

Role of Radiation Therapy

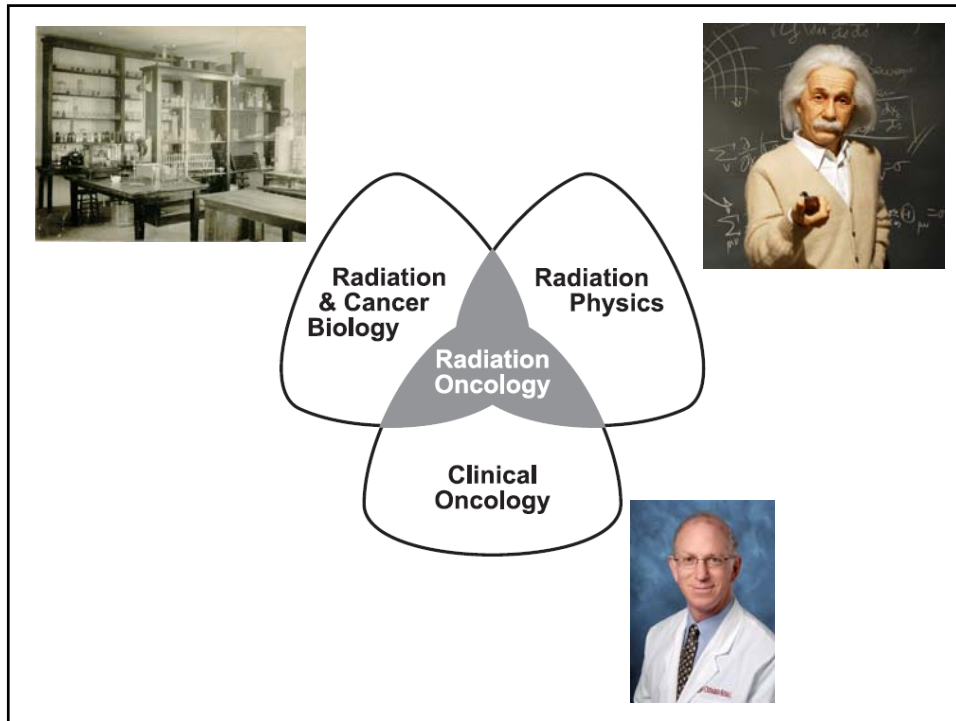
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Therapeutics
Chairman
Department
of Radiation Oncology



Topics

- How radiotherapy works (4Rs)
- Role of Radiation Therapy
- Hippocampus
- Meningioma

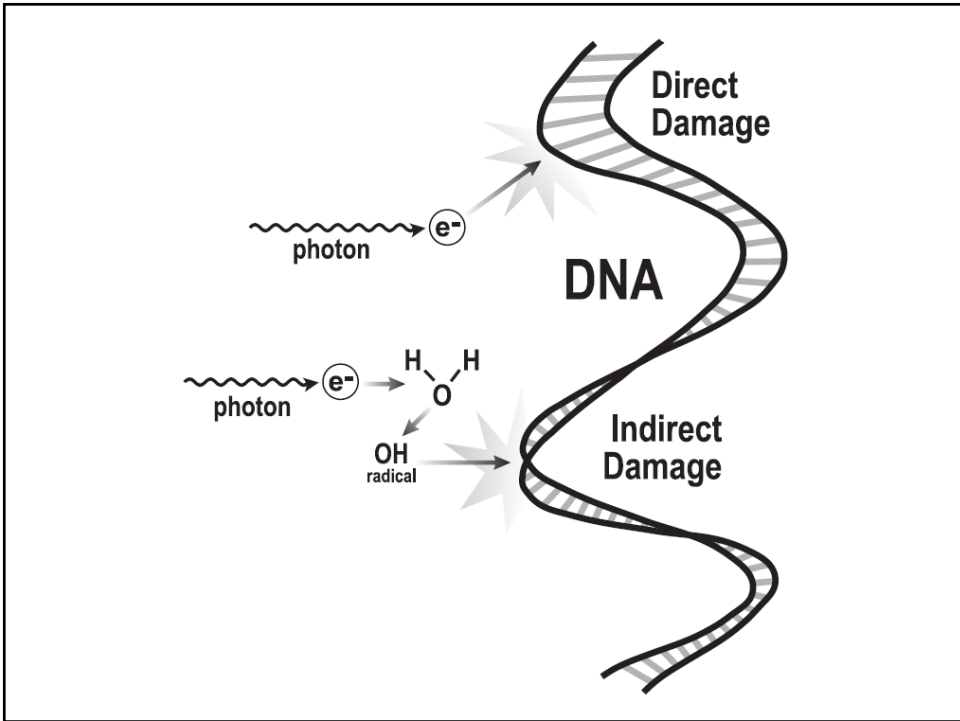
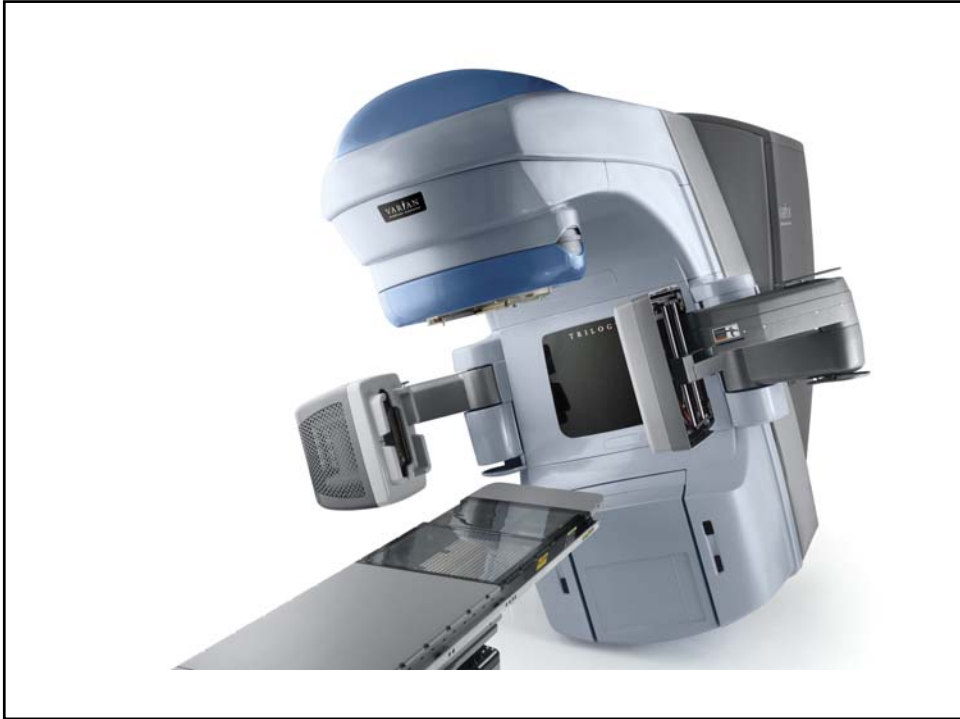


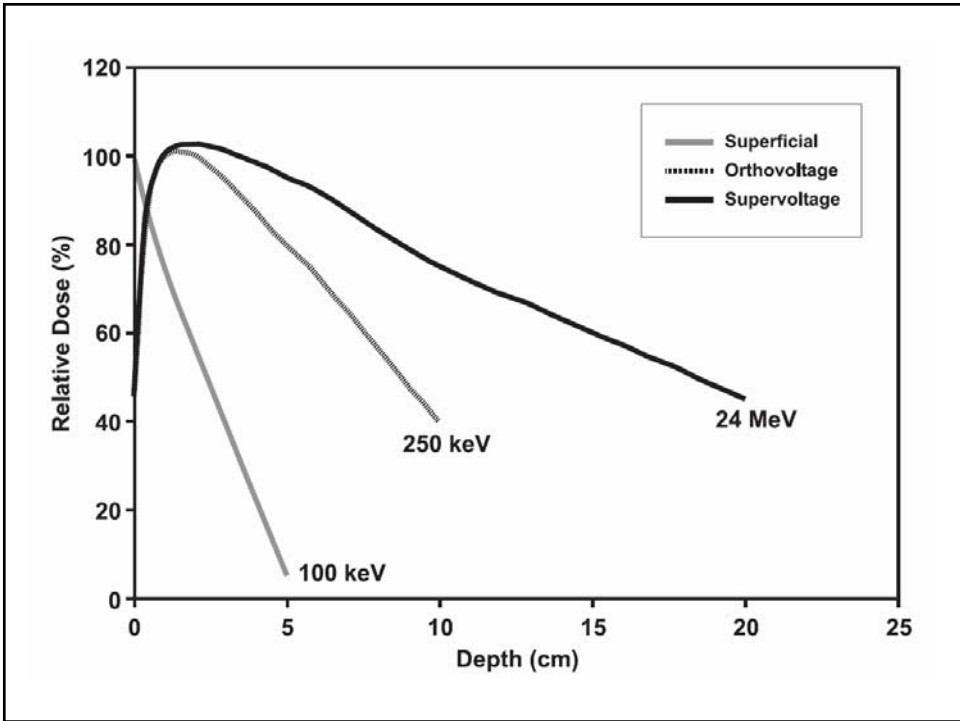
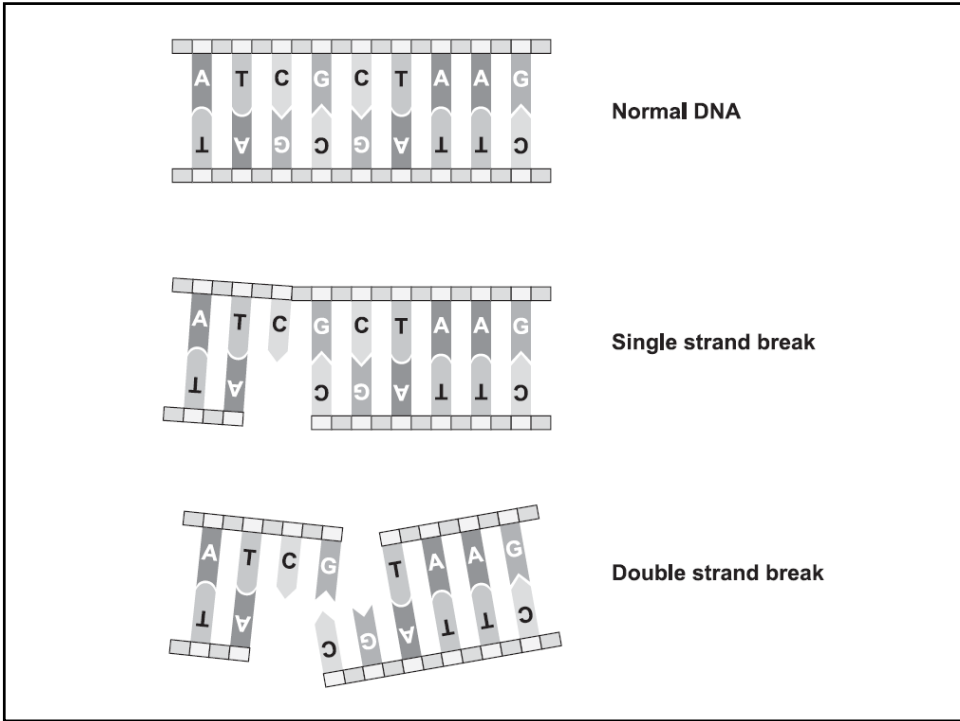


Radiotherapy

- What is it?
 - Ionizing RT
 - DNA strand breaks
 - Cell death







Fractionation

- Why do we fractionate?



Historical Background

- Early experiments:
 - Ram Testis (as tumor equivalent)
 - Sterilization (as cure)
 - Skin damage
- Fractionation of the radiation dose produces better tumor control for a given level of normal tissue toxicity than a single large dose



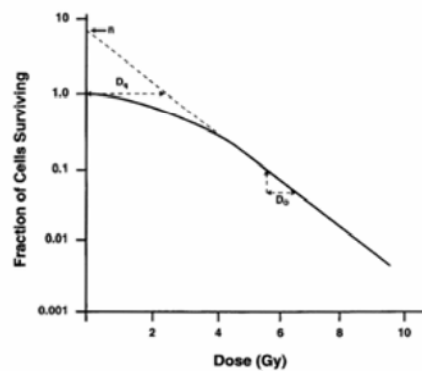
Why fractionation works - 4 R's

- Repair
- Reassortment
- Repopulation
- Reoxygenation



Cellular Radiosensitivity

- ❖ Studied through radiation-induced cell death (loss of reproductive integrity)
- ❖ Useful in assessing the relative biologic impact of various types of radiation and exposure conditions
- ❖ Cellular inability to form colonies as a function of radiation exposure → cell survival curves
- ❖ Three parameters defining response to radiation: n , D_q and D_0



Repair

- Sublethal damage is repaired
 - Increase in survival that is observed if a given radiation dose is split into two fractions separated by a time interval



Reassortment

- RT kills sensitive cells, mostly M & G2
- After RT, most survivors are in S phases
- Progression of cells through the cycle after sensitive cells are killed
- Return to a more even cell age distribution within the cycle



Repopulation - Accelerated

- After RT, cells will grow back
- Treatment with any cytotoxic agent can trigger the surviving cells to divide FASTER than before – ACCELERATED REPOPULATION



Reoxygenation

- After RT and cell killing, hypoxic areas become more oxygenated



Normal Tissue vs. Tumor

- Spares normal tissues
 - Repair (only for acute effects)
 - Repopulation (if time sufficiently long)
- Increases damage to tumor
 - Reoxygenation
 - Reassortment



Low grade astrocytoma	Schwannoma
Anaplastic astrocytoma	Craniopharyngioma
GBM	Pituitary tumors
Low grade oligo	CNS germ cell tumors
Anaplastic oligo	Pilocytic astrocytoma
Mixed gliomas	Ganglioglioma
Ependymoma	Hemangioblastoma
PNET	Hemangiopericytoma
CNS lymphoma	Sarcoma
Meningioma	Choroid plexus carcinoma



Roles of Radiotherapy

- Post-op adjunct to:
 - decrease local failure
 - delay progression/relapse
 - prolong survival, eg GBM, AA
- Primary curative therapy:
 - PNET, Germ Cell Tumors, Pilocytic astrocytoma
- To halt tumor growth:
 - Meningioma, Schwannoma
- To alter endocrine function
- To palliate



Radiotherapy Improves Survival

Disease	Survival (no XRT)	Survival (with XRT)
PNET	< 10%	50-70%
CNS Germinoma	< 5%	> 90%
Craniopharyngioma	10 yr: 37%	10 yr: 77%
Glioblastoma	MS: 18 wks	MS: 42 wks



Radiotherapy Improves Local Control

Craniopharyngioma as a case-study: 34 literature reports

Outcome	TR	STR	STR/RT
5-YR SURV	81%	53%	89%
10-YR SURV	69%	37%	77%
RECURRENCE	29%	73%	17%



Radiotherapy Diminishes Local Failure

Meningioma as a case-study: Literature reports


Outcome	TR	STR	STR/RT
5-YR PROGR	5%	37%	11%
10-YR PROGR	10%	55%	23%
15-YR PROGR	32%	91%	



The Impact of Radiation Dose

Medulloblastoma as a case-study: Literature reports

Author	Year	<50 Gy	>50 Gy
Harisiadis	1977	24%	48%
Cumberlin	1979	17%	86%
Berry	1981	42%	78%
Silverman	1982	38%	80%
Kopelson	1983	50%	78%
CCG	1987	33%	58%

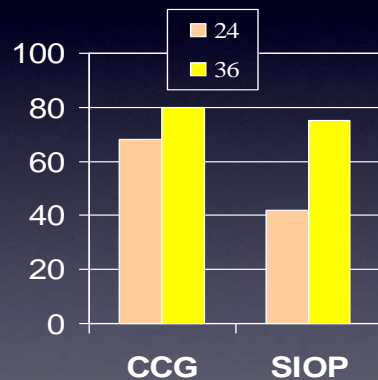
Decreasing posterior fossa dose increases relapses 

The Impact of Radiation Dose

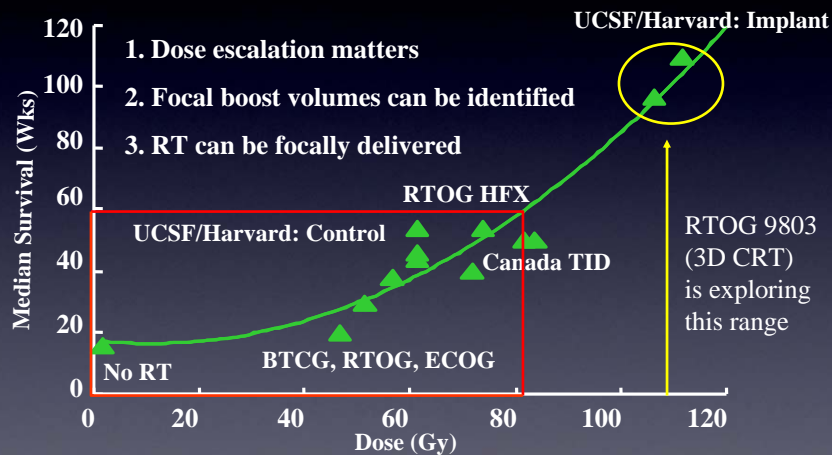
Medulloblastoma as a case-study: Clinical Trials

- 2 -ve Ph III trials
- 3 yr isolated neuraxis failure: 2/44 vs. 11/45.
- SIOPII: 4 arms; 35 vs. 25 Gy CSI +/- pre-RT chemo
- 5 yr RFS= 75 vs. 42% for chemo RT arms

3/5 yr RFS (CCG & SIOPII)



GBM: Dose Escalation



The Role of the Hippocampus

- Many patients exhibit learning/memory deficits with no pathologic changes, especially when the RT field involves the temporal lobes.
- Recent work has shown that hippocampus-dependent learning and memory are strongly influenced by the activity of neural stem cells and their proliferative progeny.
- The hippocampal granule cell layer undergoes continuous renewal and restructuring by the addition of new neurons.
- Radiation at low doses affects the highly proliferative progenitors. A single low dose to the cranium of a mature rat is sufficient to ablate hippocampal neurogenesis.

Monje MJ; Radiation injury and neurogenesis. Current Opinion in Neurology. 16:129-34, 2003.

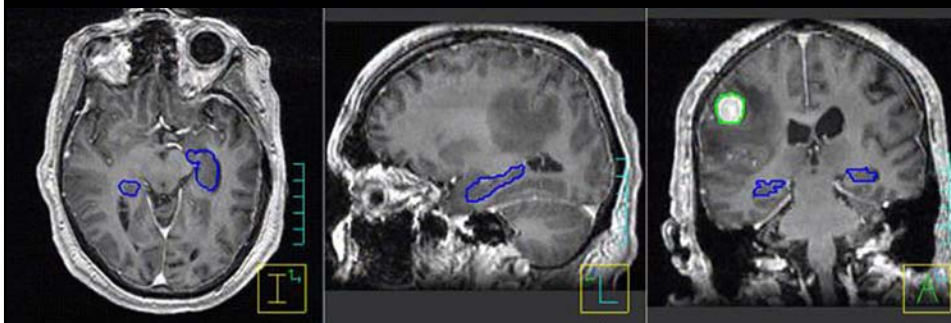


Hippocampus Avoidance Hypothesis

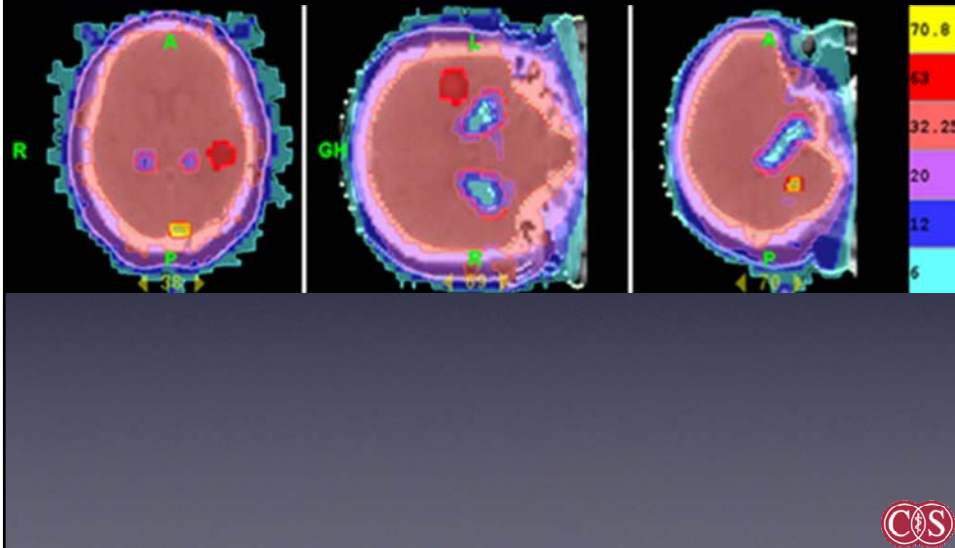
- The hippocampus plays a significant role in RT induced dementia
- Doses as low as 2 Gy cause significant toxicity to the hippocampus
- Conformal avoidance of the hippocampus may help reduce neurocognitive deficits



Hippocampus Delineation



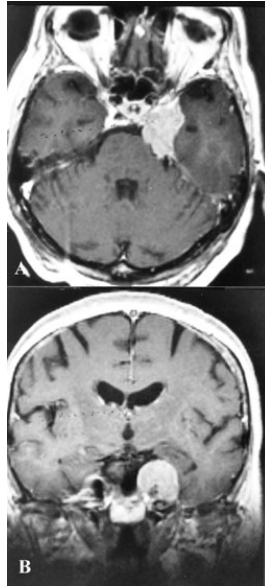
Hippocampus Avoidance with IMRT



Radiotherapy for Meningiomas

- Second most frequent primary brain tumor
- Options for management
 - Conservative approach
 - Surgery
 - Radiotherapy
 - Fractionated External Beam (~ 30 fractions)
 - Stereotactic Radiosurgery (single fraction)
 - Stereotactic Radiotherapy (2-5 fractions)





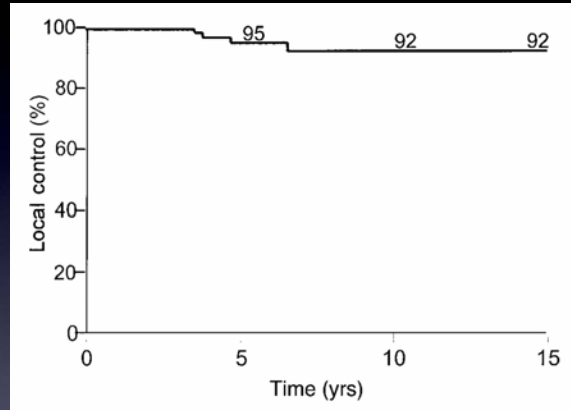
Radiotherapy for Meningiomas

- Indications for RT
 - Subtotally resected tumors
 - Unresectable/hard-to-resect locations
 - Atypical/Anaplastic histologies
- Fractionated external beam
 - Low daily dose reduces risk of toxicity to normal structures within or adjacent to target volume



Radiotherapy for Meningiomas

- External Beam Results
 - Univ Florida
 - 101 patients with skull-based meningiomas
 - 40 recurrent after surgery
 - Excellent local control

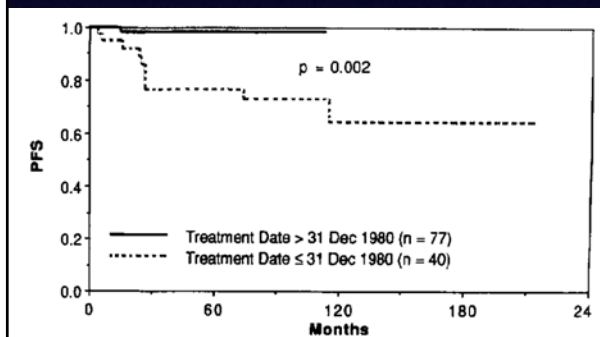


Mendenhall, et al. *Cancer* 98:1473,2003



Radiotherapy for Meningiomas

- UCSF
 - 140 patient series, older era
 - Local control reviewed as function of year



Goldsmith, et al. *J Neurosurg* 80:195,1994



Radiotherapy for Meningiomas

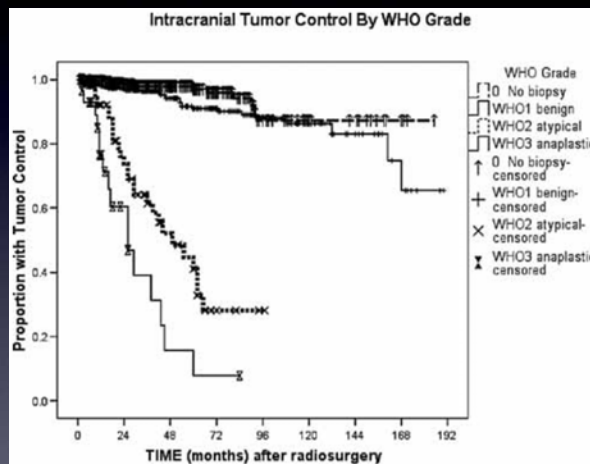
- What about SRS/Gamma Knife?
- Univ Pittsburgh
- 1045 cases!
- Exclusions
 - Diameter > 3.5 cm
 - Mass effect
 - Optic sheath with vision
 - Atypical imaging without histology



Kondziolka et al. Neurosurgery 62:53,2008



Radiotherapy for Meningiomas



Kondziolka et al. Neurosurgery 62:53,2008



Conclusions

- Radiotherapy has an important role to play



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The radiation oncologists in the Radiation Therapy Program work with professional experts, including psychosocial, pain management and nutritional support staff members to develop individualized therapy programs for each patient.


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