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Role of Radiation Therapy

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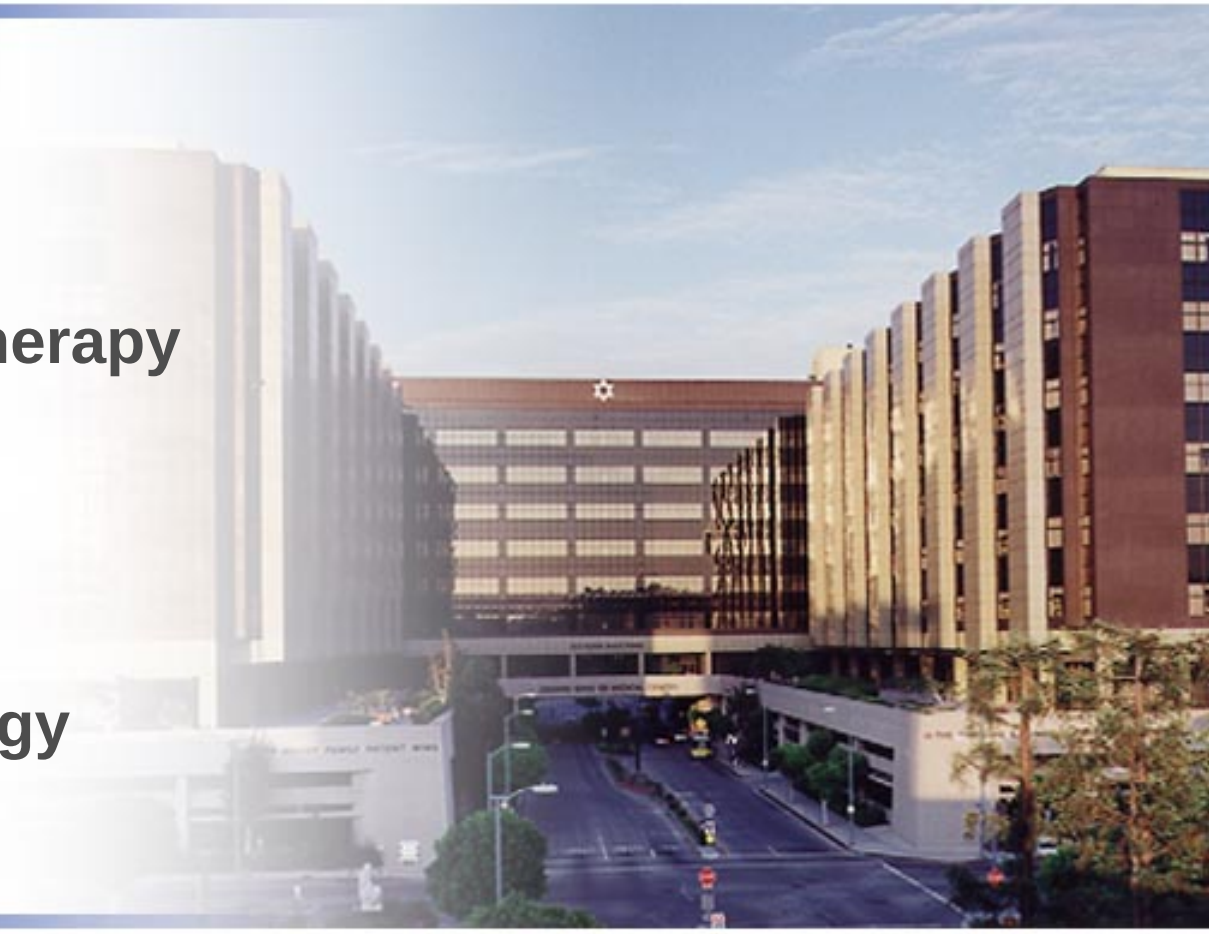

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Topics

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

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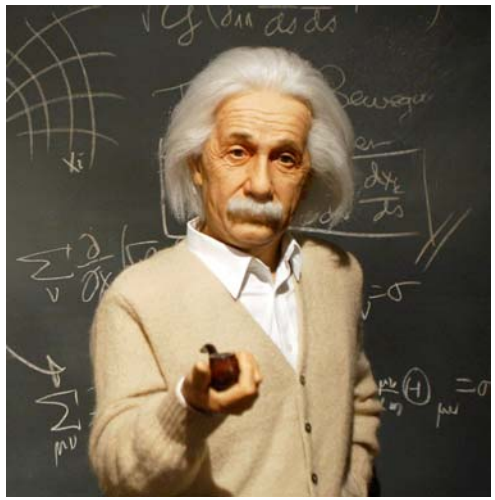

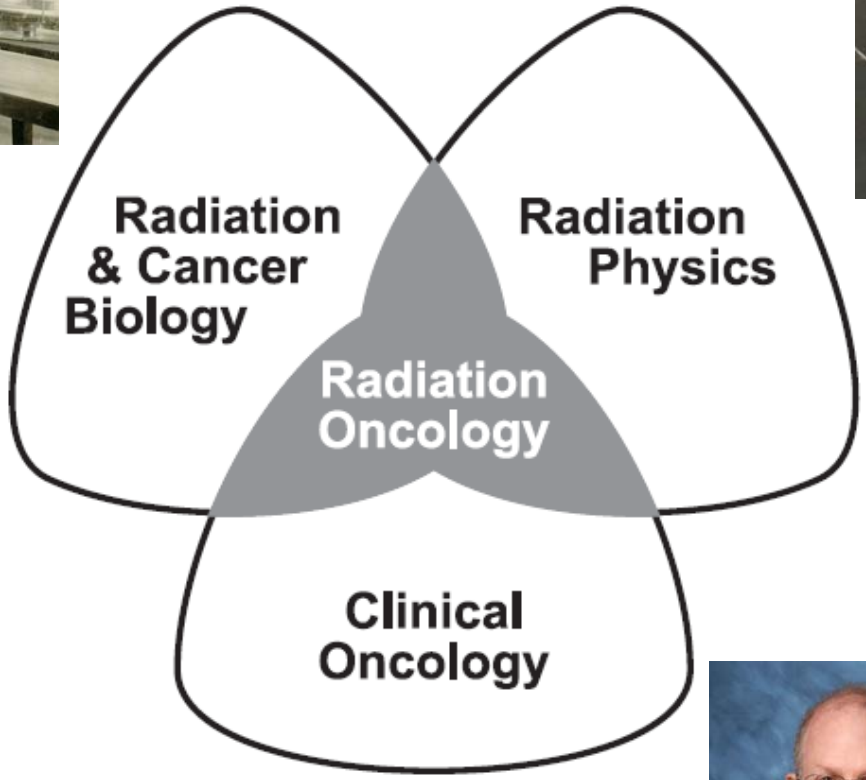
Radiation
& Cancer
Biology
Radiation
Physics
Radiation
Oncology
Clinical
Oncology

Radiotherapy

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

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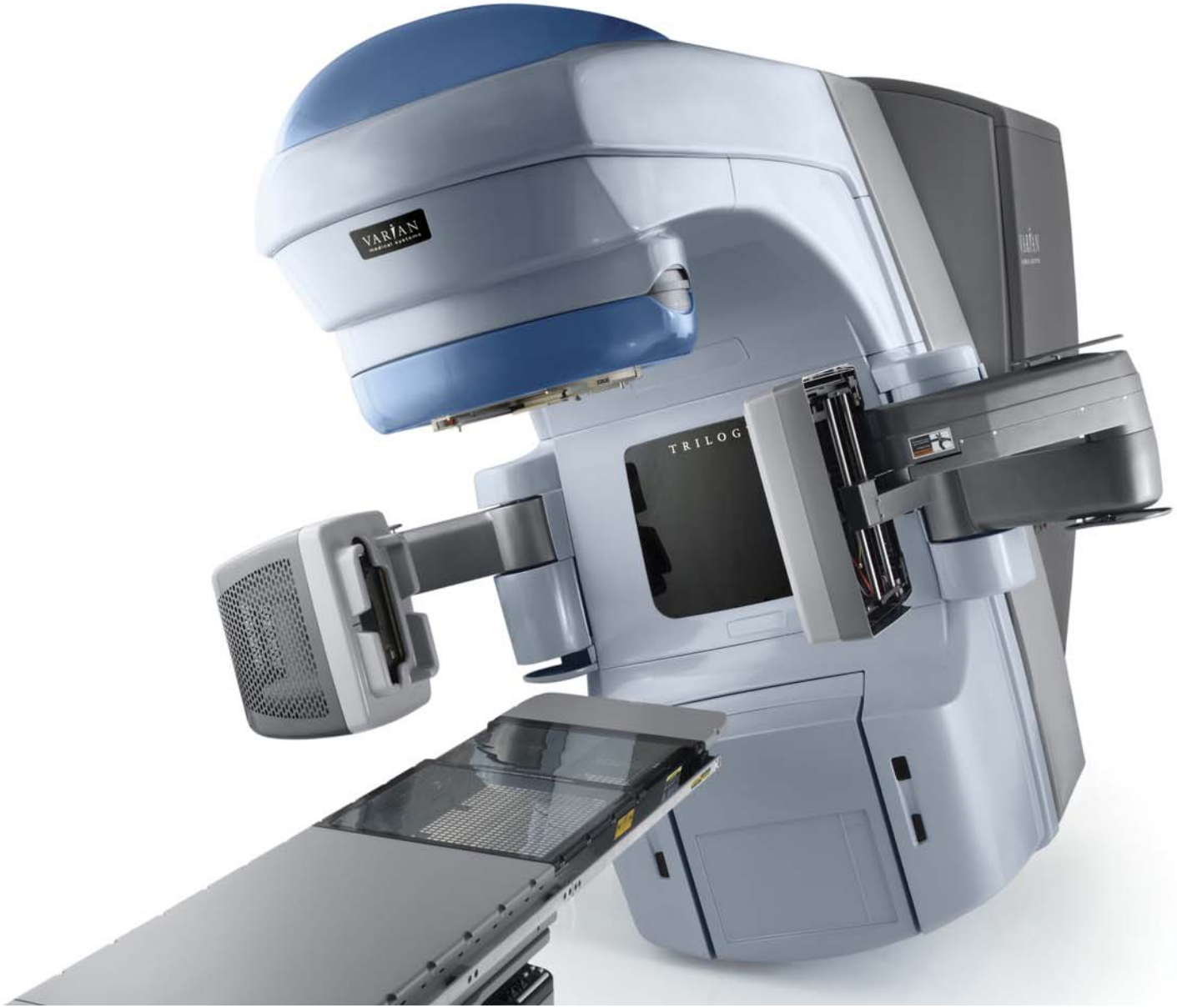
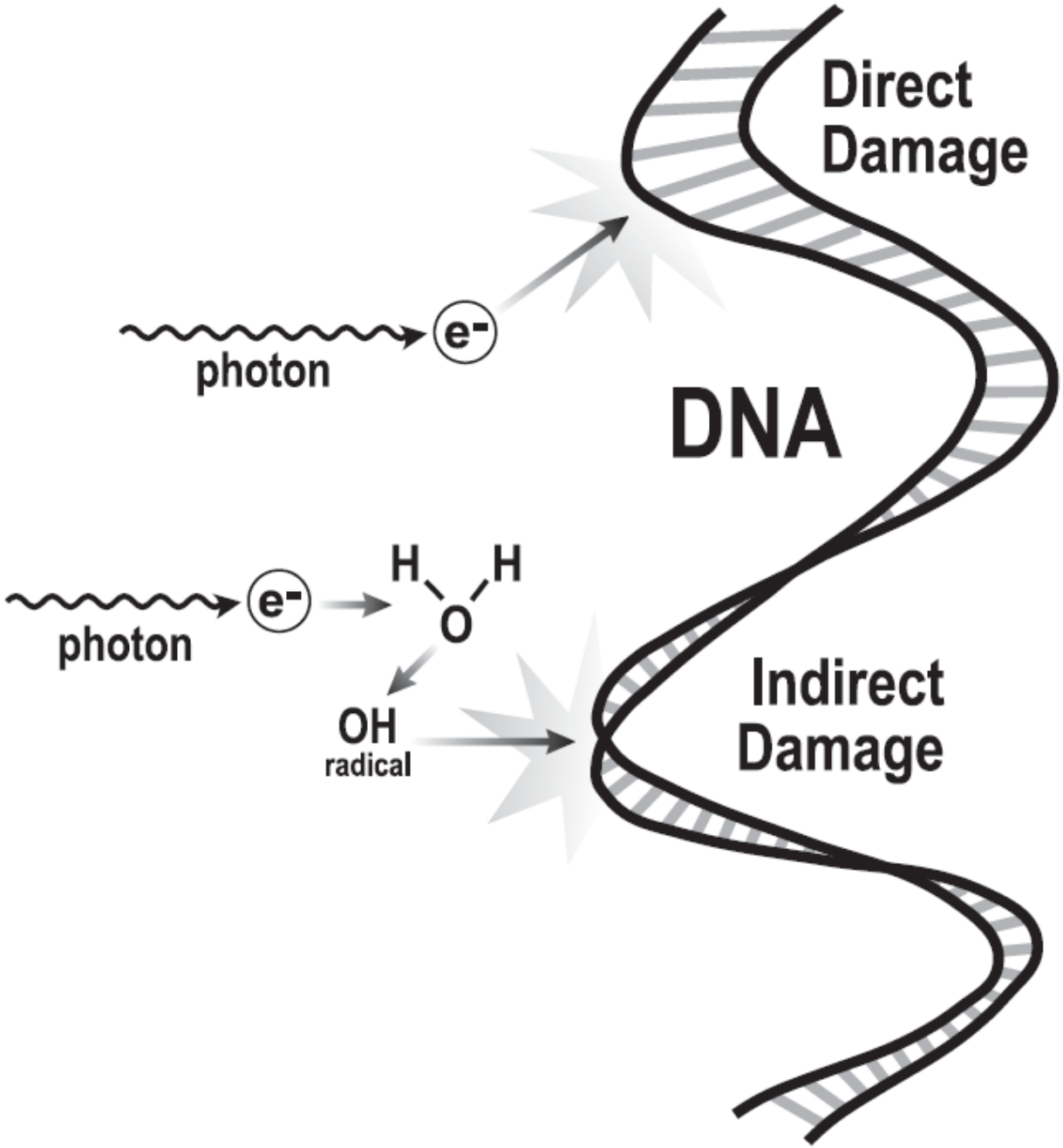
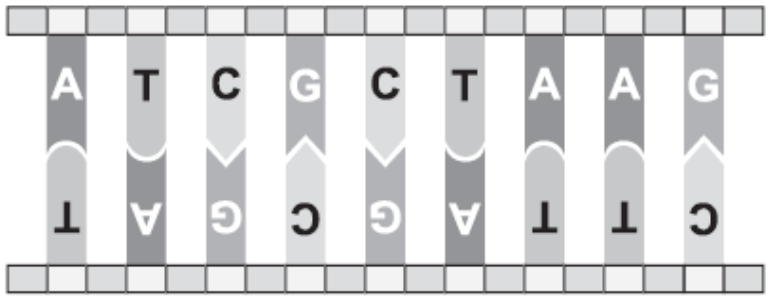
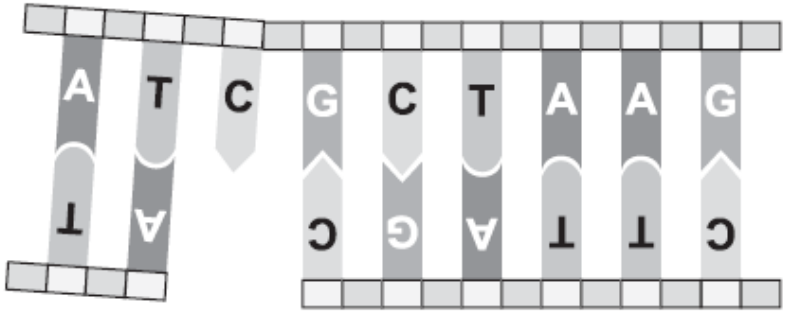

VARIAN
TRILOG

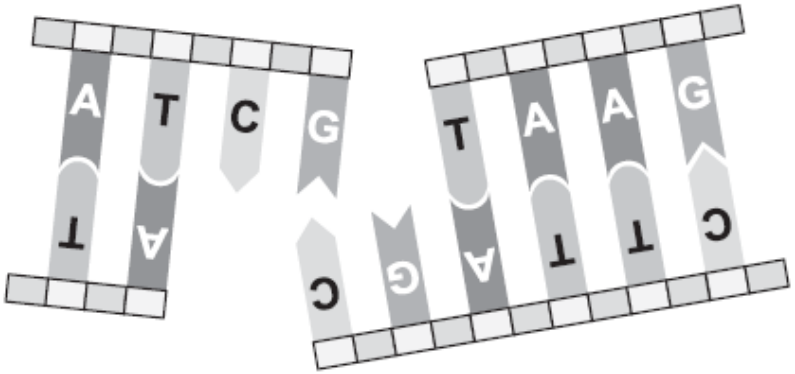

Direct
Damage
photon
e-
DNA
photon
e-
H
O
H
OH
radical
Indirect
Damage



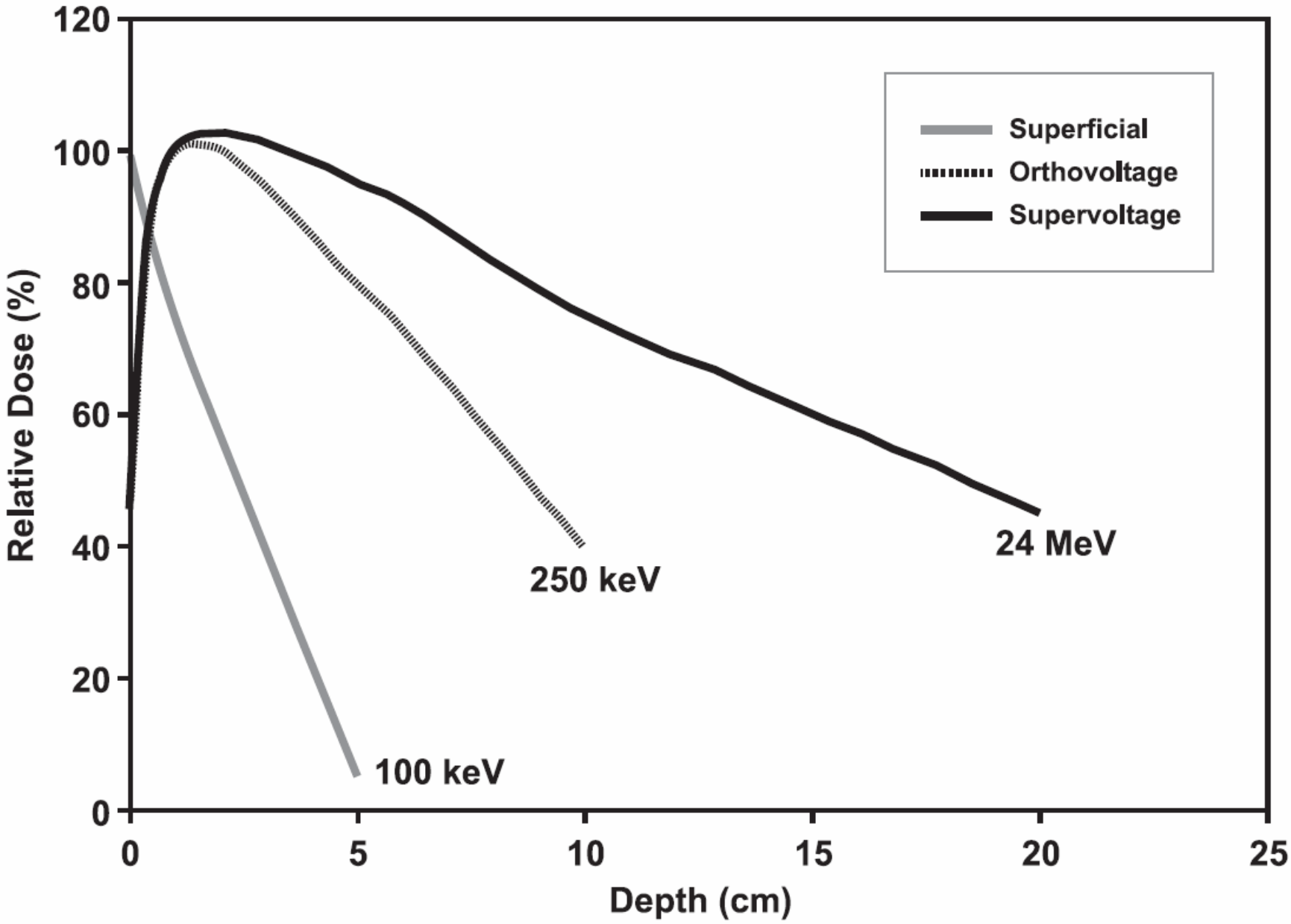
Normal DNA



Single strand break



Double strand break


120
100
80
60
40
20
0
Relative Dose (%)
0
5
10
15
20
25
Depth (cm)
Superficial
Orthovoltage
Supervoltage
100 keV
250 keV
24 MeV

Fractionation

Why do we fractionate?

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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

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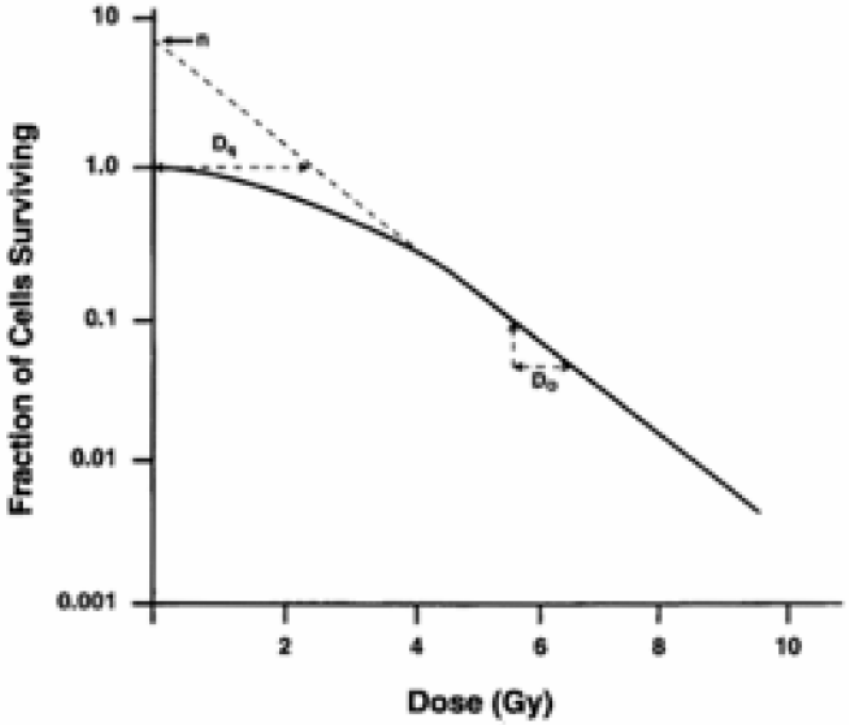
Cellular Radiosensitivity

- 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 & G_2
- 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

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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

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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

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**

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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

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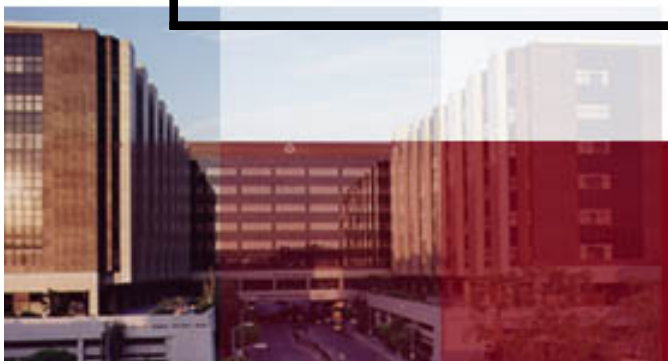
Radiotherapy Improves Local Control

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%



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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%	

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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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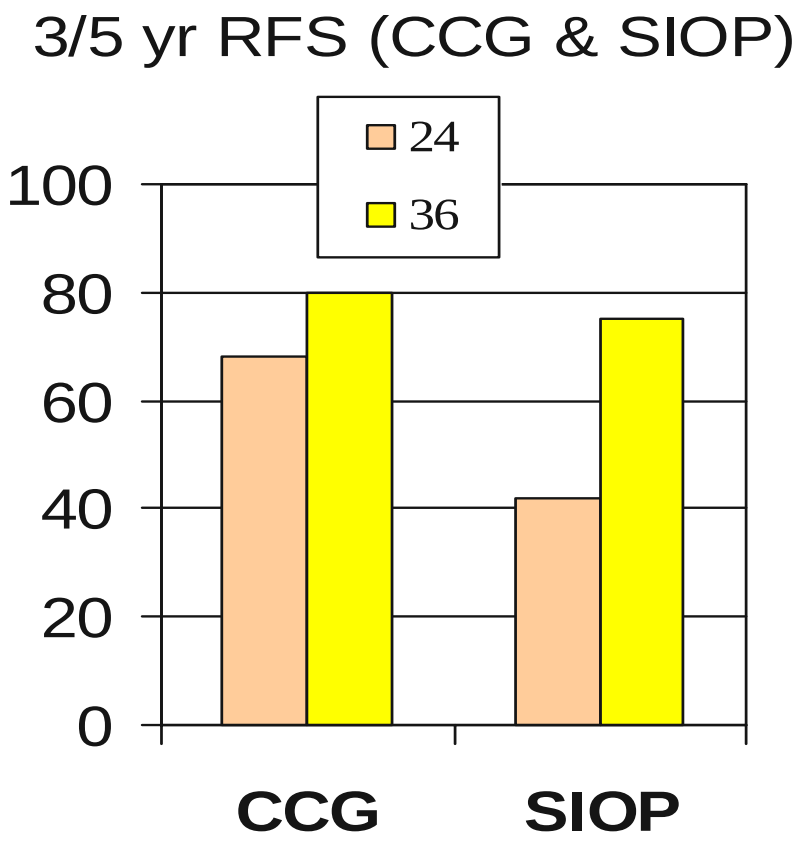
The Impact of Radiation Dose

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



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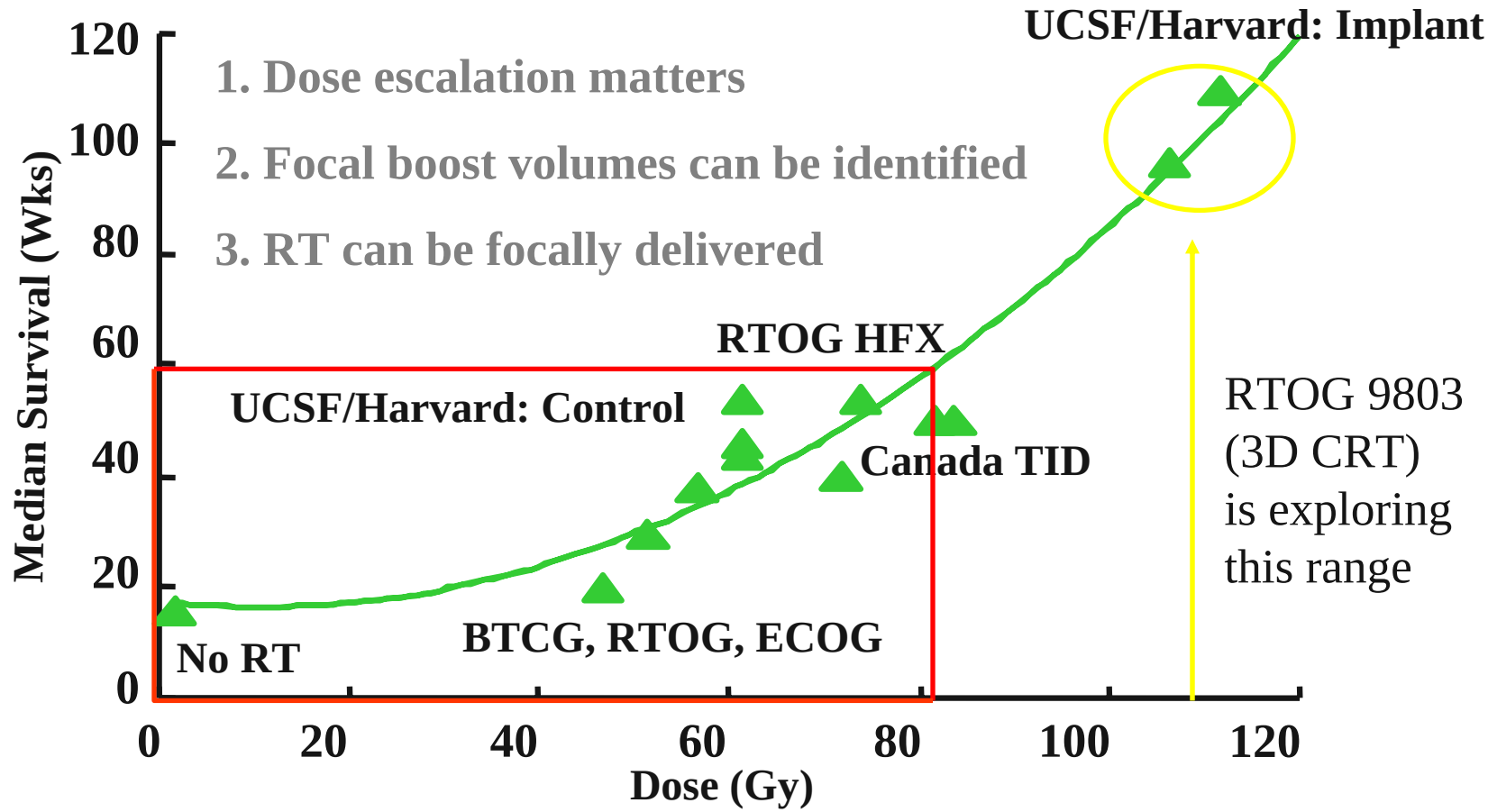
GBM: Dose Escalation



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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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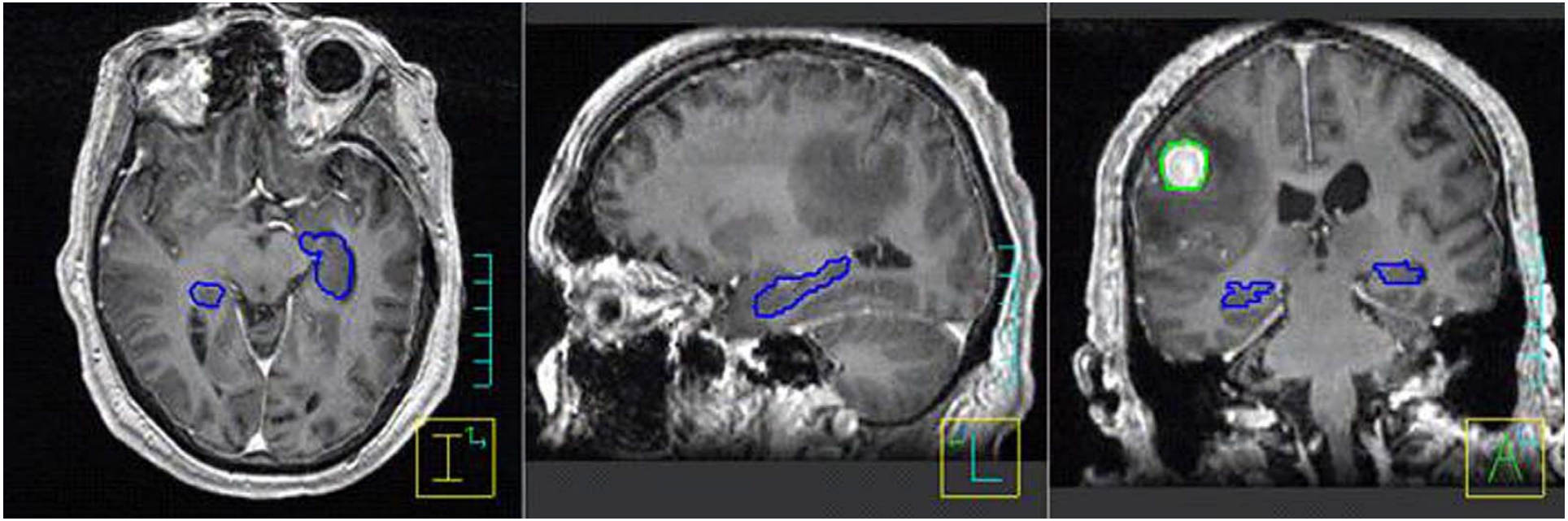
Hippocampus Delineation



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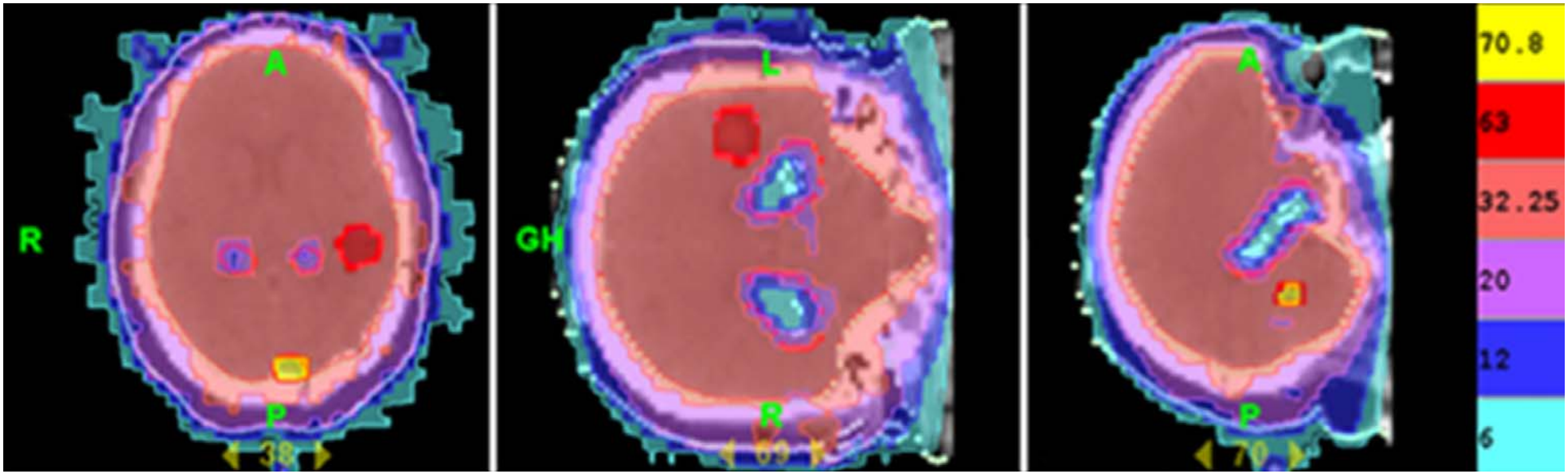
Hippocampus Avoidance with IMRT



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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)

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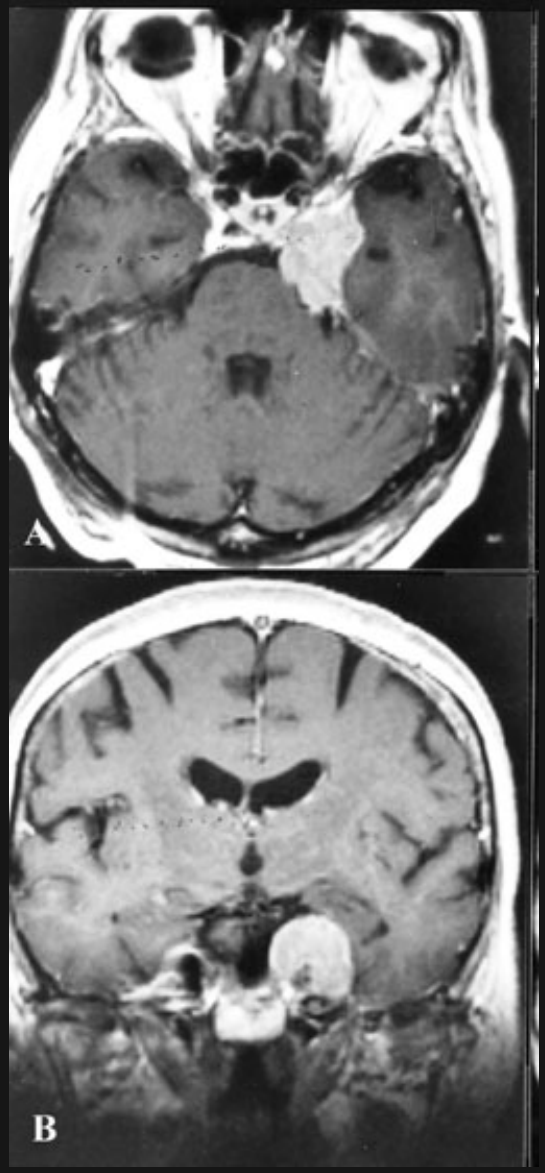
A
B

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

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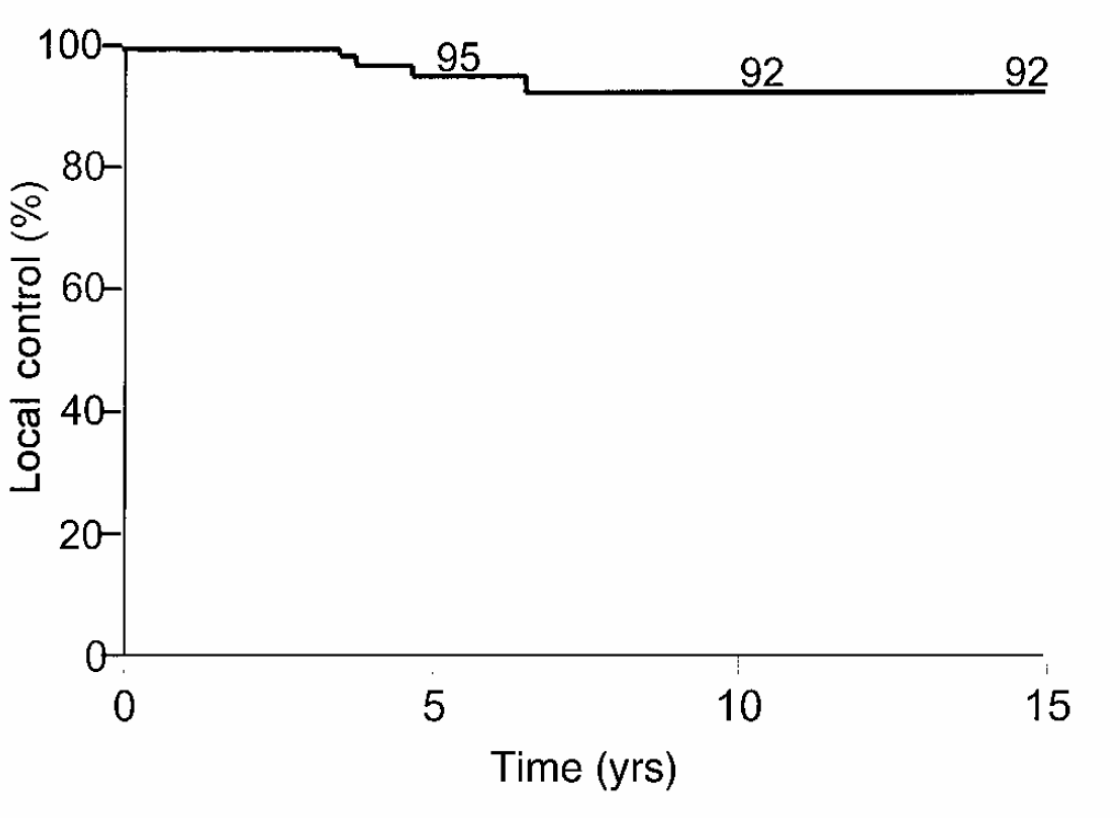
Radiotherapy for Meningiomas

- 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

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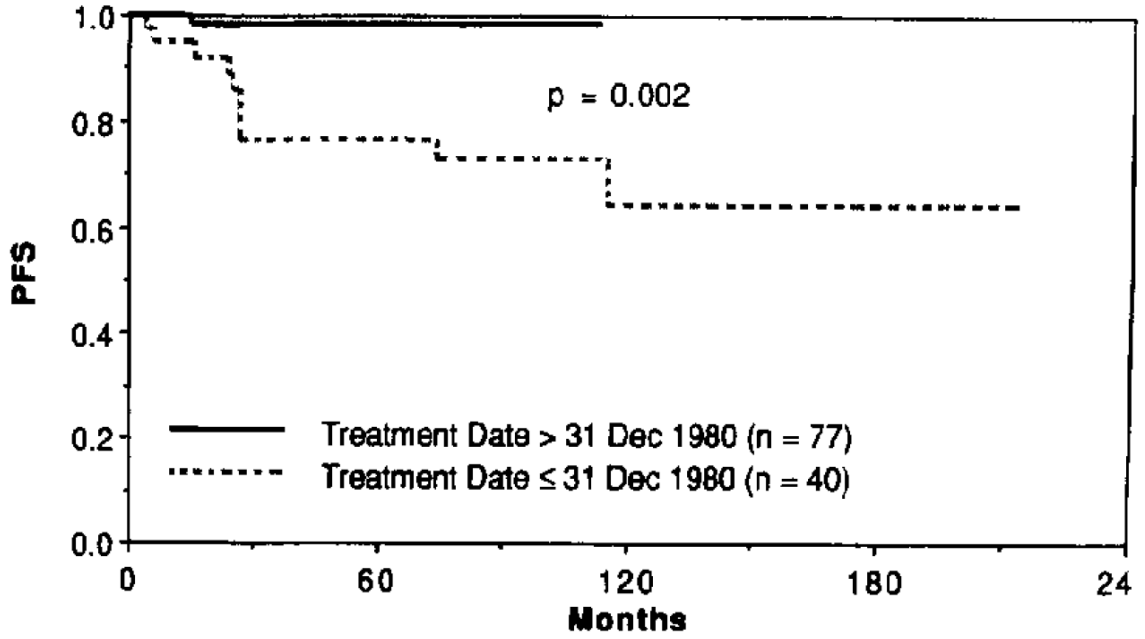
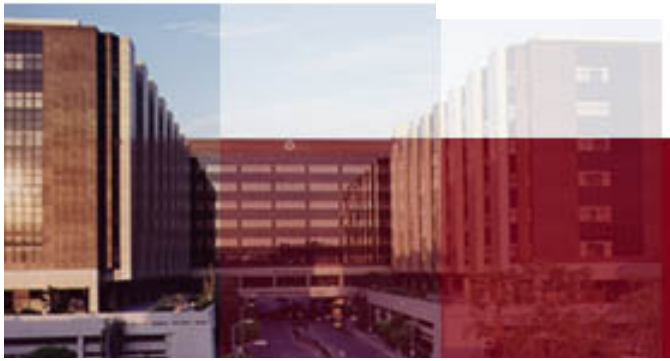
Radiotherapy for Meningiomas

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



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



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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

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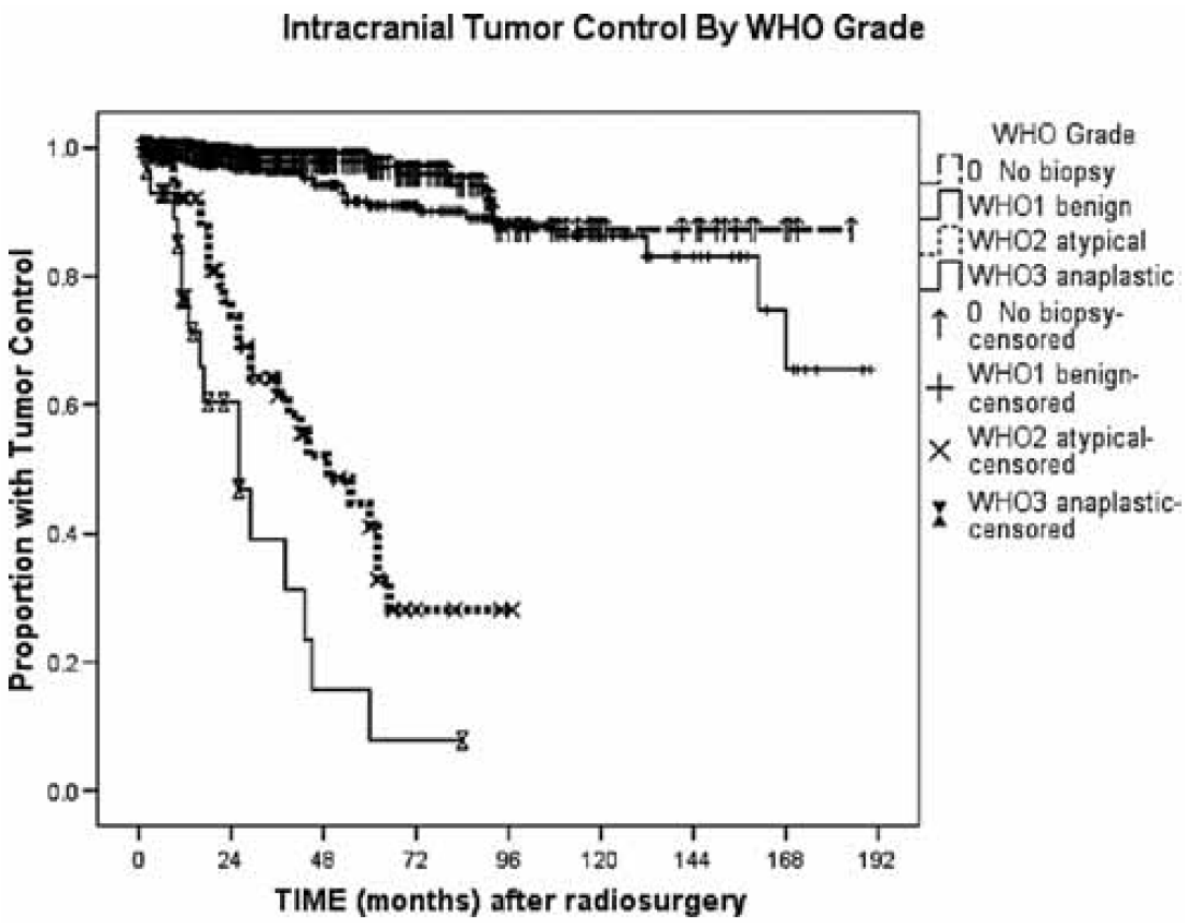
Radiotherapy for Meningiomas



Kondziolka et al. Neurosurgery 62:53,2008

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Conclusions

- Radiotherapy has an important role to play

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Radiation Oncology at Cedars-Sinai

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