

# Contemporary Management of Brain Metastases

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## Definitions

- Primary tumor- original site of cancer
  - Lung, breast, melanoma, renal cell carcinoma, etc.
- Metastasis- tumor cells which have migrated from the original site
  - Brain, bone, other organs (liver metastases with lung primary, etc.)



## Overview

- Epidemiology
- Diagnosis
- Imaging
- Radiation: whole brain, stereotactic radiosurgery
- Surgery
- Future treatments



## Epidemiology

- Approximately 150-170,000 annually
- Posner and Cherek: 24% of 2375 cancer patients
- Increased age 45-64 but most prevalent over 65
- Presenting symptom of cancer in 15%
- Solitary site of cancer 9%



## Incidence is increasing

- Increasing length of survival
- Increasing rate of diagnosis
  - MRI
  - PET scans
  - Protocols
- BBB- blood-brain barrier
  - Relatively immunoprotected environment

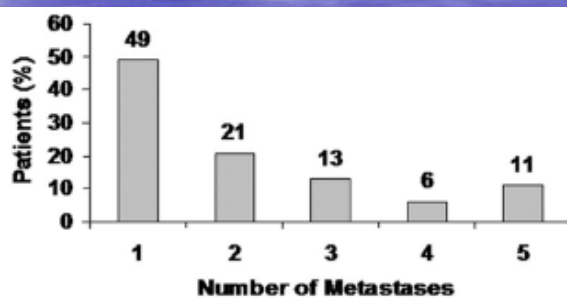


FIGURE 1.2. Number of cranial lesions per patient with brain metastases (from, Delattre JY, Krol G, Thaler HT, Posner JB: Distribution of brain metastases. *Arch Neurol* 45:741-744, 1988 [11]).



## Timing of presentation

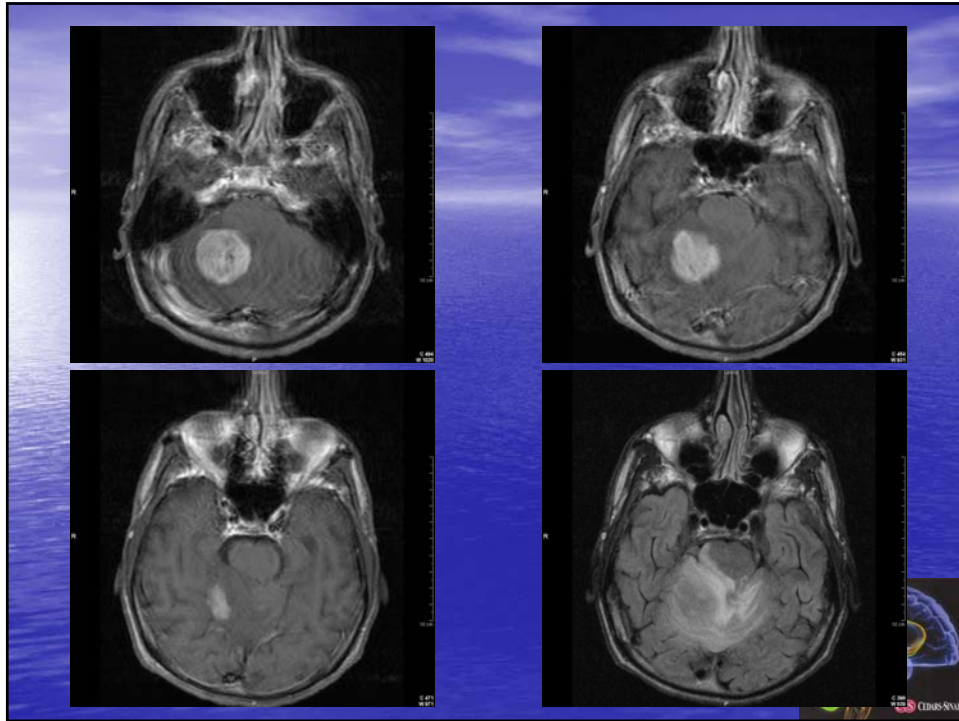
- Metachronous 80%
  - 2+ mos from initial Dx
- Synchronous
  - Within 2 mos of Dx
- Precocious
  - Diagnosis of brain metastasis before primary tumor



## Symptoms

- More dependent on location in brain and growth rate than tumor type
- Headache alone 50%
- Seizures 20%
- Hydrocephalus- blockage of spinal fluid drainage
- Mental status changes (confusion, sleepiness)
- Tumor TIA (mini-stroke)- symptoms which improve
- Asymptomatic 10%





## MRI- metastases vs. glioma (primary brain tumor)

- Multiple
- Well-circumscribed
- Grey-white junction
- Common in posterior fossa
- Single
- Infiltrative
- Cortical
- Uncommon in posterior fossa





## Imaging

- Screening
  - Non small cell lung cancer
  - Breast cancer
- Increased sensitivity on triple dose contrast, thin-cut MRI
- Hemorrhagic
  - Melanoma, thyroid, renal, breast, lung
- Possibly CT with contrast, MRI without contrast
  - Less sensitive

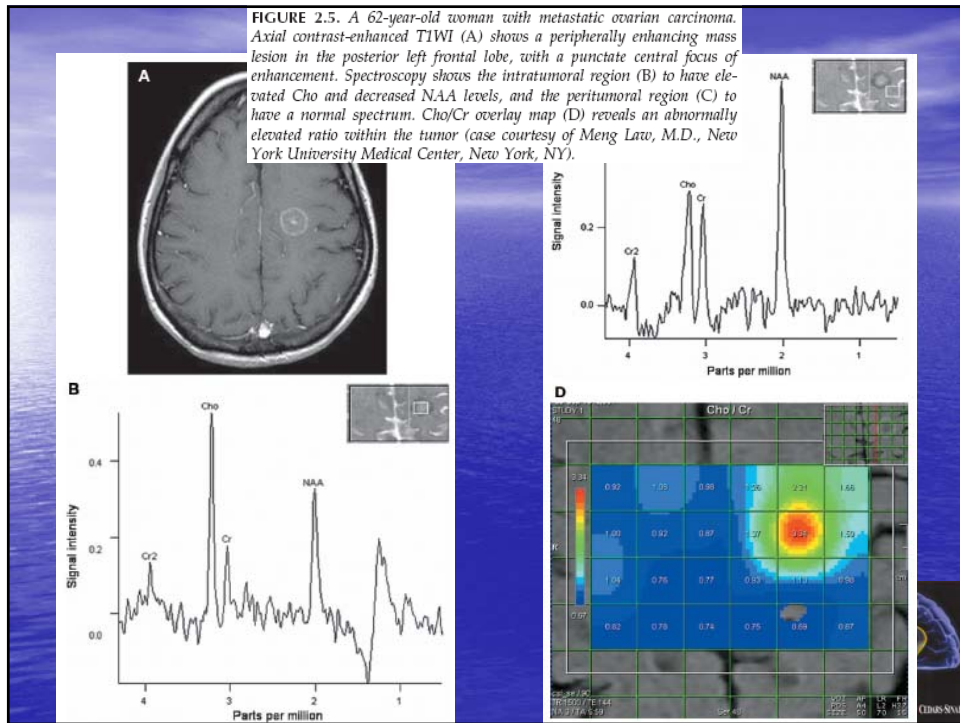
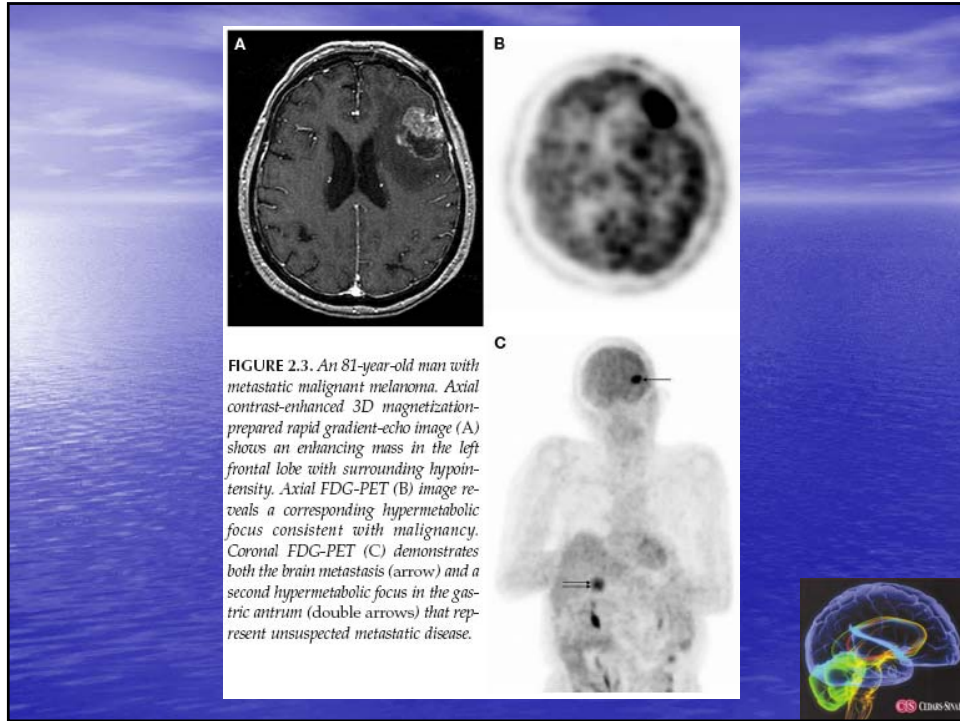


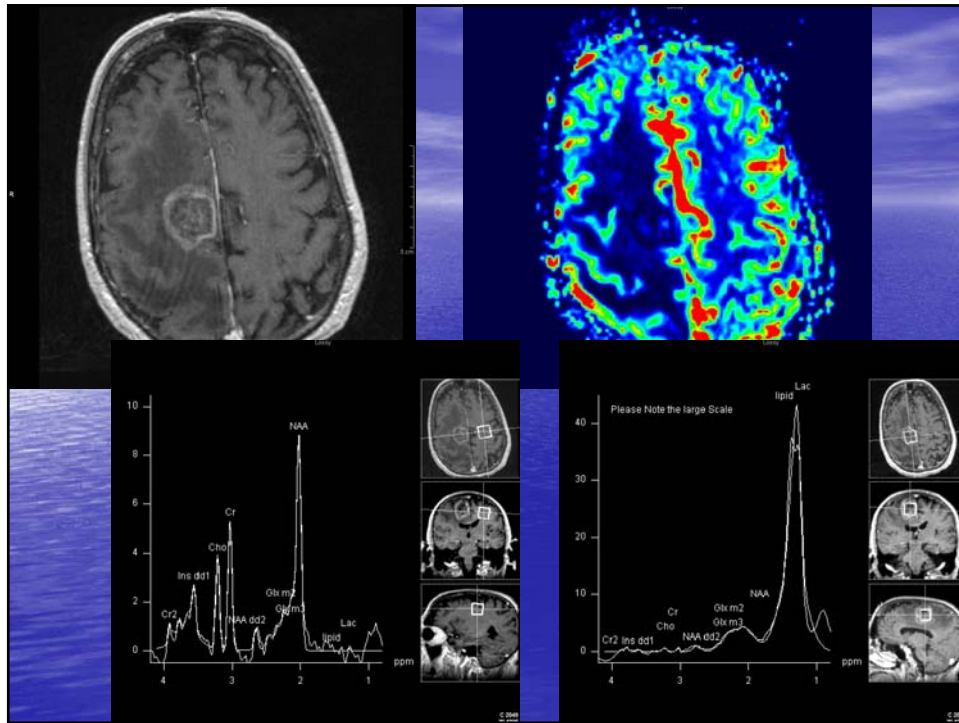


## Physiologic imaging

- PET scan
  - $^{18}\text{F}$ -deoxyglucose
  - Increased cellular activity
- SPECT
- Perfusion MRI
- MR spectroscopy (MRS)



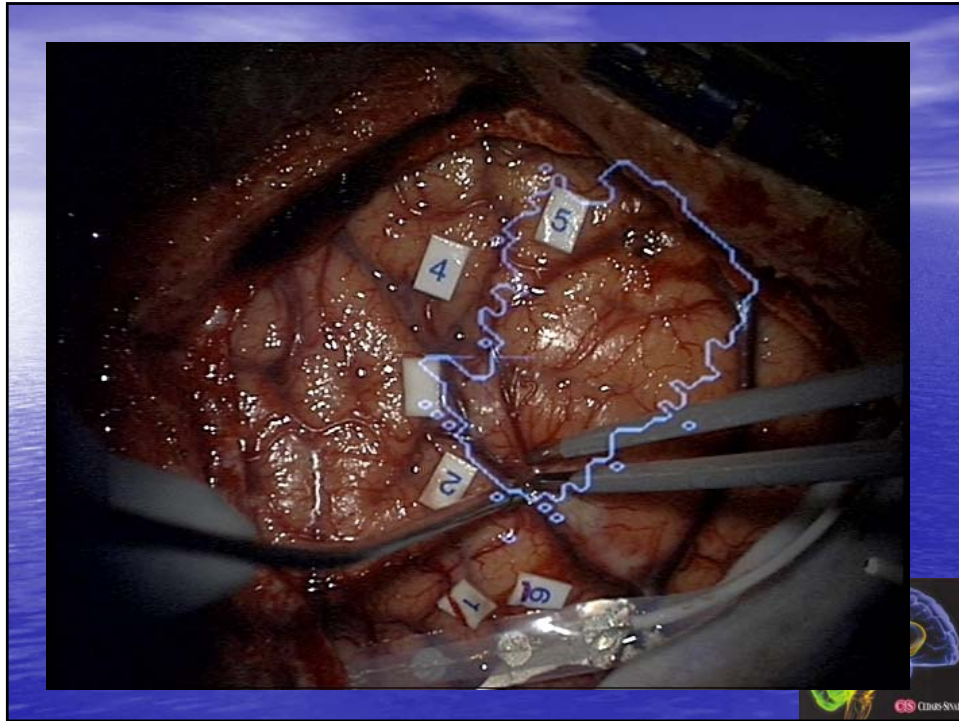




## Anticonvulsants

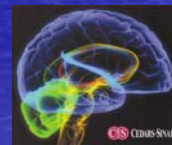
- American Academy of Neurology
- Antiepileptic drugs (AEDs) not needed unless history of seizures
  - Dilantin, phenobarbital
  - Blood levels, interference with other medications
- Peri-operative coverage- one week
- Unclear with newer AEDs- Keppra, Zonegran





## Surgical Techniques

- MRI guidance
- Intraoperative MRI
- Intraoperative ultrasound
- Motor strip mapping
- Language mapping
- Awake craniotomy



## Patchell 1990

- Randomized study in single brain mets
- 48 patients
- Improvement in median survival for surgery + XRT vs. XRT alone (40w. vs. 15w.,  $p < .01$ )
- Longer functional independence (38w vs 8w,  $p < .005$ )
- Patchell 1998- whole brain radiation after surgery delayed neurologic morbidity and mortality (vs. surgery alone)
- Few randomized surgical trials



## Factors favoring excision of a solitary lesion

- Primary disease controlled
- Accessible lesion
- Symptomatic, large ( $> 4\text{cm}$ ), or life-threatening lesion
- Not radiosensitive tumor (not small-cell lung carcinoma)
- Only accessible pathology
- No delay in appropriate treatment from craniotomy



## Factors favoring excision of multiple lesions

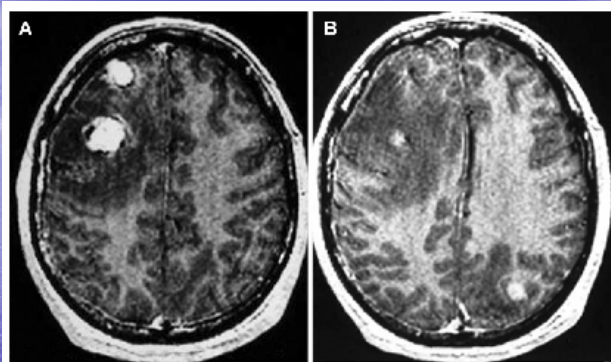
- Primary disease controlled
- Accessible lesions, less than 4
- Symptomatic, large (> 4cm), or life-threatening lesions
- Not radiosensitive tumor
- Only accessible pathology
- No delay in appropriate treatment from craniotomy



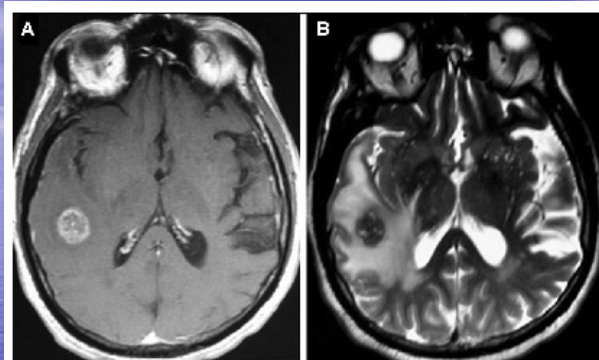
## Bindal, Sawaya 1993

- Resection of up to 3 accessible metastases improved survival to the same as those with a single metastasis
- SRS (stereotactic radiosurgery) is a possibility





**FIGURE 3.2.** A and B, multiple metastatic brain tumors with large dominant lesions. This 45-year-old man presented with headaches and personality change. He had no known primary lesion at the time. He opted to have surgical removal of the largest two lesions for diagnosis and for relief of mass effect. Histology confirmed lung carcinoma. He went on to have WBRT. He maintained a KPS score of 100 and worked full time for an additional 2 years. He had an overall survival of 27 months from the diagnosis of the brain lesions. This case illustrates some of this issues discussed in the text regarding the use of surgery in multiple brain metastases.



**FIGURE 3.3.** This 72-year-old man had a remote history of colon cancer. He presented with seizure and mental status change. Brain imaging (A and B) demonstrated a solitary right temporal lesion measuring  $1.6 \times 2.0$  cm, but with significant surrounding edema. His seizures were difficult to control medically. He opted to undergo craniotomy for removal of the lesion, despite the small size. This case illustrates some of this issues discussed in the text regarding the use of surgery versus radiosurgery for patients with a single brain metastasis.

## Whole Brain Radiation Therapy (WB XRT)

- 30 Gy in 10 fractions over 2w. vs. 50 Gy in 2 Gy fractions
- Radiosensitive
  - SCLC, germ cell tumors, lymphoma, leukemia, multiple myeloma
- “Radioresistant”
  - Melanoma, renal cell carcinoma, sarcoma
  - Different for radiosurgery



TABLE 4.4. Response to whole-brain radiation therapy in patients with brain metastases from various tumor types (N = 108)<sup>a</sup>

Tumor type	Complete response (%)	Partial response (%)
Small cell lung carcinoma	37	44
Breast cancer	35	30
Squamous cell carcinoma	25	31
Adenocarcinoma (nonbreast)	14	36
Renal cell carcinoma	0	46
Melanoma	0	0
All metastases	24	35

<sup>a</sup> Adapted from, Nieder C, Berberich W, Schnabel K: Tumor-related prognostic factors for remission of brain metastases after radiotherapy. *Int J Radiat Oncol Biol Phys* 39:25–30, 1997 (55).



TABLE 4.5. Whole-brain radiation therapy with or without surgery, and surgery with and without whole-brain radiation therapy in randomized studies<sup>a</sup>

Series (ref. no.)	No. of patients	Treatment	Local recurrence (% of patients)	Median survival (mo)
Patchell et al., 1990 (60)	48	WBRT	52	4
		WBRT + surgery	20	10
Vecht et al., 1993 (90)	63	WBRT	Not reported	6
		WBRT + surgery		10
Mintz et al., 1996 (51)	84	WBRT	Not reported	6.3 <sup>b</sup>
		WBRT + surgery		5.6
Patchell et al., 1998 (59)	95	Surgery	46 <sup>c</sup>	12.0
		Surgery + WBRT	10	10.8

<sup>a</sup> WBRT, whole-brain radiation therapy.

<sup>b</sup>  $P = 0.24$ .

<sup>c</sup>  $P = 0.001$ .



## XRT Complications

- Acute < 90d
  - N/V, alopecia, hearing loss, skin reactions, somnolence
  - Some symptoms reversible
- Late > 90d
  - Radiation necrosis, personality changes, memory loss, cognitive deficits, ataxia, incontinence
- Should be minimal if 30 Gy in 10 fractions or more
- Severe complications 5%; total rate higher



## Small cell lung cancer

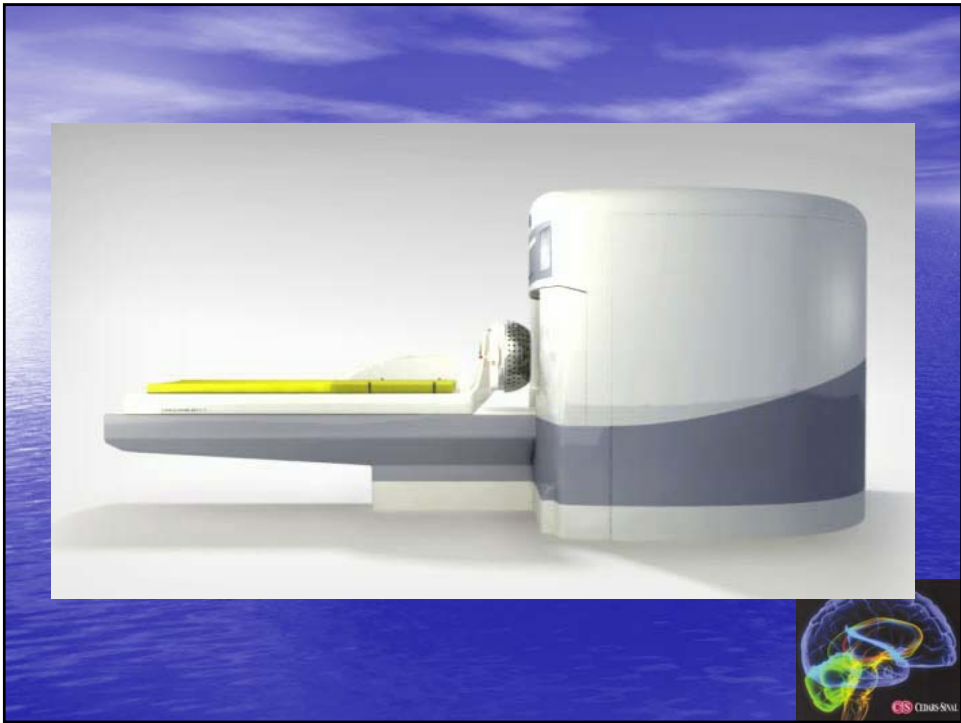
- 20% of lung cancer
- Oat cell cancer
- Younger, smokers
- Median survival 6-10 mos.
- Mets in 80% of those who survive 2y.
- Radiosensitive- prophylactic WB XRT
- Biopsy of lung lesion important when possible when facing undiagnosed lung mass and brain mass

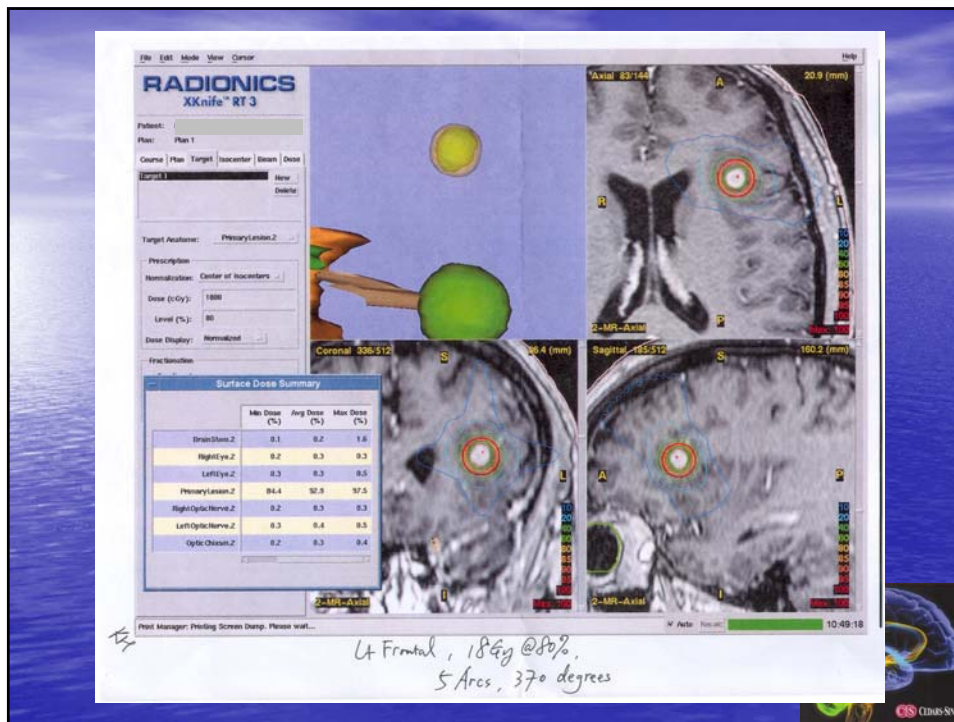


## Stereotactic radiosurgery (SRS)

- Targeted radiation delivery
- Energy sources:
  - gamma knife- Cobalt-60
  - linear accelerator (LINAC)- electron accelerator
  - proton beam
- Cyberknife, Novalis- frameless LINAC
  - Accuracy vs patient comfort
- 18-22 Gy







## Surgery vs. Radiosurgery

- Limited data on comparative efficacy
- Need good systemic health for craniotomy
- Mass effect
- Significant edema
- Small, relatively inaccessible lesions



## Outcome

- Karnofsky >70 (good neurologic status)
- Age <60
- No systemic metastases
- Controlled primary disease
- >1y. since primary Dx
- Solitary metastasis



## Outcome

- No treatment- 1 mo. median survival
- Steroids alone- 2 mos.
- WB XRT 3-6 mos. 50% deaths from intracranial progression
- Surgery, WB XRT 12 mos.
  - Improved for young age, unifocal and accessible disease, good neurologic status

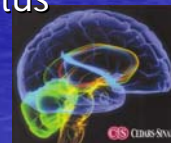


TABLE 5.3. Median survival by primary tumor type<sup>a</sup>

Primary tumor type	Chen et al., 2000 (12)		Sneed et al., 2002 (58)		Petrovich et al., 2002 (48)	
	No. of patients	Median survival (mo)	No. of patients	Median survival (mo)	No. of patients	Median survival (mo)
Melanoma	88	6.9	93	7.1	231	8
Breast	12	16.6	50	8.6	38	17
Colon	9	5.3			13	6
Lung			282	8.7	94	9
NSCLC	40	9.7				
SCLC	5	2.8				
Renal	49	12.3	62	9.6	29	12
Other	24	5.4	82	8.4	39	6

<sup>a</sup> NSCLC, non small cell lung cancer; SCLC, small cell lung cancer.



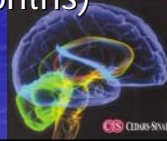
## Whole brain radiation vs. radiosurgery boost after surgery

- Whole brain essentially cannot be repeated
- Assumes that primary tumor seeding the brain is a one-time event
- Assumes that survival does not generally last long enough to see side effects of whole brain radiation



## Surgery + whole brain vs. radiosurgery boost

- Cancer treatment centers disagree
- May recommend whole brain for any patient with one metastasis, even after surgery
  - Risk of complications of whole brain radiation
- May recommend radiosurgery boost after surgery, assuming close follow-up with MRIs
  - Risk of distant recurrence
  - May need radiosurgery, whole brain radiation in future
- Follow closely with MRIs (e.g., every 3 months)



## Summary

- Surgical resection of brain metastases should be considered for patients with limited disease in good condition
  - After surgery- whole brain radiation vs. radiosurgery boost
- Radiosurgery- difficult to remove, poor condition for surgery, poor control of overall cancer
- Whole brain radiation 4+ lesions, SCLC



## Unanswered questions

- Is the rate of distal failure when avoiding WB XRT significant to the patient?
- Is there a more sensitive method for detecting micro-metastases than MRI?
- Is there a benefit to WB XRT after radiosurgery?
- Is there a benefit with low risks to radiosurgery after whole brain radiation?



## Ongoing studies

- European Organisation for Research and Treatment of Cancer (EORTC) 22952- comparison of surgery and radiosurgery +/- XRT



# New treatments

- Temodar
  - Alkylating agent which crosses BBB
- Gliadel (BCNU)
  - Chemo wafer placed across the BBB
  - XRT or SRS?
  - Is local vs. distant disease the problem?
- Radiosensitizers
  - Etoposide, motexafin gadolinium
- Microwave ablation

