

Cedars-Sinai

Role of Radiation Therapy

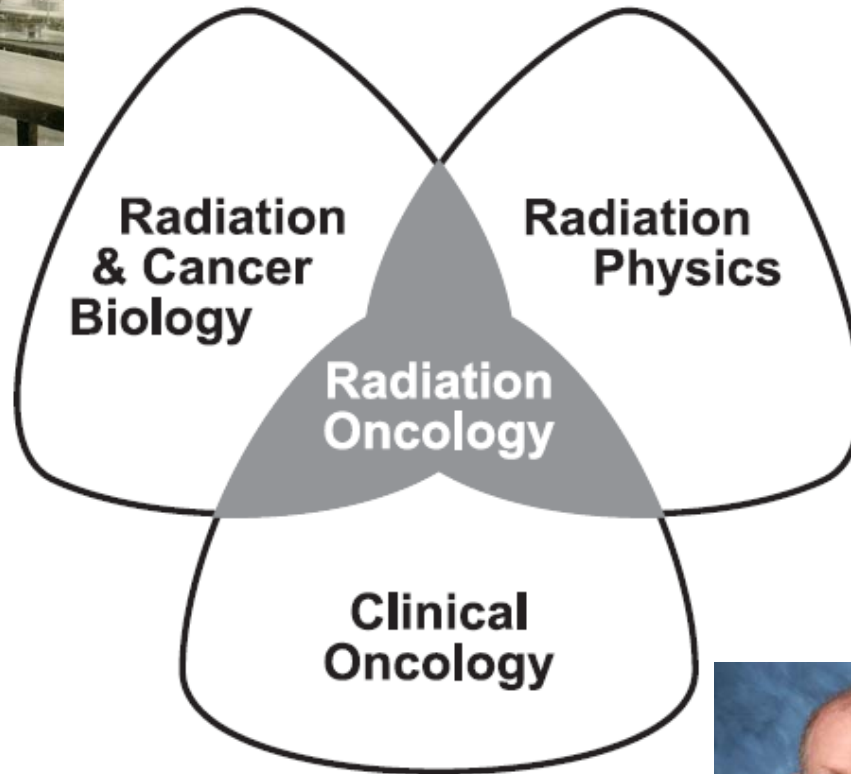
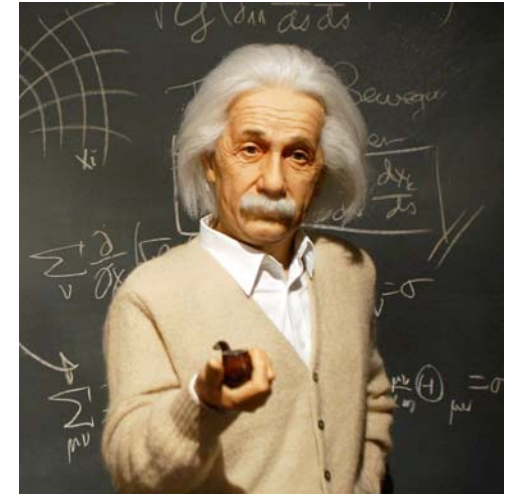
Howard Sandler
Chairman
Department
of Radiation Oncology



Topics

1. How radiotherapy works (4Rs)
2. Role of Radiation Therapy
3. Hippocampus
4. Meningioma



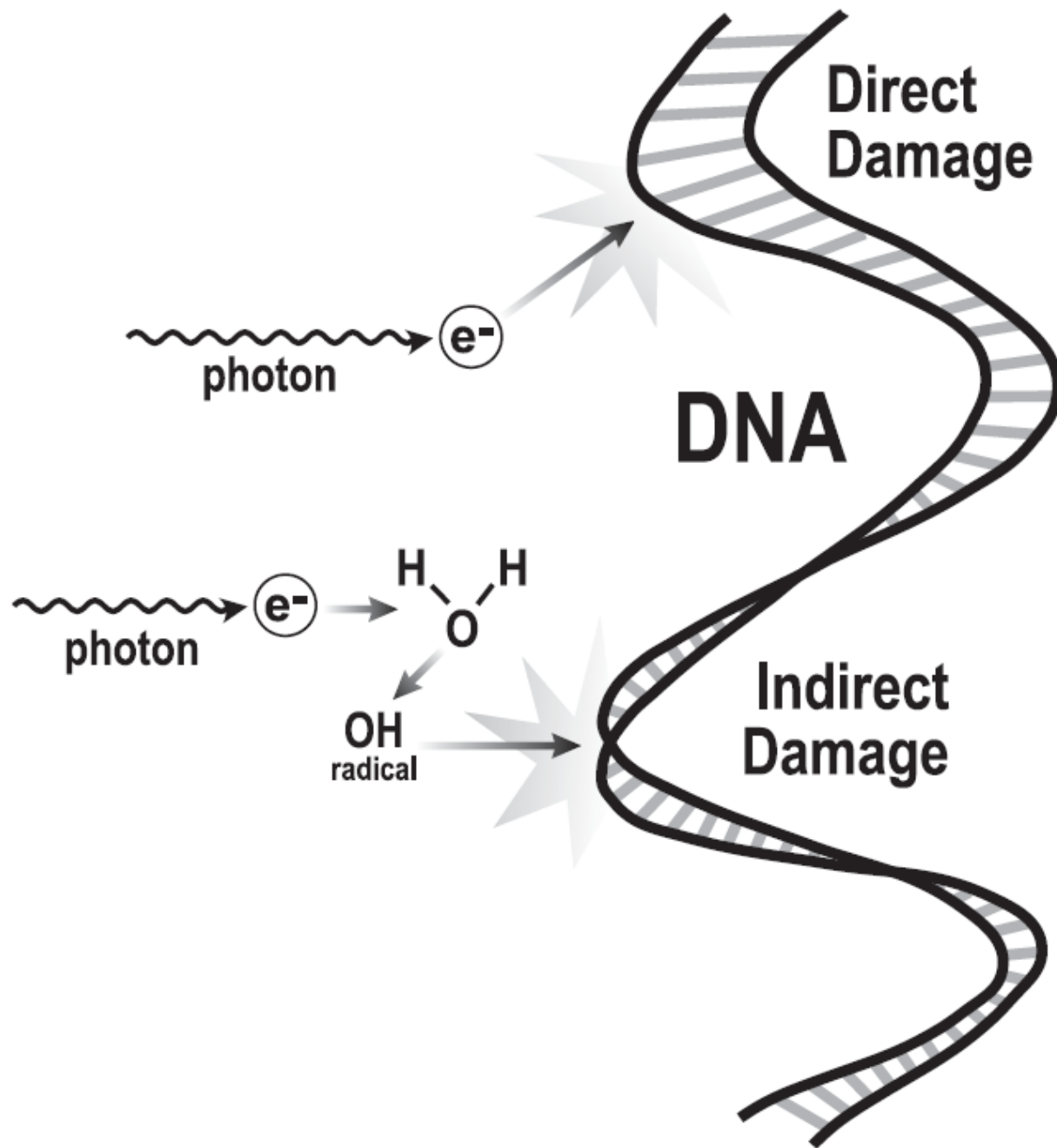


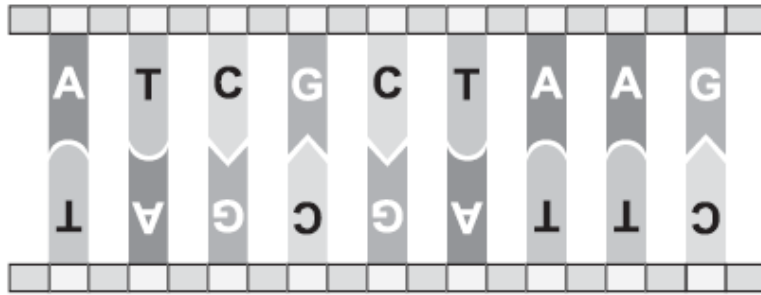
Radiotherapy

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

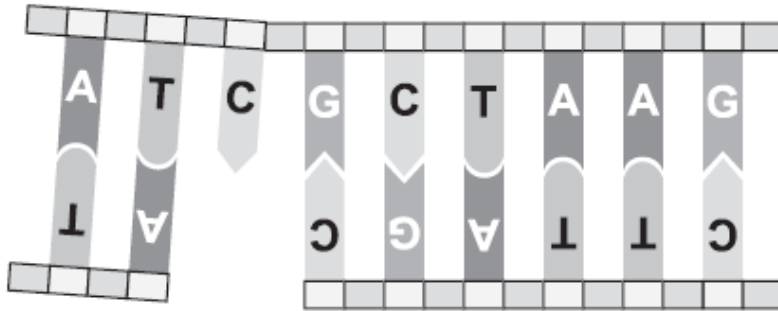




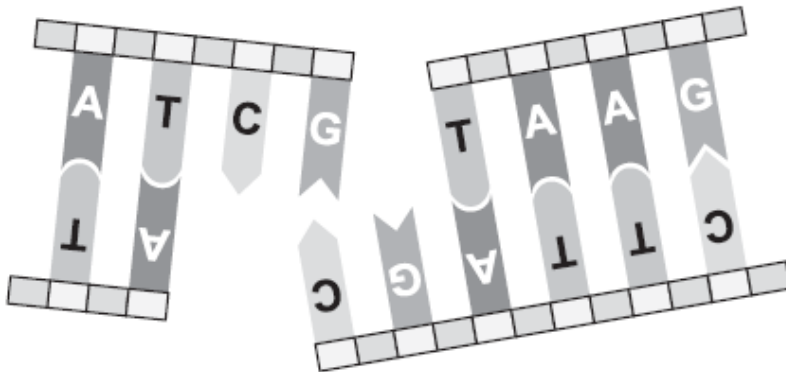




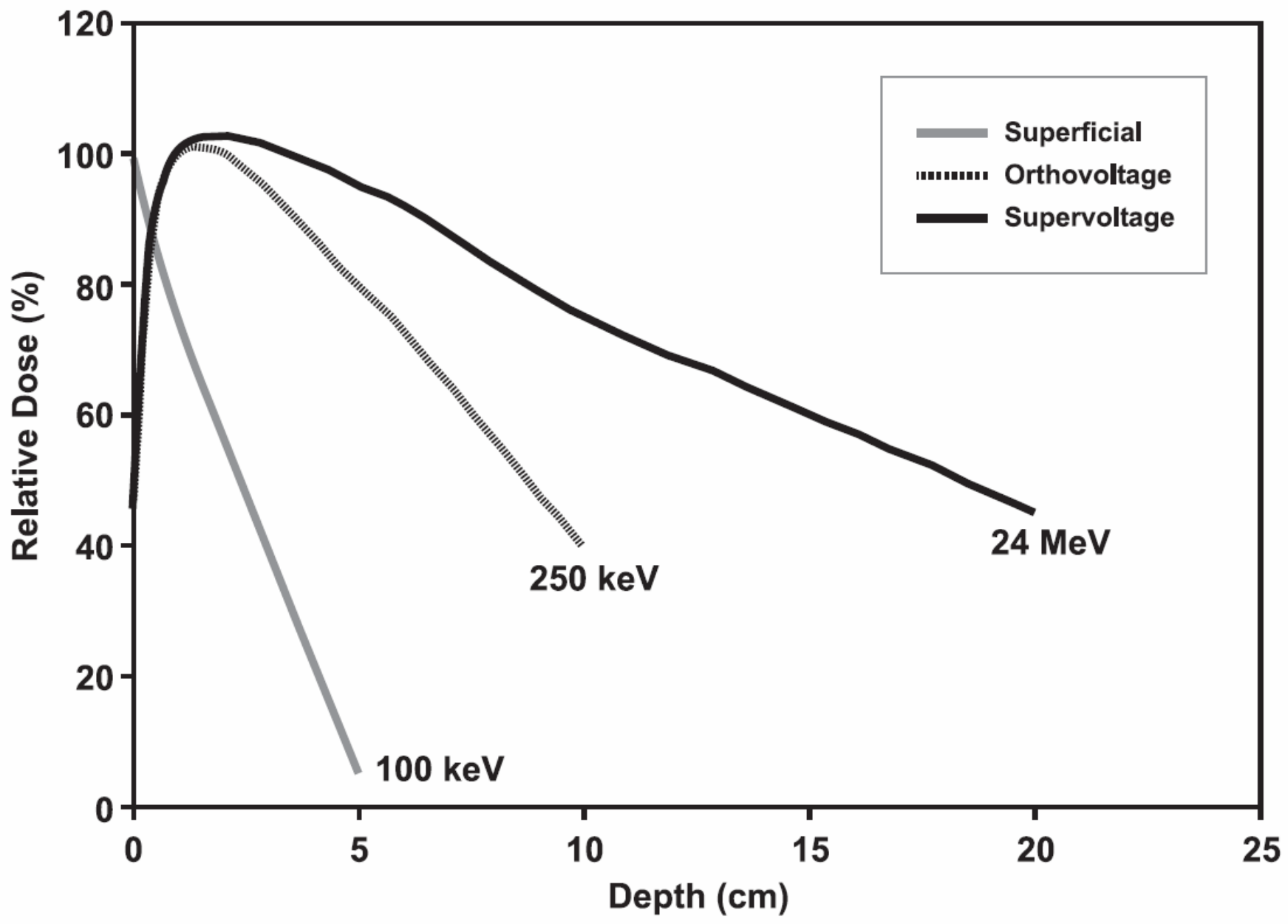
Normal DNA



Single strand break



Double strand break



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



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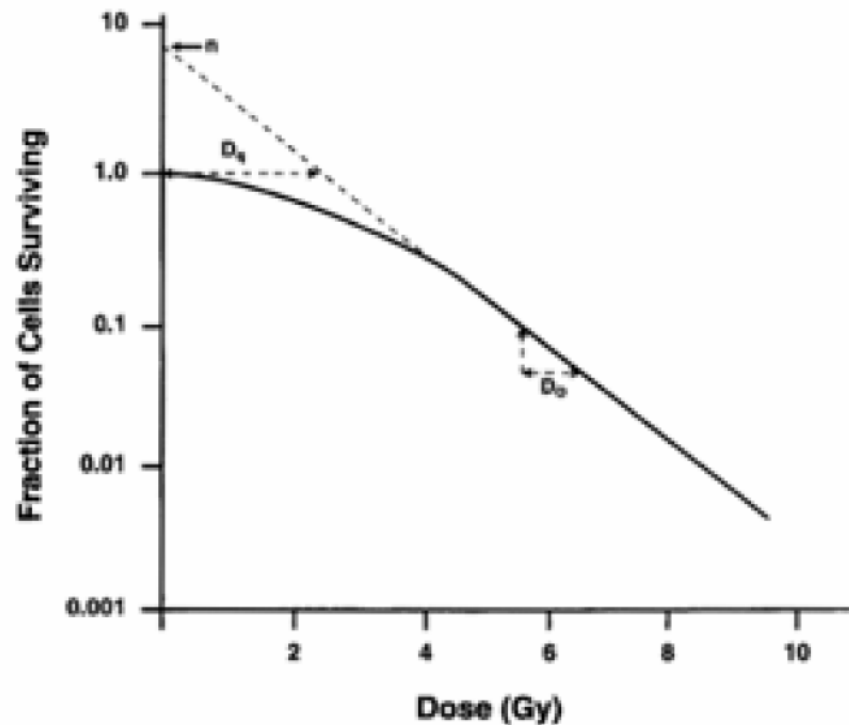
Why fractionation works - 4 R's

- 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



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Normal Tissue vs. Tumor

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



CNS Tumors with a Role for Radiotherapy

Low grade astrocytoma

Anaplastic astrocytoma

GBM

Low grade oligo

Anaplastic oligo

Mixed gliomas

Ependymoma

PNET

CNS lymphoma

Meningioma

Schwannoma

Craniopharyngioma

Pituitary tumors

CNS germ cell tumors

Pilocytic astrocytoma

Ganglioglioma

Hemangioblastoma

Hemangiopericytoma

Sarcoma

Choroid plexus carcinoma



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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



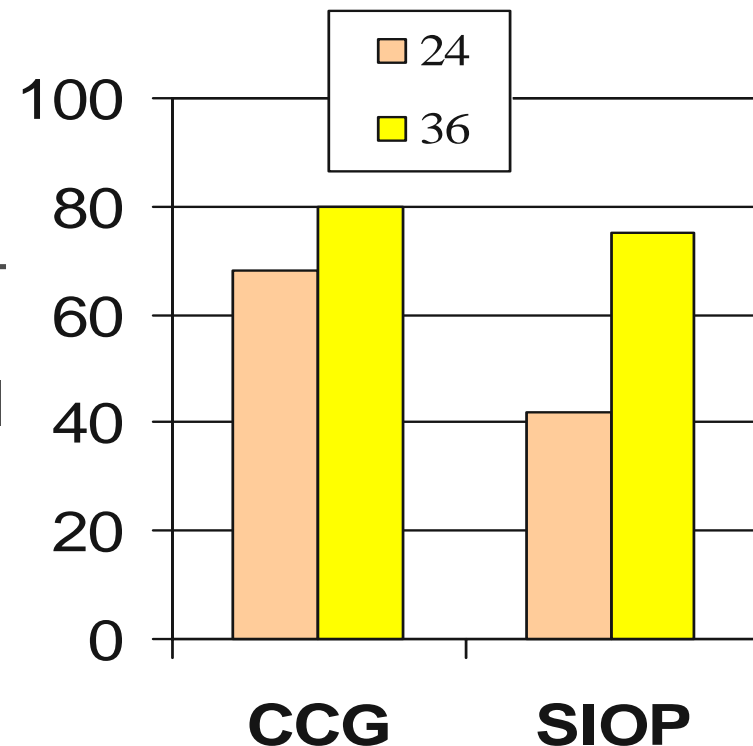
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The Impact of Radiation Dose

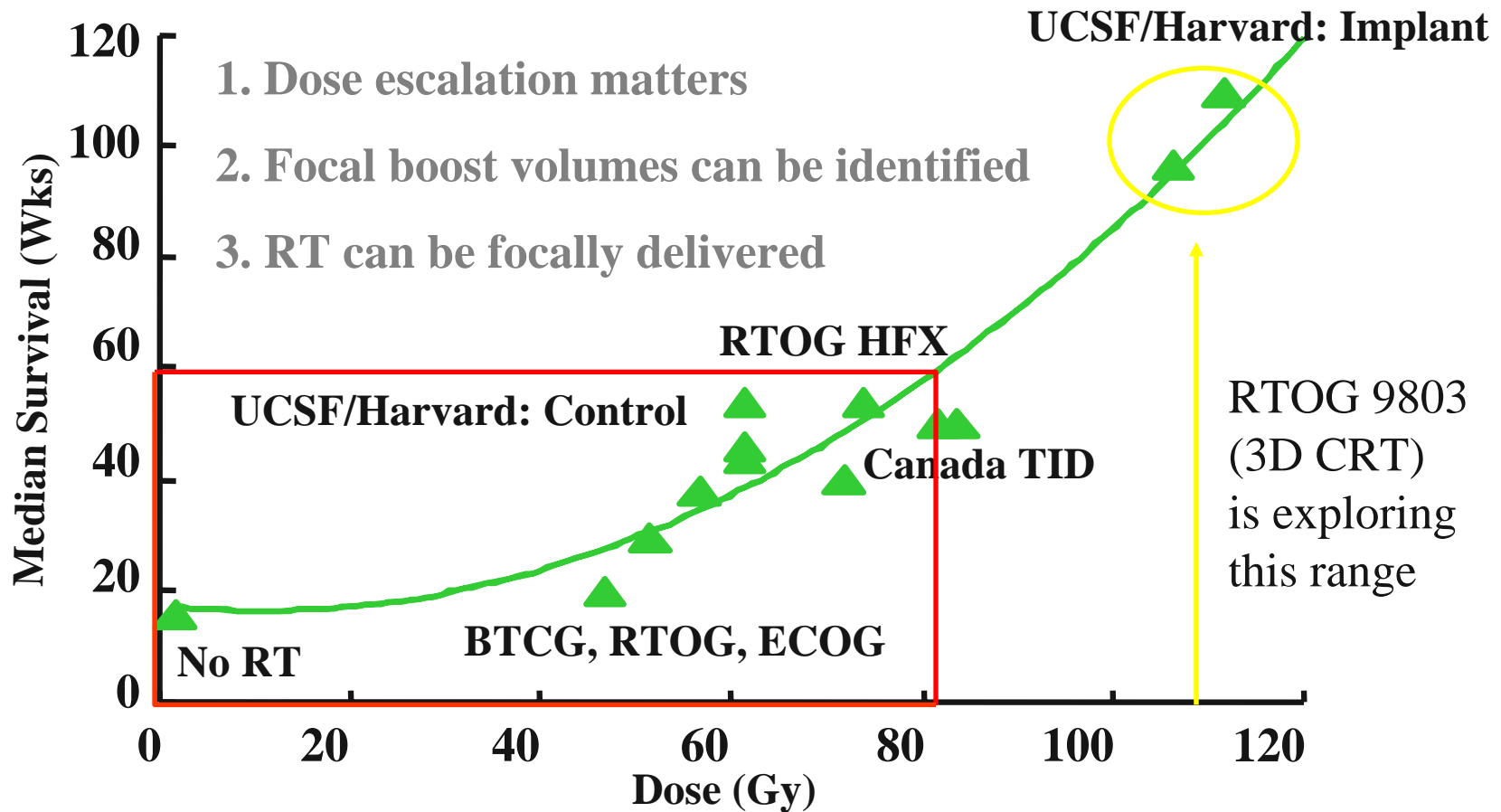
Medulloblastoma as a case-study: Clinical Trials

- 2 -ve Ph III trials
- 3 yr isolated neuraxis failure: 2/44 vs. 11/45.
- SIOP II: 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 & SIOP)



GBM: Dose Escalation



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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 ML. Radiation injury and neurogenesis. *Current Opinion in Neurology*. 16:129-34, 2003.



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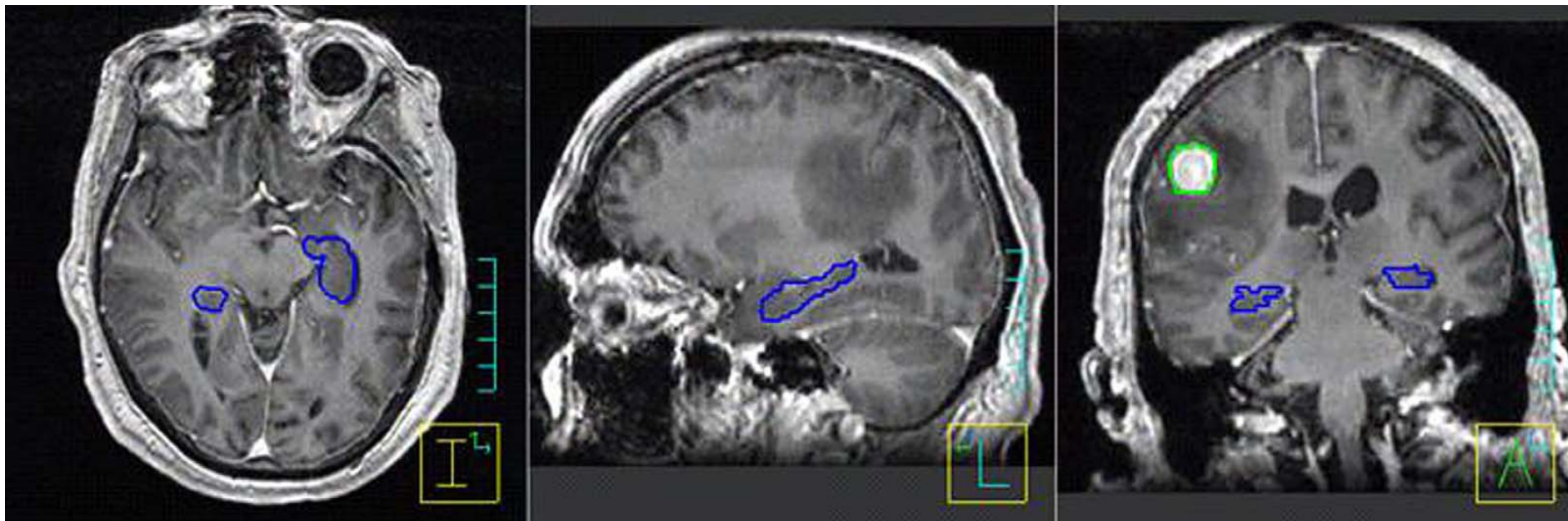
Hippocampus Avoidance Hypothesis

- 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

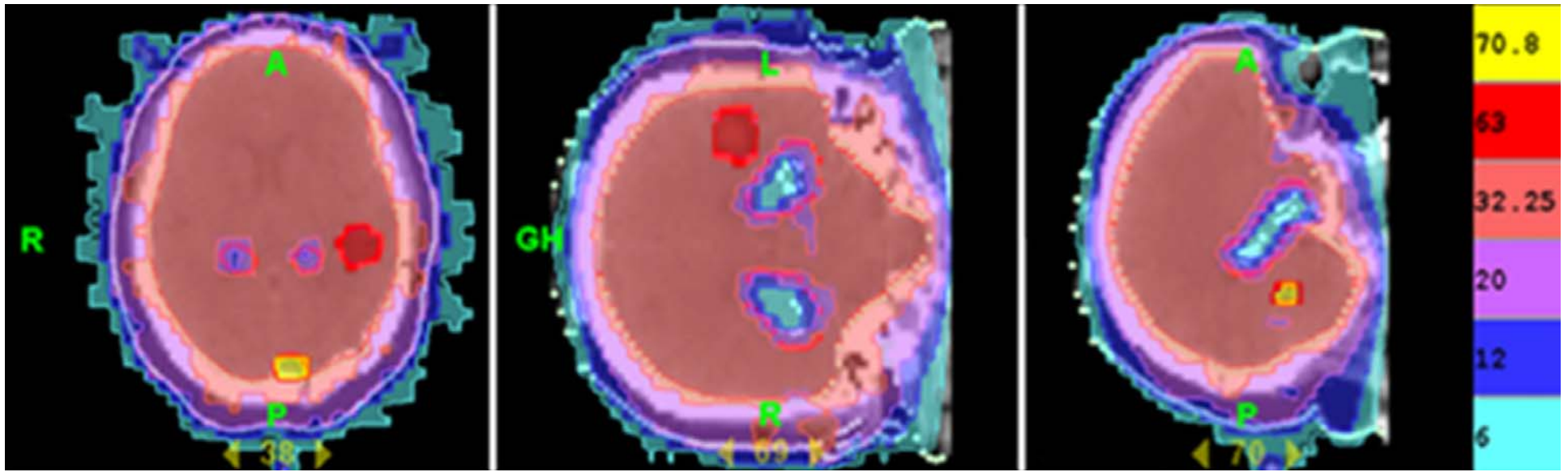


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Hippocampus Delineation



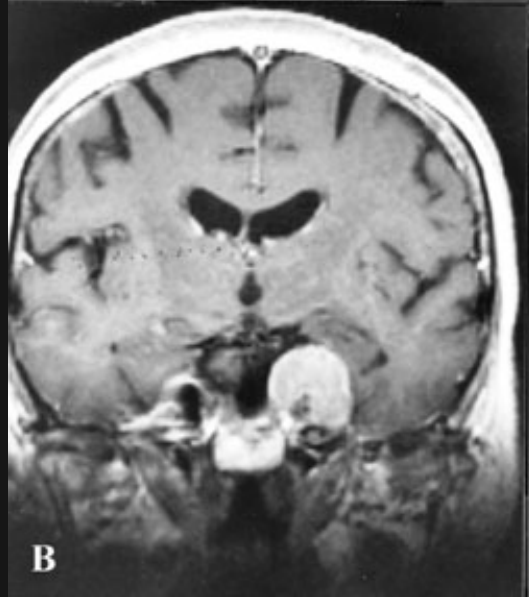
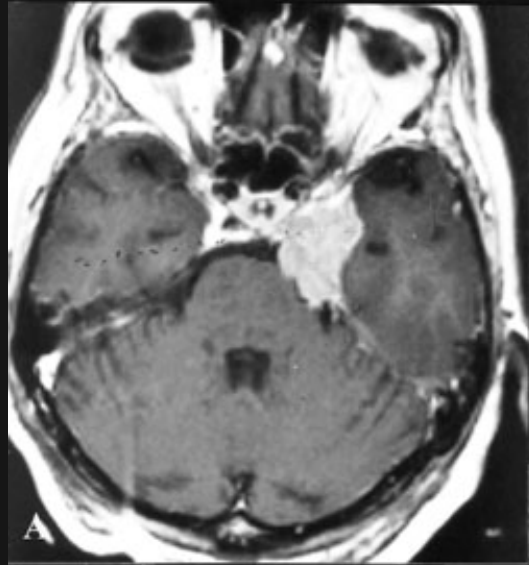
Hippocampus Avoidance with IMRT



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)





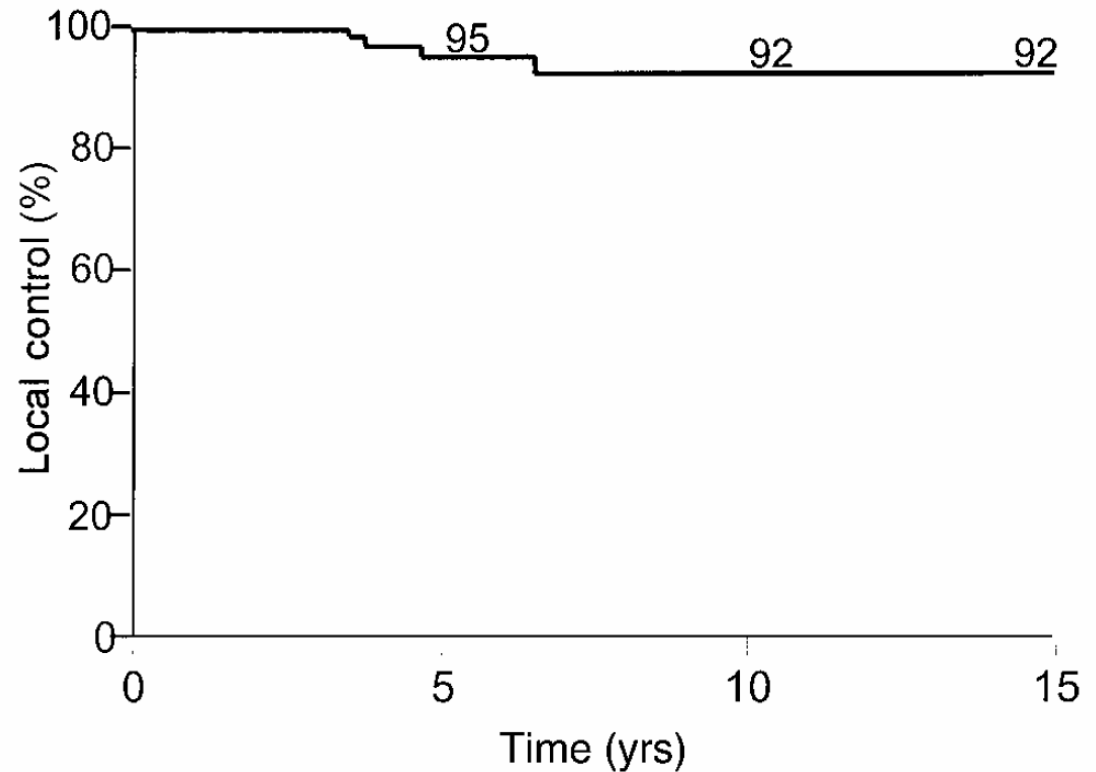
Radiotherapy for Meningiomas

- 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

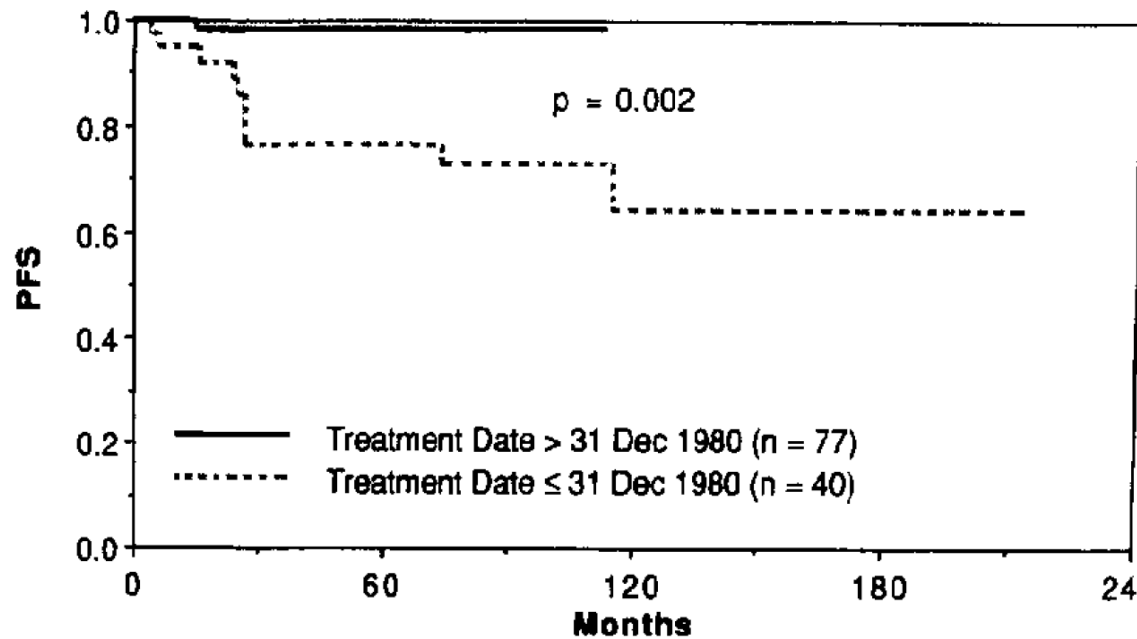


Mendenhall, et al. Cancer 98:1473,2003



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



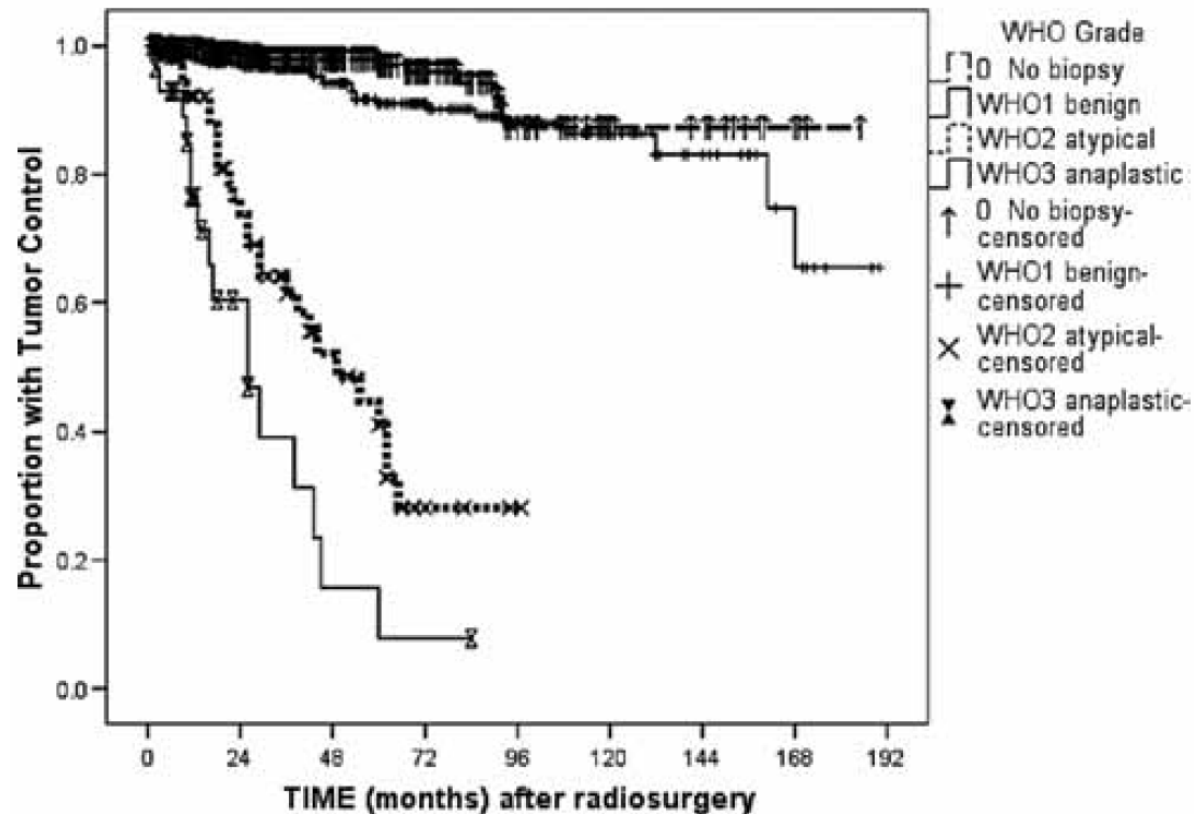
The screenshot shows the Cedars-Sinai website for the Department of Neurosurgery, specifically the Gamma Knife treatment page. The page features a navigation menu with links for Home, Medical Dictionary, and Contact Us. Below the navigation is a search bar and a menu with categories like About Cedars-Sinai, Careers at Cedars-Sinai, Giving & Support, Health Conditions, Healthcare Professionals, Patients & Visitors, Programs & Services, Quality Measures, and Research & Education. The main content area is titled "Department of Neurosurgery" and "Gamma Knife Treatment for Lesions and Tumors in the Brain". It includes a "Printer Friendly" button, an "Email to a Friend" button, and a "Have Questions?" button. The text describes Gamma Knife surgery as a preferred treatment for selected lesions, tumors, and conditions that afflict the brain. It mentions that Gamma Knife can be used to treat brain tumors, arteriovenous malformations, and brain dysfunctions, such as trigeminal neuralgia. The Gamma Knife is noninvasive and is an alternative for many patients for whom traditional brain surgery is not an option because it avoids the physical trauma and most of the risks associated with conventional surgery. The single-session treatment is also usually administered in an outpatient setting with periodic follow-up. The page also lists the Gamma Knife Center's location at the Samuel Oschin Comprehensive Cancer Institute, Department of Neurosurgery, and the S. Mark Taper Foundation Imaging Center. A list of links for "Who May Be a Candidate for This Procedure" includes Treatment, Safe and Precise, The Process, The Benefits, A Healing Environment, Personalized, Team Centered Approach, and A Patient-Centered Environment. A photograph of the Gamma Knife machine is visible on the right side of the page.



Kondziolka et al. Neurosurgery 62:53,2008

Radiotherapy for Meningiomas

Intracranial Tumor Control By WHO Grade



Kondziolka et al. Neurosurgery 62:53,2008

Conclusions

- Radiotherapy has an important role to play



Radiation Oncology at Cedars-Sinai

Radiation Therapy

at the Samuel Oschin Comprehensive Cancer Institute

Programs and Services

Radiation Therapy

Cancers Treated with Radiation Therapy

Contact Us

► Our Expert Team

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Mirhadi, Amin

Sandler, Howard M.

Outpatient Cancer Center

Radiation Technologies

Second Opinions

Support Services

Our Expert Team

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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