Collection of Recorded Radiotherapy Seminars

http://humanhealth.iaea.org
The Management of Brain Metastases

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The Problem

• ≅ 2000 000 new cases/year in N. America
• Incidence is rising
• Autopsy incidence: 15-20%
• Mean age: 60 years
• Median survival: < 1 year

Brain Metastases (Most Common Intracranial Tumor): Epidemiology of Brain Metastases

<table>
<thead>
<tr>
<th>Primary Tumor</th>
<th>Relative Prevalence of Brain Metastases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon: 5%</td>
<td></td>
</tr>
<tr>
<td>Melanoma: 9%</td>
<td></td>
</tr>
<tr>
<td>Unknown primary: 11%</td>
<td></td>
</tr>
<tr>
<td>Other known primary: 13%</td>
<td></td>
</tr>
<tr>
<td>Breast: 15%</td>
<td></td>
</tr>
<tr>
<td>Lung: 48%</td>
<td></td>
</tr>
</tbody>
</table>

Method of Spread and Distribution

- Hematogenous spread
- Most commonly grey/white junction
- 80% cerebral hemispheres, 15% cerebellum, 5% brain stem
- 2/3 are multiple (by MRI)
## CNS Failures - NSCLC

<table>
<thead>
<tr>
<th>Study</th>
<th>Stage</th>
<th>Overall Failure</th>
<th>1&lt;sup&gt;st&lt;/sup&gt; Failure Site</th>
</tr>
</thead>
<tbody>
<tr>
<td>Choi</td>
<td>T&lt;sub&gt;1-3&lt;/sub&gt; pN&lt;sub&gt;2&lt;/sub&gt;</td>
<td>NA</td>
<td>30%</td>
</tr>
<tr>
<td>Stuschke</td>
<td>T&lt;sub&gt;1-4&lt;/sub&gt; pN&lt;sub&gt;2&lt;/sub&gt;</td>
<td>54%</td>
<td>30%</td>
</tr>
<tr>
<td>Ceresoli</td>
<td>II&lt;sub&gt;B&lt;/sub&gt;, III&lt;sub&gt;A-B&lt;/sub&gt;</td>
<td>29%</td>
<td>22%</td>
</tr>
</tbody>
</table>

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## Survival vs Primary Site

<table>
<thead>
<tr>
<th>Primary</th>
<th>Dx to mets (months)</th>
<th>Mets to death (months)</th>
<th>Dx to death (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSCLS</td>
<td>3</td>
<td>4</td>
<td>10</td>
</tr>
<tr>
<td>Breast</td>
<td>40</td>
<td>4</td>
<td>53</td>
</tr>
<tr>
<td>SCLC</td>
<td>6</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>Melanoma</td>
<td>31</td>
<td>5</td>
<td>41</td>
</tr>
<tr>
<td>Renal cell</td>
<td>28</td>
<td>6</td>
<td>46</td>
</tr>
</tbody>
</table>

Nussbaum et al. Cancer 1996
Radiation and Clinical Oncologists Indicate Maintaining Neurologic and Neurocognitive Function is More Important than Prolonging Survival

![Bar chart showing primary goal in treating brain metastases](chart.png)

- Improve quality of life: 61% (Radiation Oncologists), 49% (Clinical Oncologists)
- Maintain or improve neurocognitive function: 19% (Radiation Oncologists), 9% (Clinical Oncologists)
- Prevent neurologic deterioration: 19% (Radiation Oncologists), 16% (Clinical Oncologists)
- Improve neurologic function: 15% (Radiation Oncologists), 13% (Clinical Oncologists)
- Extend survival: 10% (Radiation Oncologists), 13% (Clinical Oncologists)

Percent of respondents: 0% to 100%

P < .05

Whole Brain Radiation Therapy

- Treatment of choice for most patients
- Improves survival
- Improves/stabilize neurologic function
- Common schedules
  - 20-40 Gy/5-20 fx
- Response rates: 40-60%
- RTOG randomized trials did not show benefit for higher doses

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Whole Brain Radiation Therapy
RTOG Randomized Trials

• Several fractionation schemes
  - 20 Gy/5fxs; 30 Gy/10fxs; 40 Gy/20fxs; 50 Gy/20fxs, etc

• No difference in median survival
  - 15 - 18 weeks

• Cause of death
  - 50% neurological
  - 50% distant disease

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Reluctance to use WBRT
WBRT May Impair Neuro-Cognitive Function!

- De Angelis’ paper reported 11% severe neurocognitive deficit (Neurology, 1989)
- Retrospective data
- Baseline deficit not documented
- WBRT poorly documented
- Patients received very large fractions

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Percent of Patients Impaired at Presentation
(Meheta et al J Clin Oncol 2003)

Fact: Brain met patients have high rates of baseline neurocog deficits

Impairment = Z ≥ 1.5

Motor Function
Peg D   Peg ND

Memory
Recall  Delay

Executive Function
Trail B

Fluency
COWA

Recog
WBRT + MGd using comprehensive NCF tools

401 BM pts

193 pts
WBRT + MGd

208 pts
WBRT

MRI q2m → q3m
NCF q1m → q3m
QOL q1m → q3m

Endpoints
✓ Survival
✓ NCF
✓ QOL

NCF - Neuro-cognitive function
Median Time to Neurologic Progression: Lung Cancer

MGd: Not reached [95% CI: (8.63, NR)]
WBRT: 7.4 months [95% CI: (5.43, 9.73)]

WBRT + MGd Response Analysis

Volume reduction $\geq 45\%$

- Good responders
- Poor responders

135 pts at 2 mo

Volume reduction $< 45\%$

- Median tumor volume reduction at 2 mo: 45\%
Tumor Shrinkage vs. Prolonged Survival

<table>
<thead>
<tr>
<th>Response</th>
<th>MS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good</td>
<td>300±26 d</td>
</tr>
<tr>
<td>Poor</td>
<td>240±19 d</td>
</tr>
<tr>
<td>P-value</td>
<td>0.03</td>
</tr>
</tbody>
</table>
Tumor Shrinkage vs Better Neurocognitive Function

PEGND Test
WBRT for Brain Metastases

- Neuro-cognitive deficit a concern
- NC function poorly studied so far
- WBRT-induced tumor regression leads to better survival and cognitive preservation
## RTOG Recursive Partitioning Analysis (RPA)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Class 1</th>
<th>Class 2</th>
<th>Class 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>KPS</td>
<td>≥ 70</td>
<td>≥ 70</td>
<td>&lt; 70</td>
</tr>
<tr>
<td>Primary status</td>
<td>Controlled</td>
<td>Uncontrolled</td>
<td></td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>&lt; 65</td>
<td>≥ 65</td>
<td></td>
</tr>
<tr>
<td>Extracranial disease</td>
<td>None</td>
<td>Other sites</td>
<td></td>
</tr>
</tbody>
</table>

All brain metastases are not created equal
Single versus Multiple Lesions
### Randomized Surgical Trials

**Single Metastasis**

<table>
<thead>
<tr>
<th>Study</th>
<th>Rx</th>
<th># Pts</th>
<th>MS (wks)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patchell</td>
<td>S+RT</td>
<td>25</td>
<td>40</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td>RT</td>
<td>23</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Noordijk</td>
<td>S+RT</td>
<td>32</td>
<td>43</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td>RT</td>
<td>31</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>Mintz</td>
<td>S+RT</td>
<td>41</td>
<td>24</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td>RT</td>
<td>43</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>Rades</td>
<td>S + RT</td>
<td>99</td>
<td>46</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>RT</td>
<td>96</td>
<td>24</td>
<td></td>
</tr>
</tbody>
</table>

Single, operable lesions

- Patients with high performance
- Surgery followed by RT should be the standard (level 1 evidence)
- Improves survival, local control and functional independence
Post-op WBRT: Is it Necessary?

Single Met → Randomize
(completely resected)

Stratify: tumor type
location extent of disease

No further treatment
WBRT


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## Survival: Observation vs WBRT

<table>
<thead>
<tr>
<th></th>
<th>Obs</th>
<th>WBRT</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuro death</td>
<td>44%</td>
<td>14%</td>
<td>0.003</td>
</tr>
<tr>
<td>Median survival</td>
<td>43 wks</td>
<td>48 wks</td>
<td>0.39</td>
</tr>
</tbody>
</table>


McGill
# Tumor Recurrence: Observation vs. WBRT (50.4 Gy)

<table>
<thead>
<tr>
<th>Recurrence</th>
<th>Obs (%) (46 pts)</th>
<th>WBRT (%) (49 pts)</th>
<th>RR</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any brain</td>
<td>70</td>
<td>18</td>
<td>3.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Original</td>
<td>46</td>
<td>10</td>
<td>4.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Distant</td>
<td>37</td>
<td>14</td>
<td>2.6</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

*McGill*  
Postop WBRT for Single Brain Metastasis

- Even in the best selected patients (i.e. MRI-confirmed completed resected single metastasis in highly functional patients), withholding WBRT increases regional and local relapses by 26 to 46%

- WBRT decreases regional relapse risk by 160%

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Can Radiosurgery Improve Control?

- Spherical, non-infiltrative
- Most lesions < 40 mm
- Grey-white location
## Brain Metastases - Recurrent
### STEREOTACTIC RADIOSURGERY

<table>
<thead>
<tr>
<th>Center</th>
<th>Median Dose (Gy)</th>
<th>Local Control</th>
<th>Median Surv (mos)</th>
<th>Late Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harvard</td>
<td>15</td>
<td>85%</td>
<td>9.4</td>
<td>7.0%</td>
</tr>
<tr>
<td>UCSF</td>
<td>18.5</td>
<td>76%</td>
<td>10</td>
<td>13%</td>
</tr>
<tr>
<td>Wisconsin</td>
<td>18.3</td>
<td>82%</td>
<td>6.5</td>
<td>7.0%</td>
</tr>
<tr>
<td>Multi-Inst.</td>
<td>17.5</td>
<td>85%</td>
<td>11</td>
<td>4.3%</td>
</tr>
<tr>
<td>Heidelberg</td>
<td>17.2</td>
<td>95%</td>
<td>6.0</td>
<td>10%</td>
</tr>
<tr>
<td>McGill</td>
<td>18</td>
<td>80%</td>
<td>6.0</td>
<td>7.0%</td>
</tr>
</tbody>
</table>

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Brain Metastases - Primary
Survival: Radiosurgery

Patient selection?

Shangavi et al IJROBP 2001
RTOG 95-08: Phase III Trial

Brain Mets → RANDOMIZE
(1996-2001)

Stratify: # of brain mets (1 vs 2-3)
Extracranial mets (none vs present)

WBRT + SRS (n=164)

WBRT (n=167)

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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


**Background** Brain metastases occur in up to 40% of all patients with systemic cancer. We aimed to assess whether stereotactic radiosurgery provided any therapeutic benefit in a randomised multi-institutional trial directed by the Radiation Therapy Oncology Group (RTOG).

**Methods** Patients with one to three newly diagnosed brain metastases were randomly allocated with equal probability to WBRT+SRS or WBRT alone. Median overall survival for patients with a single unresectable brain metastasis. WBRT and stereotactic radiosurgery should, therefore, be standard treatment for patients with a single unresectable brain metastasis and considered for patients with two or three brain metastases.

*Lancet* 2004; 363: 1665–72
<table>
<thead>
<tr>
<th>Survival Analyses</th>
<th>WBRT &amp; SRS</th>
<th>WBRT</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>6.5 mo</td>
<td>5.7 mo</td>
<td>0.13</td>
</tr>
<tr>
<td>Solitary brain met.</td>
<td>6.5 mo</td>
<td>4.9 mo</td>
<td>0.04</td>
</tr>
<tr>
<td>1-3 mets &amp; Age &lt; 50</td>
<td>9.9 mo</td>
<td>8.3 mo</td>
<td>0.04</td>
</tr>
<tr>
<td>1-3 mets &amp; NSCLC</td>
<td>5.9 mo</td>
<td>3.9 mo</td>
<td>0.05</td>
</tr>
<tr>
<td>1-3 mets &amp; RPA Class 1</td>
<td>11.6 mo</td>
<td>9.6 mo</td>
<td>0.05</td>
</tr>
</tbody>
</table>

If you use radiosurgery, do you need whole brain RT?
## Randomized Trials: WBRT + SRS vs. SRS

<table>
<thead>
<tr>
<th>Author</th>
<th>Therapy</th>
<th># Pts</th>
<th>Local Control</th>
<th>Brain Recurrence</th>
<th>Median Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aoyama</td>
<td>WBRT + SRS</td>
<td>65</td>
<td>88%*</td>
<td>18%*</td>
<td>7.5 m</td>
</tr>
<tr>
<td></td>
<td>SRS</td>
<td>67</td>
<td>70%</td>
<td>52%</td>
<td>8.0 m</td>
</tr>
<tr>
<td>Chougule</td>
<td>WBRT + SRS</td>
<td>37</td>
<td>91%</td>
<td>19%*</td>
<td>5.0 m</td>
</tr>
<tr>
<td></td>
<td>SRS</td>
<td>36</td>
<td>87%</td>
<td>43%</td>
<td>7.0 m</td>
</tr>
<tr>
<td>Chang</td>
<td>WBRT + SRS</td>
<td>27</td>
<td>73%*</td>
<td>27%*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SRS</td>
<td>28</td>
<td>27%</td>
<td>60%</td>
<td></td>
</tr>
<tr>
<td>Kocher</td>
<td>WBRT + SRS</td>
<td>100</td>
<td>81%*</td>
<td>33%*</td>
<td>10.9 m</td>
</tr>
<tr>
<td></td>
<td>SRS</td>
<td>79</td>
<td>69%</td>
<td>48%</td>
<td>10.7 m</td>
</tr>
</tbody>
</table>

* P < 0.05
MD Anderson Study
SRS + WBRT

58 patients
1-3 brain mets
KPS ≥ 70

Randomized

SRS

SRS & WBRT
30 Gy/12fxs

Primary outcome:
Neurocognitive function at 4 months

## MD Anderson Study

**SRS + WBRT**

<table>
<thead>
<tr>
<th>RPA Class</th>
<th>SRS</th>
<th>SRS + WBRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>23%</td>
<td>11%</td>
</tr>
<tr>
<td>2</td>
<td>77%</td>
<td>89%</td>
</tr>
<tr>
<td>Liver metastases</td>
<td>7%</td>
<td>18%</td>
</tr>
<tr>
<td>Adrenal metastases</td>
<td>10%</td>
<td>18%</td>
</tr>
<tr>
<td>Median tumor volume (cm³)</td>
<td>1.4</td>
<td>2.3</td>
</tr>
</tbody>
</table>

Chang et al. Lancet Oncol 2009
MD Anderson Study
SRS + WBRT

Median Survival
SRS: 15.2 mos
SRS plus WBRT: 5.7 mos

Survival
Freedom from Local Progression

Chang et al. Lancet Oncol 2009

McGill
MD Anderson Study
SRS + WBRT

Intracranial recurrence rate at 1 year:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>1 Year Recurrence Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stereotactic radiosurgery alone (N=30)</td>
<td>7% (0/6) distant brain progression</td>
</tr>
<tr>
<td>Stereotactic radiosurgery plus whole-brain radiotherapy (N=28)</td>
<td>27% (1/10) distant brain progression</td>
</tr>
<tr>
<td>Salvage stereotactic radiosurgery (n symptomatic/n salvage)</td>
<td>0% (0/2) distant brain progression (8 tumours)</td>
</tr>
<tr>
<td>Salvage whole-brain radiotherapy (n symptomatic/n salvage)</td>
<td>10% (1/10) distant brain progression</td>
</tr>
<tr>
<td>Salvage surgery (n symptomatic/n salvage)</td>
<td>70% (7/10) local brain progression (12 tumours)</td>
</tr>
<tr>
<td>No salvage treatment (n symptomatic/n recurred)</td>
<td>66% (2/3) distant brain progression (12 tumours)</td>
</tr>
</tbody>
</table>

Table 4: Percentage of patients with intracranial progression who were symptomatic by treatment assignment and type of salvage therapy

Chang et al. Lancet Oncol 2009
MD Anderson Study
SRS + WBRT

• Primary End-Point

Cognitive decline
at 4 months
SRS
SRS+WBRT
4/20
7/11
(20%)
(63.5%)
MD Anderson Study
Concerns

- Small study; small number of events
- Groups not really comparable
- Larger disease volume in SRS+WBRT
- Survival differences may have influenced cognitive outcome
- Salvage therapy may have also influenced cognitive outcome
- Late relapses from SRS group not taken in account for cognitive outcome

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Neurological Functional Preservation Rate (RTOG stage \leq 2)

Rate at 1 year
WBI+SRS: 70%
SRS alone: 71%

P=0.34

Aoyama, ASCO 2004, JROSG99-1
Impact of WBRT on MMSE

- 82 pts on JROSG 99-1 had MMSE ≥ 27
- Median time to 3 point drop:
  - 16.5 vs. 7.6 months, in favor of WBRT+SRS (p =0.05)
- 12 and 24 month freedom from ≥3 point drop:
  - 76 and 69% for WBRT+SRS vs. 59 and 52% for SRS alone
- Progressive disease is worse than WBRT

EORTC Study 22952-26001
SRS/Surgery + WBRT

359 patients
1-3 brain mets
WHO PS 0-2

Surgery or SRS

Randomized

Observation

WBRT
30 Gy/10

160 surgical resection
96% 1 met
199 SRS
67% 1 met
23% 2 mets
10% 3 mets

Primary outcome
Functional Independence

Kocher et al. J Clin Oncol 2011
# EORTC Study 22952-26001

## SRS/Surgery + WBRT vs Observation WBRT

<table>
<thead>
<tr>
<th></th>
<th>Observation</th>
<th>WBRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Time to WHO PS &gt; 2*</td>
<td>10 mos</td>
<td>9.5 mos</td>
</tr>
<tr>
<td>Median Overall Survival</td>
<td>10.9 mos</td>
<td>10.7 mos</td>
</tr>
<tr>
<td>Intracranial progression</td>
<td>78%</td>
<td>48%</td>
</tr>
<tr>
<td></td>
<td>p &lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Death from intracranial progress</td>
<td>44%</td>
<td>28%</td>
</tr>
<tr>
<td></td>
<td>p &lt; 0.002</td>
<td></td>
</tr>
</tbody>
</table>

* Primary end-point

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Kocher et al. J Clin Oncol 2011
Chemotherapy in Brain Metastases

- Limited role
  - Blood brain barrier
  - Drug resistance (prior chemo)
- Heterogeneity of tumor types/patients
- Prospective trial with CDDP + VP-16*
  - 30% response rate in the brain
- New agents being studied

*Franciosi et al: Cancer 1999
Randomized Phase II: RT vs RT+TMZ

- 52 pts, solid tumors (65% NSCLC)
- WBRT 40 Gy/20 fx
- TMZ 75 mg/m^2 daily, then 200 mg/m^2 x5d Q28d

Antonadou et al JCO 2002

![Graph showing response rates for RT vs RT+TMZ.](Image)
Confirmatory Randomized Phase III: RT vs RT + TMZ

- 134 pts, solid tumors (80% NSCLC)
- WBRT 30 Gy/ 10fxs
- TMZ 75 mg/m$^2$ daily, then 200 mg/m$^2$ x5d Q28d

Antonadou ASTRO 2002
Phase III Trial
Schering-Plough PO3247

NSCLC
KPS ≥ 70
≤2 extra cranial sites

Brain Mets →

RANDOMIZE

WBRT + Temodal

WBRT

WBRT: 30 Gy/10 fx
Temodal: 75 mg/m² days 1-28

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Biological Agents

- EGFR TK inhibitor shown to have activity
- EGFR TKI shown to enhance RT response

Hotta et al. Lung Ca 2004

14 patients NSCLC
12 adenoca

Before
After

Chiu et al: Lung Ca 2005
Prospective Trial - Gefitinib

- 41 pts, NSCLC
- Gefitinib 250 mg
  - 37 pts received previous CT
  - 17 pts received previous WBRT

Ceresoli et al. Ann Oncol 2004
Gefitinib in NSCLC brain mets

PR = 10% (4 pts)
SD = 17% (7 pts)
RTOG 0320 Randomized Trial

NSCLC 1-3 mets

Brain Mets

WBRT+SRS

WBRT+SRS+Tarceva

WBRT+SRS+Temodal
NSCLC - CNS Failures

- 35-50% (II-III) will develop CNS metastases
- Systemic therapy improving systemic control
- Chemotherapy does not address CNS foci

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## PCI in NSCLC
### Randomized Studies

<table>
<thead>
<tr>
<th>Author</th>
<th># Pts</th>
<th>Brain Mets</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCI vs no PCI</td>
<td></td>
<td>PCI  vs</td>
<td>P value</td>
</tr>
<tr>
<td></td>
<td></td>
<td>no PCI</td>
<td></td>
</tr>
<tr>
<td>Cox 1981 (VALG)</td>
<td>281</td>
<td>6%</td>
<td>13%</td>
</tr>
<tr>
<td>Umsawasdi 1984</td>
<td>97</td>
<td>4%</td>
<td>27%</td>
</tr>
<tr>
<td>Russell 1991 (RTOG 8403)</td>
<td>187</td>
<td>9%</td>
<td>19%</td>
</tr>
</tbody>
</table>
PCI in NSCLC

- Cochrane review - 4 RCTs
- 791 evaluable pts
- PCI significantly ↓ incidence of brain mets
- No survival benefit
RTOG 0214 Randomized Trial

Accrual target: 1058
Closed prematurely!!
PCI Trial - RTOG 0214

356 pts entered the trial

Gore et al. J Clin Oncol 2011
Conclusions

• Neglected area
• Improved systemic control and earlier detection, incidence brain metastases
• Choice of end-point important
• Multiple brain metastases should receive WBRT
Conclusions

• Single metastasis should be treated by WBRT and surgery or radiosurgery
  - Survival improvement
• WBRT + SRS for multiple brain lesions
  - Improves local control
  - Decreases failure in the brain
  - Does not improve survival
Conclusions

• Neurocognitive decline post-WBRT possible, but poorly evaluated
  - On-going studies
• Tumor growth has worse impact on NCF than WBRT