>
<td>34</td>
<td>85.7</td>
<td>NR</td>
<td>80% (1 yr), 57% (2 yr) (all)</td>
<td>30–35/5</td>
<td>48–59.5 (range)</td>
</tr>
<tr>
<td>Sohn et al., 2014</td>
<td>13/13</td>
<td>RCC</td>
<td>NR</td>
<td>85.7 (1 yr) 23.1</td>
<td>23.1</td>
<td>15 mos (median)</td>
<td>38/4 (mean)</td>
<td>74.1 (mean)</td>
</tr>
<tr>
<td>Guckenberge r et al., 2014</td>
<td>387/301</td>
<td>Mixed</td>
<td>11.8</td>
<td>90 (1 yr), 84 (2 yrs)</td>
<td>58</td>
<td>65% (1 yr), 44% (2 yrs) (median 19.5 mos)</td>
<td>24/3 (median) (10–60/1–20)</td>
<td>43.2 (median) (range 20–78 )</td>
</tr>
<tr>
<td>Thibault et al., 2014</td>
<td>51/51</td>
<td>RCC</td>
<td>12.3</td>
<td>84.3 (crude)</td>
<td>NR</td>
<td>64.1% (1 yr)</td>
<td>24/2 (median)</td>
<td>52.8 (median)</td>
</tr>
<tr>
<td>Study</td>
<td>No. of Patients</td>
<td>Fractionation</td>
<td>Complete /Partial Pain Response</td>
<td>Complete Pain Response</td>
<td>Duration</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>----------</td>
<td>----------------</td>
<td>---------------</td>
<td>---------------------------------</td>
<td>------------------------</td>
<td>-------------------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prince 1986</td>
<td>288</td>
<td>1x8 Gy 10 x 3 Gy</td>
<td>73% 64%</td>
<td>45% 28%</td>
<td>59% @ 3 mo 50% @ 3 mo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gaze 1997</td>
<td>280</td>
<td>1 x 10Gy 5 x 4.5 Gy</td>
<td>84% 89%</td>
<td>39% 48%</td>
<td>Median 3.5 mo Median 3.5 mo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steenland 1999</td>
<td>1171</td>
<td>1 x 8 Gy 6 x 4 Gy</td>
<td>72% 69%</td>
<td>37% 33%</td>
<td>Median 5 mo Median 6 mo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Roos 2005</td>
<td>272</td>
<td>1 x 8 Gy 5 x 4 Gy</td>
<td>61% 53%</td>
<td>26% 27%</td>
<td>Median 3.5 mo Median 5.5 mo</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

~70%  
~25-40%  
~35% @ 3-6 mo
Target Volume Definition

- International Spine Radiosurgery Consortium Consensus Guidelines

Cox BW. IJROBP 2012;83(5):e597-605

International Spine Radiosurgery Consortium anatomic classification system for consensus target volumes for spine radiosurgery
<table>
<thead>
<tr>
<th>Target volume</th>
<th>Guidelines</th>
</tr>
</thead>
</table>
| GTV           | Contour gross tumor using all available imaging  
|               | Include epidural and paraspinal components of tumor |
| CTV           | Include abnormal marrow signal suspicious for microscopic invasion  
|               | Include bony CTV expansion to account for subclinical spread  
|               | Should contain GTV  
|               | Circumferential CTVs encircling the cord should be avoided except in rare instances where the vertebral body, bilateral pedicles/lamina, and spinous process are all involved or when there is extensive metastatic disease along the circumference of the epidural space without spinal cord compression |
| PTV           | Uniform expansion around CTV  
|               | CTV to PTV margin ≤3 mm  
|               | Modified at dural margin and adjacent critical structures to allow spacing at discretion of the treating physician unless GTV compromised  
|               | Never overlaps with cord  
|               | Should contain entire GTV and CTV |

*Abbreviations: CTV = clinical target volume; GTV = gross tumor volume; PTV = planning target volume.*
<table>
<thead>
<tr>
<th>GTV involvement</th>
<th>ISRC GTV anatomic classification</th>
<th>ISRC bony CTV recommendation</th>
<th>CTV description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any portion of the vertebral body</td>
<td>1</td>
<td>1</td>
<td>Include the entire vertebral body</td>
</tr>
<tr>
<td>Lateralized within the vertebral body</td>
<td>1</td>
<td>1, 2</td>
<td>Include the entire vertebral body and the ipsilateral pedicle/transverse process</td>
</tr>
<tr>
<td>Diffusely involves the vertebral body</td>
<td>1</td>
<td>1, 2, 6</td>
<td>Include the entire vertebral body and the bilateral pedicles/transverse processes</td>
</tr>
<tr>
<td>GTV involves vertebral body and unilateral pedicle</td>
<td>1, 2</td>
<td>1, 2, 3</td>
<td>Include entire vertebral body, pedicle, ipsilateral transverse process, and ipsilateral lamina</td>
</tr>
<tr>
<td>GTV involves vertebral body and bilateral pedicles/transverse processes</td>
<td>3</td>
<td>2, 3, 4</td>
<td>Include entire vertebral body, bilateral pedicles/transverse processes, and bilateral laminae</td>
</tr>
<tr>
<td>GTV involves unilateral pedicle</td>
<td>2</td>
<td>2, 3 ± 1</td>
<td>Include pedicle, ipsilateral transverse process, and ipsilateral lamina, ± vertebral body</td>
</tr>
<tr>
<td>GTV involves unilateral lamina</td>
<td>3</td>
<td>2, 3, 4</td>
<td>Include lamina, ipsilateral pedicle/transverse process, and spinous process</td>
</tr>
<tr>
<td>GTV involves spinous process</td>
<td>4</td>
<td>3, 4, 5</td>
<td>Include entire spinous process and bilateral laminae</td>
</tr>
</tbody>
</table>

Abbreviations: CTV = clinical target volume; GTV = gross tumor volume; ISRC = International Spine Radiosurgery Consortium.
CTV

Include Abnormal Marrow Signal

Include Bony CTV Extensions

Should contain GTV

Circumferential CTV encircling Cord should be avoided
OAR Delineation

Spinal Cord

Two Spinal Cord Contour sets –

1. Conventional Spinal Cord
   Fusion with T1 contrast & T2 MRI
   At least 10cm above & Below the target volume

2. Partial Spinal Cord Volume
   At least 6mm above & Below the target volume

Draw thecal sac separately
PRV – 2mm over Spinal Cord

• Other OARs- Within 10cm of target volume as per RTOG guideline
Dose Fractionation

- 16–24 Gy/1 fraction - 41.6–81.6
- 24 Gy/2 fractions - 52.8
- 24–27 Gy/3 fractions - 43.2–51.3
- 30–35 Gy/5 fractions - 50.4–59.5

GTV $D_{\text{min}} > 14 \text{Gy}$ (Single Fraction) or $> 21 \text{Gy}$ (3 Fractions) – recommended

BishopAetal.IJROBP2015.92(5):1016-1026
Late Complication

• **Nerve Damage**

• **Vertebral Compression Fracture**-
  
  • 1- and 2-year cumulative incidences 12.35% and 13.49%, respectively (24Gy/SF) and 8.5% and 13.8%. (24Gy/2#), (Tseng et al)
  
  • dose per fraction increases beyond 19 Gy, risk increases
  
  • significantly higher risk of VCF for the 24 Gy/fraction group and 20 to 23 Gy/fraction group.
  
  • baseline VCF, lytic tumor, and spinal misalignment (kyphosis/ scoliosis and subluxation/translation) were predictive

  Sahgal et al, JCO, Sept 2013
Response Assessment
Response assessment after stereotactic body radiotherapy for spinal metastasis: a report from the SPIne response assessment in Neuro-Oncology (SPINO) group. Thibault et al

- **Local Control**

<table>
<thead>
<tr>
<th>RECIST version 1.1&lt;sup&gt;35*&lt;/sup&gt;</th>
<th>MDACC&lt;sup&gt;37†&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Complete response</strong></td>
<td>Disappearance of target lesions</td>
</tr>
<tr>
<td><strong>Partial response</strong></td>
<td>≥30% decrease in sum of target lesion diameters</td>
</tr>
<tr>
<td><strong>Progressive disease</strong></td>
<td>≥20% increase in sum of target lesion diameters plus absolute increase of ≥5 mm, appearance of one or more new lesions, unequivocal progression of non-target lesions, or a combination</td>
</tr>
<tr>
<td><strong>Stable disease</strong></td>
<td>Any response other than complete or partial response and progressive disease</td>
</tr>
</tbody>
</table>

RECIST = Response Evaluation Criteria in Solid Tumors. MDACC = MD Anderson Cancer Center. *For bone metastases, osteolytic and mixed lesions are deemed measurable if identifiable soft tissue extension is ≥10 mm; osteoblastic metastases are non-measurable. †Measurements for bone metastases are based on the sum of a perpendicular bidimensional measurement of the greatest diameters of each individual lesion.

*Table 2: Imaging-based tumour response classifications*
Pain Response

- BPI preferred, with assessment based on worst pain score
- ICPRE should be adopted as standard guidelines for pain response
- Pain response should be assessed at 3 months after SBRT

<table>
<thead>
<tr>
<th>Complete response</th>
<th>ICPRE(^{41})*</th>
<th>MDACC(^{43})†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Score of 0 at the treated site in patients with baseline pain, and no increase in analgesic requirements (converted to OMED)</td>
<td>Average pain score of 0 for two consecutive questionnaire assessments</td>
<td></td>
</tr>
</tbody>
</table>

| Partial response | Pain reduction of ≥2 at the treated site without increase in OMED, or analgesic reduction of ≥25% from baseline without pain increase | Decrease of 2 points in the worst pain score for two consecutive questionnaire assessments |

| Pain progression | Pain score increase of ≥2 above baseline with stable OMED, or analgesic increase of ≥25% in OMED with a stable pain score or 1 point above baseline | Pain score > 0 that doesn’t change within 8 weeks from start of treatment, or a 2-point pain score increase sustained at a higher level for 1 month after the start of treatment, or pain score decrease ≥2 and subsequent sustained rise (≥2 increase on two consecutive questionnaire assessments) |

| Indeterminate response | Any response other than complete or partial response and pain progression | NA |

ICPRE=International Consensus Pain Response Endpoints. MDACC=MD Anderson Cancer Center. OMED=oral morphine equivalent dose. NA=not applicable. *Only the worst pain score for the previous 3 days should be assessed and scored on a scale of 0–10. †Criteria taken directly from study protocol.

Table 3: Pain response definitions
Optimal dose fractionation schedule?

- Ongoing randomized study from MSKCC (NCT01223248) is comparing two fractionation schedules- 27 Gy in three fractions (3 days) or 24 Gy in one fraction (1 day).
Comparison with EBRT

Sprave et al

- Phase II randomised trial comparing pain response b/w single-fraction SBRT (24 Gy) vs 3DCRT (30 Gy in 10 fractions).
- primary endpoint was pain relief of >2 points on the visual analog scale (VAS) measured within the irradiated region at 3 months
- At 3 months no differences in VAS score, 6 months following RT, significantly lower VAS values were reported in the SBRT group (p = 0.002).

Ongoing study phase III- Canadian Clinical Trials Group (CCTG) Symptom Control (SC)-24 (SC-24) trial (NCT02512965), comparing 24 Gy in 2 SBRT fractions vs 20 Gy in 5 EBRT fraction
## Re-Irradiation

<table>
<thead>
<tr>
<th>Study</th>
<th># patients / cases</th>
<th>Follow-up (months)</th>
<th>Myelopathy</th>
<th>Lcoal / pain control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Milker-Zabel 2003</td>
<td>18 / 19</td>
<td>12.3</td>
<td>0%</td>
<td>95%</td>
</tr>
<tr>
<td>Mahan 2005</td>
<td>8 / 8</td>
<td>15.2</td>
<td>0%</td>
<td>100%</td>
</tr>
<tr>
<td>Sahgal 2009</td>
<td>25 / 37</td>
<td>7</td>
<td>0%</td>
<td>70%</td>
</tr>
<tr>
<td>Choi 2010</td>
<td>42 / 51</td>
<td>7</td>
<td>n=1 G4</td>
<td>73%</td>
</tr>
<tr>
<td>Sterzing 2010</td>
<td>36 / 36</td>
<td>7.5</td>
<td>0%</td>
<td>63%</td>
</tr>
<tr>
<td>Damast 2010</td>
<td>94 / 97</td>
<td>12.1</td>
<td>0%</td>
<td>66%</td>
</tr>
<tr>
<td>Garg 2011</td>
<td>59 / 63</td>
<td>13</td>
<td>n=2 G3 peripheral nerve injury</td>
<td>76%</td>
</tr>
<tr>
<td>Mahadevan 2011</td>
<td>60 / 81</td>
<td>12</td>
<td>n=3 persistent radicular pain n=1 lower-extremity weakness</td>
<td>93%</td>
</tr>
<tr>
<td>Chang 2012</td>
<td>49 / 54</td>
<td>17.3</td>
<td>0%</td>
<td>79%</td>
</tr>
</tbody>
</table>

- Very low incidence of myelopathy
- Nerve damage a more frequent toxicity
- Promising local control 63 – 100%

### Clinical Practice:
- 0% risk of myelopathy if
  - Initial course <50Gy (EQD2/2)
  - SBRT course <25Gy (EQD2/2)
  - Interval >5 months

*Sahgal IJROBP 2010*
Post Operative SBRT

- Highly selected patients with single area of symptomatic MESCC decompressive surgery followed by RT can be considered.

- Consensus guidelines for postoperative stereotactic body radiation therapy for spinal metastases: results of an international survey.

<table>
<thead>
<tr>
<th>Indications</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radio-resistant primary 1–2 levels of</td>
<td>Involvement of more than 3 contiguous vertebral bodies</td>
</tr>
<tr>
<td>adjacent disease</td>
<td>ASIA Grade A status (complete spinal cord injury without preservation of</td>
</tr>
<tr>
<td></td>
<td>motor or sensory function)</td>
</tr>
<tr>
<td>Prior overlapping radiation therapy</td>
<td>Postoperative Bilsky Grade 3 residual (spinal cord compression without any</td>
</tr>
<tr>
<td></td>
<td>CSF around the spinal cord)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Volume</th>
<th>Include</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gross tumor volume (GTV)</td>
<td>Postoperative residual based on MRI</td>
</tr>
<tr>
<td>Clinical tumor volume (CTV)</td>
<td>Entire extent of preoperative tumor, anatomic compartment involved, &amp; any postoperative residual</td>
</tr>
<tr>
<td></td>
<td>Surgical instrumentation &amp; incision not included unless involved</td>
</tr>
<tr>
<td></td>
<td>Prophylactic circumferential treatment of epidural space controversial</td>
</tr>
<tr>
<td></td>
<td>Additional expansion up to 5 mm for paraspinal extension controversial</td>
</tr>
<tr>
<td></td>
<td>Consider an additional expansion of up to 5 mm cranio-caudally beyond known epidural disease extent based on pre- &amp; postoperative imaging</td>
</tr>
<tr>
<td>Planning target volume (PTV)</td>
<td>0- to 2-mm expansion from CTV</td>
</tr>
<tr>
<td>Spinal cord</td>
<td>True spinal cord based on postoperative T2-weighted MRI or CT myelogram in cases of significant hardware artifact</td>
</tr>
<tr>
<td>Spinal cord planning risk volume (PRV)</td>
<td>0- to 2-mm expansion of spinal cord volume</td>
</tr>
</tbody>
</table>
SBRT with 27Gy/3# to GTV, 27Gy/3# to CTV (SIB) alternate day (27.6.18 to 2.7.18)
Newer Radiopharmaceutical- Radium 223

• For wide spread osteoblastic metastases → P32 / Sr89 / Sm153 _ Beta emitters
• Radium 223 in alpha emitting radionuclide, high LET, half-life of 11.4 days.
• FDA approved in 2013 for treatment of bone pain in patients with mCRPC with no other visceral metastases.
• ALSYMPCA trial, showed a significant improvement in overall survival, delay in symptomatic skeletal events, and quality of life.
• Given intravenously over 1 minute at 50 kBq/kg body weight every 4 weeks for a total of 6 injections.
Questions unanswered

• “Better than expected” survival after ablative treatment.
• Effect on long term survival.
• Deffering initiation of systemic therapy.
• Immunologic response?
• Lack of level I evidence.
Oligo-metastatic breast cancers are rare and may have curative potential.

These patients can be identified through clinical features and maybe molecular parameters.

The biology of oligo-metastatic breast cancer is not well understood.

Adding curative therapy in this setting may have added value.