Palliative Radiation For Metastatic Brain Lesions

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August 27, 2014

Perception of radiation oncology among palliative care physicians

Question	ASTRO	AAHPM
Radiation oncologists are integral members of the pain control/palliative care team.	39%	8%

Cancer J. 2007; 13:130-137

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Bottom line: radiation oncology is often perceived as a walled-off, single-focus specialty of questionable palliative utility

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Frequent barriers to referral for palliative radiotherapy

Barrier	ASTRO	AAHPM
Lack of education of referring physicians	44%	44%
Lack of practice guidelines regarding radiation in palliative care	41%	53%
Travel/transportation	35%	56%
Duration of radiation	31%	58%
Poor communication with physicians	21%	52%
Toxicity of radiation	21%	42%
Delayed onset of symptom relief	17%	30%

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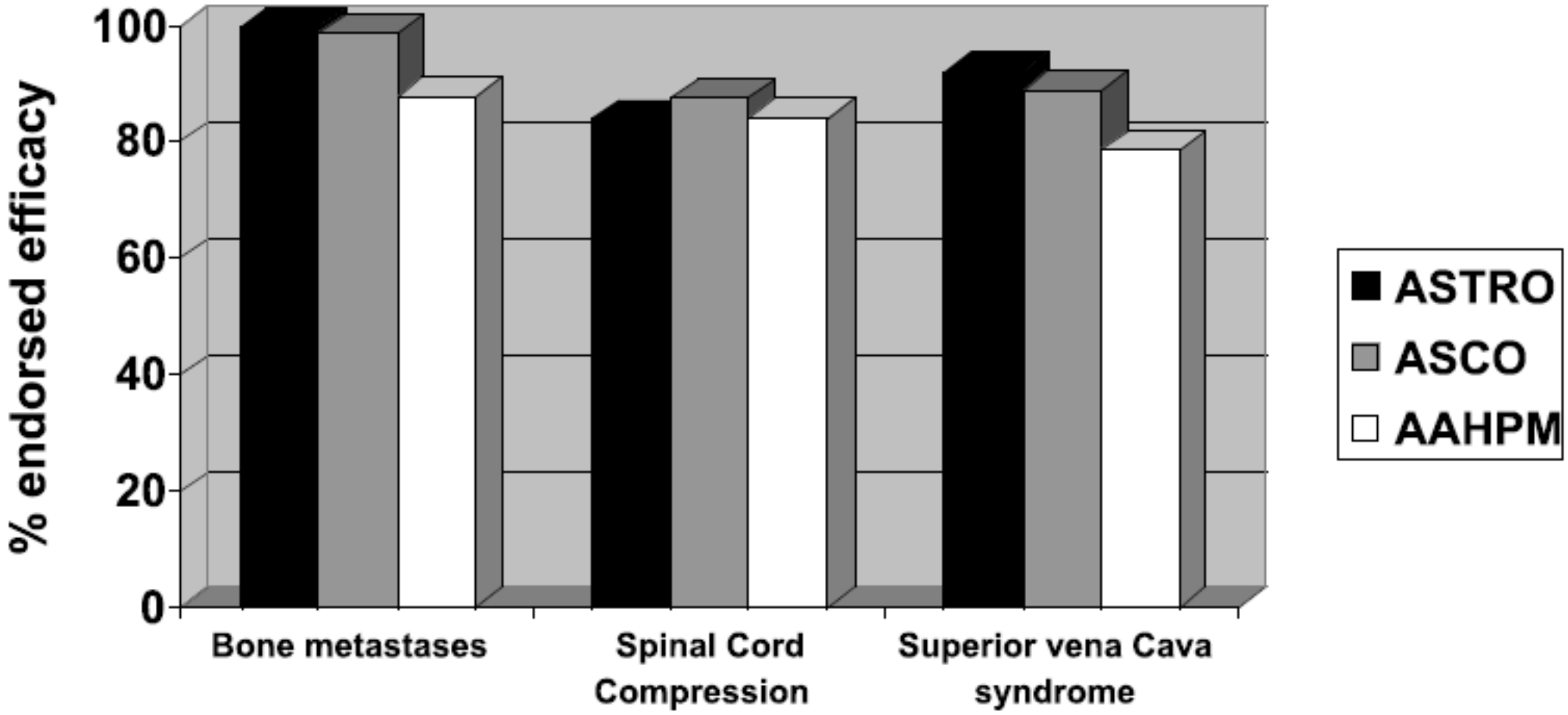
Disciplines agree on some indications for palliative radiation



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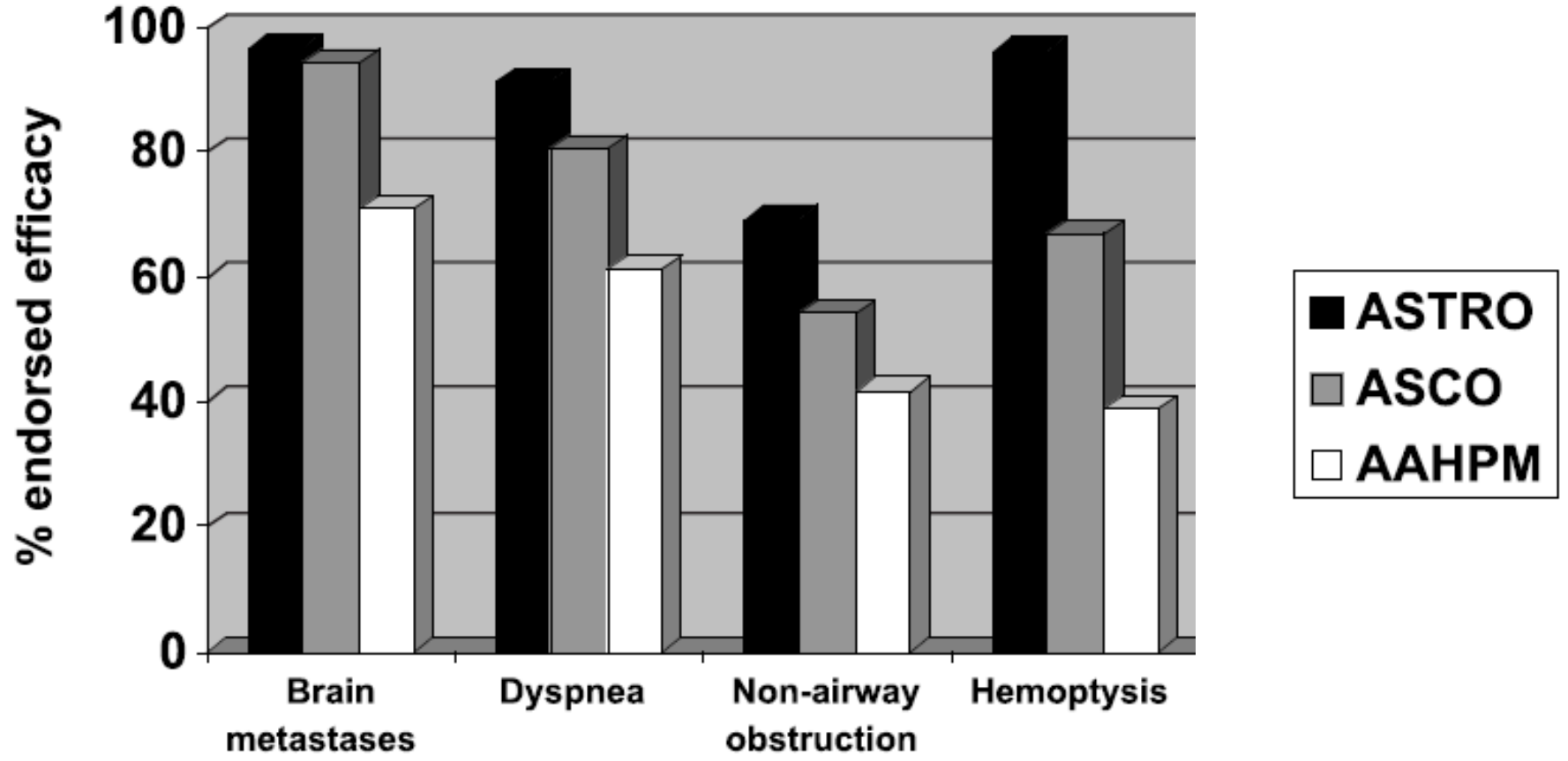
Perception of the utility of palliative radiation varies widely for some indications



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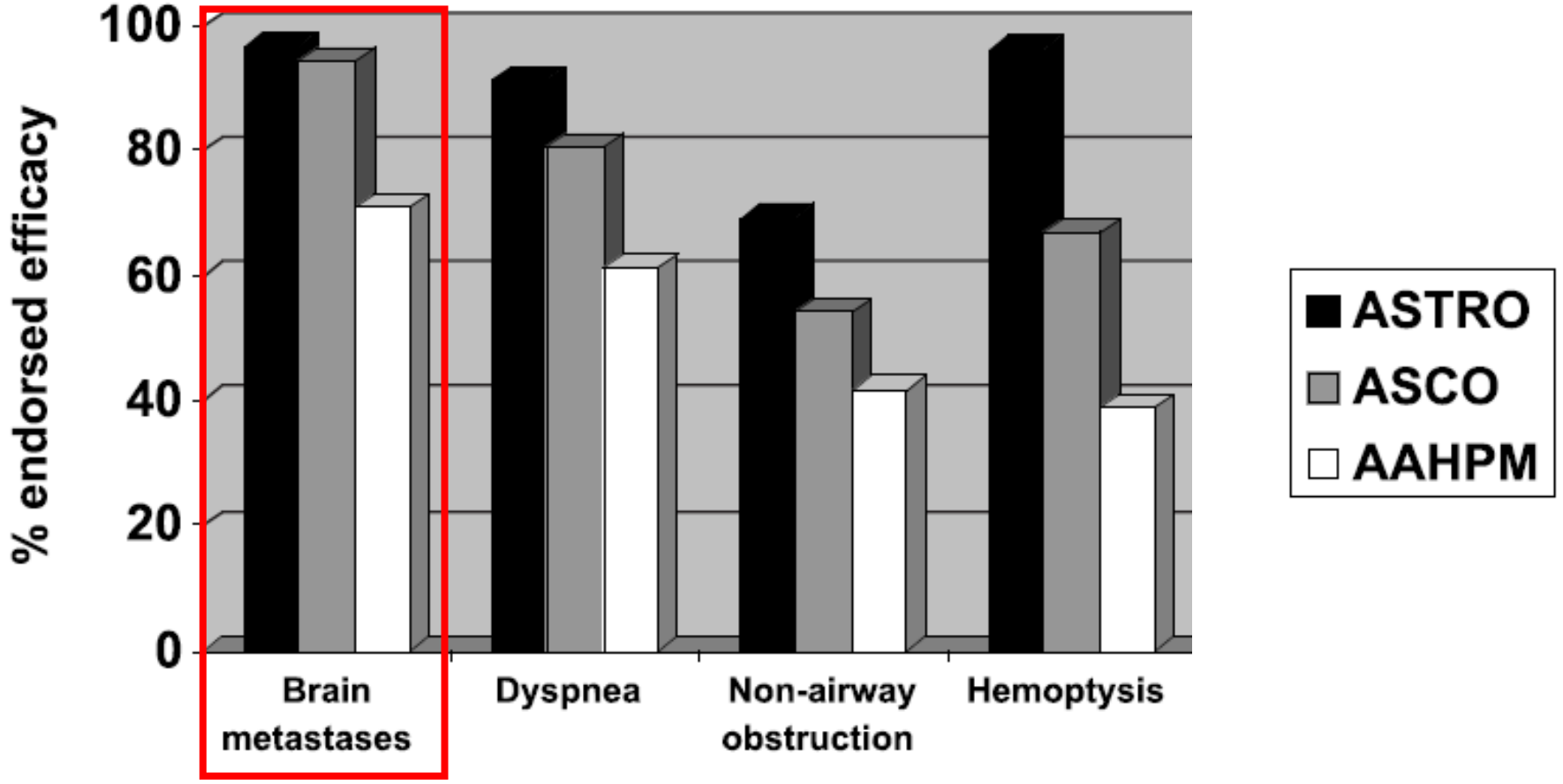

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Brain metastases

- Metastatic lesions are the most common brain tumor
- Overall incidence: 8.3/100,000
- Brain involvement in 10-40% of patients with metastatic cancer
- Without treatment, median survival with symptomatic brain metastases is 1 month

Lancet. 2004; 363(9422):1665-1672

Radiotherapy for brain metastases

- Who is likely to benefit?
- What are the options?
- What is the typical duration of treatment?
- Does toxicity negatively impact quality of life?

2012 ASTRO guidelines for palliative radiotherapy of brain metastases

- Single metastasis and > 3 months estimated survival:
  - < 3-4 cm and unresectable: SRS alone or SRS + WBRT (level 1)
  - > 3-4 cm and unresectable: WBRT (level 3)

- Multiple metastases and > 3 months estimated survival:
  - SRS alone, WBRT alone, or SRS + WBRT (level 1)

- < 3 months estimated survival
  - Palliative care with or without WBRT (level 3)

Practical Radiation Oncology. 2012; 2:210-225

XRT: radiotherapy
WBRT: whole brain radiotherapy
SRS: stereotactic radiosurgery

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No proven benefit in neurologic functional status, symptom relief, palliative index, or performance status conferred by palliative WBRT courses longer than 5 days

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Prognostic indices for brain metastasis

Recursive partitioning analysis (RPA)

Class I	Age < 65y, KPS ≥ 70, controlled primary tumor, no extracranial metastases
Class II	All patients not in Class I or III
Class III	KPS < 70

Int J Radiat Oncol Biol Phys. 2008; 70(2):510-514

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Graded prognostic assessment (GPA)

	Score		
	0	0.5	1.0
Age	≥ 60	50-59	< 50
KPS	< 70	70-80	90-100
No. of CNS metastases	> 3	2-3	1
Extracranial metastases	Present		None

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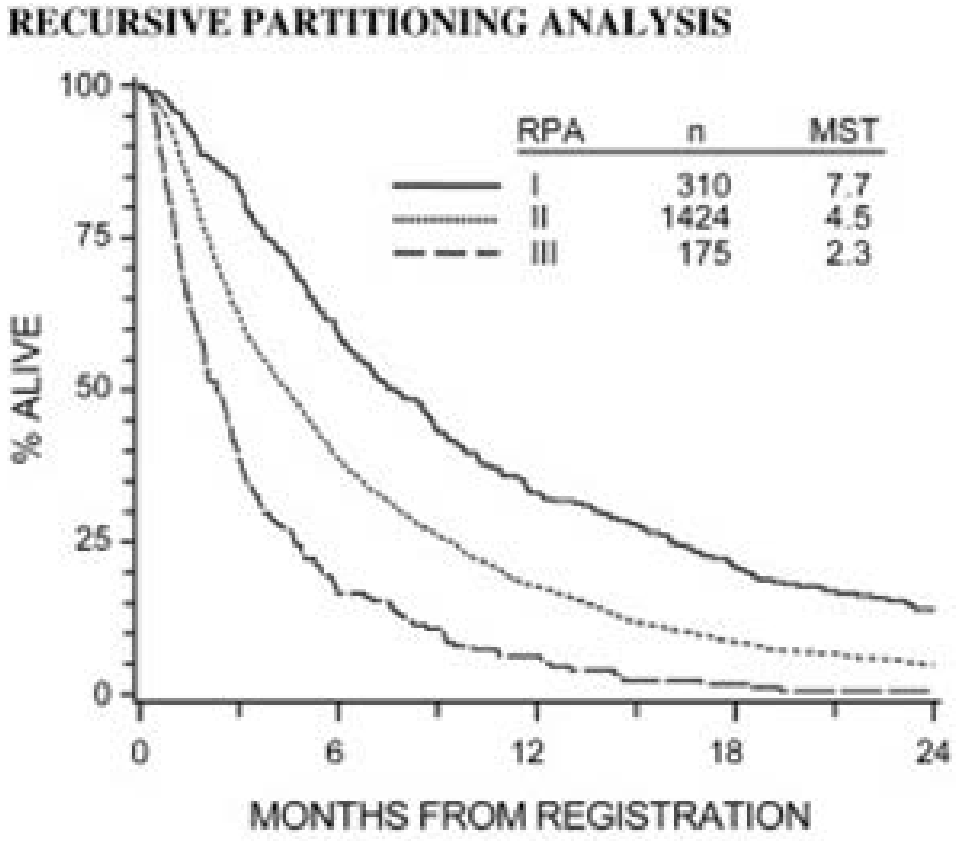
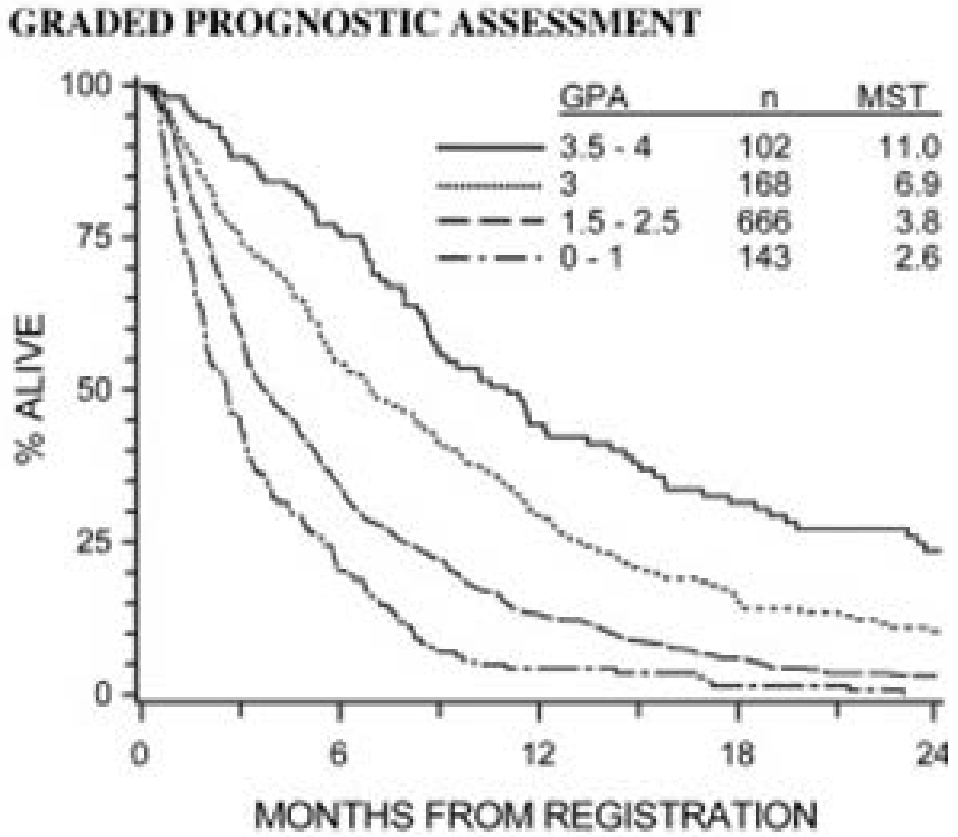
Median survival time based on RPA and GPA





Difference between all classes significant to $p < 0.0001$

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Disease specific graded prognostic assessment (DS-GPA)

Non–small-cell and small-cell lung cancer

Prognostic Factor	0	0.5	1.0	Patient Score
Age, years	> 60	50-60	< 50	____
KPS	< 70	70-80	90-100	____
ECM	Present	—	Absent	____
No. of BM	> 3	2-3	1	____
Sum total				____

Median survival (months) by GPA: 0-1.0 = 3.0; 1.5-2.0 = 5.5; 2.5-3.0 = 9.4; 3.5-4.0 = 14.8

Melanoma

Prognostic Factor	0	1.0	2.0	Patient Score
KPS	< 70	70-80	90-100	____
No. of BM	> 3	2-3	1	____
Sum total				____

Median survival (months) by GPA: 0-1.0 = 3.4; 1.5-2.0 = 4.7; 2.5-3.0 = 8.8; 3.5-4.0 = 13.2

Breast cancer

Prognostic Factor	0	0.5	1.0	1.5	2.0	Patient Score
KPS	≤ 50	60	70-80	90-100	n/a	____
Subtype	Basal	n/a	LumA	HER2	LumB	____
Age, years	≥ 60	< 60	n/a	n/a	n/a	____
Sum total						____

Median survival (months) by GPA: 0-1.0 = 3.4; 1.5-2.0 = 7.7; 2.5-3.0 = 15.1; 3.5-4.0 = 25.3

Renal cell carcinoma

Prognostic Factor	0	1.0	2.0	Patient Score
KPS	< 70	70-80	90-100	____
No. of BM	> 3	2-3	1	____
Sum total				____

Median survival (months) by GPA: 0-1.0 = 3.3; 1.5-2.0 = 7.3; 2.5-3.0 = 11.3; 3.5-4.0 = 14.8

GI cancers

Prognostic Factor	0	1	2	3	4	Patient Score
KPS	< 70	70	80	90	100	____

Median survival (months) by GPA: 0-1.0 = 3.1; 2.0 = 4.4; 3.0 = 6.9; 4.0 = 13.5

J Clin Oncology. 2012; 30:419-425

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RTOG 9508

- WBRT + SRS vs WBRT alone
  - Median survival: 6.5 vs 4.9 months ($p = 0.04$) for single metastasis
  - Median survival: 11.6 vs 9.6 months ($p = 0.045$) for RPA class I
  - Stable/improved KPS: 43% vs 27% ($p = 0.033$) at 6 months
  - Decrease in steroid use: 65% vs 45% ($p < 0.016$) at 6 months

Lancet. 2004; 363:1665-1672.

Acute toxicity reported in RTOG 9508

	WBRT + SRS (n = 160)				WBRT alone (n = 166)			
Acute Toxicity Grade	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
★ **Nausea/Vomiting**	20	7	1	0	16	9	0	0
Hearing loss	1	1	0	0	2	1	0	0
★ **Skin (acute)**	64	9	0	0	56	20	0	0
Skin (subacute)	9	3	0	0	7	1	0	0
★ **Neurological (central)**	12	10	2	1	9	11	0	0
Neurological (peripheral)	5	2	1	0	3	2	0	0
Other	16	7	0	0	10	10	0	0
Worst reported	69 (43%)	28 (18%)	3 (2%)	1 (1%)	59 (36%)	43 (26%)	0	0

Lancet. 2004; 363:1665-1672.

JROSG 99-1

- SRS + WBRT vs SRS alone
  - Median survival: 7.5 vs 8 months
  - No difference in death by neurological causes or 1 year actuarial survival
  - Similar toxicities in each group
  - No differences in neurological outcome (MMSE) at 12 months
  - Local recurrence: 46.8% vs 76.4% ($p < 0.001$)
  - Distant recurrence: 41.5% vs 63.7% ($p = 0.03$)

JAMA. 2006; 295:2483-2491

Chang *et al.* (MD Anderson)

- SRS + WBRT vs SRS alone
  - Stopped early (n = 58) due to 96% chance that SRS + WBRT more likely to result in memory and learning deficits
  - Probability of deficit:
    - 52% vs 24% at 4 months
    - 28% vs 8% at 6 months
  - Median survival: 5.7 vs 15.2 months, but complicated by high rate of salvage surgery in SRS only group
  - First trial to include detailed neurocognitive testing of patients treated for brain metastases
  - QOL measured with FACT-BR, but not reported

Lancet Oncol. 2009; 10:1037-1044

Cost and QOL for SRS vs. SRS + WBRT

- Analysis concurrent to Chang *et al*
- SRS + WBRT
  - $74,000 total cost
  - 0.60 LYS at $123,000/LYS
  - 0.51 QALY at $145,000/QALY
- SRS alone
  - $119,000 total cost
  - 1.64 LYS at $72,600/LYS
  - 1.54 QALY at $77,300/QALY
  - $44,000/QALY added vs. SRS + WBRT

Am J Clin Oncol. 2012; 35(1):45-50

Summary of randomized evidence for radiotherapy of brain metastases

- RTOG 9508
  - Addition of SRS to WBRT improves survival, KPS preservation, and steroid dependence.
- JROSG 99-1
  - Addition of WBRT to SRS improves local and distant control without affecting survival or MMSE at 1 year.
- Chang *et al*
  - Addition of WBRT to SRS increases risk of neurocognitive deficits at 4 and 6 months.
  - SRS as initial stand-alone therapy may improve survival in patients with close follow-up and potential for salvage surgery
- Lal *et al*
  - SRS as initial stand-alone therapy may be more cost-effective with respect to patient QOL and well within accepted standards for cost/QALY

Closing remarks

- Radiotherapy is likely to improve survival and preservation of performance status in patients with estimated survival > 3 months
- Duration of treatment is typically 1 hour per day for 1-10 weekdays
- Serious toxicity is rare, however neurocognitive effects may be most pronounced at 4 months

Fin.

Toxicity of WBRT

- Acute effects (first days to weeks)
  - Fatigue
  - Alopecia
  - Dermatitis
  - Nausea/vomiting
  - Anorexia
  - Cerebral edema
- Subacute effects (first weeks to months)
  - Fatigue
  - Somnolence
  - Memory loss
  - Focal neurologic deficits
- Late effects (more than 3 months post-WBRT)
  - Neurocognitive decline in 31-57% at 3 months, 48-89% at 1 year
  - Tumor progression affects neurocognitive decline more than WBRT

Surg Neurol Int. 2013; 4(Suppl 4): S236-244