

8th EIKCS Symposium: May 2013

What should we do about patients with brain mets?



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Disclosures

- **Advisory**
 - Ipsen
 - Astellas
- **Educational**
 - Takeda
 - Philips
 - Ipsen
 - Accuray

RCC Brain Mets: Its Significance

- **Incidence**
 - 10% (5-20%) of renal cases
- **Symptoms**
 - Onset: Acute or Gradual
 - Headaches (25 - 55 %)
 - Focal weakness (15 - 40 %)
 - Altered mental status (25 - 35 %)
 - Seizures (15 - 20 %)
 - Ataxia (9 - 20 %)
- **Prognosis**
 - New & different
- **Patient Impact**
 - Alters PS, QOL & MST

Are all brain mets the same?

Issues for consideration

- **Mode of presentation**

- Symptomatic vs Asymptomatic
- Synchronous vs Metachronous
- New vs Recurrent
- Via screening vs NOT

- **Extent of cerebral lesions**

- Small 'mm' vs large 'cm'
- Single vs multiple
- Location

- **Types of Management**

- Systemic therapy, Surgery, Radiotherapy, Combined modality

- **Disease History**

- Changing disease patterns within TKI-era

What should we do?

Factors for consideration

Patient Factors

- Age
- Symptoms
 - Acute
 - Chronic
- Performance status
- Expectations
- Preference

Tumour Factors

- Control of Primary
- Time between events
- Number of brain mets
- Location of brain mets
- Other systemic disease
 - Active
 - Asymptomatic

Therapy Factors

- Previous therapy
 - Local Rx
 - Systemic Rx
- Current therapy
 - Local Rx
 - Systemic Rx
- Other therapy
 - Local Rx
 - Systemic Rx
- Previous responses

Brain Mets: Prognosis

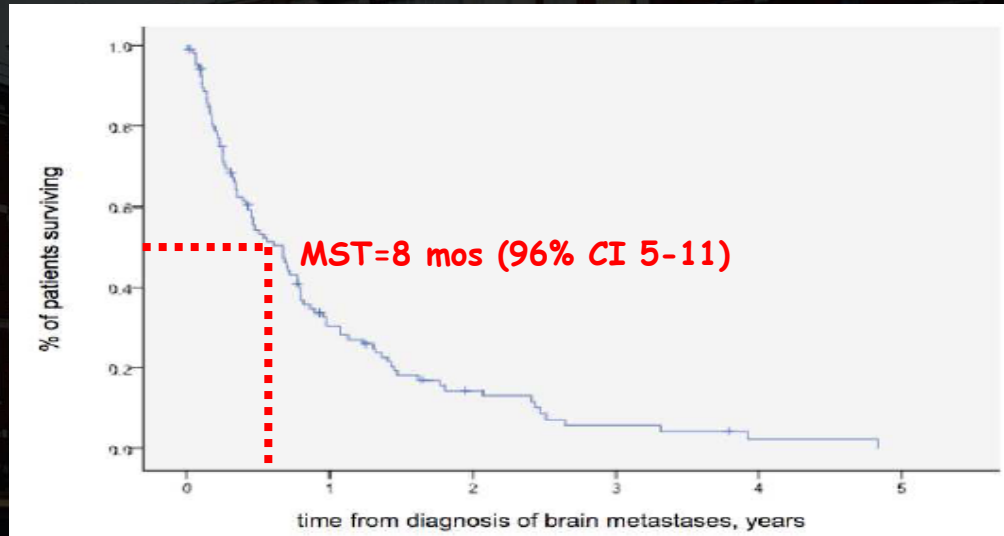
RMH (1984-2007): Retrospective RCC Brain Mets. N = 107.
Median age: 55 (33-78)

- **Median time**
 - 1° to BM: 24m
 - stage IV to BM: 11m
- **Asymptomatic: 10%**
- **Single BM: 55%**
- **Presence systemic disease: 80%**
- **Progressive systemic disease: 45%**
- **1 line systemic Rx before BM: 55%**
- **Univariate analysis:**
 - Nom BM,
 - Progressive systemic disease
 - Synchronous disease diagnosis
 - Previous systemic Rx esp TKI
- **Multivariate analysis**
 - Progressive systemic disease
 - Suitability for surgery

Brain Mets: Prognosis

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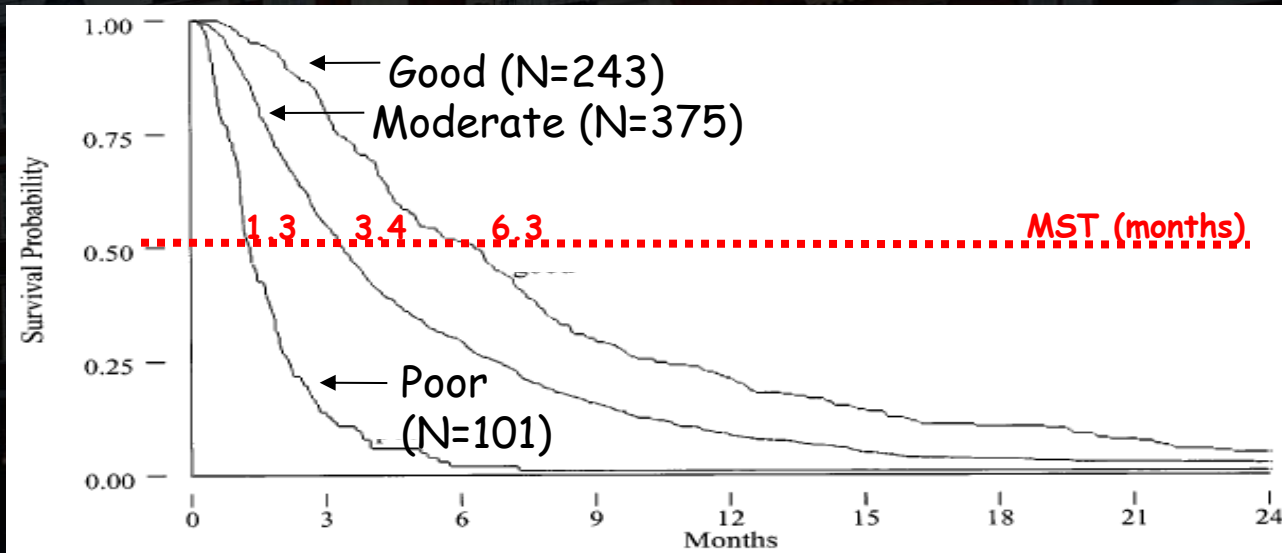
- Surgery (24%)
- XRT (81%)



Brain Mets: Prognostic Factors

Subgroup Categories

- Good
- Moderate
- Poor
- ECOG 0-1 + no/limited systemic actv + steroid response
- All others
- ECOG 2-3 + limited/extensive systemic actv, little steroid response



Brain Mets: Prognostic Factors

Independent factors for survival > 6m

R
A
N
D
O
M
I
Z
E

1) RTOG 79-16(N=792)

→	30 Gy	10 fx / 10 days / 2 wks
→	30 Gy	10 fx / 10 days / 2 wks + MISO
→	30 Gy	6 fx / 6 days / 3 wks
→	30 Gy	6 fx / 6 days / 3 wks + MISO

• PS: KPS 70 - 100

• 1° Tumour: Absent / Controlled

• Age: < 60 years

• Mets extent: Brain only

Predicted probability of surviving 200 days

- 4 favourable factors: 52 %
- 3 favourable factors: 33 %
- 0 favourable factors: 8 %

Brain Mets: Prognostic Factors

RTOG: 3 consecutive PRTs: fractionation & radiosensitizers
1979-1993 (RTOG 79-16; 85-28; 89-05). N=1200
Recursive partition analysis (RPA)

- **Patient related factors:**

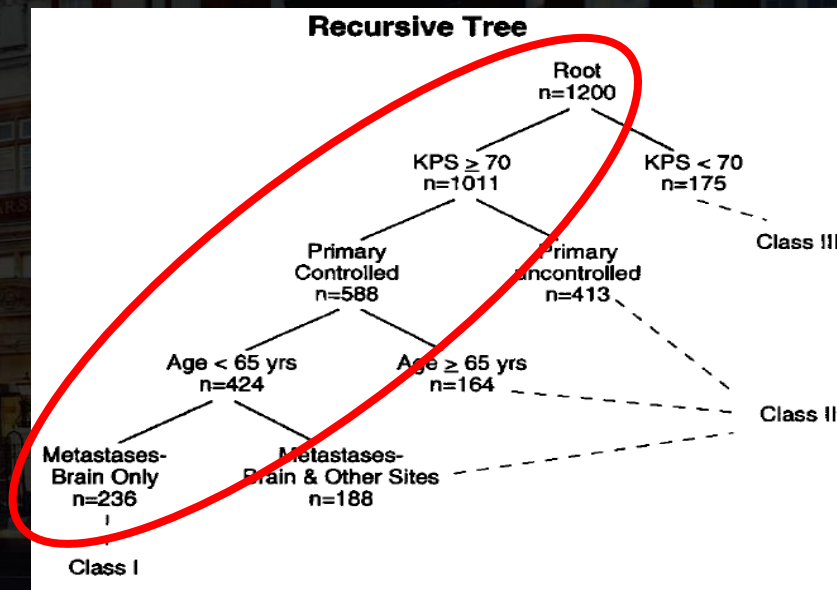
- age, KPS, neuro function/symptoms/signs

- **Tumour related factors:**

- primary, controlled status of primary, presence of extra-cranial disease, number of brain mets, time interval between primary & met

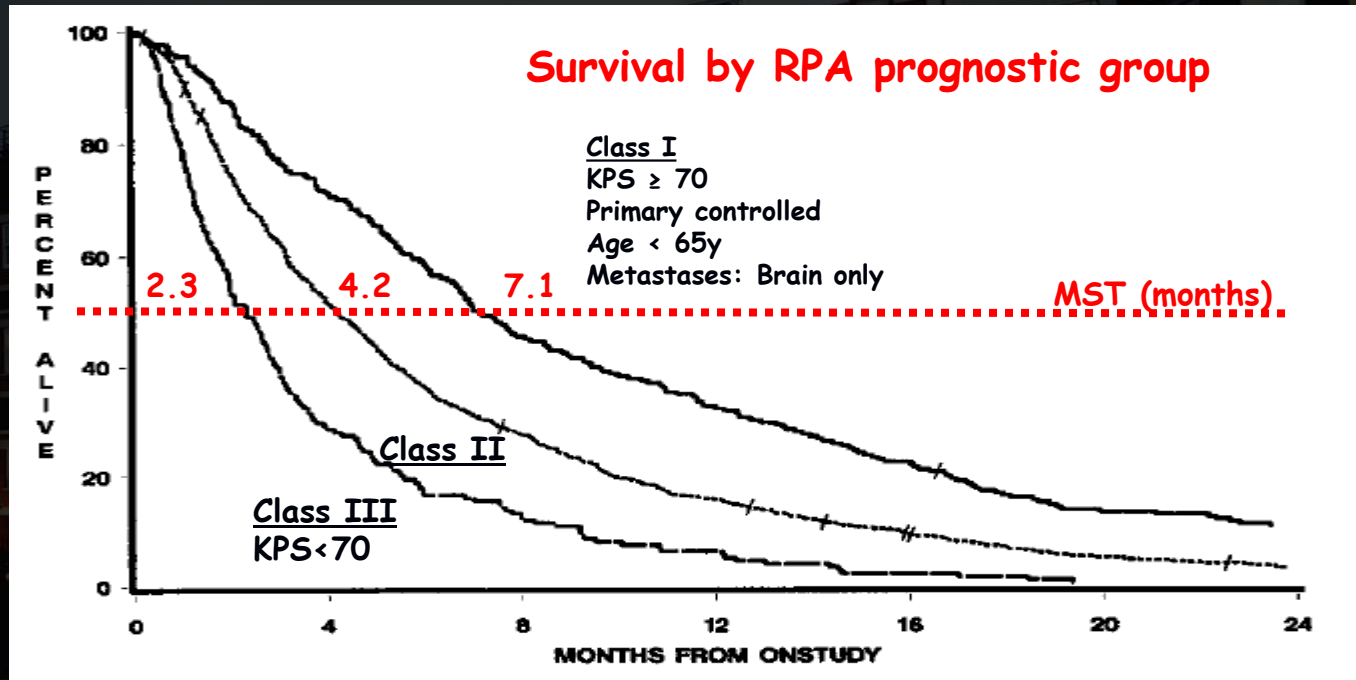
- **Treatment related factors:**

- dose, response

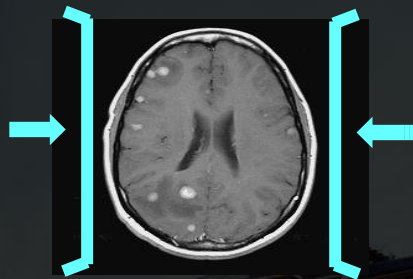


Brain Mets: Prognosis

RTOG: 3 consecutive PRTs: fractionation & radiosensitizers
1979-1993 (RTOG 79-16; 85-28; 89-05). N=1200
Recursive partition analysis (RPA)



Brain Mets: WBRT Palliation



RTOG PRT Trials: 1971 - 1995.
N \approx 2,600 patients

- **Neurological symptoms**
 - 60 - 90% complete or partial responses
- **Improvement to higher neuro functional class**
 - 45 - 50%
- **Median duration of improvement**
 - 10 - 12 weeks
- **Remaining survival period of patients**
 - 75 - 80% stable or improved neurologic state

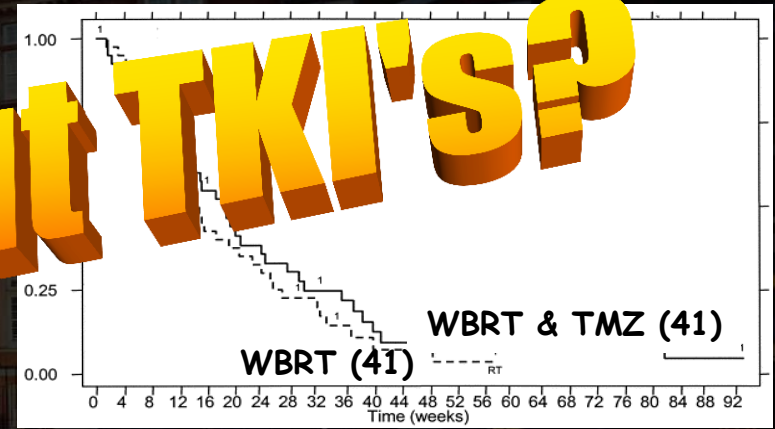
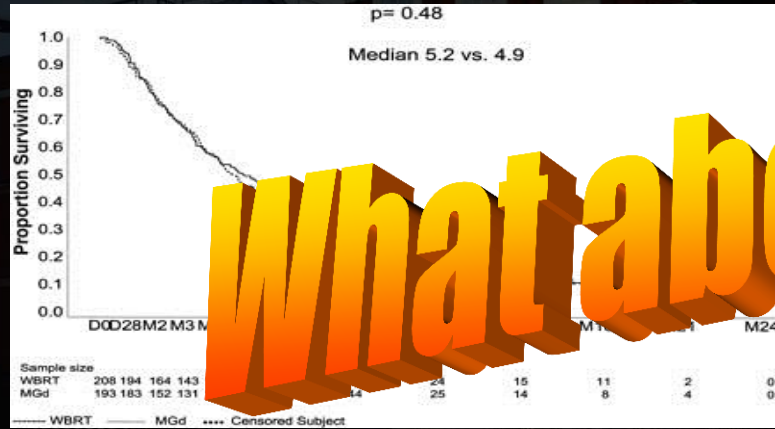
IJROBP: Borgelt '80, Kurtz et al '81, Borgelt et al '81, Coia et al '92, Murray et al '97,

Brain Mets: WBRT

No to minimal improvement when combined with drug agents

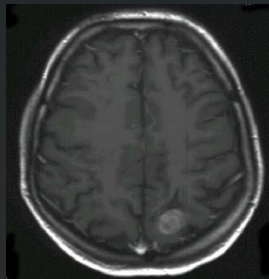
WBRT ± Motexafin gadolinium
(Radiosensitiser)

WBRT ± Temozolomide



Brain Mets: Solitary Lesion

Randomise



WBRT
Surgery

Surgery
Surgery

⇒ WBRT
⇒ WBRT

Study	No.	WBRT	ECD(%)	MST WBRT	MST S+WBRT
Patchell	48	36/12#	83-76%	3.4m	9.2m (p<0.01)
Noordijk	63	40/20#	68-69%	6.0m	10m (p=0.04)
Mintz	83	30/10#	84-73%	6.3m	5.6m (p=0.24)

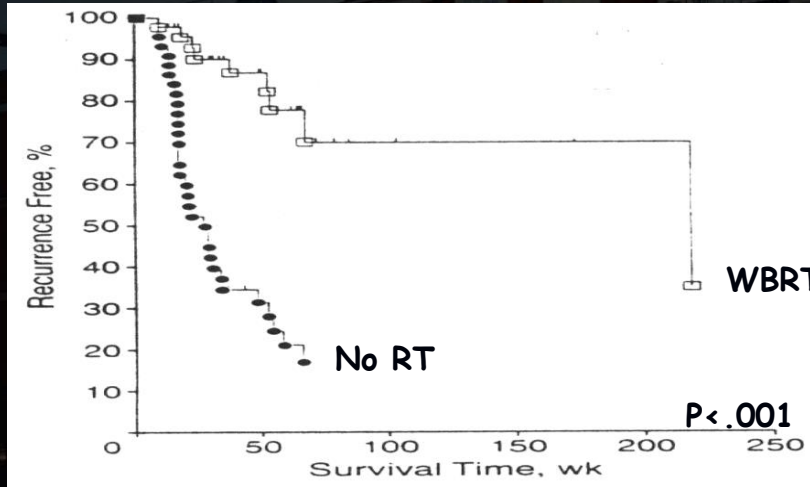
Study	No.	WBRT	ECD(%)	MST S only	MST S+WBRT
Patchell	95	50.4/28#	65-63%	9.9m	11.0m (p=0.39)

Patchell et al NEJM '90, Noordijk et al IJROBP '94, Mintz et al Cancer '96, Patchell JAMA '98

Brain Mets: Solitary Lesion

PRT: Surgery ± WBRT (N = 95)

Potential impact of WBRT to Surgery



Brain Failures

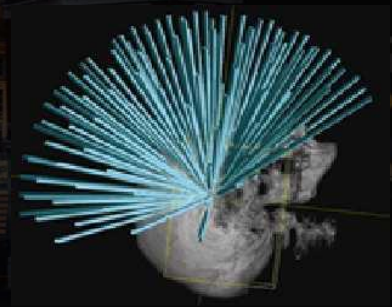
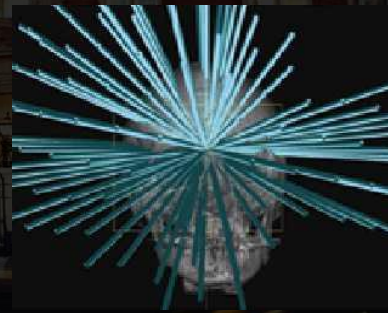
Local BF:	10%	46%
Other BF:	14%	37%
Any BF:	18%	70%

Radiosurgery

Gamma Knife



CyberKnife

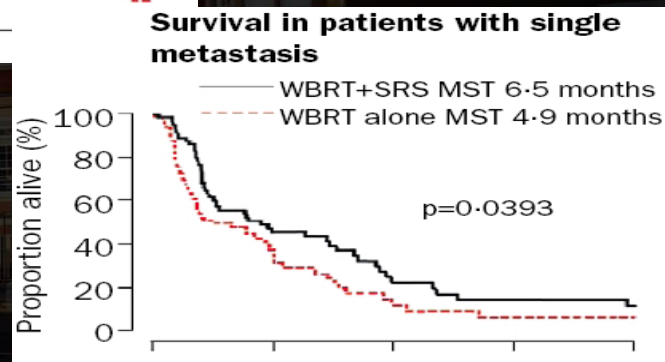
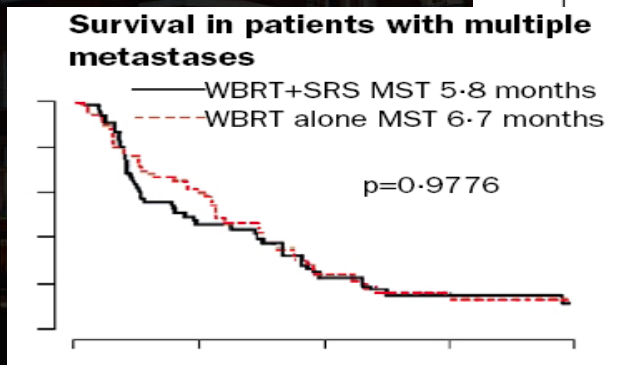
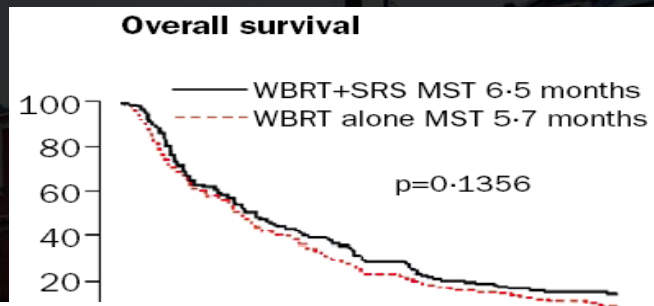


Brain Mets: WB-XRT & RS

RTOG 95-08 (1996-2001), N = 331

Unresectable 1-3 brain mets, KPS \geq 70, Systemic Rx > 1m

WBRT (37.5/15#) \pm RS (15-24Gy/2-4cm)



Brain Mets: Evidence-based Review

Systematic reviews, RCTs or observational studies meeting criteria: N = 38. Grade evaluation

- **Likely to be beneficial**
 - Corticosteroids
 - WBRT
 - WBRT + RS in limited disease (ie 1 met & stable ECD)
- **Uncertain effectiveness**
 - Systemic cytotoxic therapy (When combined with WBRT, it may increase response but survival same)
 - Surgery with WBRT in limited disease (ie 1 met & stable ECD)
- **Insufficient evidence**
 - Surgery vs RS; Surgery \pm RS; Surgery \pm RS \pm WBRT; RS vs WBRT

Brain Mets: Survival

Management

- No Treatment
- BSC (with steroids)
- Whole brain RT
- Combined therapy

Median Survival Times

- 1 - 2 months
- 2 - 2.5 months
- 3 - 6 months
- 9 - 11 months

Brain Mets: Summary

- For symptomatic palliation
 - WBRT provides in 60-90%
- For those with good prognostic features, more aggressive therapy may be appropriate.
 - S ± WBRT
 - RS ± WBRT (unresectable regions or eloquent regions)
 - S or RS alone
- Opportunity to tailor treatments to the patient.
 - Application of prognostic factors
 - Response to TKI
 - Potential imaging biomarkers
- Minimal evidence base for new therapies & combinations.
 - New patient cohorts ie at staging
 - Need to re-consider RCT trials for brain mets in TKI era

Thank You