Radical Treatment of Brain Metastases: The importance of a neuro-oncology multi-disciplinary approach

ESMO Preceptorship in Lung Cancer
Manchester
6th – 8th March 2019

Dr Catherine McBain
Consultant Clinical Oncologist
The Christie NHS FT
DISCLOSURE OF INTEREST

I have no disclosures or competing interests

Catherine McBain
Topics

- Background and introduction
- Patient selection: Who gets what and why?
- Areas of debate
- Summary and take home messages
The changing problem

- Up to 50% of all lung cancer patients develop brain mets; incidence is increasing
- Role of surgery and SRS established for some time
- Benefit confined to those with controlled / radically treated systemic disease

**But:**
- The boundaries of radically treatable / controllable systemic disease are changing
- Synchronous presentation is common
- Learning more about different disease subtypes
- Falling enthusiasm for whole brain radiotherapy
The QUARTZ study

Dexamethasone and supportive care with or without whole brain radiotherapy in treating patients with non-small cell lung cancer with brain metastases unsuitable for resection or stereotactic radiotherapy (QUARTZ): results from a phase 3, non-inferiority, randomised trial


Patients approached if:
• There was uncertainty in the clinicians’ or patients’ minds about the potential benefit of WBRT

• A multidisciplinary team that included both neurosurgeons and radiation oncologists had concluded that the patient was unsuitable for either surgery or stereotactic radiotherapy
The QUARTZ study

Dexamethasone and supportive care with or without whole brain radiotherapy in treating patients with non-small cell lung cancer with brain metastases unsuitable for resection or stereotactic radiotherapy (QUARTZ): results from a phase 3, non-inferiority, randomised trial


Patients approached if:
• There was uncertainty in the clinicians’ or patients’ minds about the potential benefit of WBRT
• A multidisciplinary team that included both neurosurgeons and radiation oncologists had concluded that the patient was unsuitable for either surgery or stereotactic radiotherapy
Evolution of Brain Metastases management

- Pre 1990s: Poor Prognosis: WBRT / Best supportive care

- 1990s: Surgery + WBRT superior to WBRT alone
  - Improved OS: 10 months vs 4 months
  - Patchell RA et al. NEJM 1990;322:494–500

- 2000s: SRS + WBRT superior to WBRT alone
  - Improved OS: 6.5 months vs 4.9 months, improved PS, reduced steroids

- Surgery or SRS? Retrospective series – No RCTs
  - Survival benefit from surgery = SRS

- Patient selection?
- Role of WBRT?
- Additional treatment after neurosurgical resection?
- Sequencing / integration with systemic therapies?
Stereotactic Radiosurgery (SRS)

- Highly targeted RT
- Sub-mm accuracy
- High dose, single fraction (single / < 5 visits)
- Spares normal brain
- Not appropriate for diffuse disease e.g. leptomeningeal disease, skull bone mets
When we talk about SRS, it is *platform independent*

- Gamma knife
- Cyberknife
- Linacc-based / Novalis Tx
Methods of SRS delivery: Gamma knife
Methods of SRS delivery: Cyberknife
Methods of SRS delivery
Linear–accelerator based: Novalis TX
Patient selection for treatment of brain metastases is an interplay between:

- Extra-cranial disease:
  - Controlled / controllable / progressing
  - Prognosis

- Intra-cranial disease:
  - Number / volume / location of metastases
  - Mass effect
  - Certainty of diagnosis

- Patient-related factors:
  - Performance status
  - Preference
  - Intercurrent medical problems e.g. COPD
So, how do we decide who benefits?

Who should we refer to a neuro-MDT?
Evolution of Graded Prognostic Assessment
Different factors scored; total score predicts survival

1997
1200 patients
• Age < 65
• KP ≥ 70
• Controlled primary
• No extracranial mets
RPA class I-III

2010
4,259 patients
• Age
• KP
• Primary tumour type
• Treatment
• Number of brain mets

2017
2,186 patients
• Tumour sub-type
• EGFR / ALK mut
• KP
• Age
• Number of mets
• Extra-cranial disease

*Gaspar L Int J Rad Oncol Biol Phys 1997;37:745-751
#Sperduto PW et al Int J Radiation Oncol Biol Phys 2010:77;655-661
#Sperduto PW et al JCO 2012;30(4):419-425
$Sperduto PW et al JAMA Oncology 2017:3:827-832
Estimating Survival in Patients With Lung Cancer and Brain Metastases
An Update of the Graded Prognostic Assessment for Lung Cancer Using Molecular Markers (Lung-molGPA)

Paul W. Sperduto, MD, MPP; T. Jonathan Yang, MD; Kathryn Beal, MD; Hubert Pan, MD; Paul D. Brown, MD; Ananta Bangdiwala, MS; Ryan Shanley, MS; Norman Yeh, MD; Laurie E. Gaspar, MD, MBA; Steve Braunstein, MD; Penny Sneed, MD; John Boyle, MD; John P. Kirkpatrick, MD, PhD; Kimberley S. Mak, MD; Helen A. Shih, MD; Alex Engelman, MD; David Roberge, MD; Nils D. Arvold, MD; Brian Alexander, MD; Mark M. Awad, MD, PhD; Joseph Contessa, MD; Veronica Chiang, MD; John Hardie, MD, PhD; Daniel Ma, MD; Emil Lou, MD; William Sperduto, BA; Minesh P. Mehta, MD
<table>
<thead>
<tr>
<th>Prognostic Factor</th>
<th>GPA Scoring Criteria(^a)</th>
<th>0</th>
<th>0.5</th>
<th>1.0</th>
<th>Patient Score(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age. y</td>
<td>(\geq 70)</td>
<td>(&lt;70)</td>
<td>NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>KPS</td>
<td>(&lt;70)</td>
<td>80</td>
<td>90-100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECM</td>
<td>Present</td>
<td>Absent</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brain metastases, No.</td>
<td>(&gt;4)</td>
<td>1-4</td>
<td>NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gene status</td>
<td>(EGFR) neg/unk and (ALK) neg/unk</td>
<td>NA</td>
<td>(EGFR) pos or (ALK) pos</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 2. Updated DS-GPA for NSCLC With Brain Metastases (Lung-molGPA) Scoring Chart and Worksheet to Estimate Survival

<table>
<thead>
<tr>
<th>Prognostic Factor</th>
<th>GPA Scoring Criteria</th>
<th>Patient Score^b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age. y</td>
<td>≥70</td>
<td>&lt;70</td>
</tr>
<tr>
<td>KPS</td>
<td>&lt;70</td>
<td>80</td>
</tr>
<tr>
<td>ECM</td>
<td>Present</td>
<td></td>
</tr>
<tr>
<td>Brain metastases, No.</td>
<td>≥4</td>
<td>1-4</td>
</tr>
<tr>
<td>Gene status</td>
<td>EGFR neg/unk and ALK neg/unk</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

---

A. Adenocarcinoma

![Graph showing survival rates for adenocarcinoma](image)

- No. at risk: GPA 0-1 = 337, GPA 1.5-2 = 664, GPA 2.5-3 = 455, GPA 3.5-4 = 65
- Months From Start of Brain Metastasis Treatment: 6.9

B. Nonadenocarcinoma

![Graph showing survival rates for nonadenocarcinoma](image)

- No. at risk: GPA 0-1 = 175, GPA 1.5-2 = 324, GPA 2.5-3 = 166
- Months From Start of Brain Metastasis Treatment: 5.3
Table 2. Updated DS-GPA for NSCLC With Brain Metastases (Lung-molGPA) Scoring Chart and Worksheet to Estimate Survival

<table>
<thead>
<tr>
<th>Prognostic Factor</th>
<th>GPA Scoring Criteriaa</th>
<th>Patient Scoreb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>0</td>
<td>0.5</td>
</tr>
<tr>
<td>KPS</td>
<td>≥70</td>
<td>&lt;70</td>
</tr>
<tr>
<td>ECM</td>
<td>Present</td>
<td>80</td>
</tr>
<tr>
<td>Brain metastases, No.</td>
<td>&gt;4</td>
<td>NA</td>
</tr>
<tr>
<td>Gene status</td>
<td>EGFR neg/unk and ALK neg/unk</td>
<td>NA</td>
</tr>
<tr>
<td>Total</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

A) Adenocarcinoma

B) Nonadenocarcinoma

No. at risk

<table>
<thead>
<tr>
<th>GPA 0-1</th>
<th>GPA 1.5-2</th>
<th>GPA 2.5-3</th>
<th>GPA 3.5-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>GPA 0-1</td>
<td>337</td>
<td>47</td>
<td>9</td>
</tr>
<tr>
<td>GPA 1.5-2</td>
<td>664</td>
<td>189</td>
<td>53</td>
</tr>
<tr>
<td>GPA 2.5-3</td>
<td>455</td>
<td>228</td>
<td>93</td>
</tr>
<tr>
<td>GPA 3.5-4</td>
<td>65</td>
<td>50</td>
<td>18</td>
</tr>
</tbody>
</table>

No. at risk

<table>
<thead>
<tr>
<th>GPA 0-1</th>
<th>GPA 1.5-2</th>
<th>GPA 2.5-3</th>
<th>GPA 3.5-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>GPA 0-1</td>
<td>175</td>
<td>15</td>
<td>4</td>
</tr>
<tr>
<td>GPA 1.5-2</td>
<td>324</td>
<td>75</td>
<td>21</td>
</tr>
<tr>
<td>GPA 2.5-3</td>
<td>166</td>
<td>54</td>
<td>15</td>
</tr>
</tbody>
</table>
In a nutshell ..... 

In referring to neuro–MDT consider prognosis and treatment of extra–cranial disease *first*

*If we know that your patient is of good prognosis, we’ll think about the intra–cranial options…*

*(Referral is not indicated or appropriate for everyone)*
So: Aggressive treatment in the brain can result in prolonged survival, particularly for some subgroups

but

*how do we decide who gets what?*
The Neuro–Oncology Multidisciplinary Team

Neuro–surgeons  Clinical Nurse Specialists
Neuro–oncologists  Physio / OT
Neuro–radiologists  MDT Co–ordinators
Neurologists  Data Manager
Surgery:
- Mass effect
- Diagnostic uncertainty
Surgery: Hydrocephalus
SRS: Multiple lesions / inoperable locations
So.......SRS or surgery?
Surgery vs SRS: Pros and cons

**Surgery**
- Confirms histology
- Larger lesion
- Faster resolution of symptoms
- Faster tapering of dex
- Risk of neurological decline
- Complications usually immediate (6%)
- Relies on fitness for GA

**SRS**
- Known histology
- Smaller lesion <3cm, no mass effect
- Possible in eloquent regions
- Out-patient treatment; possible in older, less fit patients
- Complications usually delayed
- Risk of radiation necrosis
- Longer use of steroids
Critical areas of the brain

Motor cortex

Speech areas
Solitary brain metastases involving the motor strip
2 or more lesions: 1 best treated with surgery, others for SRS
Advantages of a Neuro–oncology MDT

- Specialist confirmation of imaging diagnosis
- Simultaneous assessment of whether surgery or SRS is the most appropriate modality
- Panel of opinion – 5 surgeons, 4 clinical oncologists
- Clinical oncology input to help guide surgical decision-making with respect to prognosis / future treatment options
- Swift, smooth patient pathway; optimal communication
- No delays (hopefully!)
Other controversies in patient selection:

- Number of metastases able to treat with SRS

- Evidence that volume is more important than number

- UK Guidelines: Total mets vol ≤ 20cc

- Role of WBRT?
How many mets can you / should you treat with SRS?
(Assume fit patient and volume < 20cc)

- RCTs used 3 or 4 metastases, but there is no clear biological rationale for that number
- No clear survival difference between incremental increases in the number of metastases; difficult to set an arbitrary maximum
- Some centres are able to treat > 10 metastases safely and with good outcomes
- UK NICE Guidance: No recommendation regarding the maximum number of metastases to be treated with SRS
- Inter-clinician variation re your view of microscopic disease
- 10 (maybe up to 15) is a commonly-employed practical maximum (decision inherently linked to lung sub-type)
SRS for multiple brain mets

- Prospective observational study from 23 facilities in Japan
- 1 to 10 newly diagnosed brain metastases
- Karnofsky PS ≥ 70 or higher
- Largest tumour <10 mL in volume, <3 cm in longest diameter
- Total cumulative volume ≤15 mL

Yamamoto et al Lancet Oncol 2014; 15(4):387-95
What happens after surgery?

- Observation
- Adjuvant WBRT
- Cavity SRS

- 3 recent definitive trials:
  - Adjuvant WBRT vs Observation
    Kocher M et al. J Clin Oncol 2011;29; 134-141
  - Cavity SRS vs Observation
  - Adjuvant WBRT vs Cavity SRS
In a nutshell.....

- Both WBRT and cavity SRS reduced local recurrence following resection of a brain met ◦ (from approx. 60–70% to 20–30% at 12 months)
- Neither improved OS
- WBRT results in reduced relapse elsewhere in the brain
- SRS results in better QOL, longer functional independence, longer time until cognitive deterioration
- Recent change in thinking: *Active* surveillance or cavity boost
  - (Clinical challenges: Difficulty defining cavity, margin of normal tissue, dose especially for larger cavities)
### Post-resection options: Pros and cons

<table>
<thead>
<tr>
<th><strong>WBRT</strong></th>
<th><strong>SRS</strong></th>
<th><strong>Surveillance</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduces local failure (at resection site)</td>
<td>Reduces local failure</td>
<td>Spares patients treatment they might not need</td>
</tr>
<tr>
<td>Reduces distant failure (new mets elsewhere in the brain)</td>
<td>Local control inferior to WBRT</td>
<td>Allows use of systemic therapy</td>
</tr>
<tr>
<td>Risk of neuro-cognitive decline</td>
<td>Better cognition, QOL &amp; functional independence</td>
<td>Need 3-monthly MR scans</td>
</tr>
<tr>
<td>Fatigue &amp; toxicity</td>
<td>Unresolved technical issues / logistical questions</td>
<td>(Allows time to ascertain behaviour of disease)</td>
</tr>
</tbody>
</table>
Hippocampal sparing WBRT

- Possible with modern radiotherapy techniques
- Single arm US study reported improved neurocognitive outcomes compared to historic data on WBRT
- UK multicentre HIPPO Phase II RCT of WBRT vs HS-WBRT post-op or post-SRS – closed early due to failure to recruit
Radiation necrosis / post treatment change

- A reaction following SRS
- Enlargement of the lesion treated; surrounding oedema
- Can come on spontaneously 6–12 months post-treatment
- Very difficult to differentiate from progressive disease
- Appearances may be exacerbated by immunotherapy agents

Management:
- Observe (+/- dexamethasone) and re-scan after 6–8 weeks
- Additional MR imaging e.g. MR Perfusion
- Often settles
- If very symptomatic / concerning may be resected
March 2017: SRS to solitary met

June & Aug 2017: Response

Dec 2017: Florid change; resected
Can you re-treat with SRS?

- You can treat different, additional areas of the brain
- You can re-treat previously treated areas BUT the risk of radiation necrosis rises
- Need to carefully weigh-up
  - Response to initial SRS
  - Duration since previous SRS
  - The disease as a whole – *treat the patient, not the scan*
- Some units are more enthusiastic about re-treating than others
The benefit of SRS or surgery in selected subgroups of NSCLC patients is well-established.

Management strategies for oncogene-addicted NSCLC are developing rapidly.

Control / treatment of extra-cranial disease and performance status dictate prognosis.

If extra-cranial disease is controlled and prognosis good, a more aggressive approach in the brain is beneficial and justifiable.
Take home messages

- Management of brain metastases must be individualised

- Patients may have different treatments at different times – a ‘brain mets journey’

- If omitting adjuvant post-op XRT, 3-monthly MR brain follow-up is required

- Many questions remain regarding sequencing and combining treatments
Summary

- A well-constituted neuro-oncology multi-disciplinary team enhances patients’ care and treatment pathways

- Good communication is vital in optimising care

Suggested reading:

*Metastatic Brain Disease from NSCLC – Getting Back to the Drawing Board*

A Greystoke and P Mulvenna

*Clinical Oncology* 2018; 30;137–143

Thank you
Early Versus dElayed on demand Radiosurgery (EVER) for newly diagnosed measurable brain metastases in driver mutated non-small cell lung cancer (NSCLC) - A phase 2 randomized multi-center study.

Nicolaus Andratschke, University Hospital, Zurich
Areas of debate: Synchronous presentation

- Presentation with new neurological symptoms
  - Brain scan → Brain mets
  - Body scan → Unsuspected primary Ca lung

- Brain metastases detected during routine diagnostic staging / work-up
  - MR brain imaging
    - Prior to surgery
    - Clinical trial screening
  - PET imaging
## Synchronous presentation: Outcomes following surgery or SRS

<table>
<thead>
<tr>
<th>Year</th>
<th>SRS / Sx</th>
<th>No of pts</th>
<th>Med OS</th>
<th>5yr OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flannery 2008</td>
<td>SRS</td>
<td>42</td>
<td>18mo</td>
<td>21%</td>
</tr>
<tr>
<td>Bonnette 2001</td>
<td>Sx</td>
<td>103</td>
<td>12mo</td>
<td>11%</td>
</tr>
<tr>
<td>Billing 2001</td>
<td>Sx</td>
<td>28</td>
<td>24mo</td>
<td>21%</td>
</tr>
<tr>
<td>Hu 2006</td>
<td>Either</td>
<td>84</td>
<td>SI 26mo SIII 9mo</td>
<td>7.6%</td>
</tr>
</tbody>
</table>

*Outcome depends on primary disease stage and treatment*

60% – 80% died of non-neurological causes

Long term survival in patients with synchronous, solitary brain mets from NSCLC treated with SRS

- 42 patients, diagnosed 1993 – 2006 (i.e. < 4 pa)

- Most important prognostic factor was management of thoracic disease (and KPS)

- Definitive thoracic therapy (26/42):
  - Median Survival 26 months
  - 5 yrs survival 34%

- Non–definitive thoracic therapy (16/42):
  - Median Survival 13months,
  - 5 yrs survival 0%

5% of NSCLC have ALK-rearranged NSCLC

Brain mets are common in this sub-population

90 patients, diagnosed in 6 US institutions 2007 – 14
- 74% stage 4 at diagnosis
- 47% had ≥ 4 brain mets
Outcomes

- Median OS after diagnosis of brain metastases: 49.5 months (> 4 years!)
- 1 year overall survival: 72%
- 2 year overall survival: 66%
- Most patients had various treatments at different times – SRS, WBRT, surgery
- ‘Brain mets journey’
Prognostic Factors

- KP > 90
- No extracranial mets
- TKI-naive

Not prognostic:
- Number of mets
- Age
- Smoking history
- Initial type of radiotherapy

Conclusion
- Many of these patients have prolonged survival; sparing of late toxicity is vital
- Consider first-line SRS, close CNS observation and treatment of emergent CNS disease