Indications for stereotactic radiosurgery (SRS) for brain metastases
(Clatterbridge Centre for Oncology, Walton Centre for Neurology and Neurosurgery)
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1. Introduction
Brain metastases constitute a significant disease burden and have a major impact on morbidity and mortality, including significant cognitive impairment at the time of presentation (1, 2). Brain metastases are not recorded by the Office for National Statistics, so figures for the UK are estimates. In the North West there are an estimated 4200 new case per year. For the majority of patients with metastatic brain cancer the prognosis is poor and survival is around 3 months (data from CCO audit of all patients with brain metastases – personnel communication with Brian Haylock). In the reported literature, the median survival is ~7 months (3), although this is likely to represent publication bias. In view of the generally poor prognosis for patient with brain metastases, careful selection of suitable patients is essential to avoid unnecessary risk to those unlikely to benefit from treatment. The recursive partitioning analysis (RPA) classification system can be used to determine the likely prognosis in cerebral metastases (4).

Table 1
Components of the RPA classification system.
KPS = Karnofsky Performance Status.
KPS ≥ 70: self-caring, but not capable of normal activity or work

<table>
<thead>
<tr>
<th>Class</th>
<th>Clinical parameters</th>
<th>Median overall survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>&lt;65 years; KPS ≥ 70; controlled primary; no extracranial spread</td>
<td>7.1</td>
</tr>
<tr>
<td>II</td>
<td>≥65 years; KPS ≥ 70; uncontrolled primary; extracranial spread</td>
<td>4.2</td>
</tr>
<tr>
<td>III</td>
<td>KPS &lt; 70</td>
<td>2.3</td>
</tr>
</tbody>
</table>

Patients likely to benefit most from aggressive treatment are those with:
- Good functional status
- Controlled primary and extra-cranial disease
2. Current treatment paradigms for brain metastases

Treatment strategies aim to improve locoregional control of cerebral metastasis and utilise surgery, radiosurgery and whole brain radiotherapy in various combinations. The benefits of locoregional control as a means to potentially prolong overall survival must be balanced against patient quality of life and neurological function. The trial data supporting the following treatment paradigms are presented in table 2.

Table 2

Best available trial evidence for treatment of brain metastasis using a combination of surgical resection, WBRT and SRS (5-12). Where median local and distant progression free survival was not reported in the original paper, the 1 year control rate is listed instead. OS = overall survival. PFS = progression free survival. NS = Not significant. RCT = randomised controlled trial.

<table>
<thead>
<tr>
<th>Study type</th>
<th>Intervention (+ patients)</th>
<th>Median OS</th>
<th>Local control</th>
<th>Overall brain control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resection + WBRT -&gt; Resection</td>
<td>Resection (n=23)</td>
<td>9.0 months</td>
<td>Median PFS</td>
<td>Median PFS</td>
</tr>
<tr>
<td>Keifer et al (2005)</td>
<td>Resection + WBRT (n=25)</td>
<td>11.0 months</td>
<td>Median PFS</td>
<td>Median PFS</td>
</tr>
<tr>
<td>Resection + WBRT -&gt; Resection</td>
<td>Resection (n=49)</td>
<td>10.0 months</td>
<td>Median PFS</td>
<td>Median PFS</td>
</tr>
<tr>
<td>Patil et al (2008)</td>
<td>Resection + WBRT (n=49)</td>
<td>11.0 months</td>
<td>Median PFS</td>
<td>Median PFS</td>
</tr>
<tr>
<td>Resection + WBRT -&gt; Resection</td>
<td>Resection (n=31)</td>
<td>10.0 months</td>
<td>Median PFS</td>
<td>Median PFS</td>
</tr>
<tr>
<td>Mancuso et al (2006)</td>
<td>Resection + WBRT (n=33)</td>
<td>11.0 months</td>
<td>Median PFS</td>
<td>Median PFS</td>
</tr>
<tr>
<td>Resection + WBRT -&gt; WBRT</td>
<td>WBRT (n=167)</td>
<td>8.0 months</td>
<td>Median PFS</td>
<td>Median PFS</td>
</tr>
<tr>
<td>Andrews et al (2004)</td>
<td>SRS + WBRT (n=164)</td>
<td>9.0 months</td>
<td>Median PFS</td>
<td>Median PFS</td>
</tr>
<tr>
<td>Resection + WBRT -&gt; SRS + WBRT</td>
<td>SRS alone (n=33)</td>
<td>12.0 months</td>
<td>Median PFS</td>
<td>Median PFS</td>
</tr>
<tr>
<td>SRS alone -&gt; WBRT</td>
<td>SRS alone (n=23)</td>
<td>9.0 months</td>
<td>Median PFS</td>
<td>Median PFS</td>
</tr>
<tr>
<td>Li et al (2008)</td>
<td>SRS + WBRT (n=67)</td>
<td>11.0 months</td>
<td>Median PFS</td>
<td>Median PFS</td>
</tr>
<tr>
<td>SRS + WBRT -&gt; SRS alone</td>
<td>SRS alone (n=67)</td>
<td>13.0 months</td>
<td>Median PFS</td>
<td>Median PFS</td>
</tr>
<tr>
<td>Aoyama et al (2006)</td>
<td>SRS alone (n=67)</td>
<td>12.0 months</td>
<td>Median PFS</td>
<td>Median PFS</td>
</tr>
<tr>
<td>SRS alone -&gt; WBRT</td>
<td>SRS alone (n=67)</td>
<td>14.0 months</td>
<td>Median PFS</td>
<td>Median PFS</td>
</tr>
<tr>
<td>Siongco et al (2000)</td>
<td>SRS + WBRT (n=34)</td>
<td>15.0 months</td>
<td>Median PFS</td>
<td>Median PFS</td>
</tr>
<tr>
<td>Santos et al (2000)</td>
<td>SRS alone (n=62)</td>
<td>16.0 months</td>
<td>Median PFS</td>
<td>Median PFS</td>
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</table>

Despite the substantial number of publications on the treatment of brain metastasis, there is a relative paucity of good quality studies investigating the various management options. Based in the current literature evidence the following recommendations can be applied to the management of newly diagnosed brain metastasis (13).

1. WBRT plus surgical resection is better than surgery alone with respect to reduced risk of distant brain metastasis
2. WBRT plus surgical resection is superior to WBRT alone with respect to prolonged survival and preserved functional status in single metastasis
3. Local tumour control can be achieved with either surgical excision or SRS, but treatment choice may depend on tumour location radiosurgery availability
4. Local tumour control (surgery or SRS) in combination with WBRT improves survival in single brain metastasis
5. Omission of WBRT results in worse local and regional control but does not appear to affect survival
6. SRS alone can provide effective local control (imaging surveillance for distant recurrence is necessary) and is associated with less cognitive decline compared to WBRT treated patients

Ultimately, the optimal management strategy for patients will be individually tailored according to clinical disease status and after appropriate discussion by the treating multi-disciplinary team. The rationale behind the available strategies is local control by resection or SRS, followed by management of the rest of the brain to address regional control. Historically this has been with whole brain radiotherapy, but more recently, focus has shifted towards investigation of the cognitive impact of WBRT and whether SRS can be used as an alternative (14, 15). Whilst the primary aim is disease control, this may come at the expense of cognitive function and several recent studies have demonstrated that omission of WBRT and treatment with SRS alone preserves neurocognition for longer (14, 15). These findings may represent the start of a paradigm shift away from whole brain radiotherapy in the treatment of brain metastasis and highlights the continuing need for clinical trials to assess not only traditional outcome measures of survival and disease control, but also cognitive function and quality of life.

3. Case load estimates for SRS in Liverpool
Estimates of the number of patients with brain metastases who would benefit from SRS have been collected from various sources.

a) Walton Centre audit data

Objectives
To determined the proportion of surgically resected brain metastasis that would have been suitable targets for SRS

Design / Subjects
All patients undergoing surgery for brain metastases between April 2007 and March 2009 at The Walton Centre for Neurology and Neurosurgery.

Methods
Eligible patients identified from pathology database. Pre-operative CT/MRI reviewed by 2 neurosurgeons (MD Jenkinson & M Javadpour) to determine tumour size (mm), composition (solid vs- cystic) and location, presence of hydrocephalus or midline shift, and number of metastases. Suitable SRS targets were defined as: <30mm diameter, no hydrocephalus, no symptomatic mass effect, solid tumour.

Results
116 patients (median age 63 years) underwent surgical resection for metastasis followed by whole brain radiotherapy (WBRT). Five patients had further surgery at recurrence. 86 were supratentorial, 30 infratentorial. 101 cases (87%) had solitary metastasis; 15 (13%) had multiple metastases. Median tumour diameter was
34mm (range: 12-70mm). 41 cases (35%) were suitable targets for SRS. Size (n=65), cystic tumour (n=18) and hydrocephalus (n=7) alone and in combination were the commonest reasons for lack of suitability. Median overall survival after surgery and WBRT was 6.2 months.

**Conclusion**

One third of surgically resected brain metastases are suitable targets for stereotactic radiosurgery. This equates to approximately 20 cases / year. It should be noted that not all patients with surgically treatable brain metastases are referred for a neurosurgical opinion, therefore the number is likely to be higher.

**b) Data from other stereotactic radiosurgery services (personal communication)**

The South West has a relatively static population of 1.8 million (our own North West population is also relatively static). The South West SRS service is based in Plymouth and has been running for approximately 6 years. They treat ~20-30 brain metastasis cases per year following discussion at the neuro-oncology multi-disciplinary team (MDT) meeting. This equates to approximately 50 patients per annum for the Walton catchment population.

**c) Non-resectable brain metastases**

Due to the previous limited availability of SRS, patients with in-operable metastases were often treated with whole brain radiotherapy only. There is likely to be a number of patients who would benefit from SRS. It is difficult to estimate the number.

**Based on our own audit data, extrapolating from the Plymouth SRS service figure and the estimates from the business case, we anticipate that in the initial phase, 50-100 patients with brain metastases would be suitable and eligible for SRS.**

**4. Eligibility criteria for SRS**

- Surgery not indicated to relieve symptomatic mass effect
- Karnofsky Performance status ≥ 70 (equates to ECOG / WHO performance status 0-2)
- ≤ 30 mm maximum tumour diameter (≤ 40mm if surgically inaccessible disease) [the treatment size limit also depends on volume, not just the largest diameter]
- ≤ 3 brain metastases (up to 4 if otherwise good prognosis).
- Primary tumour and extracranial disease controlled or only slowly progressing (or a radically treatable primary tumour without extracranial metastases in a newly diagnosed patient).
- Case discussed at neuro-oncology MDT

**These criteria apply to newly diagnosed brain metastases and recurrent brain metastases after previous surgery, SRS or WBRT.**
5. Proposed Liverpool brain metastases treatment pathway

This allows treatment to be tailored to each individual patient, following discussion at the MDT.

6. References


