Validation of the RTOG Recursive Partitioning Analysis (RPA) Classification for Small Cell Lung Cancer – Only Brain Metastases: Single Institution Experience

Gregory MM Videtic, MD; David J. Adelstein, MD; Tarek Mekhail, MD; Thomas W. Rice, MD; Glen H.J. Stevens, MD; Shih-Yuan Lee, MSPH; John H. Suh, MD

Departments of Radiation Oncology, Medical Oncology and Thoracic Surgery; and the Brain Tumor Institute

Cleveland Clinic Foundation
Introduction

- Brain metastases occur in 25% of all cancer patients
- Reported median survivals with treatment range 4-6 months
- How do we improve outcomes beside treatment innovations?
- In other words, can brain mets patients be stratified into prognostic categories?
Introduction

- Gaspar LE et al. IJ ROBP 1997; 37:745-751
  - “Recursive partitioning analysis (RPA) of prognostic factors in three Radiation Therapy Oncology Group (RTOG) brain metastases trials.”
  - RPA- a statistical method of building decision trees to model predictors, using prognostic variables as “nodes”, from which patient subsets are split with respect to statistically significant survival outcomes
Introduction

Methods for Gaspar et al. study:

1. Using 3 RTOG randomized trials database, analyze pre-treatment variables using RPA.

2. Look for relationship between survival and combination of variables.

3. Stratify patients by variables into homogeneous survival groups.
Population for Gaspar et al. study:

- 1,276 patients enrolled in 3 RTOG randomized brain mets studies with radiotherapy as primary treatment
- 1,200 patients analyzed
  - 61% patients had lung primary
  - NB- 4% patients had small-cell lung cancer (SCLC)
## Results of Gaspar et al. study

<table>
<thead>
<tr>
<th>Class</th>
<th>Patients Characteristics</th>
<th>Median Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>KPS ≥ 70</td>
<td>7.1 months</td>
</tr>
<tr>
<td></td>
<td>&lt; 65 years</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Controlled primary</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No extracranial mets</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>Other than class I and III</td>
<td>4.2 months</td>
</tr>
<tr>
<td>III</td>
<td>KPS &lt; 70</td>
<td>2.3 months</td>
</tr>
</tbody>
</table>
Introduction

Validation of the RTOG RPA classification

By treatment modality:


2. **Surgical resection of brain mets** e.g. Agboola et al. Prognostic factors derived from recursive partition analysis (RPA) of Radiation Therapy Oncology Group (RTOG) brain metastases trials applied to surgical resected and irradiated brain metastatic cases. *Int J Radiat Oncol Biol Phys.* 1998 Aug 1;42(1):155-9

3. **Other RTOG studies** (91-04: randomized study comparing 2 fractionations) e.g. Validation of the RTOG recursive partitioning analysis (RPA) classification for brain metastases. *Int J Radiat Oncol Biol Phys.* 2000 Jul 1;47(4):1001-6
Introduction

Validation of the RTOG RPA classification

By histology:

Introduction

Validation of the RTOG RPA classification

Controversial?

1. **Effect of number of brain mets** e.g. Recursive partitioning analysis (RPA) class does not predict survival in patients with four or more brain metastases. Strahlenther Onkol. 2003 Jan;179(1):16-20
Introduction

Evidence to date:

- RPA classes for brain mets appear valid and reliable for historical comparisons.

- RPA classes should be used as stratification factors in the development of clinical trials.
Introduction

*Brain Mets from Small-Cell Lung Cancer (SCLC)*

- Often not enrolled in trials by clinicians
- **Rationale**
  - Anecdotal evidence suggests natural history, response to treatment “different” than others brain mets
- Explicitly excluded in some lung cancer trials
  - *e.g.* [SMART](#) trial ([S]tudy of neurologic progression with [M]otexafin gadolinium and [R]adiation [T]herapy)
    - Open to non-SCLC only
Introduction

Are the RPA defined classes valid as prognostic categories for patients with brain metastases arising from SCLC?
Materials and Methods

- 20-year single institution retrospective review


- Population: 164 patients in total
  - 154 analyzable in this study
    - 10 patients treated with surgery
Materials and Methods

RTOG RPA Criteria for class assignment

1. Karnofsky Performance Status (KPS)
2. Primary tumor status
3. Presence of extracranial metastases
4. Age

Endpoint 1. overall survival
2. comparison with reported RTOG database.
Results

154 SCLC brain met pts: 4/6/83 to 5/30/03

Median Follow-Up Time → 4.7 months (range 0.3 – 40.3)

Median Age → 65 (range 42-85); age ≥ 65: 51%

Median KPS → 70 (range 40-100); KPS ≥ 70: 67%

Median # of lesions → 3 (range 1-30)
- no data on 15 pts for #
## Results

<table>
<thead>
<tr>
<th>Primary Controlled</th>
<th>Systemic Disease</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>No</td>
<td>20 (13%)</td>
</tr>
<tr>
<td>Yes</td>
<td>Yes</td>
<td>27 (18%)</td>
</tr>
<tr>
<td>No</td>
<td>No</td>
<td>34 (22%)</td>
</tr>
<tr>
<td>No</td>
<td>Yes</td>
<td>73 (47%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td>154 (100%)</td>
</tr>
</tbody>
</table>
## Results

### Patient Distribution According to RTOG RPA Classes

<table>
<thead>
<tr>
<th>RPA Class</th>
<th>SCLC</th>
<th>RTOG Database</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>8 (5%)</td>
<td>792 (66%)</td>
</tr>
<tr>
<td>II</td>
<td>95 (62%)</td>
<td>338 (28%)</td>
</tr>
<tr>
<td>III</td>
<td>51 (33%)</td>
<td>70 (6%)</td>
</tr>
<tr>
<td></td>
<td>154 (100%)</td>
<td>1200 (100%)</td>
</tr>
</tbody>
</table>
# Results

## Number of Patients by Treatment Type

<table>
<thead>
<tr>
<th>Treatment Type</th>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBRT</td>
<td>130</td>
</tr>
<tr>
<td>WBRT + SRS</td>
<td>18</td>
</tr>
<tr>
<td>WBRT + Chemo</td>
<td>3</td>
</tr>
<tr>
<td>SRS</td>
<td>2</td>
</tr>
<tr>
<td>IMRT</td>
<td>1</td>
</tr>
</tbody>
</table>
Results

- Median survival for 154 pts = 4.9 months
- 4 patients (2.6%) alive at analysis
Results

Overall Survival Stratified by RTOG RPA Class for Brain Metastases Patients from SCLC

Median: RPA I (n=8), 8.6 months
Median: RPA II (n=95), 5.3 months
Median: RPA III (n=51), 2.5 months

P=0.0023
## Overall Survival by RPA Class

<table>
<thead>
<tr>
<th>RPA Class</th>
<th>SCLC</th>
<th>RTOG Database</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>8.6</td>
<td>7.1</td>
</tr>
<tr>
<td>II</td>
<td>5.3</td>
<td>4.2</td>
</tr>
<tr>
<td>III</td>
<td>2.5</td>
<td>2.3</td>
</tr>
</tbody>
</table>
Conclusions

- Outcomes for SCLC-only brain metastases similar to RTOG database, class by class.

- This suggests RPA classes valid for stratification of brain mets from SCLC.

- Supports inclusion of SCLC patients in future brain mets trials.

- RPA classification of SCLC brain mets appropriate basis for historical comparisons.