

Management of Brain Metastases

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Epidemiology of Brain Metastasis

MANAGEMENT OF BRAIN METASTASES	Primary site	
	Lung	50%
	Breast	15-20%
	Other known primary	10-15%
	Unknown primary	10-15%
	Melanoma	10%
	Colon	5%
	Relevant facts	
	Median survival	<1 year
	Mean age	60 yrs
	Annual US incidence	>170,000
	Autopsy incidence	10-30%
	Clinical incidence	15-30%
Metastatic/primary ratio	10:1	

Pathophysiology

- Arterial circulation
- Batson venous plexus (pelvic and GI tumors)

Cerebrum (80-85%)

Cerebellum (10-15%)

Brain stem (3-5%)

Clinical Presentation of Brain Metastasis

MANAGEMENT OF BRAIN METASTASES	Symptom	Percent of Patients	Sign	Percent of Patients
	Headache	49	Hemiparesis	59
	Mental problems	32	Cognitive deficits	58
	Focal weakness	30	Sensory deficits	21
	Ataxia	21	Papilledema	20
	Seizures	18	Ataxia	19
	Speech problems	12	Apraxia	18

Clinical Diagnosis of Brain Metastasis

- Contrast enhanced CT or MRI

MRI is more sensitive and specific

Differential Diagnoses:

Brain abscess

Hypertensive hemorrhage

Lymphoma

Stroke

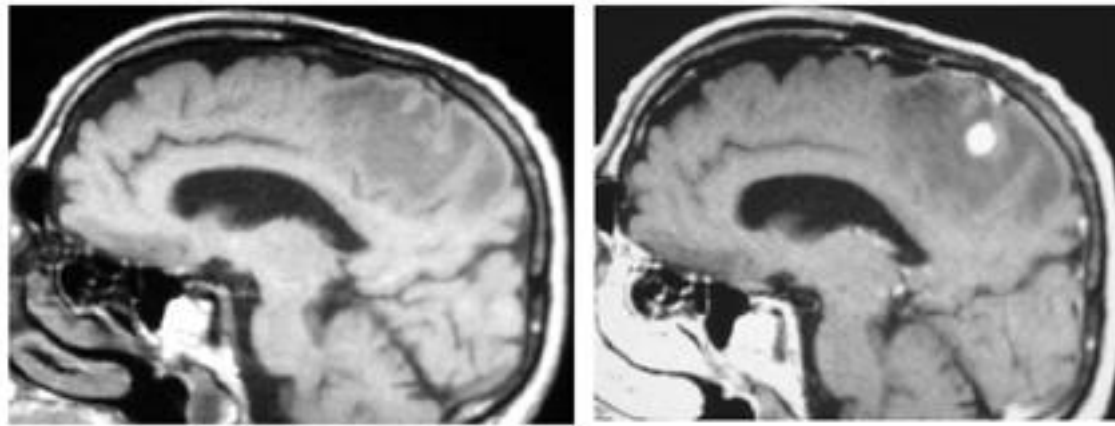
Meningioma

Multicentric glioma

Brain vasculitis

- Lesions are isointense to mildly hypointense on T1-weighted
- Hyperintense on T2-weighted images

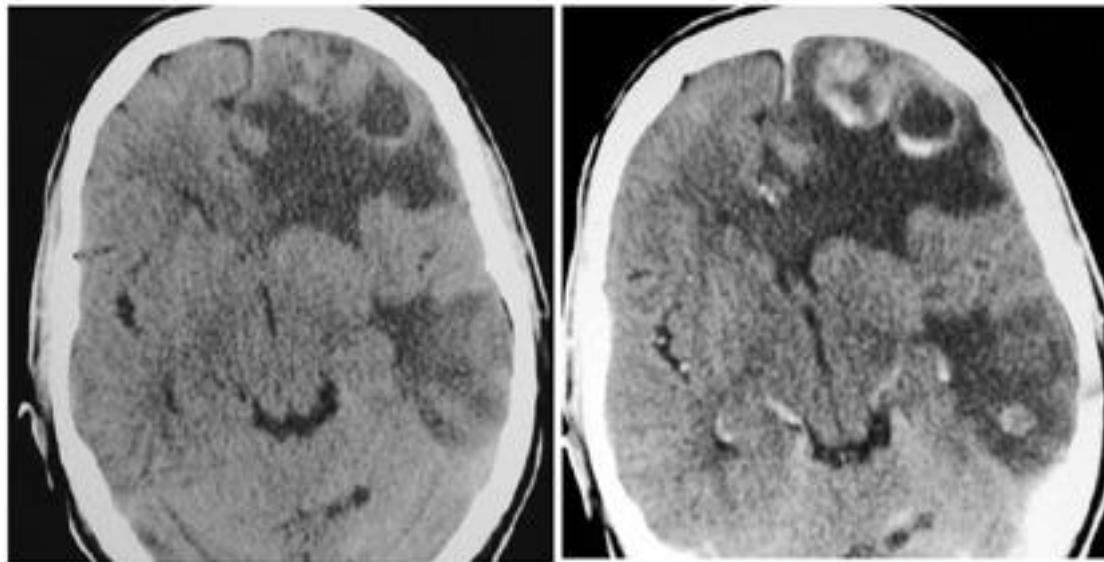
Solitary Metastases -edema



T1-Sag

T1-Sag Gd

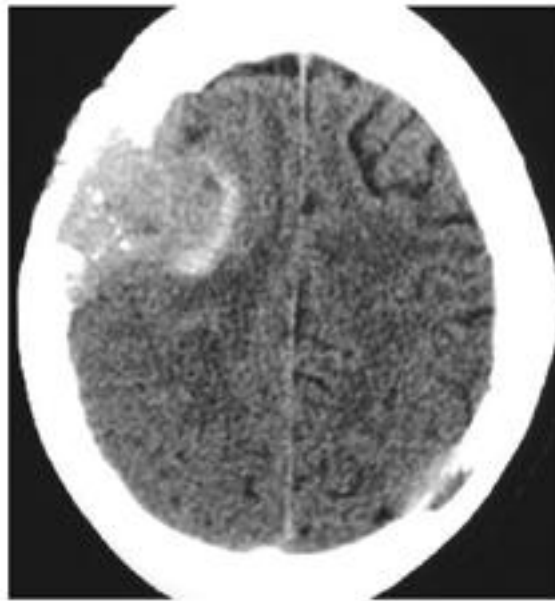
Multiple Metastases -Lung



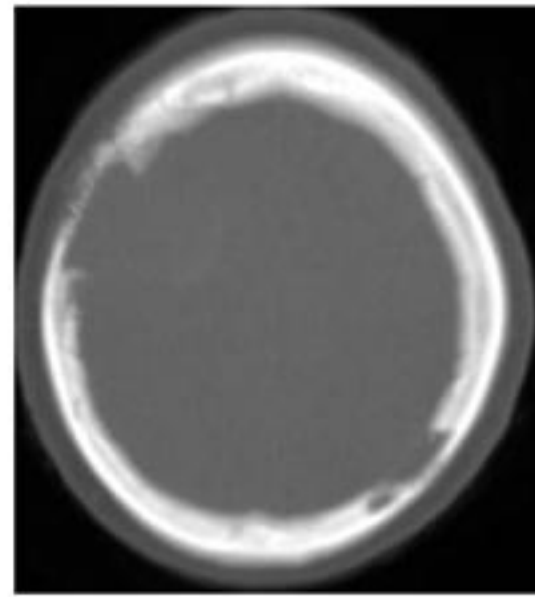
NCCT

CECT

Dural and calvarial metastases-Breast Cancer

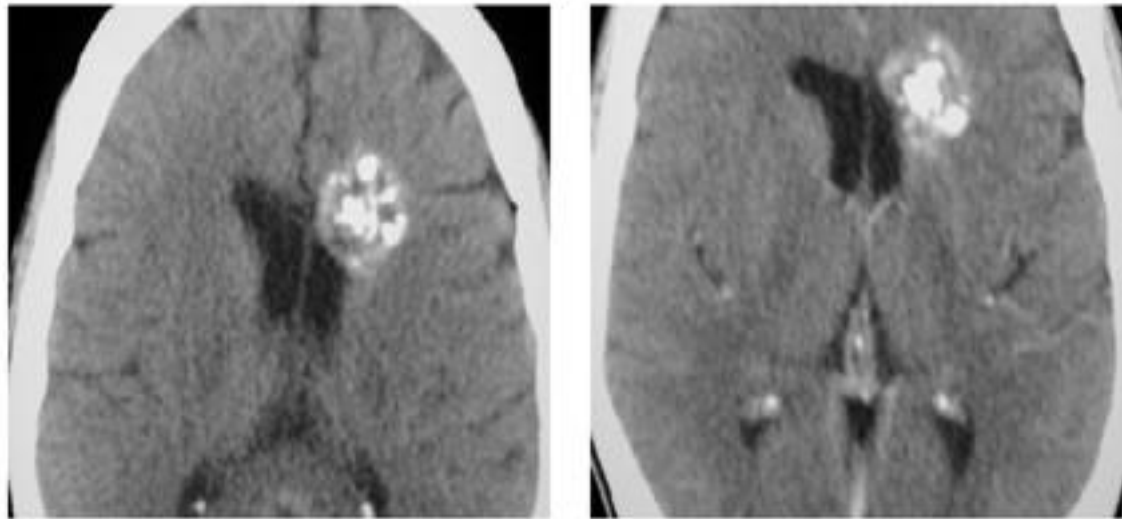


CECT



CT

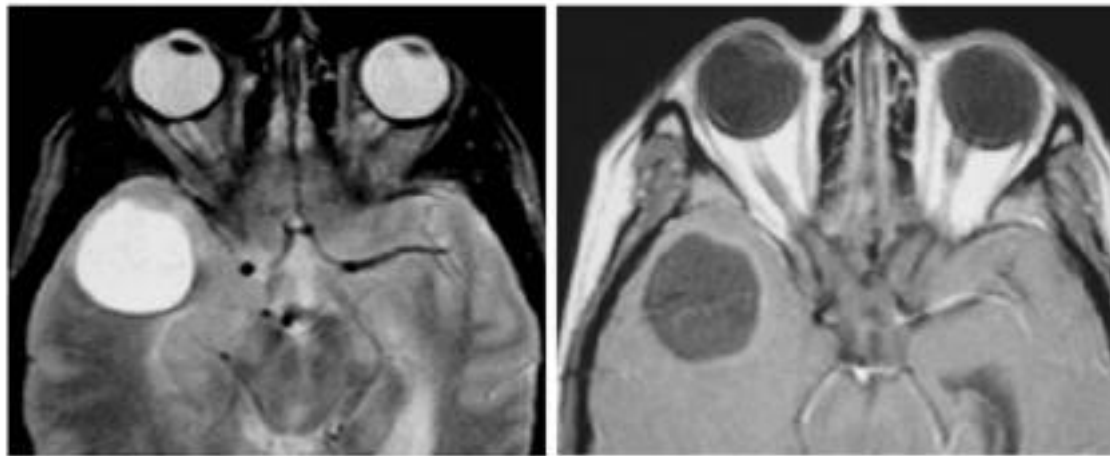
Calcified Metastases-Gastric Ca



NCCT

CECT

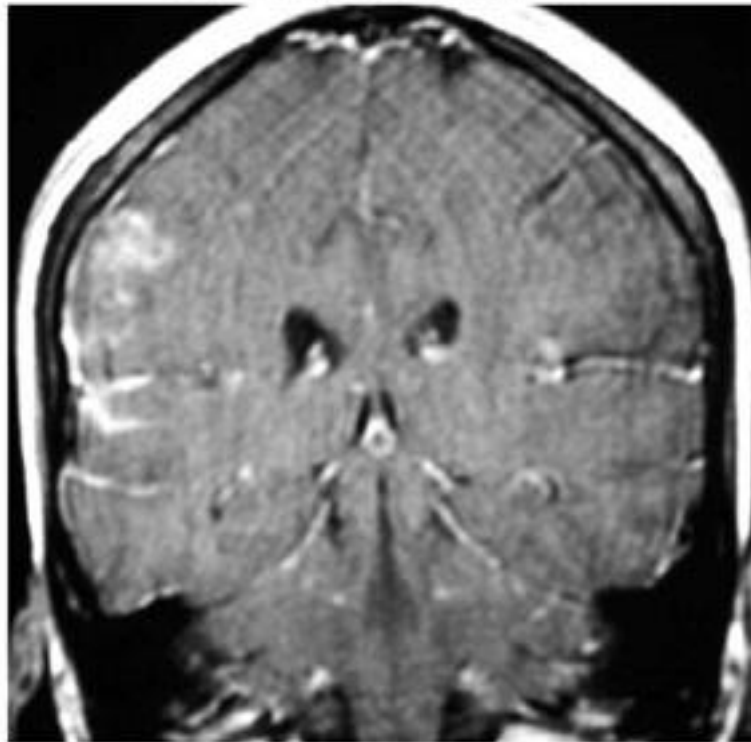
Cystic Brain Metastases -uterine CA



T2

T1-Gd

Leptomeningeal Carcinomatosis- Melanoma



T1-Gd

Basic Score-Brain Metastases

- | <u>CHARACTERISTICS</u> | <u>Points</u> |
|---------------------------|---------------|
| • KPS \geq 70 | 1 |
| • Age <65 | 1 |
| • No Extracranial Disease | <u>1</u> |

SCORE

0-3

BS-BM- Highly Prognostic

<u>Score</u>	<u>Median Survival (months)</u>
3	24.6
2	6.6
1	4.7
0	2.8

- BMC Cancer 2007

Treatment Modalities

MANAGEMENT OF BRAIN METASTASES

- Corticosteroids (dexamethazone 16-24 mg/day)
- Surgery
- Whole brain radiotherapy (WBRT)
- Stereotactic radiosurgery (SRS) or stereotactic radiotherapy (SRT)
- Chemotherapy/radiosensitizers

Role of Surgery

- *HISTOLOGIC DIAGNOSIS*

Surgical Resection or Stereotactic Biopsy

- *MASS EFFECT*

requires surgical resection if tumor is accessible



Table 91.4

RANDOMIZED TRIALS OF SURGICAL RESECTION OF SINGLE BRAIN METASTASIS

Author/Study Group	Surgery + RT	RT Alone	P Value
Patchell et al. (48)/University of Kentucky (n = 48)			
Primary end point		(36 Gy/12 fx)	
Overall survival	40 wk	15 wk	<0.01
Secondary end points			
Local control			
Local failure	20%	52%	<0.02
Time to local failure	>59 wk	21 wk	<0.0001
Time to neurologic death	62 wk	26 wk	<0.0009
KPS \geq 70 maintenance	38 wk	8 wk	<0.005
Noordijk et al. (45)/Dutch (n = 63)			
Primary end points		(40 Gy/20 fx) ^a	
Overall survival	10 mo	6 mo	0.04
FIS ^b	7.5 mo	3.5 mo	0.06
Mintz et al. (43)/Canadian (n = 84)			
Primary end point		(30 Gy/10 fx)	
Overall survival	5.6 mo	6.3 mo	NS
Secondary end points			
FIS (proportion of days, mean) ^c	32%	32%	NS
Quality of life (Spitzer score)			
1–3 months (mean)	6.38	5.36	NS
4–6 months (mean)	6.32	6.15	NS

RT, whole-brain radiotherapy; fx, fraction number; KPS, Karnofsky performance score; FIS, functionally independent survival; NS, not significant.

^a40 Gy total in 2-Gy twice daily hyperfractionation for the entire course of therapy.

^bFIS defined by World Health Organization performance status \leq 1 and neurologic condition \leq 1.

^cFIS defined by KPS \geq 70.

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Surgical resection recommendations

MANAGEMENT OF BRAIN METASTASES

- Good performance status
- Minimal or no evidence of extracranial disease
- Resectable single brain met
- WBRT should be considered to reduce the risk of local recurrence
- Alternative to surgical resection is SRS boost

Whole Brain Radiotherapy

MANAGEMENT OF BRAIN METASTASES



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Whole Brain Radiotherapy

MANAGEMENT OF BRAIN METASTASES

- Standard treatment of brain metastasis
- Usually hypofractionated schemas
- Local control
- Quality of survival functions
- Neurocognitive impairments

Patchell, JAMA, 1998

Surgery

S+WBRT

Local Recurrence	46%	10%	p<0.001
Distant Brain Recurrence	70%	18%	p<0.001
Neurological Death	44%	14%	p<0.003



Table 91.6

RANDOMIZED TRIALS OF POST-OPERATIVE WHOLE BRAIN RADIOTHERAPY

Study	Surgery + RT	Surgery Only	P Value
Patchell et al. (47)/University of Kentucky (n = 95; single lesion)			
Primary end point	(50.4 Gy/28 fx)	Craniotomy	
Brain tumor recurrence			
<i>Total brain recurrence</i>	18%	70%	<0.001
Original site only	4%	33%	
Distant site only	8%	24%	
Original and distant	6%	13%	
Distant site total	14%	37%	<0.01
Original site total	10%	46%	<0.001
Secondary end points			
Cause of death			
Neurologic	14%	44%	0.003
Systemic	84%	46%	<0.001
Functional independence*	37 wk	35 wk	NS
Overall survival	48 wk	43 wk	NS
Aoyama et al. (3)/Japanese JROSG99-1 (n = 132; 1 to 4 lesions)			
Primary end point	(30 Gy/10 fx)	radiosurgery	
Overall survival			
1-year	39%	28%	NS
Median	7.5 mo	8.0 mo	NS
Secondary end points			
Brain recurrence (total) ^a	47%	76%	<0.001
Functional preservation ^{a, b}	34%	27%	NS
Neurologic death	23%	19%	NS
Need for salvage therapy	10 patients	29 patients	<0.001
Radiation morbidity			
Acute	4 patients	8 patients	NS
Late	7 patients	3 patients	NS

RT, whole-brain radiotherapy; fx, fraction number; NS, not significant.

^aOne-year actuarial rates.

^bAs defined by Karnofsky performance score ≥ 70 maintenance.

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**Table 91.3****SELECTED RANDOMIZED TRIALS EXAMINING VARIOUS FRACTIONATION SCHEDULES FOR BRAIN METASTASIS**

Author/Study Group	Dose (Gy)/Fractions	N	Median Survival	P Value	
Borgelt et al. (4)/RTOG First study (1971–1973)	30/10	233	21 wk	NS	
	30/15	217	18 wk		
	40/15	233	18 wk		
	40/20	227	16 wk		
	Second study (1973–1976)	20/5	447	15 wk	NS
		30/10	228	15 wk	
40/15		227	18 wk		
Haie-Meder et al. (19)/French (1986–1989)	25/10	110	4.2 mo	NS	
	36/6 ^a	106	5.3 mo		
Priestman et al. (52)/Royal College of Radiology (1990–1993)	30/10	263	84 d	0.04	
	12/2	270	77 d		
Murray et al. (44)/RTOG 91-04 (1991–1995)	30/10	213	4.5 mo	NS	
	54.4/34 ^b	216	4.5 mo		

NS, not significant; RTOG, Radiation Therapy Oncology Group.

^a18 Gy/three split course with another 18 Gy/three within 1 month.

^b54.4 Gy in 1.6 Gy twice daily hyperfractionation for the entire course of therapy.

Stereotactic radiosurgery or Stereotactic radiotherapy

MANAGEMENT OF BRAIN METASTASES

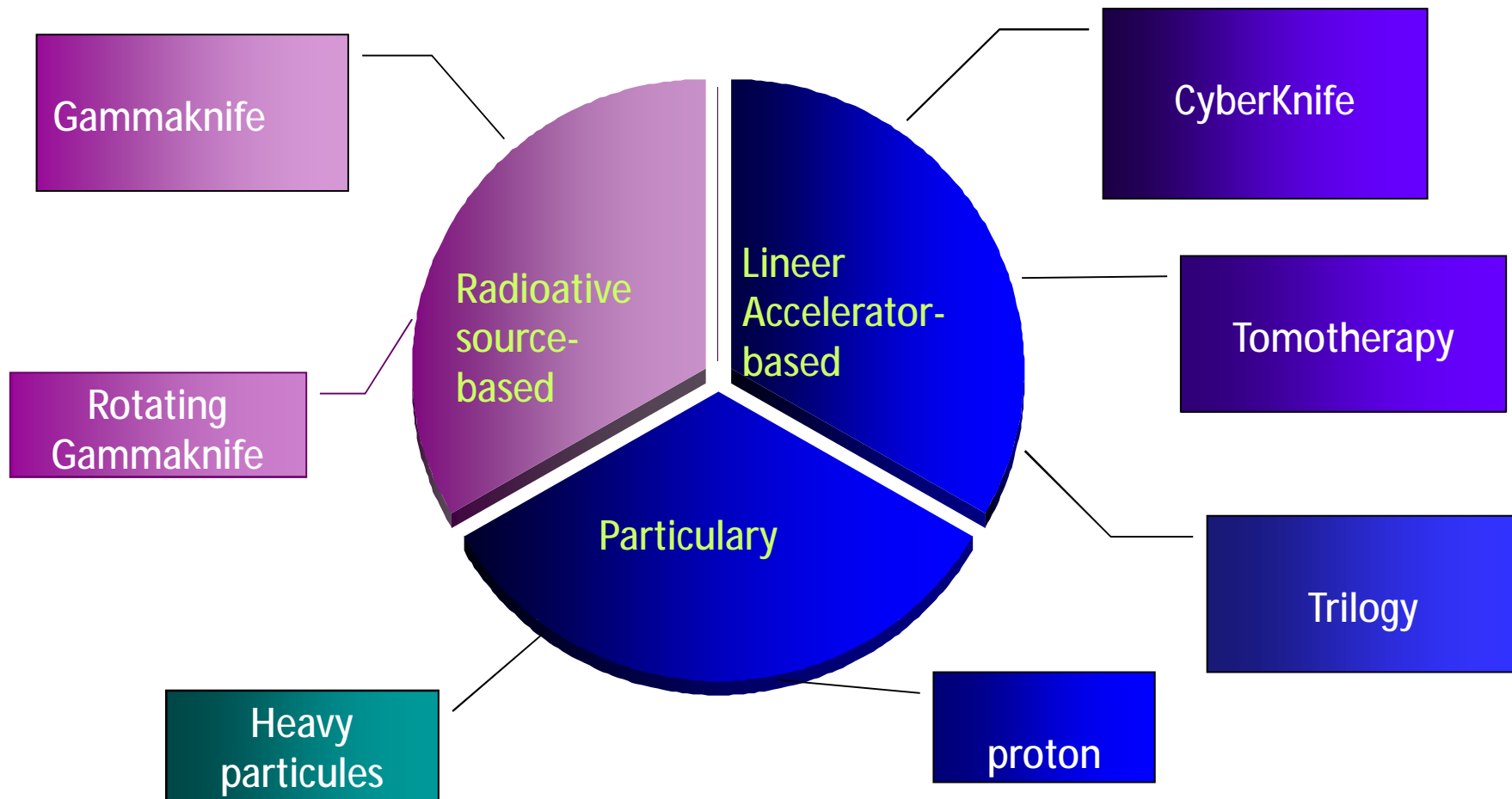
- Fractionated or not fractionated
- After WBRT
- Survival ?
- Local control?
- Neurological side effects???


Table 91.5
RANDOMIZED TRIALS OF STEREOTACTIC RADIOSURGERY BOOST IN BRAIN METASTASES

Author/Study Group	RT + SRS	RT Alone	SRS Alone	P Value
Andrews et al. (1)/RTOG 95-08 (n = 333; 1 to 3 lesions)				
Primary end point (overall survival)	(37.5 Gy/10 fx)			
1 to 3 lesions	5.7 mo	6.5 mo		NS
Single brain metastasis (planned subgroup analysis)	6.5 mo	4.9 mo		0.04
Secondary end points				
Local control (1 year)	82%	71%		0.01
Neurologic death rate	28%	31%		NS
Performance outcome				
KPS stable/improve				
at 3 mo	50%	33%		0.02
at 6 mo	43%	27%		0.03
Mental status				NS
Unplanned subgroup analysis (overall survival)				
Largest tumor >2 cm	6.5 mo	5.3 mo		0.04
RPA class I	11.6 mo	9.6 mo		0.05
Squamous/NSCLC	5.9 mo	3.9 mo		0.05
Other outcomes				
Response rate (3 mo)				
Tumor	73%	62%		0.04
Edema	70%	47%		0.002
Kondziolka et al. (30)/University of Pittsburgh (n = 27; 2 to 4 lesions)				
Primary end point		(30 Gy/12 fx)		
Local control (1 yr)	92%	0%		0.0016
Time to local failure	36 mo	6 mo		0.005
Time to any brain failure	34 mo	5 mo		0.002
Secondary end points				
Overall survival	11 mo	7.5 mo		NS
Treatment morbidity	0	0		
Progression-free survival	Not reported			
Need for retreatment	Not reported			
Chougule et al. (7)/Brown University (n = 109; 1 to 3 lesions)				
End points (abstract only)	(30 Gy + 20 Gy SRS)	(30 Gy/10 fx)	(30 Gy SRS)	
Overall survival	5 mo	9 mo	7 mo	Not reported
Local control	91%	62%	87%	Not reported
New brain lesions	19%	23%	43%	Not reported

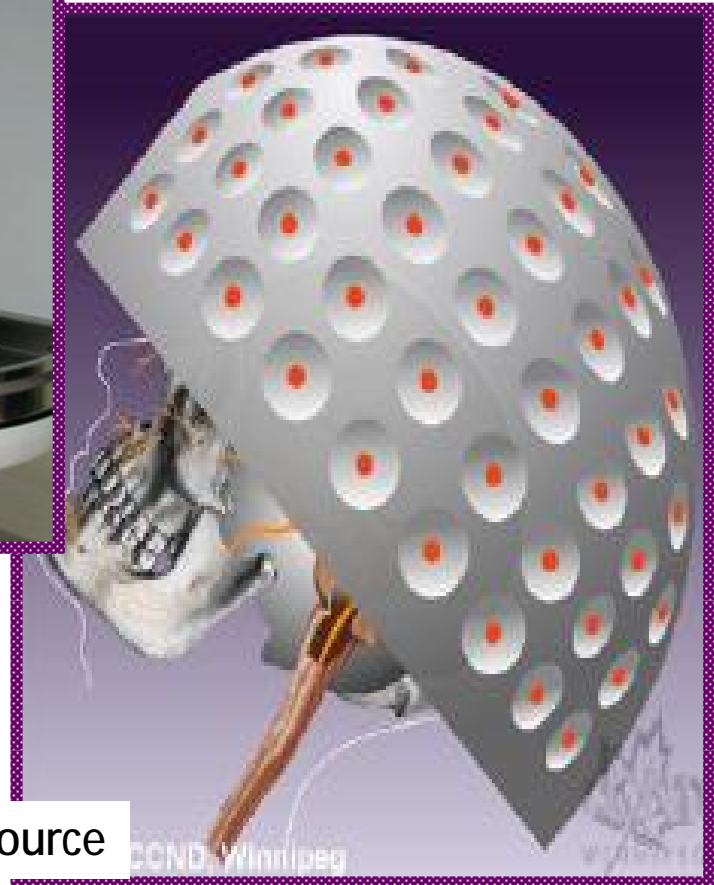
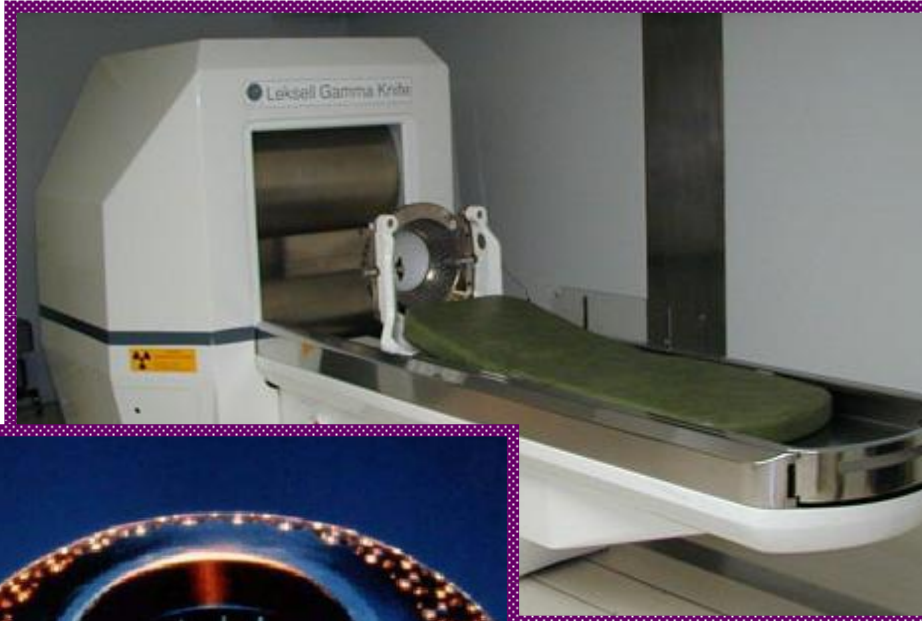
RT, whole-brain radiotherapy; SRS, stereotactic radiosurgery; RTOG, Radiation Therapy Oncology Group; fx, fraction number; KPS, Karnofsky performance score; RPA, recursive partitioning analysis; NSCLC, non-small cell lung cancer.

SBRT

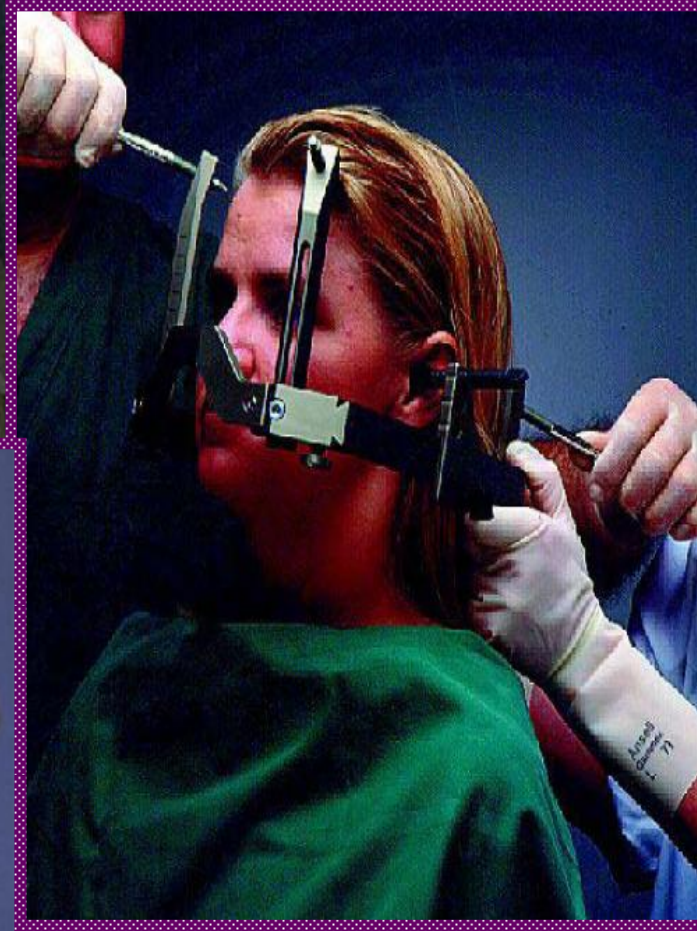
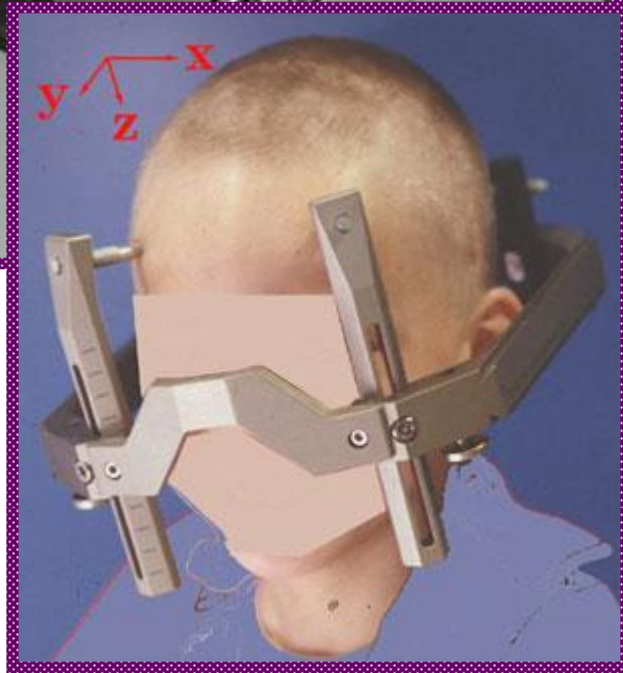




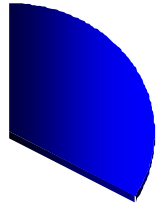
Gamma-knife



201- CO-60 source



Invasive frame.



Cyberknife

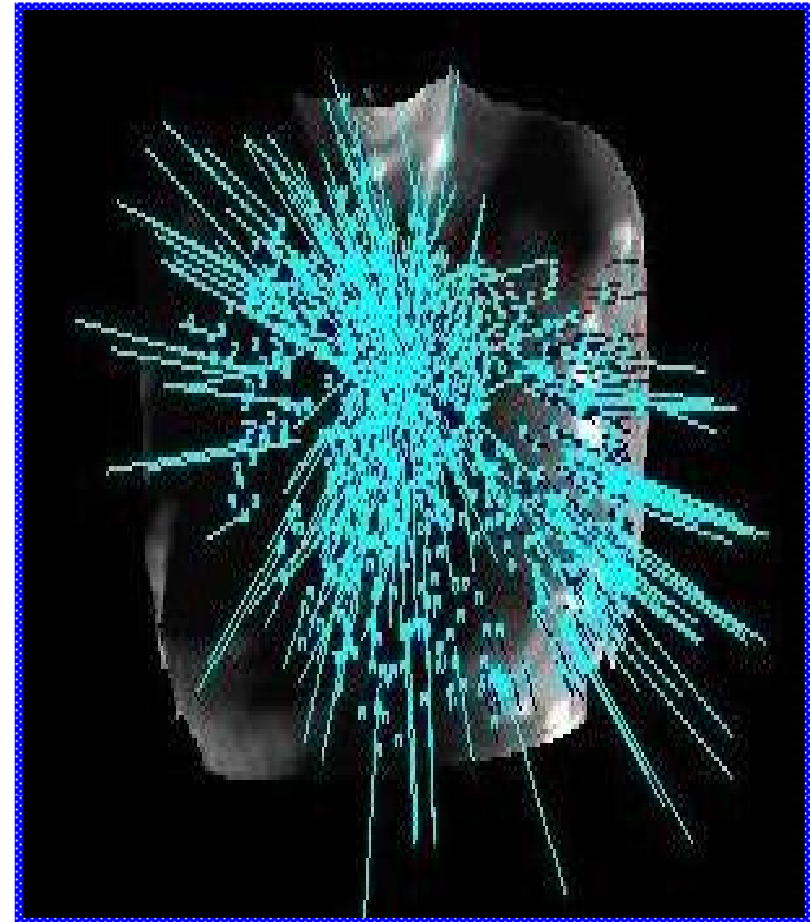


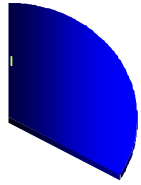
- First patient was on 1994
- FDA approval was on 2001



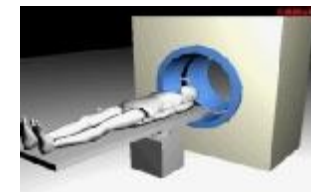
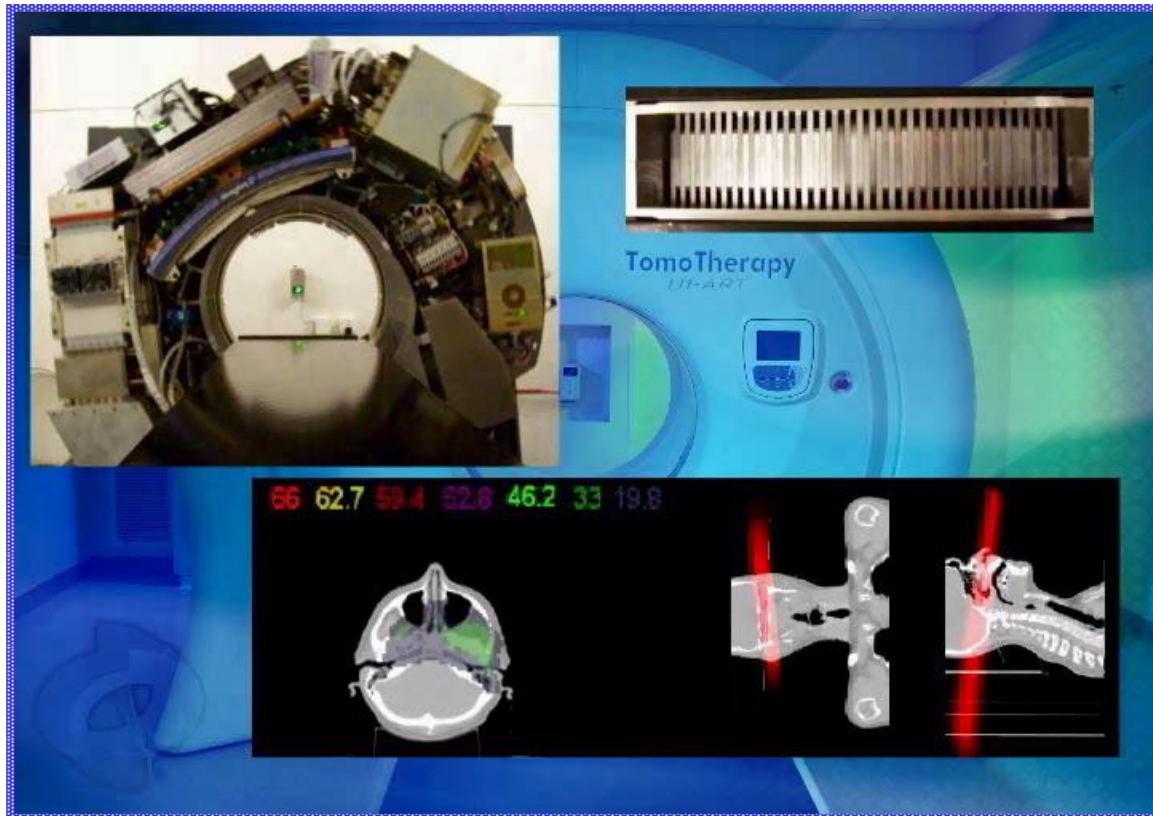
- Patient position is following up
- Cranial or extracranial
- Portal image after 3 shooting

Cranial irradiation





Tomotherapy



Chemotherapy/radiosensitizers

- Systemic control
- Additive or synergistic effect with radiotherapy
- Blood brain barrier
- New agents (efaproxial, Gliadin wafers etc.)

Chemotherapy/radiosensitizers

- N= 740 with brain met
- Survival 8.1% at 2 yrs, and 4.8% at 3 yrs
- Highest survival for ovarian ca (23.9%), and lowest survival in pts with lung CA .
- Prognostic factors:
 - Age < 60 yrs
 - KPS > 70
 - Single lesion
 - Surgical resection
 - WBRT
 - ChT



Table 91.7

SELECTED RANDOMIZED TRIALS OF RADIOSENSITIZERS IN BRAIN METASTASIS

Author/Study Group	Arms	Response		Median	
		Rate	P Value	Survival	P Value
Komarnicky et al. (29)/ RTOG 79-16 (n = 859)	RT (30 Gy/10 fx)	45% ^a		4.5 mo	
	RT + misonidazole	42% ^a	NS	3.9 mo	NS
	RT (30 Gy/6 fx)	42% ^a		4.1 mo	
	RT + misonidazole	45% ^a	NS	3.1 mo	NS
Ushio et al. (70)/Japan ^b (n = 88)	RT (40 Gy/20 fx)	36%		27 wk	
	RT + nitrosurea	69%		31 wk	
	RT + nitrosurea + tegafur	74%	<0.05	29 wk	NS
Phillips et al. (49)/RTOG 89-05 (n = 72)	RT (37.5/15 fx)	50%		6.1 mo	
	RT + BrdUrd	63%	NS	4.3 mo	NS
Guerrieri et al. (18)/Australia ^b (n = 42)	RT (20 Gy/5 fx)	10%		4.4 mo	
	RT + carboplatin	29%	NS	3.7 mo	NS
Antonadou et al. (2)/Greece (n = 52)	RT (40 Gy/20 fx)	67%		7.0 mo	
	RT + temozolomide	96%	0.017	8.6 mo	NS
Verger et al. (73)/Spain (n = 82)	RT (30 Gy/10 fx)	54% ^c		3.1 mo	
	RT + temozolomide	72% ^c	0.03	4.5 mo	NS
Mehta et al. (41)/9801 Trial (n = 401)	RT (30 Gy/10 fx)	51%		4.9 mo	
	RT + MGd	46%	NS	5.2 mo	NS
Suh et al. (67)/REACH Trial (n = 515)	RT (30 Gy/10 fx)	38%		4.4 mo	
	RT + efaproxiral	46%	NS	5.4 mo	NS

RTOG, Radiation Therapy and Oncology Group; RT, whole-brain radiotherapy; fx, fractions; NS, not significant; BrdUrd, bromodeoxyuridine; MGd, motexafin gadolinium.

^aPercent of survival time in Karnofsky performance score 90–100 range.

^bOnly lung cancer patients.

^cNinety-day freedom from brain metastasis.

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Take home messages

MANAGEMENT OF BRAIN METASTASES

- WBRT is standard for multiple metastases
- Surgery is suitable for single met with high KPS, and young pts
- Radiosurgery boost (with WBRT) may be considered in selected pts to improve local control
- The use of radiosensitizers is not recommended outside research studies
- The use of ChT as primary therapy for brain met. or the use of ChT with WBRT to treat brain metastases remains experimental



Thank you...

ESMCA 2010