A Population-Based Study on the Uptake and Utilization of Stereotactic Radiosurgery (SRS) for Brain Metastasis in Nova Scotia

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Outline

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• Background: SRS
• Current Guidelines
• Study Objectives
• Study Design / Inclusion Criteria
• Statistical Methods
• Patients and Results
• Multivariate Analysis
• Results with SRS
• SRS utilization trends
• Conclusions and future directions
Background

- 20–40% of all patients with cancer will develop brain metastasis
- the most common intracranial tumour
- survival for untreated patients is generally less than 7-12 weeks.
Management of Brain Metastasis:

- Steroids
- WBRT (1950’s)

Published randomized trials:

- Altered dose fractionation schedules (1970’s-1990’s)
- Radiosensitizers (1990’s – 2000’s)
- Chemotherapy (1990’s – 2000’s)
- Surgery for single brain metastasis (1990’s)
- Radiosurgery (1990’s – 2000’s)
Background

- The RTOG devised three prognostic groups using recursive partitioning analysis based on data of 1200 patients: (Gaspar et al, IJROBP 1997;37:745)

- Class I (median survival 7.1 months):
  - KPS ≥ 70, age < 65
  - controlled primary tumor
  - no extra cranial mets
- Class II (median survival 4.2 months):
  - all who are not I or III
- Class III (median survival 2.3 months)
  - KPS < 70

Fig. 3. Survival curves for Class I, II, III.
Background

- Randomised trials have reported that aggressive local therapy (surgery or SRS) in addition to regional therapy (WBRT) improves survival in selected patients.

- RTOG 95-08 trial (Andrews et al): survival benefit for the addition of SRS to WBRT.

- Kondziolka et al: interim analysis showed a dramatic advantage to adding SRS (median time to local failure: 6 months vs. 36 months).

- For patients with good performance the addition of aggressive local therapy in the form of resection or SRS is recommended.
Stereotactic RadioSurgery (SRS)

- Stereotactic – use of a 3D co-ordinate system to locate intracranial targets precisely
- Radiosurgery – specialized radiation technique typically using a single fraction of focused high dose radiation associated with rapid drop-off of radiation dose outside the target
Gamma-Knife

Images from www.gammaknife.com
Linear Accelerator based SRS
Current Evidence-Based Recommendations

- **Level 1**: Single-dose SRS along with WBRT leads to significantly longer survival compared with WBRT alone for patients *single* metastatic brain tumors who have KPS ≥ 70
- **Level 2**: Single-dose SRS along with WBRT is superior in terms of local tumor control and maintaining functional status when compared to WBRT alone for patients with 1-4 brain metastatic tumors who have a KPS ≥ 70
- **Level 3**: Single-dose SRS along with WBRT may lead to significantly longer patient survival than WBRT alone for patients with 2-3 metastatic brain tumors
Current Guidelines / ASTRO 2012

• Single-dose SRS boost is currently recommended after WBRT for all patients with brain metastasis who have:
  • Limited number of lesions: 1-3 (upto 4*), AND
  • Largest lesion < 4 cm in size, AND
  • “Good prognosis”:
    » KPS ≥ 70
    » Primary tumor controlled/being treated
    » expected survival ≥ 3 months
Concerns

• SRS is still a relatively new technology
• not yet widely available due to logistic and financial considerations.
• A Canadian Association of Radiation Oncology (CARO) survey found that the main barriers for access to SRS were:
  – the need to purchase and/or upgrade linear accelerators or gammaknife (67%)
  – the need to purchase and/or upgrade planning systems (58%)
  – the need to train existing oncologists to deliver SRS (42%).
• It is very likely that this treatment is underutilized, potentially shortening the survival time of a large number of patients.
Why a Population-Based Study

• Data regarding the benefit of SRS is limited
• There are very few trails and no large meta-analysis to confirm the benefit
• Strictly following guidelines would require a large expansion of existing SRS programs and a significant expenditure by provinces to obtain infrastructure and trained staff
• Hence, more data and evidence is required regarding the benefits of SRS
• Population-based studies are cohort studies of an entire ‘defined’ population. They help confirm the results of randomized trials at the population level:
  – External Validity
  – Generalization beyond the study / clinical trail setting
Study Objectives

1) Quantify the underutilization of SRS in Nova Scotia by documenting the number of patients eligible, and number of patients who did get SRS.
   • This will be used to estimate the number of patients who would benefit from further expansion of the SRS program.

2) Evaluate the patient and prognostic factors associated with the use of SRS.

3) Compare the outcomes with the use of WBRT, with and without SRS, in Nova Scotia to clinical trials reported in literature.
Study Design

- Design: Retrospective population-based cohort study
- Period: June 2006 – June 2010
- Data Source:
  - Cancer Care Nova Scotia, Cancer Registry
  - Radiation Therapy SRS Treatment Records
  - Chart Review, OPIS data, HPF, web1000
  - Provincial Death Registry
- Search Criteria:
  - All patients who received WBRT during the study period
Statistical Methods

- SPSS PASW Statistics 17 ©
- Primary endpoint: overall survival (OS).
- Chi Square ($\chi^2$) test will be used to compare rates.
- Univariate analysis for survival will be done using the Kaplan–Meier method
- Prognostic factors compared using the log-rank test
- Multiple-covariate analysis to detect independent prognostic factors using the stepwise Cox’s proportional hazards regression model, with statistical tests for the hypotheses outlined above.
Inclusion Criteria

• Age ≥ 18 years
• Received WBRT during the study period
• Primary diagnosis of:
  – Ca Breast
  – Colorectal Ca
  – NSCLC
  – SCLC
  – Renal Cell Ca
  – Melanoma
  – “unknown primary”
• Treated for Brain Metastasis:
  – Diagnosis of brain metastasis confirmed by CT or MRI
  – Palliative patients who did not receive WBRT, excluded
Patients

n = 710

Sydney: n = 180

Halifax: n = 530

Excluded n = 63

Included for Chart Review: n = 647

“Good Prognosis” N = 283

WBRT + Surgery n = 44

WBRT + SRS n = 73

WBRT alone n = 166

Poor Prognosis

n = 364
Results: all patients

- At last follow-up, the majority of patients (61.6%) had documented intracranial disease progression.
- At the time of analysis, 86.8% of patients had died.
- The 1 year OS for our entire patient population is 25.6%.
- Median survival 5.5 months.
## Results

<table>
<thead>
<tr>
<th>RPA Class</th>
<th>p value</th>
<th>1-yr OS</th>
<th>Median Survival</th>
<th>RTOG (1997)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-</td>
<td>50.2%</td>
<td>13.7 months</td>
<td>7.1 months</td>
</tr>
<tr>
<td>2</td>
<td>&lt;0.01</td>
<td>32.8%</td>
<td>7.4 months</td>
<td>4.2 months</td>
</tr>
<tr>
<td>3</td>
<td>&lt;0.001</td>
<td>8.4%</td>
<td>3.1 months</td>
<td>2.3 months</td>
</tr>
</tbody>
</table>

The diagram illustrates the survival curves over time (months) for different RPA classes.
<table>
<thead>
<tr>
<th>KPS</th>
<th>p value</th>
<th>1-yr OS</th>
<th>Median Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥70</td>
<td>-</td>
<td>35.3%</td>
<td>7.8 months</td>
</tr>
<tr>
<td>&lt;70</td>
<td>&lt;0.001</td>
<td>10.9%</td>
<td>3.5 months</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age</th>
<th>p value</th>
<th>1-yr OS</th>
<th>Median Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;65</td>
<td>-</td>
<td>29.7%</td>
<td>6.7 months</td>
</tr>
<tr>
<td>≥65</td>
<td>&lt;0.001</td>
<td>19.2%</td>
<td>4.4 months</td>
</tr>
</tbody>
</table>
# Brain mets

<table>
<thead>
<tr>
<th># Brain mets</th>
<th>Survival Rate</th>
<th>Median</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>38.9%</td>
<td>7.9</td>
<td>-</td>
</tr>
<tr>
<td>2-3</td>
<td>21.4%</td>
<td>5.8</td>
<td>P&lt;.01</td>
</tr>
<tr>
<td>&gt;3</td>
<td>12.6%</td>
<td>3.6</td>
<td>P&lt;.01</td>
</tr>
</tbody>
</table>
Patients

n = 710

Sydney: n = 180

Included for Chart Review: n = 647

Halifax: n = 530

Excluded n = 63

n = 364 Poor Prognosis

“Good Prognosis” N = 283

WBRT + Surgery n = 44

WBRT + SRS n = 73

WBRT alone n = 166
Inclusion Criteria

• In accordance with our institutional policy, the three criteria used to evaluate a patient's suitability for adjuvant SRS included:
  – Karnofsky performance status (KPS) $\geq 70$,
  – 1-3 brain metastatic lesions, AND
  – extra-cranial disease controlled or actively being treated.

• A total of 283 consecutive patients with these ‘good-prognostic’ features were identified and included in the analysis.
Patients

- Median Age: 61 yrs. (range 21-80)
- 111 (39.2%) male, 172 (60.8%) female
- Primary Tumor:
  - Breast Ca: 16.8%
  - Colorectal Ca: 6.3%
  - NSCLC: 54.5%
  - SCLC: 10.7%
  - Renal Cell Ca: 5.5%
  - Unknown Primary: 2.3%
Patients

- KPS at presentation
  - 70: 141 (49.8%)
  - ≥80: 142 (50.2%)

- Number of brain mets:
  - 1: 176 (62.2%)
  - 2: 66 (23.3%)
  - 3: 41 (14.5%)
Patients

- Treatment for brain metastasis:
  - WBRT alone: 166 (58.7%)
  - WBRT + SRS: 73 (25.8%)
  - WBRT + surgery: 44 (15.5%)

- WBRT dose:
  - 37.5 Gy/15: 5 (1.8%)
  - 30 Gy/10: 119 (42%)
  - 25 Gy/10: 6 (2.1%)
  - 20 Gy/5: 153 (54.1%)
Results

• $n = 283$
• Median Survival: **7.9 months** (95% CI: 4.5 – 9.3 months)
<table>
<thead>
<tr>
<th>Treatment</th>
<th>n</th>
<th>Median survival</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBRT+SRS</td>
<td>73</td>
<td>17.6</td>
<td>-</td>
</tr>
<tr>
<td>WBRT+Surgery</td>
<td>39</td>
<td>13.7</td>
<td>0.873</td>
</tr>
<tr>
<td>WBRT alone</td>
<td>183</td>
<td>4.8</td>
<td>p&lt;.001</td>
</tr>
</tbody>
</table>
# Multivariate Analysis
(Cox regression: backward conditional)

<table>
<thead>
<tr>
<th>Variables entered in the model</th>
<th>DF</th>
<th>p</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>KPS 70</td>
<td>1</td>
<td>0.001</td>
<td>2.320</td>
<td>1.96 - 2.82</td>
</tr>
<tr>
<td>Age ≥ 65 yrs</td>
<td>1</td>
<td>0.050</td>
<td>1.371</td>
<td>1.02 – 1.76</td>
</tr>
<tr>
<td>Extra-cranial metastasis present</td>
<td>1</td>
<td>0.106</td>
<td>1.214</td>
<td>0.95 – 1.77</td>
</tr>
<tr>
<td>Primary tumour not controlled</td>
<td>1</td>
<td>0.016</td>
<td>1.495</td>
<td>1.08 – 2.07</td>
</tr>
<tr>
<td>Intracranial oligometastasis (2-3)</td>
<td>1</td>
<td>0.074</td>
<td>1.344</td>
<td>0.97 – 1.86</td>
</tr>
<tr>
<td>WBRT Alone</td>
<td>1</td>
<td>&lt;0.001</td>
<td>2.761</td>
<td>1.99 – 3.83</td>
</tr>
</tbody>
</table>
## SRS Details

<table>
<thead>
<tr>
<th>Number of lesions</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>44 (60.3%)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>18 (24.7%)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>11 (12.3)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dose to each lesion (80% isodose)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>15Gy</td>
<td>4 (5.5%)</td>
<td></td>
</tr>
<tr>
<td>18Gy</td>
<td>3 (4.1%)</td>
<td></td>
</tr>
<tr>
<td>20Gy</td>
<td>21 (28.8)</td>
<td></td>
</tr>
<tr>
<td>24Gy</td>
<td>45 (61.6%)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Location of each lesion</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Frontal</td>
<td>35 (47.9%)</td>
<td></td>
</tr>
<tr>
<td>Temporal</td>
<td>12 (16.4%)</td>
<td></td>
</tr>
<tr>
<td>Parietal</td>
<td>28 (38.4%)</td>
<td></td>
</tr>
<tr>
<td>Occipital</td>
<td>10 (13.7%)</td>
<td></td>
</tr>
<tr>
<td>Midbrain</td>
<td>2 (2.7%)</td>
<td></td>
</tr>
<tr>
<td>Cerebellum</td>
<td>19 (26.0%)</td>
<td></td>
</tr>
</tbody>
</table>

**Symptomatic SRS-related edema requiring steroids**

<table>
<thead>
<tr>
<th>No</th>
<th>61 (83.6%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>12 (16.4%)</td>
</tr>
</tbody>
</table>

**Evidence of radionecrosis**

| 5 (6.8%) |

**Documented progression in SRS-treated lesion**

| 20 (27.4%) |
SRS Utilization Trends

- On multivariate analysis, factors associated with a likely increased utilization of SRS include:
  - Female Gender (p=0.022)
  - Age < 65 years (p=0.018)
  - Single Brain Metastasis (p=0.01)
  - Primary diagnosis of Breast Cancer (p=0.001)
  - Travel distance to SRS facility < 200 km (p<0.001)

- Referral patterns, awareness about SRS, and physician mindset, are other factors that could influence the utilization rates of SRS, but are difficult to measure.
Conclusions

- Our results are consistent with those of previous randomized trials and reports a survival benefit for the addition of SRS to WBRT for patients with limited brain metastasis and a good performance status.

- KPS, age, status of the primary tumor, and number of metastasis are powerful predictors of outcome for patients with brain metastasis.

- Outcomes for patients with brain metastasis treated in Nova Scotia are comparable to the results reported in literature and major randomized trials.
Conclusions

- We report a median survival of 17.6 months with the use of WBRT + SRS, and an absolute survival benefit of 12.8 months over WBRT alone.
- SRS is generally well tolerated by patients, with minimal acute or late complications.
- There is room for expansion of the SRS program for Brain Metastasis in Nova Scotia.
- We recommend that all patients meeting the above mentioned criteria be considered and referred for this treatment.
Future Directions

• Population-Based Study for the uptake and utilization of SRS for Brain Metastasis in British Columbia.
• Merge with available data from Ontario and Nova Scotia

Clinical Investigation

A Multi-institutional Study of Factors Influencing the Use of Stereotactic Radiosurgery for Brain Metastases

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