New Modalities in Radiation Oncology

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New Modalities

- Altered fractionation schemes tested in the clinic
- Intensity Modulated RT: dose-volume effects
- Radiosurgery: new biology?
- Charged Particles
- (Do Neutrons have life?)
- Radio-immunotherapy
- Targeted Radio-sensitization

Modifying Fractionation

Hyper-fractionation

Increased total dose, same (or slightly longer) treatment time, more fractions. Reduces late effects.

Typical schedule: 80.5 Gy in 70 fractions (1.15 Gy bid) over 7 weeks

Accelerated treatment

Reduced total dose, reduced treatment time, fractions? Reduces repopulation in tumors. Increase in late effects.

Very accelerated: 54 Gy in 36 fx (1.6 Gy tid) over 12 days; Moderately accelerated: 72 Gy in 42 fx (concomitant boost)

Hypo-fractionation

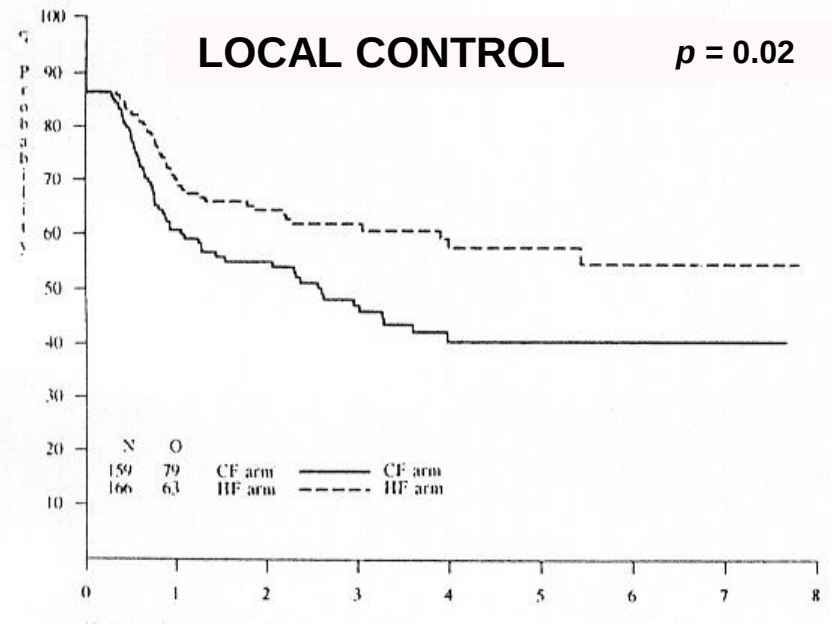
Reduced total dose, but larger fraction doses. Tumor has low $\alpha/ß$ ratio. Increases late effects (requires coning down of tumor and treatment volumes)

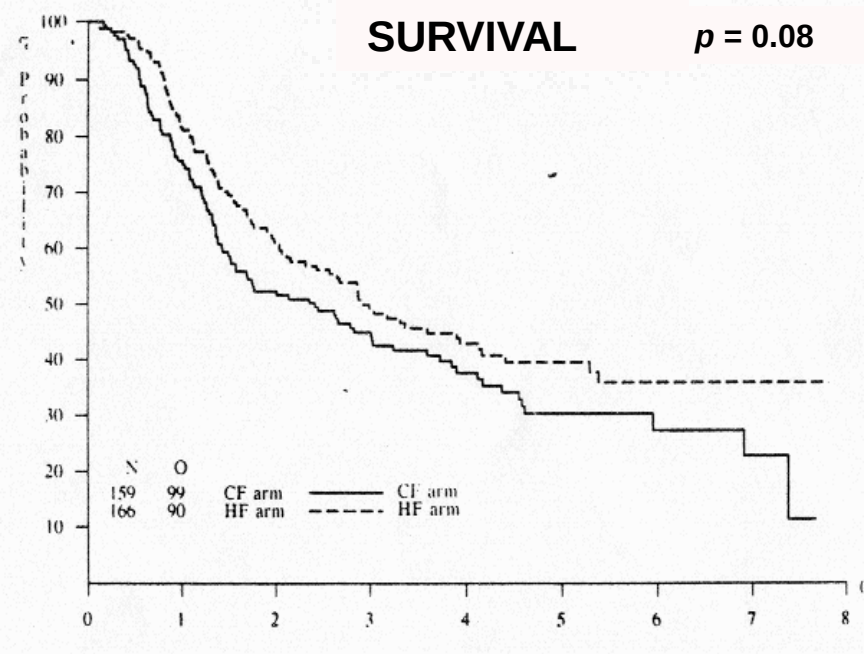
EORTC hyperfractionation trial in oropharynx cancer (N = 356)

Oropharyngeal Ca T2-3, N0-1

Horiot 1992

80.5 Gy - 70 fx - 7 wks vs control: 70 Gy - 35-40 fx - 7-8 wks





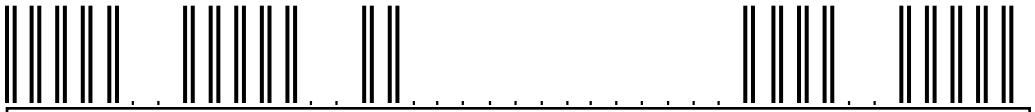
RTOG 90-03, comparison of fractionation schedules (N = 1113)

70 Gy - 35 fx - 7 wks

Conventional

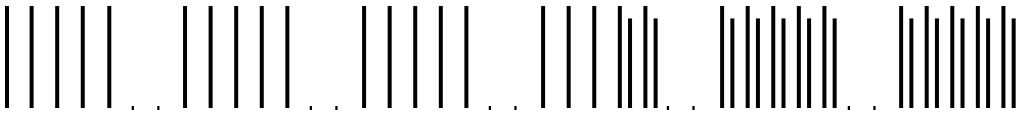
81.6 Gy - 68 fx - 7 wks

Hyperfractionated



67.2 Gy - 42 fx - 6 weeks (including 2-week split)

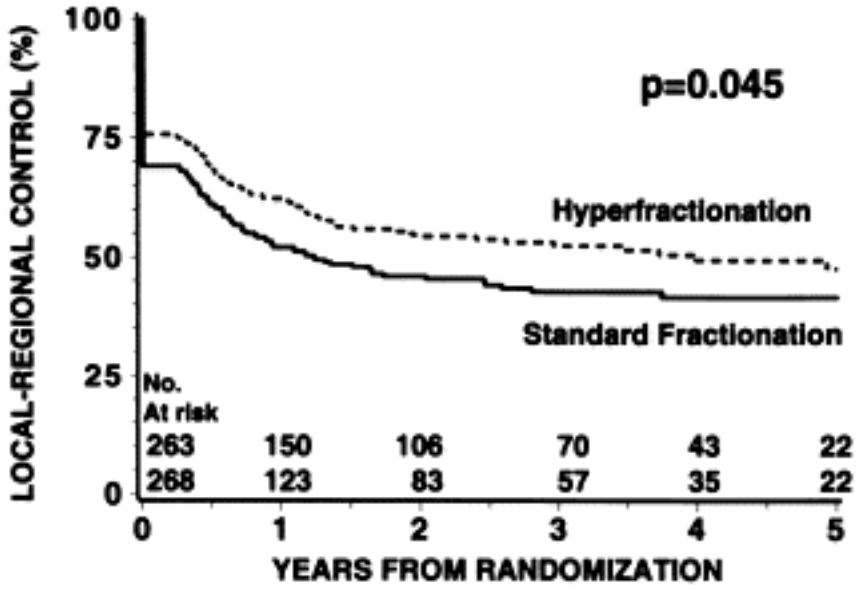
Accelerated with split

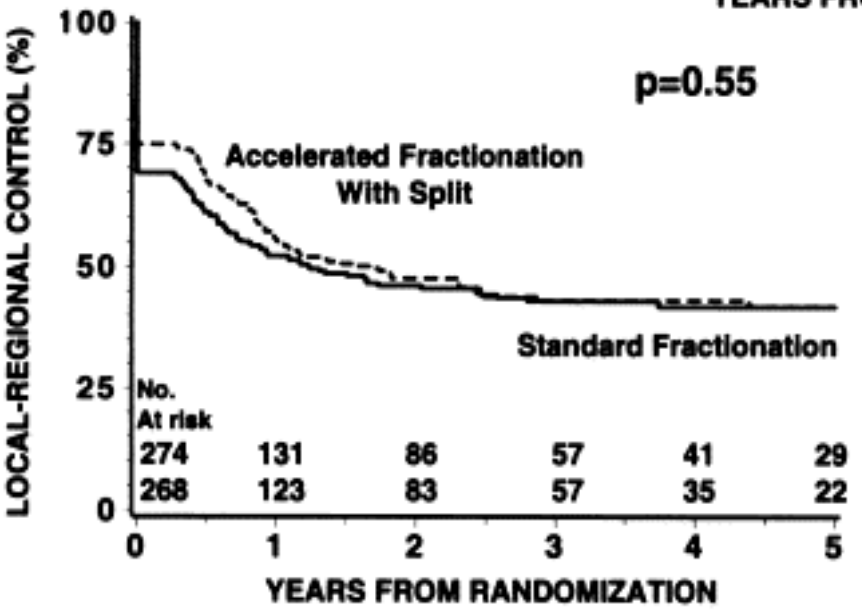


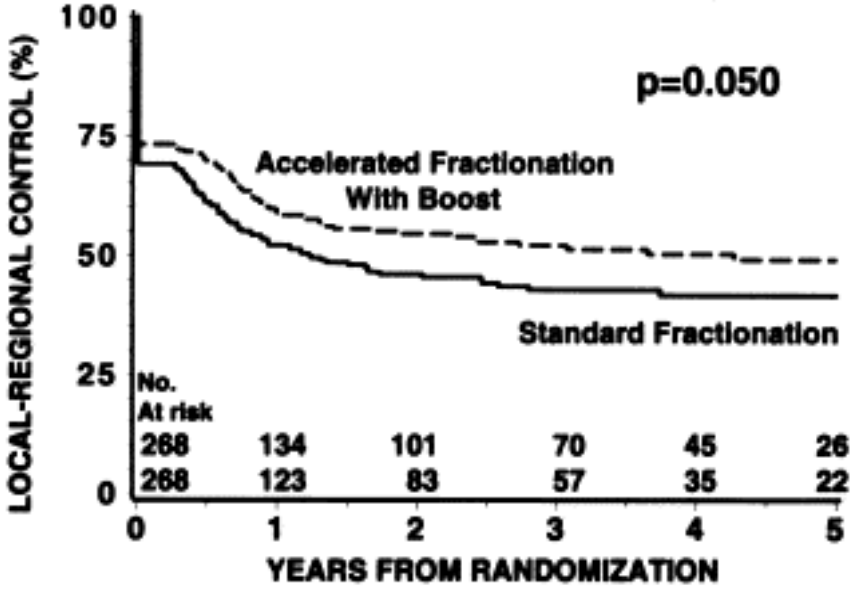
72 Gy - 42 fx - 6 wks

Accelerated with concomitant boost

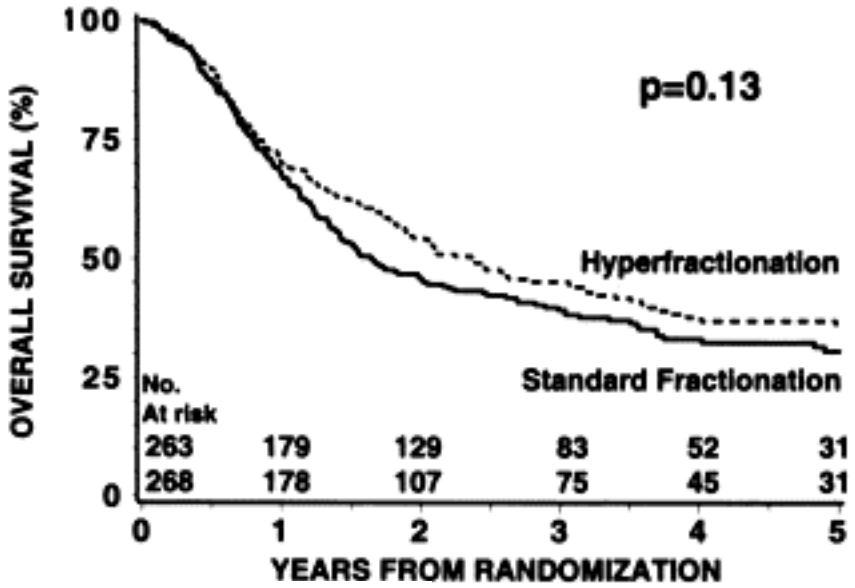
RTOG 90-03: Loco-regional control

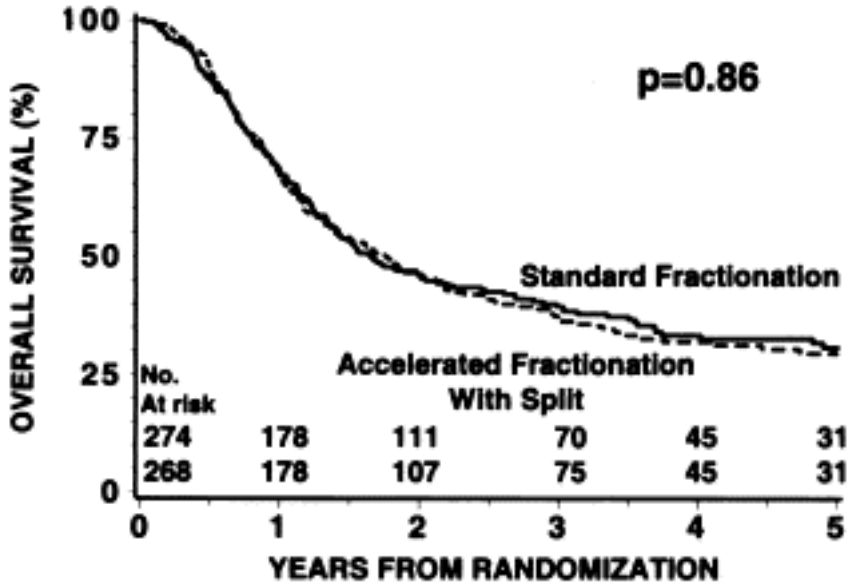


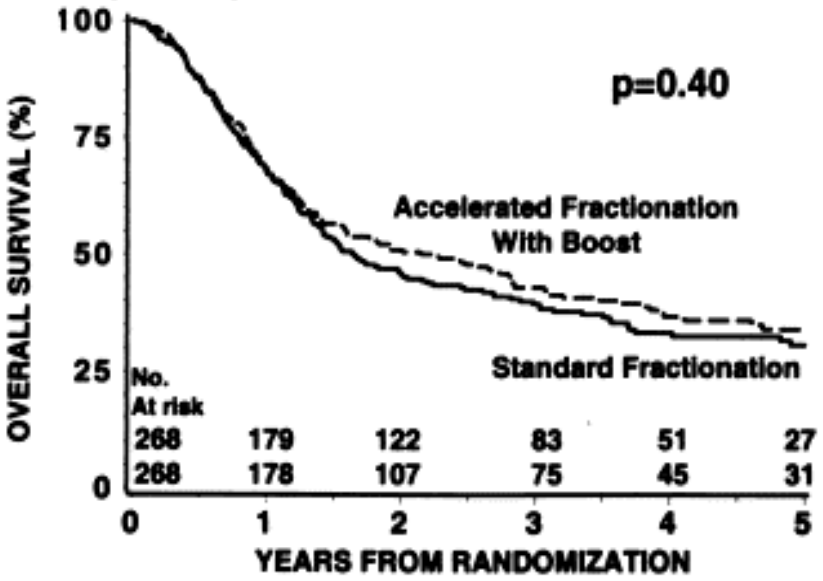




RTOG 90-03: Survival







RTOG 90-03: Adverse effects

Acute

Maximum toxicity per patient	Conventional	Hyperfract	Concom boost	Acc + split
Grade 1	5%	3%	4%	7%
Grade 2	57%	39%	36%	41%
Grade 3	35%	54%	58%	49%
Grade 4	0%	1%	1%	2%

Late (> 90 days)

Maximum toxicity per patient	Conventional	Hyperfract	Concom boost	Acc + split
Grade 1	11%	8%	7%	16%
Grade 2	50%	56%	44%	50%
Grade 3	19%	19%	29%	20%
Grade 4	8%	9%	8%	7%
Grade 5	1%	0%	1%	1%

Altered fractionation in head and neck cancer: meta-analysis

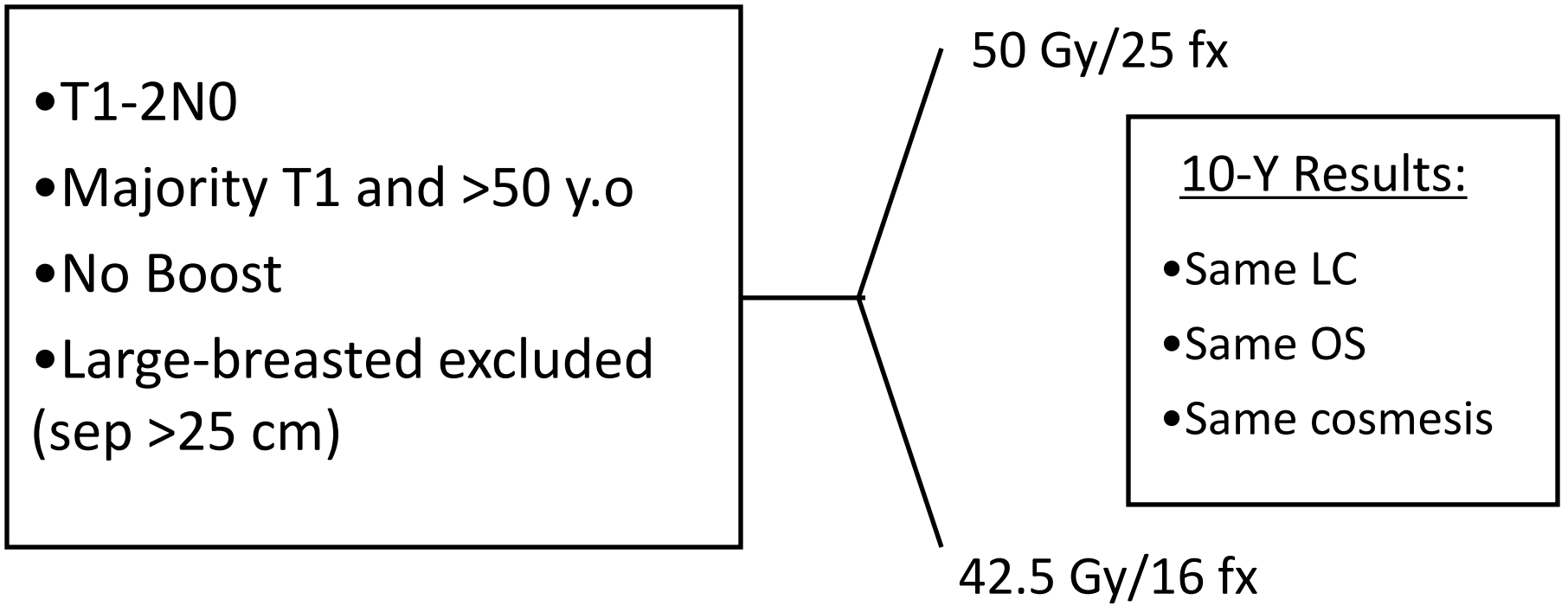
Randomized trials 1970-1998 (no postop RT)
15 trials included (6515 patients, individual data)

Survival benefit: 3% (36% → 39% at 5 years, *p* = 0.003)
Loco-regional control benefit: 7% (46% → 53% at 5 years, *p* < 0.0001)

	loco-regional control benefit	survival benefit
Very accelerated with reduction of total dose	**3% (n.s.)**	**2% (n.s.)**
Moderately accelerated	**7%**	**1% (n.s.)**
Hyperfractionated	**9%**	**9%**

Bourhis, Lancet 2006

Standard vs Hypo-fractionated Whole Breast RT: Canadian Trial



Whelan, NEJM, 2010

Conclusions to Fractionation

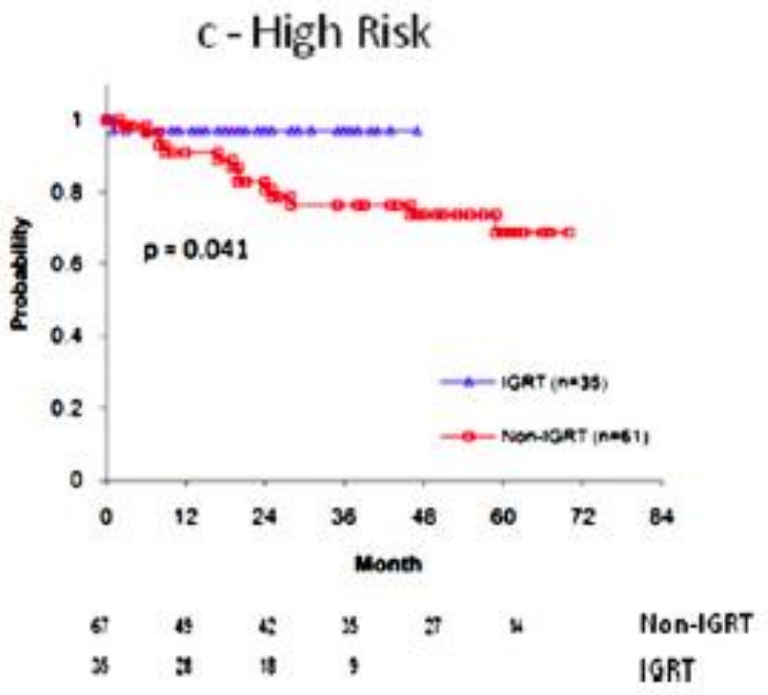
- **Altered fractionation can be of benefit**
- **Addition of chemotherapy or biological therapies requires re-adjustment of radiotherapy schedule**
- **In principle, tumors should be treated for an overall treatment time that is as short as possible consistent with acceptable acute morbidity, but with a dose per fraction that does not compromise late responding normal tissues, or total dose.**
- **Avoid treatment breaks and treatment prolongation**

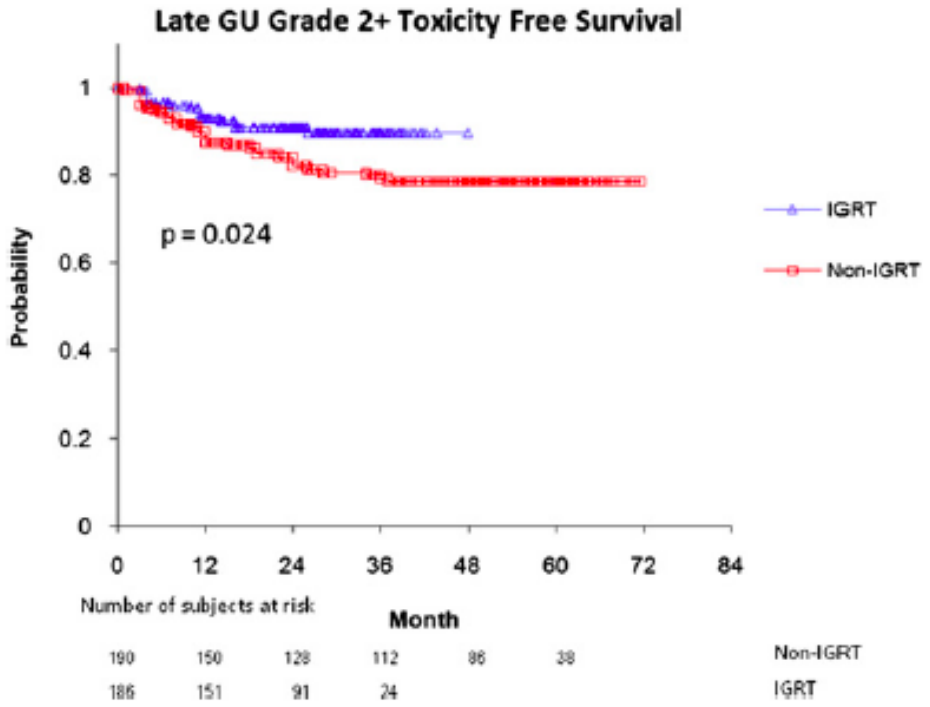
The Experience with Prostate Cancer IMRT at MSKCC

	Safety Margins	Dose		Percent Toxicity	Patients
				Cure	
Conventional Radiotherapy	20 mm	≤ 70 Gy		3.5%	428
		> 70 Gy	174	44%	6.9%
IMRT	6 mm	81 - 86.4 Gy	838	1.4%	88%

IMRT provided proof-in-principle that reduction of normal tissue safety margins enables tumor dose escalation and increased local cure

The Experience with Prostate Cancer IGRT-IMRT at MSKCC





IMRT

- **Only 4 randomized trials of IMRT vs conventional XRT**
  2 head and neck*, breast, prostate*****

  - **Endpoints for all four were toxicity and QoL**

  - **Head and neck – better salivary function and QoL – IMRT**
  - **Breast – less moist desquamation and better QoL – IMRT**
  - **Prostate – less acute and late GI and GU toxicity – IMRT**

Pow EH et al. Int J Radiat Oncol Biol Phys 66:981-991, 2006
Kam et al. J Clin Oncol 25:4873-4879, 2007
****** Pignol J-P et al. JCO 2085-2092, 2008***
******* Al-Mamgani et al. Int J Radiat Oncol Biol Phys 73:685-691,2009***

Radiation Oncology: Technology Assessment

RO history is one of continuous change when new technology becomes available. These changes were implemented with very few prospective, randomized trials.

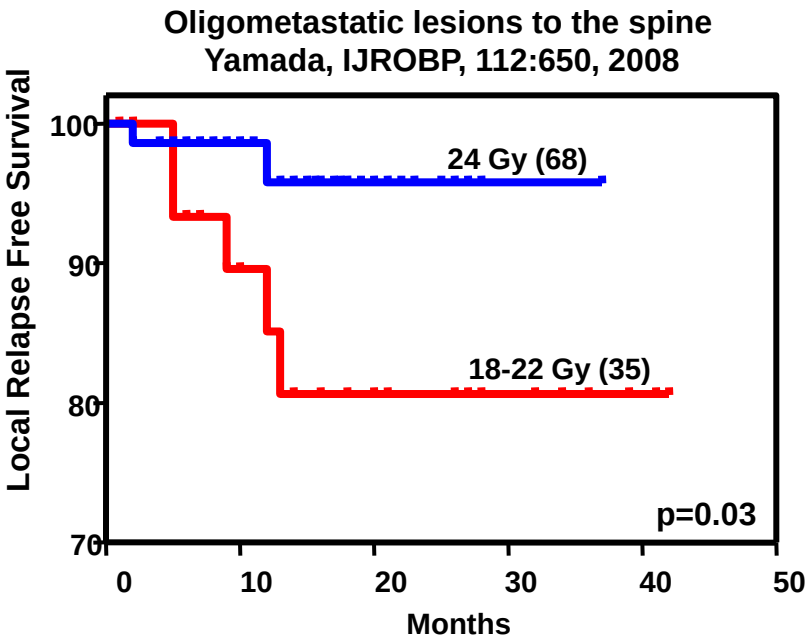
Energy 250 keV cobalt linear accelerators

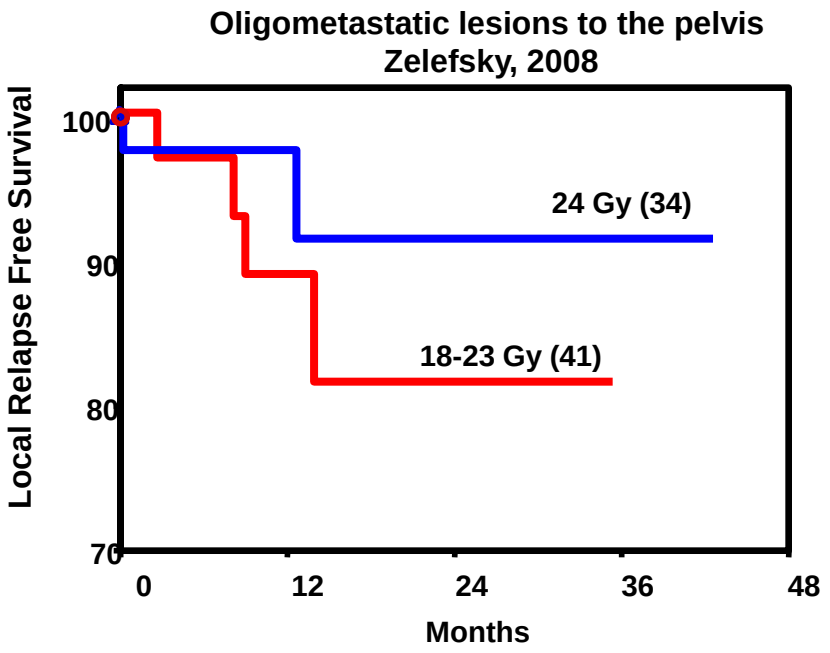
Conformality 2D 3DCRT IMRT IGRT

Clinicians rely extensively on the physics and mathematics used for treatment comparisons



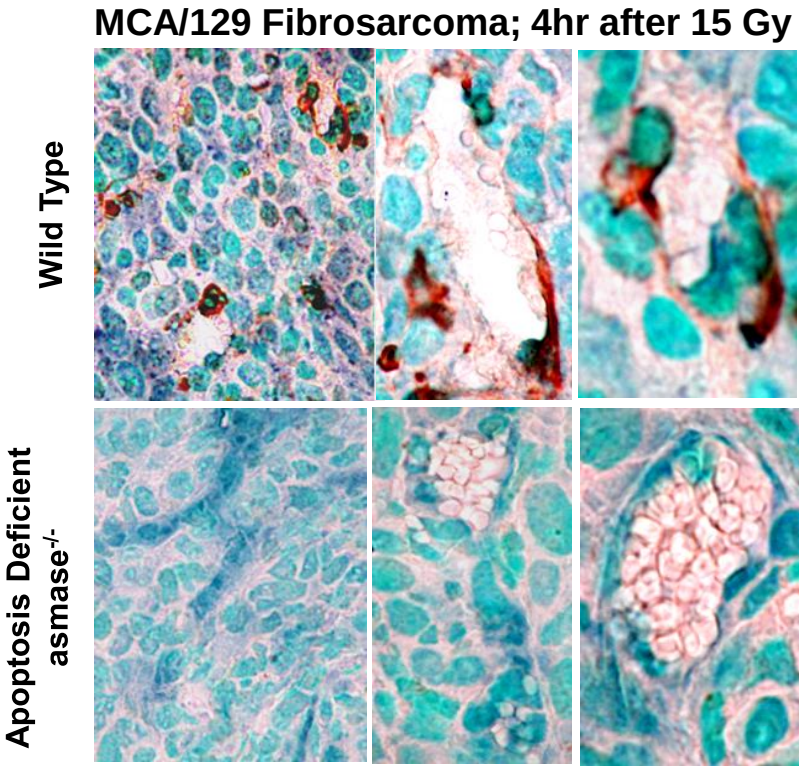

Local Control Oligometastatic Tumors The MSKCC Series of SD-IGRT, 2008

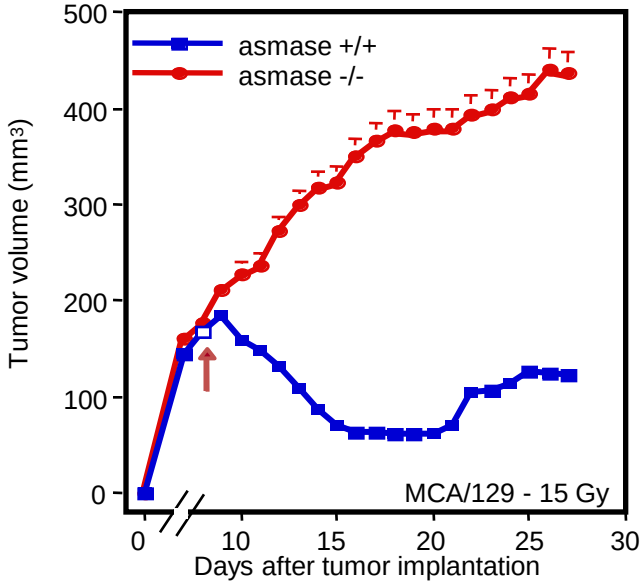




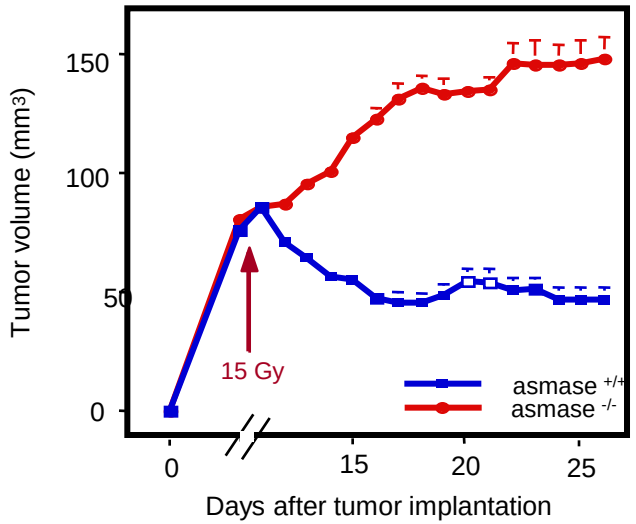
- Patients with metastatic breast, colorectal, lung, head and neck, liver, pancreatic, sarcoma, melanoma and other tumors

Lipid Signaling controls Vascular Collapse in Tumors

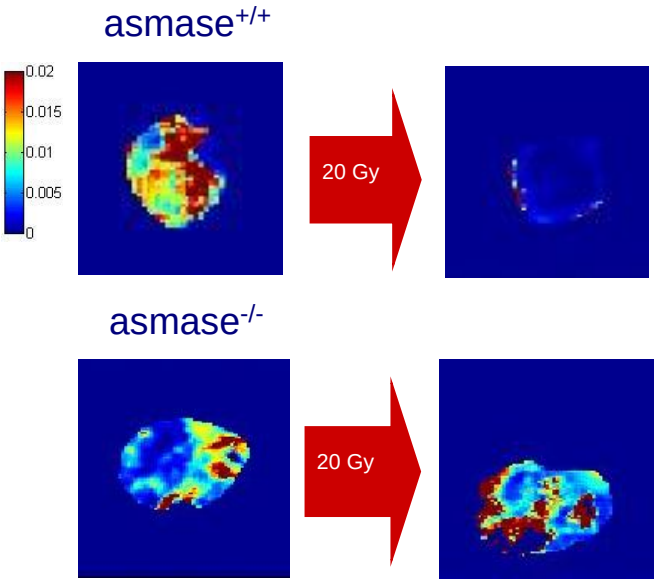




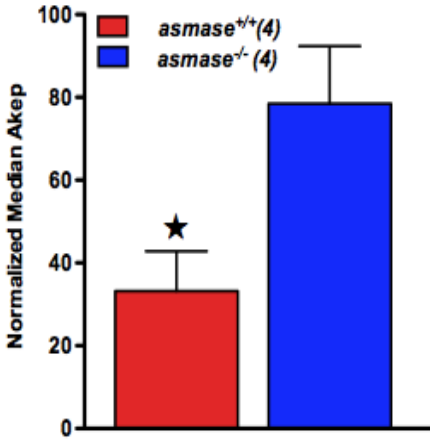
Recipient – asmase +/+
12 Gy WBR – day 0
BMT – day 1 (asmase $^{+/+}$ or $^{-/-}$)
Tu transplantation – day 30



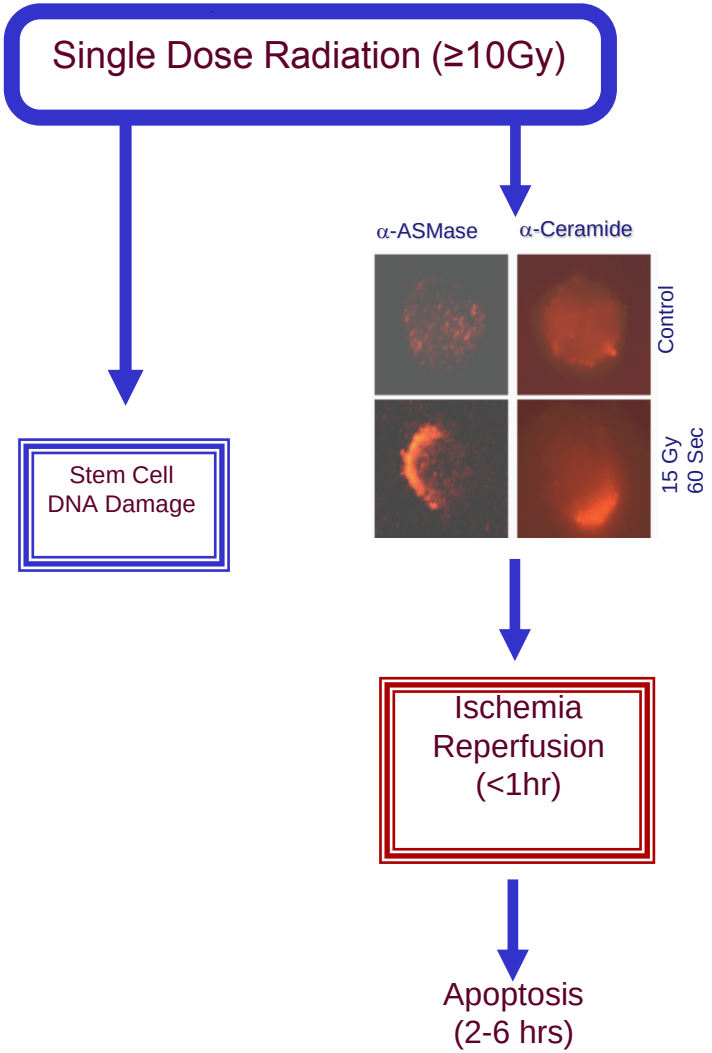
SDRT induces micro-vascular dysfunction in the tumor bed



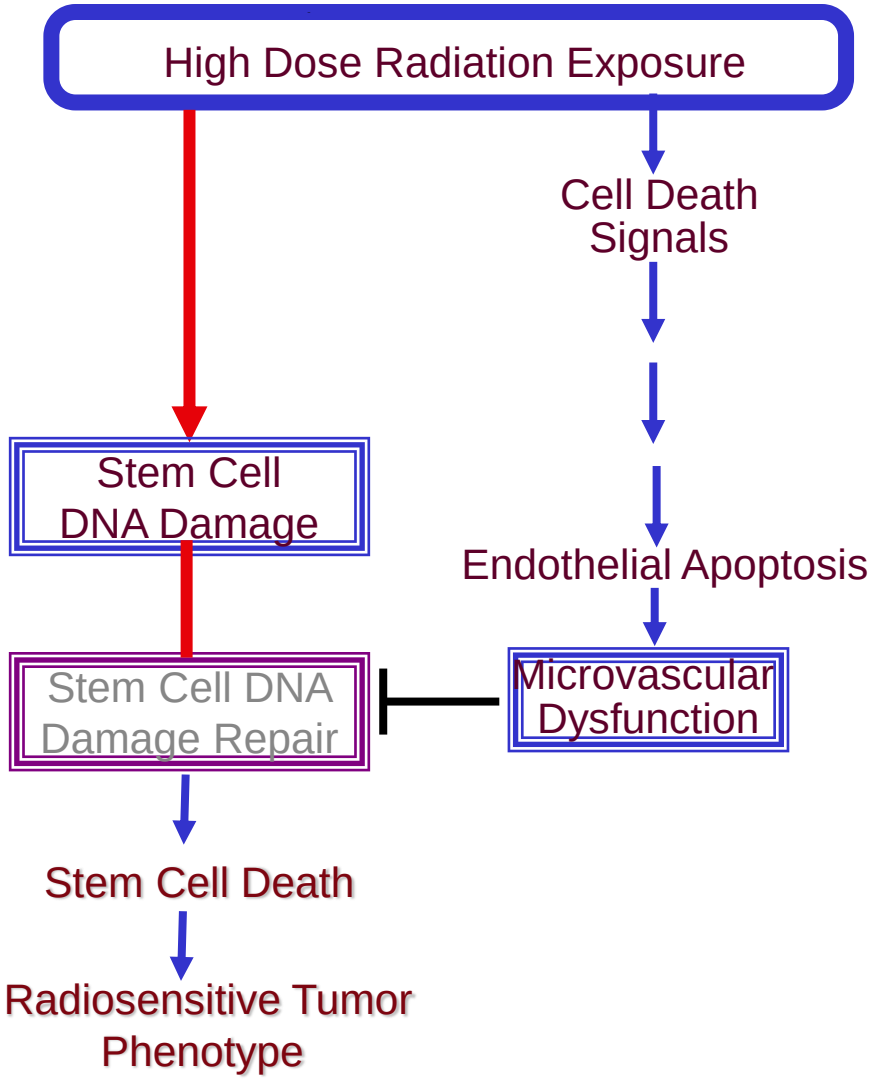
A kep intensity maps of 1 mm reconstructed Gd-DTPA DCE-MRI slice at 30 min after SDRT

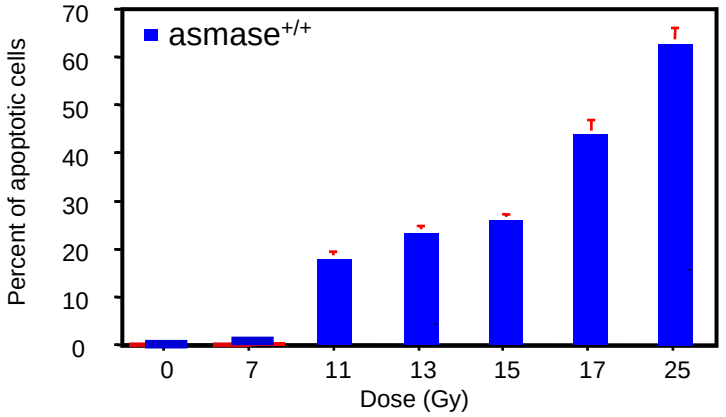


Reduction in whole tumor perfusion (DCE-MRI) at 30 minutes after 20Gy

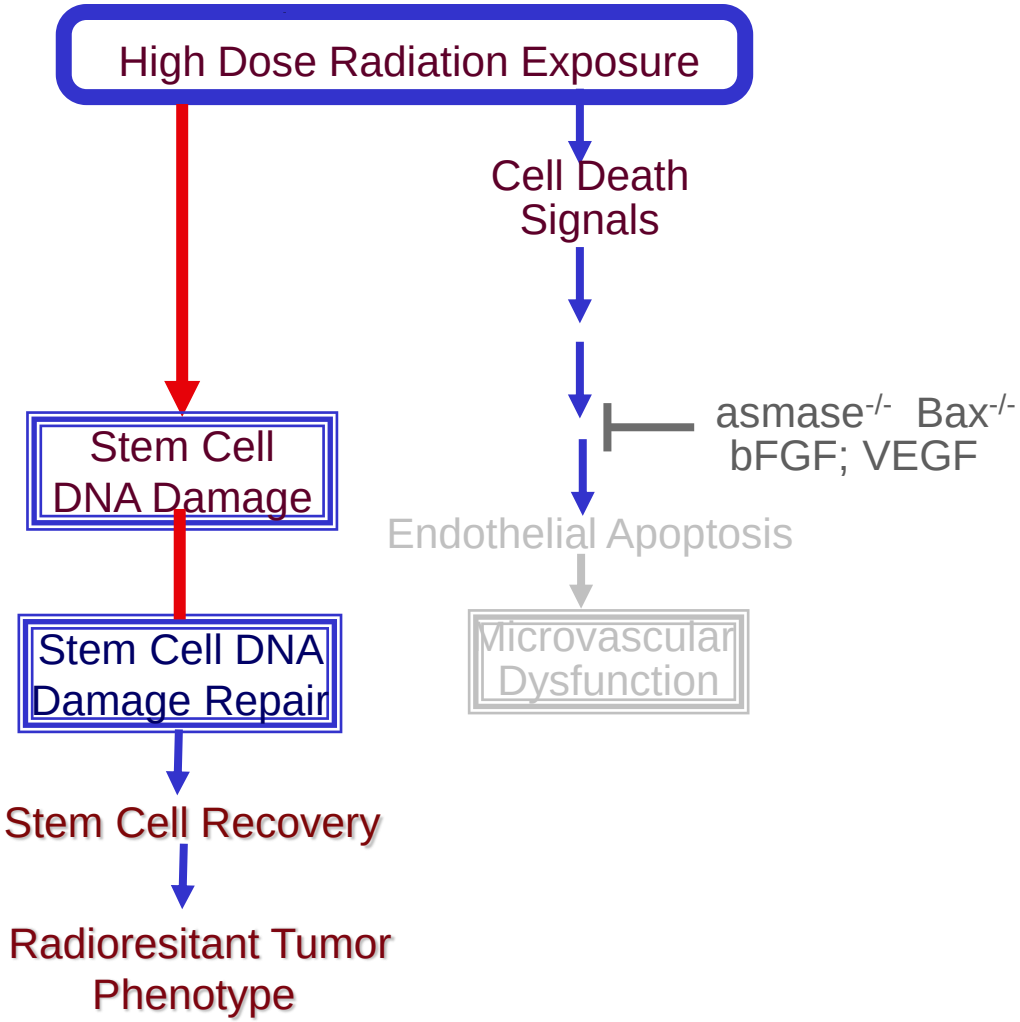


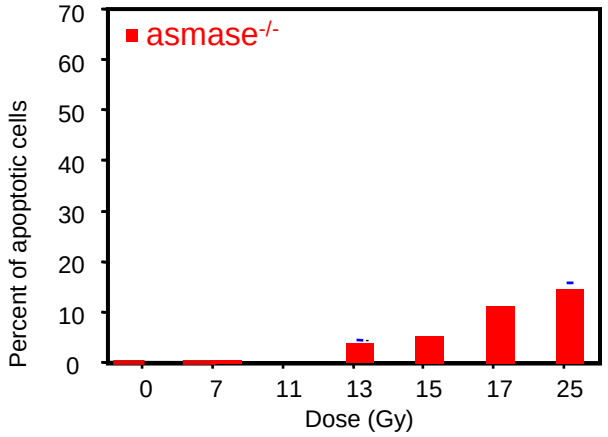
Lipid Signaling via Ceramide and Acid Sphingomyelinase governs Vascular Collapse and Tumor Cell DNA Repair



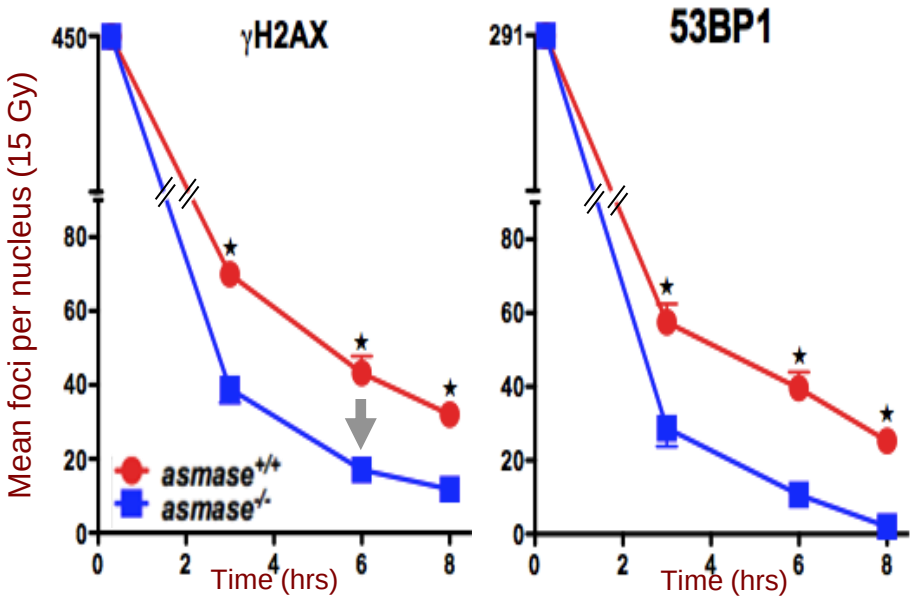


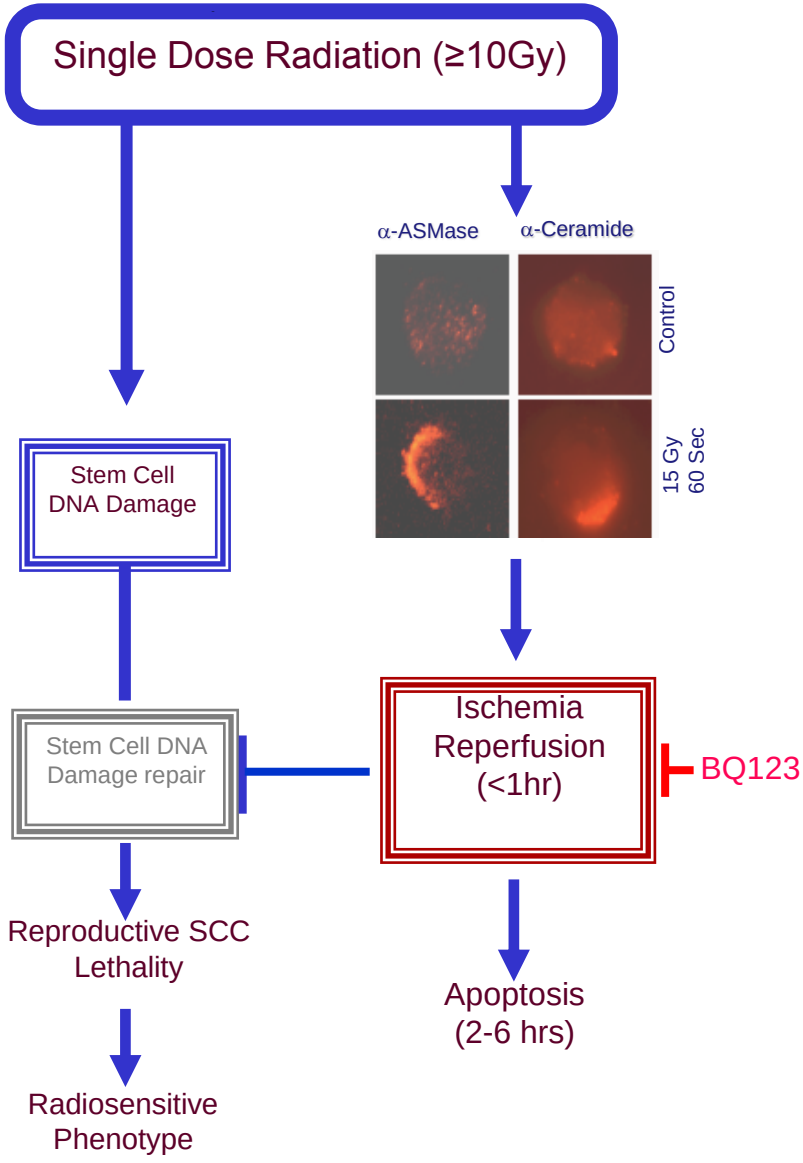
The loss of Acid Sphingomyelinase results in no observable apoptosis and no tumor cell sensitization





Microvascular dysfunction inhibits DSB repair





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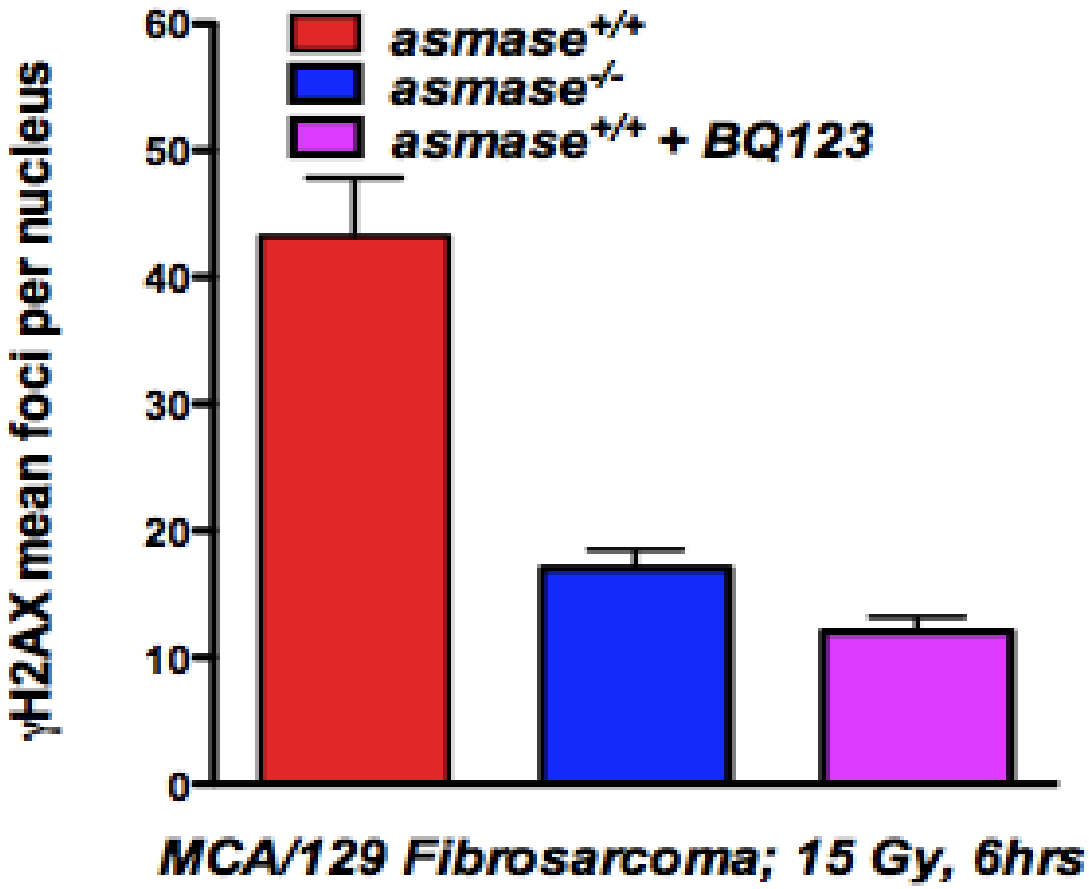


The Two-Target Model in Single-Dose Radiotherapy

- High dose radiation engages both tumor stem cells and the microvascular endothelium as a linked target system in effecting depletion of the stem cell compartment
- Engagement of the endothelial component has a threshold at 8-10Gy
- Transient micro-vascular dysfunction regulates the repair of repopulating tumor stem cells DNA dsb, converting potentially repairable damage into lethal lesions

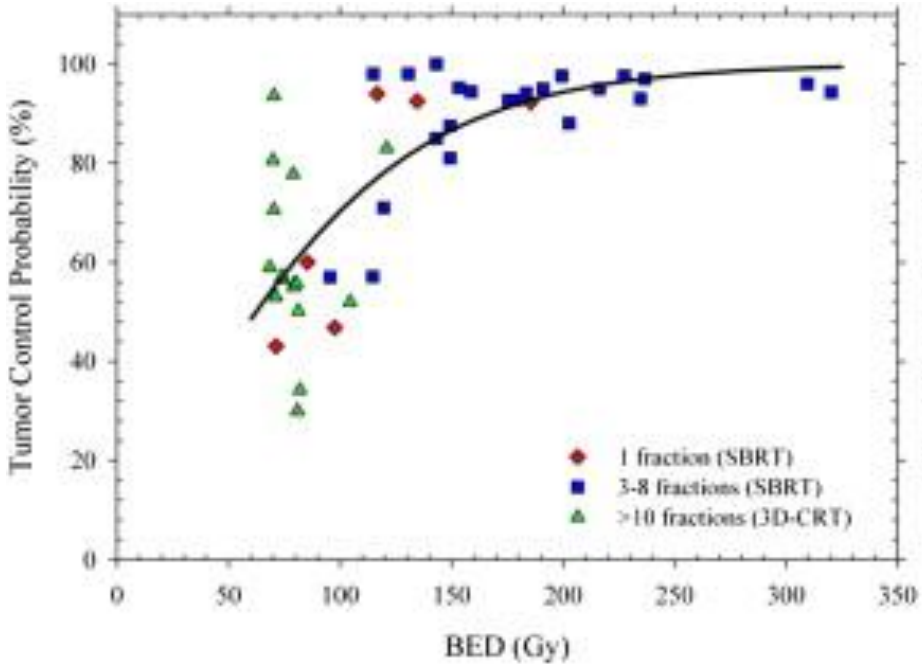
Single Dose IGRT Differs Mechanistically from Classical Fractionated Radiotherapy

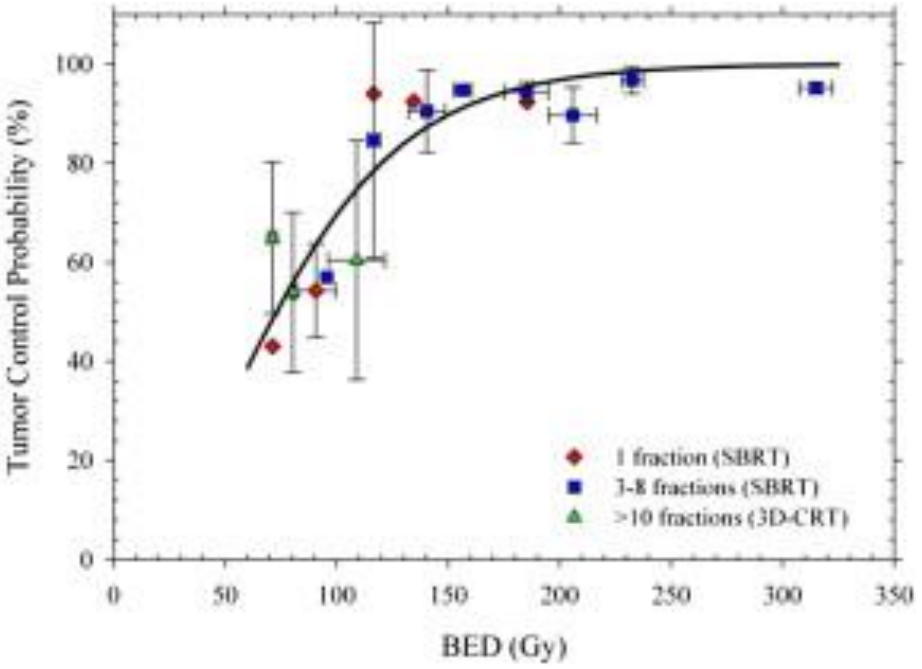
SINGLE DOSE IGRT	FRACTIONATED RADIOTHERAPY
Linked stem cell / endothelial target	Stem cell target; no endothelial component
Activated at 8-10 Gy; optimal range 22-25 Gy	Daily 1.8-2.0 Gy escalated to tolerance
Microvascular dysfunction represses DNA dsb repair	Based on more efficient dsb repair in normal tissues compared to tumors during inter-fractional intervals
IGRT required to exclude normal tissues, thus removing the barrier for delivery of tumoricidal dose levels	Fractionation enables tumor dose buildup with reduced normal tissue toxicity
≥90% local control with ≥24 Gy regardless of tumor phenotype	Rank ordering of tumor curability by phenotypic inherent radiosensitivity

Arguments against the use of SD/Hypo-Frac Radiotherapy

- The 4R paradigm of classical radiobiology features a requirement for dose fractionation to overcome hypoxic tumor cell resistance via inter-fractional re-oxygenation
- Assuming a 20% hypoxic fraction and the classical linear quadratic α/β model with adjustment for high dose exposure, the predicted single dose required for an iso-effect of 30x2Gy is ~40 Gy
- The predicted ultra-high SD doses required for human tumor cure with SD/HF mandate maximal exclusion of normal tissues, raising issues of biological uncertainties relative to microscopic tumor spread beyond GTV

SD-Radiotherapy: New Biology?



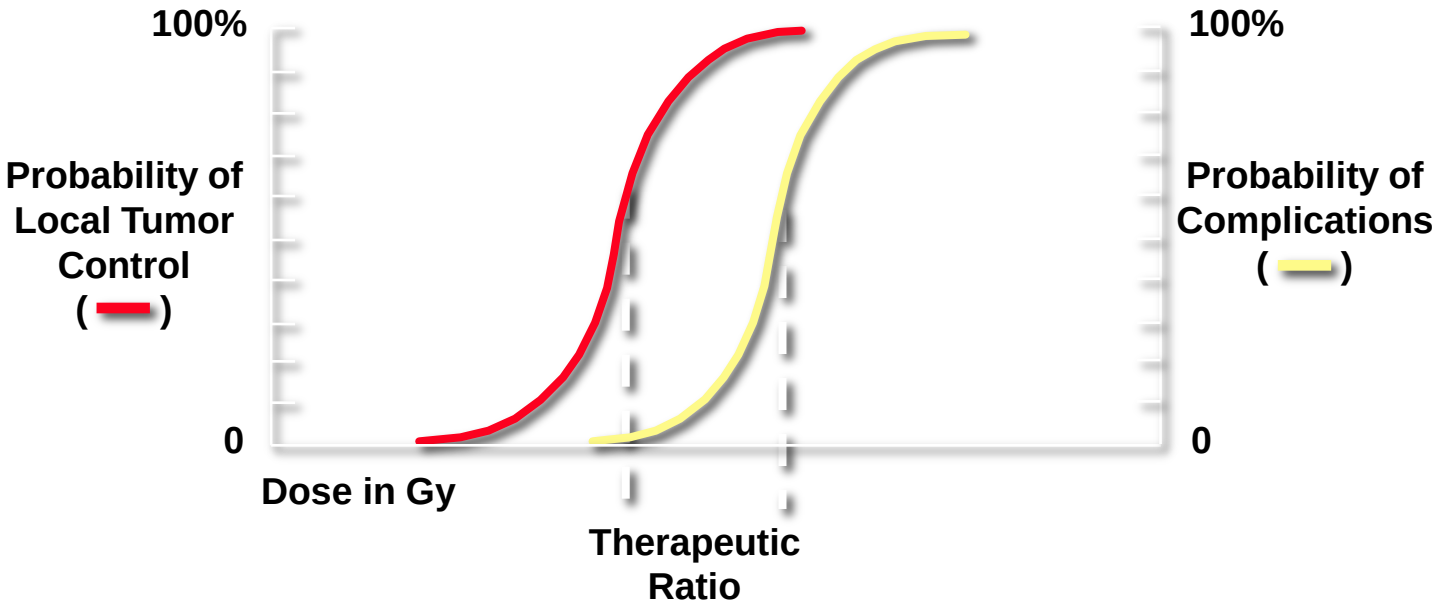


Brown, Brenner and Carlson, 2013

Why Proton Beam Radiotherapy?

- Tumorcidal radiation treatment, from photons or protons, can be administered to ~ 50% of all cancer patients.
- Many radiation treatment advances have focused on minimizing dose to normal tissues.
- Proton beam radiotherapy has superior (exit) dose precision, but currently availability is limited due to cost and logistical difficulties.

Therapeutic Ratio



Sensitization

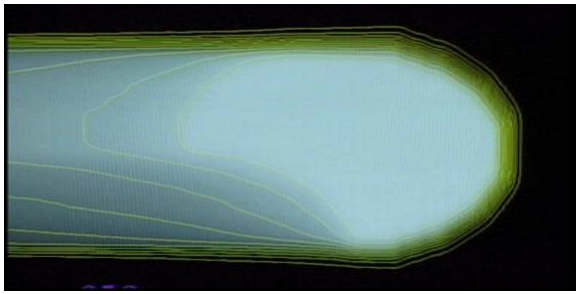
Chemotherapy
Oxygen
Hypoxic cell sensitizers
Biological Response Modifiers

Protection

3-D Conformal radiation therapy
Intensity modulated radiation therapy
Protons
Radioprotectors (Amifostine)

Advantages of Proton Therapy

- Compared to photons, particles deliver, on average, less than half the dose to normal tissues: therefore, particles provide
  - reduced acute and late morbidities
  - increased target dose
  - or both



Robert Wilson Ph.D

- **"I am fascinated by the unique distribution of ionization by protons compared to x-rays. This might be of interest to the radiological community for the treatment of tumors"**

- **".....the medical application of protons would give me atonement for involvement in the development of the bomb at Los Alamos."**

Radiological Use of Protons:
A J Radiology 47:487-491,1946

X-ray Beam

Proton Beam

Outcome Measures: Radiation Therapy

- Local control and survival rates
- Tumor control with acceptable morbidity
- Children represent a challenge to further reduce treatment related morbidities to historically low levels

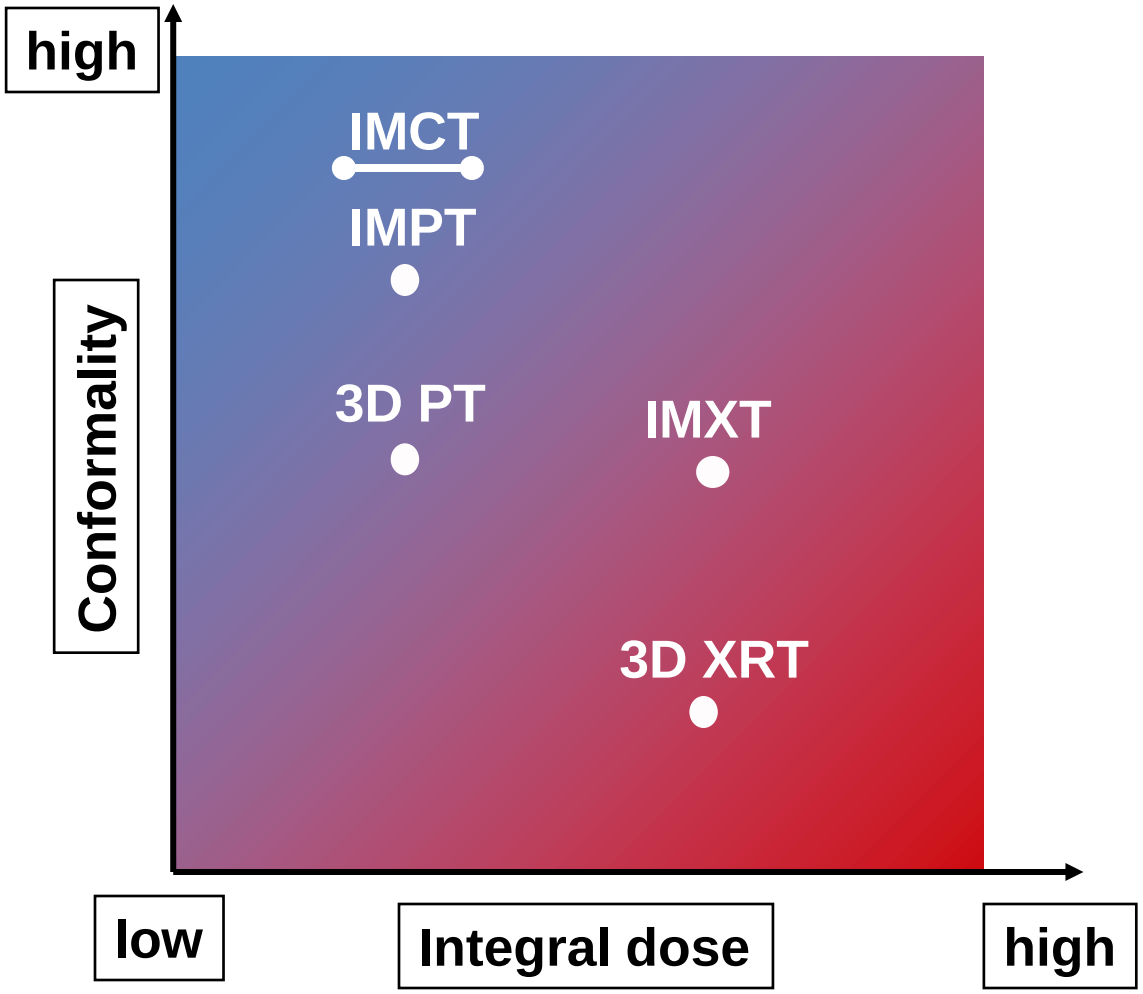
Commons Statements about Proton Therapy:

- The biology is not understood
- Proton therapy is experimental
- Photon delivery technology is so advanced that it has superceded the need of protons
- Dose distribution is so conformal that ‘margin failures’ will be seen
- Secondary neutrons will increase risk of secondary tumor formation
- Protons are too expensive

Commons Myths of Proton Therapy

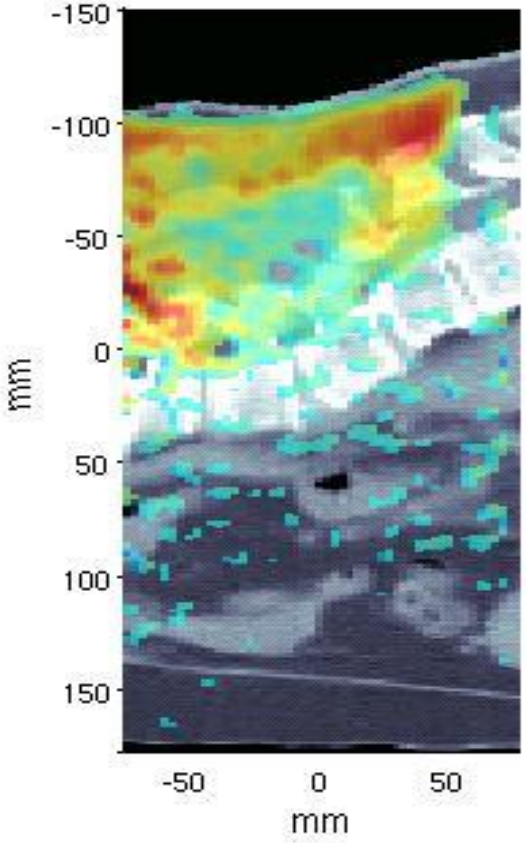
- The biology is not understood – FALSE (mostly)
- Proton therapy is experimental – FALSE (mostly)
- Photon delivery technology is so advanced that it has superseded the need of protons – FALSE (probably)
- Dose distribution is so conformal that ‘margin failures’ will be seen - FALSE
- Secondary neutrons will increase risk of secondary tumor formation - FALSE
- Protons are too expensive – partially true in 2013

Particles vs. Photons

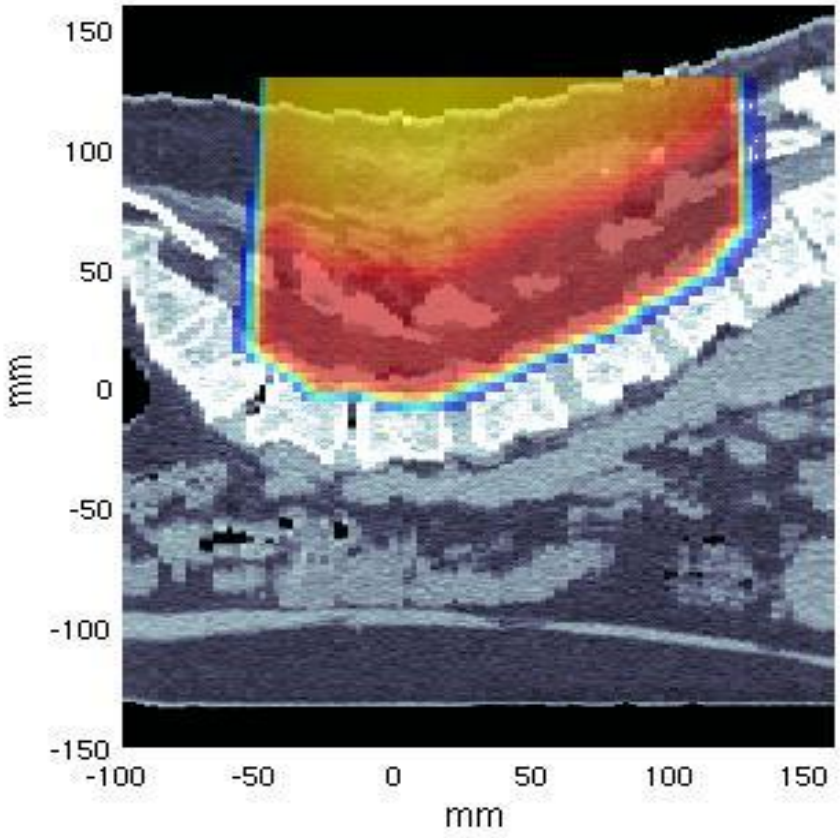


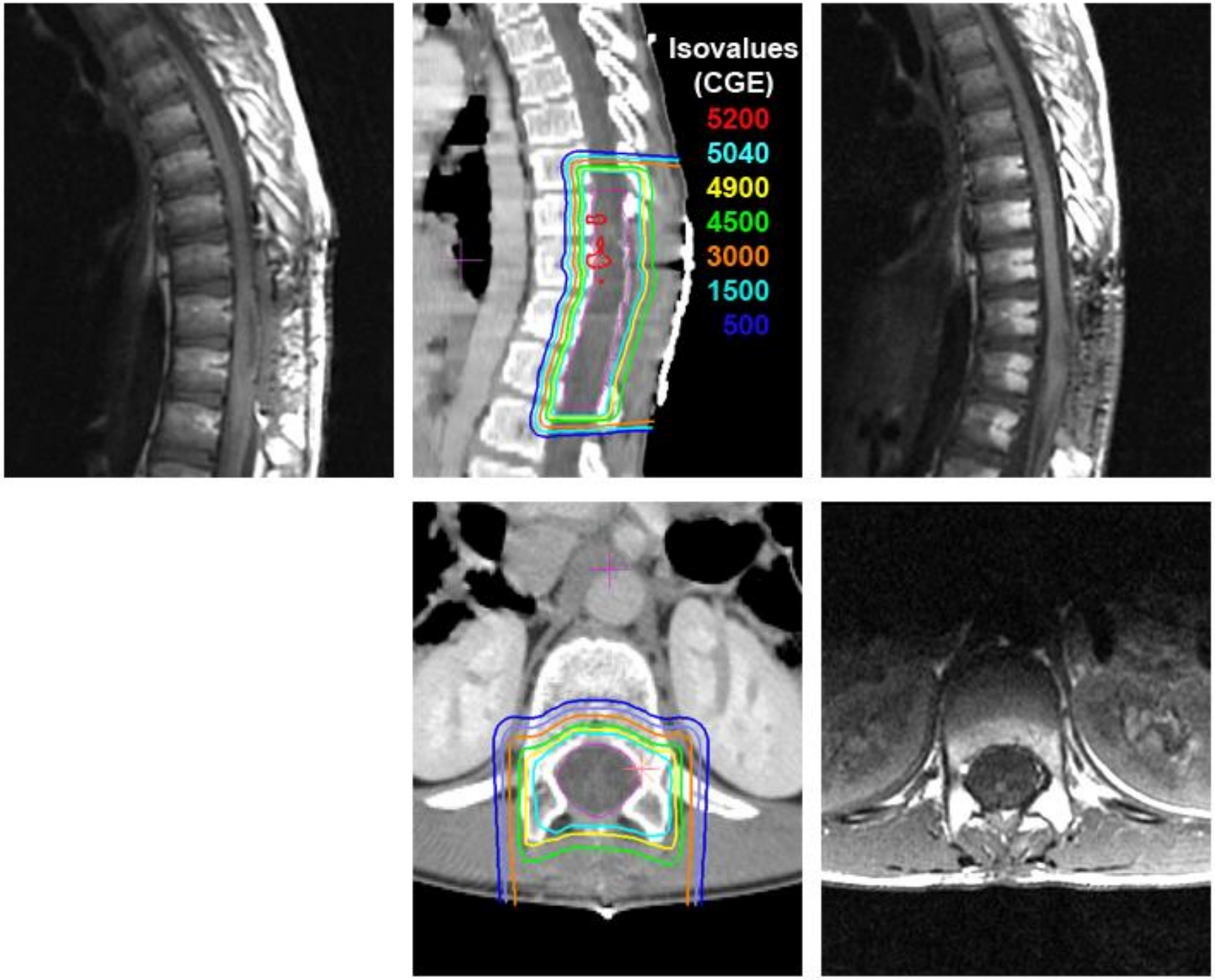
Chordoma: PET Verification of Proton Dose Distribution

PET/CT measurement



Planned dose




Isovalues
(CGE)
5200
5040
4900
4500
3000
1500
500

Proton Therapy

- **Biology – Gy for Gy essentially the same as photons?**

- **Reducing the dose outside the desired target volume is:**
  - ***preferable***
  - ***desirable***
  - ***logical***
  - ***sensible***
  - ***cost-effective***

- **In trials where “higher than standard dose” is being delivered, patients are required to be on IRB approved, prospective, clinical trials (chordoma, nasopharynx, liver, pancreas, prostate)**

Limitations of Clinical Data: Proton Therapy at the MGH

- Nearly 30 years of experience at HCL
- Low energy and fixed beam limited sites of treatment (e.g. skull base, eye)
- Data for some endpoints (secondary tumors) *contaminated* with at least 20% of treatments being conformal x-rays
- Clinical results still compelling, however





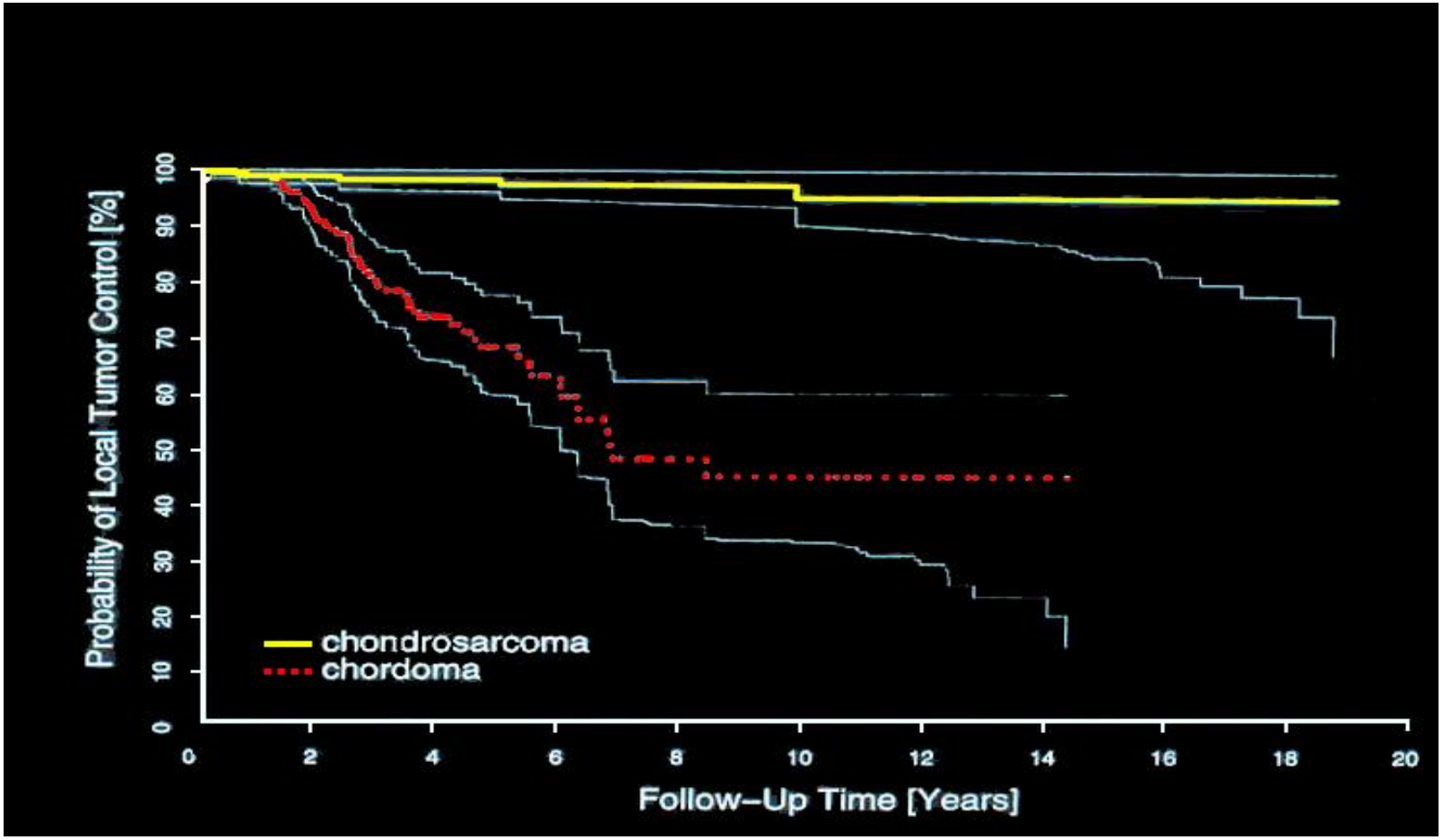
Limitations of Clinical Data: Proton Therapy at the MGH

- **Clinical results still compelling, however**
  - **>95% LC uveal melanoma at 15 years**
  - **80% LC paraspinal sarcomas at 5 years**
  - **80% LC paranasal sinus scc without visual injury**
  - **Reduced early and late effects pediatric tumors**





Local Tumor Control



Chordoma (adults)

LC = 75 % at 5 yrs.

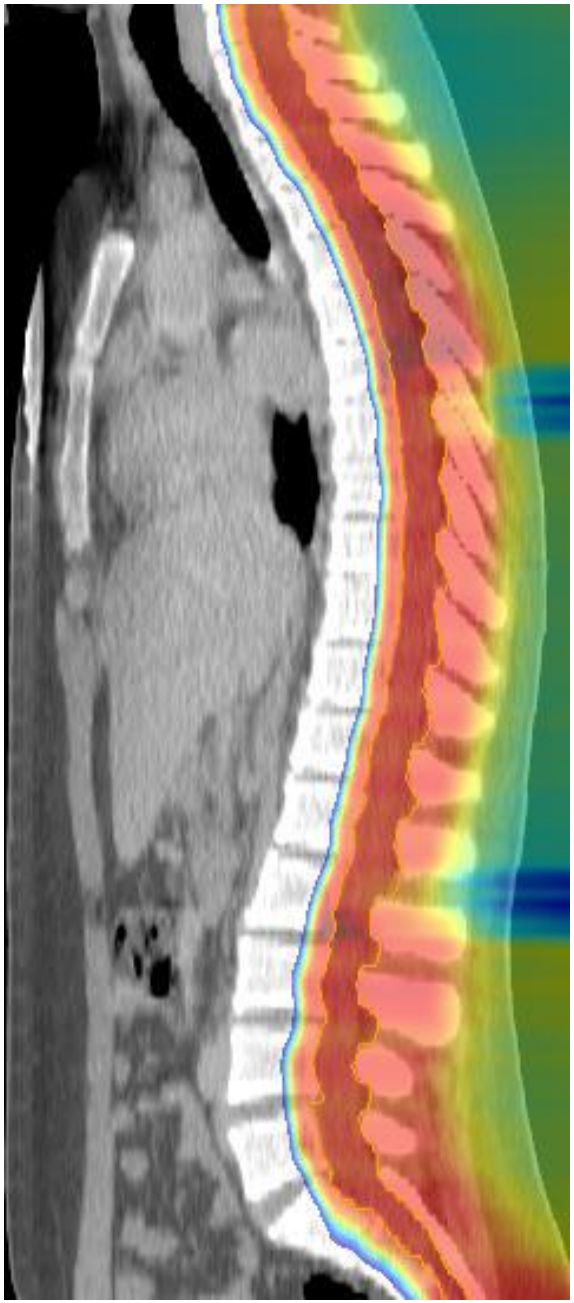
= 55 % at 10 yrs.

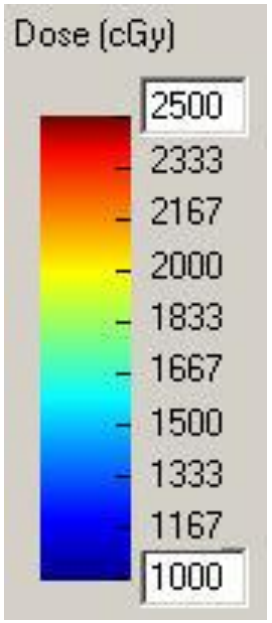
Chondrosarcoma

LC = 98 % at 5 yrs.

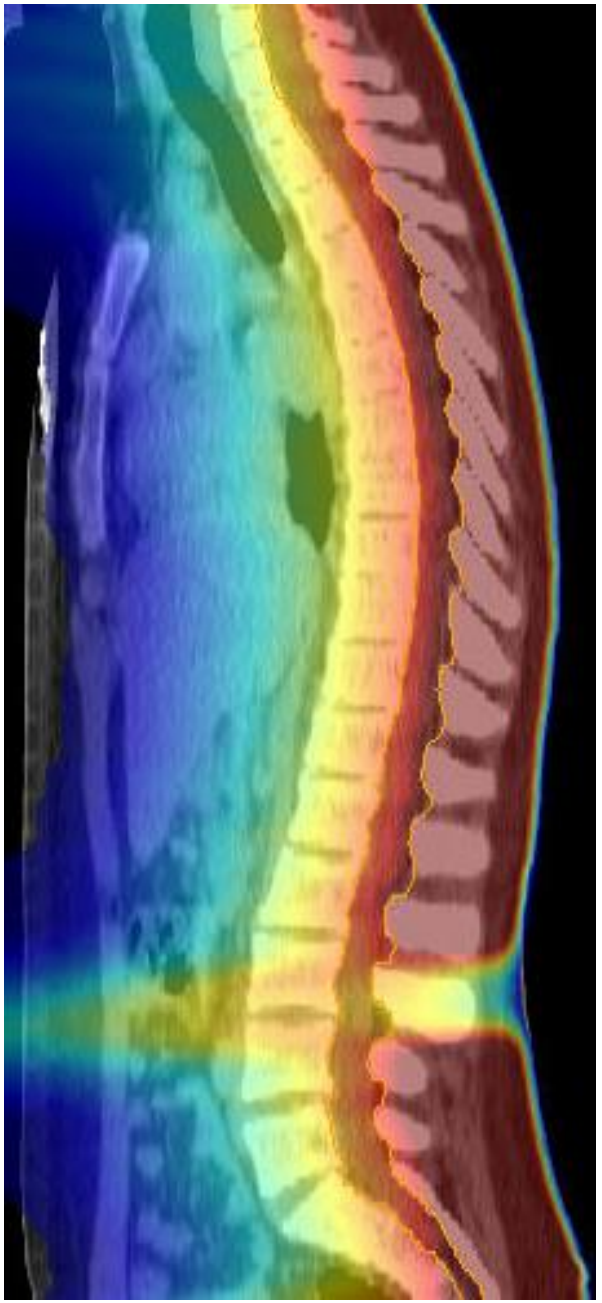
= 95 % at 10, 15 yrs.

Protons





Photons

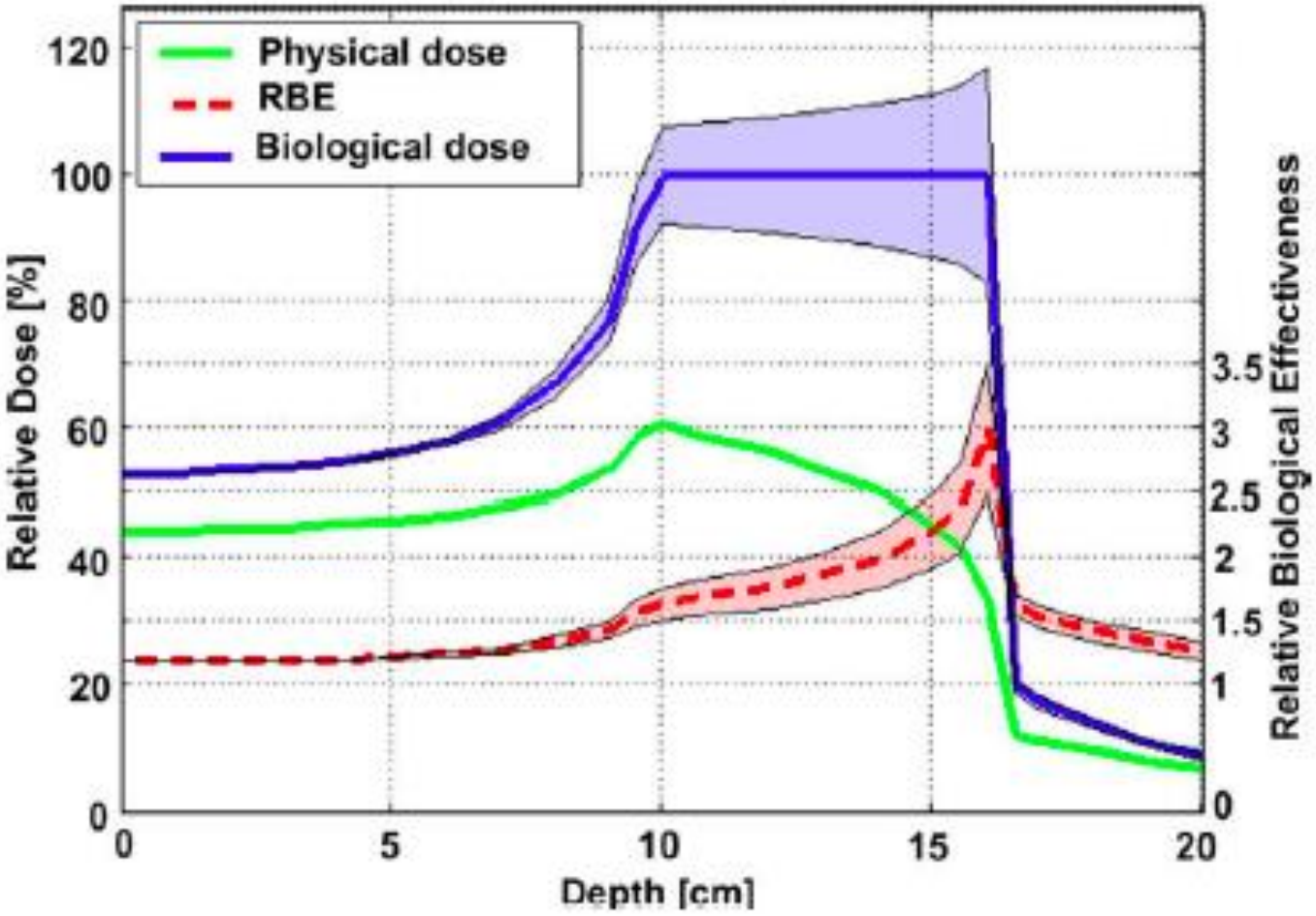


Secondary Malignancies Following Proton/Photon Therapy at HCL/MGH

- **503 proton patients**
- **1591 matched photon patients from SEER registry**
- **Observation times >5 years**
- **Matched for age, gender, age at treatment**
- **6.4% of proton patients developed SMs**
- **12.8% of photons patients developed SMs**
- **No pediatric patient has developed secondary tumor**
- **Conclusions**

  Photons radiation therapy was associated with significant increase risk of SMs compared to photons (Adjusted Hazard Ratio of 2.73, $p<0.0001$)

Particle Therapy: Summary

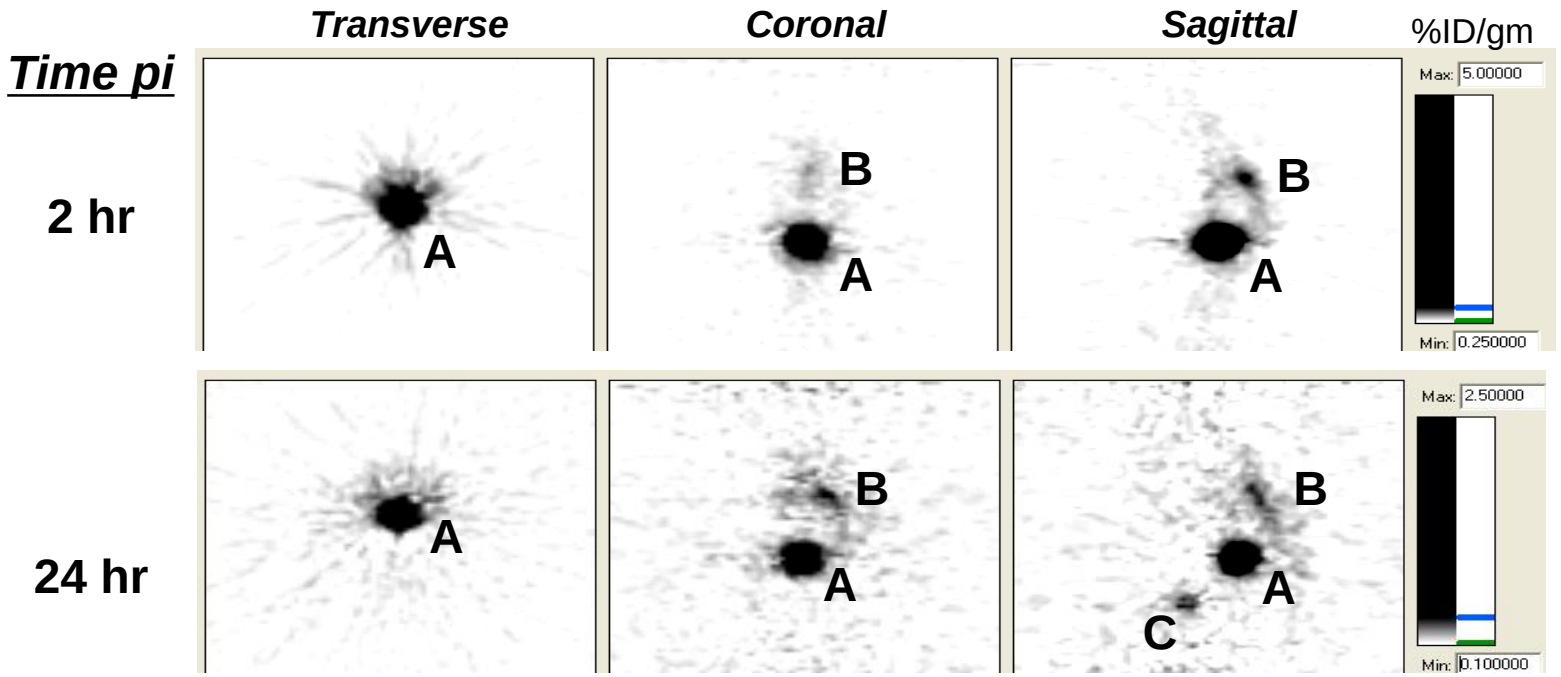


Neutron Therapy: a short history

- **Neutrons have high-LET and increased RBE**
- **Clinical trials were initially limited by low energy, which made dose distribution less favorable**
- **Is the RBE higher for tumors or normal tissues?**
- **Conclusions:**
  - **Late effects of neutrons were excessive, but volume restriction not optimized.**

Convection-Enhanced Delivery (CED) of Theranostic ^{124}I-8H9 Antibody
Pre-clinical Results

Focus 120 microPET Images
following 10-μCi (10 μl) Infusion into Cerebellum of Normal Rat



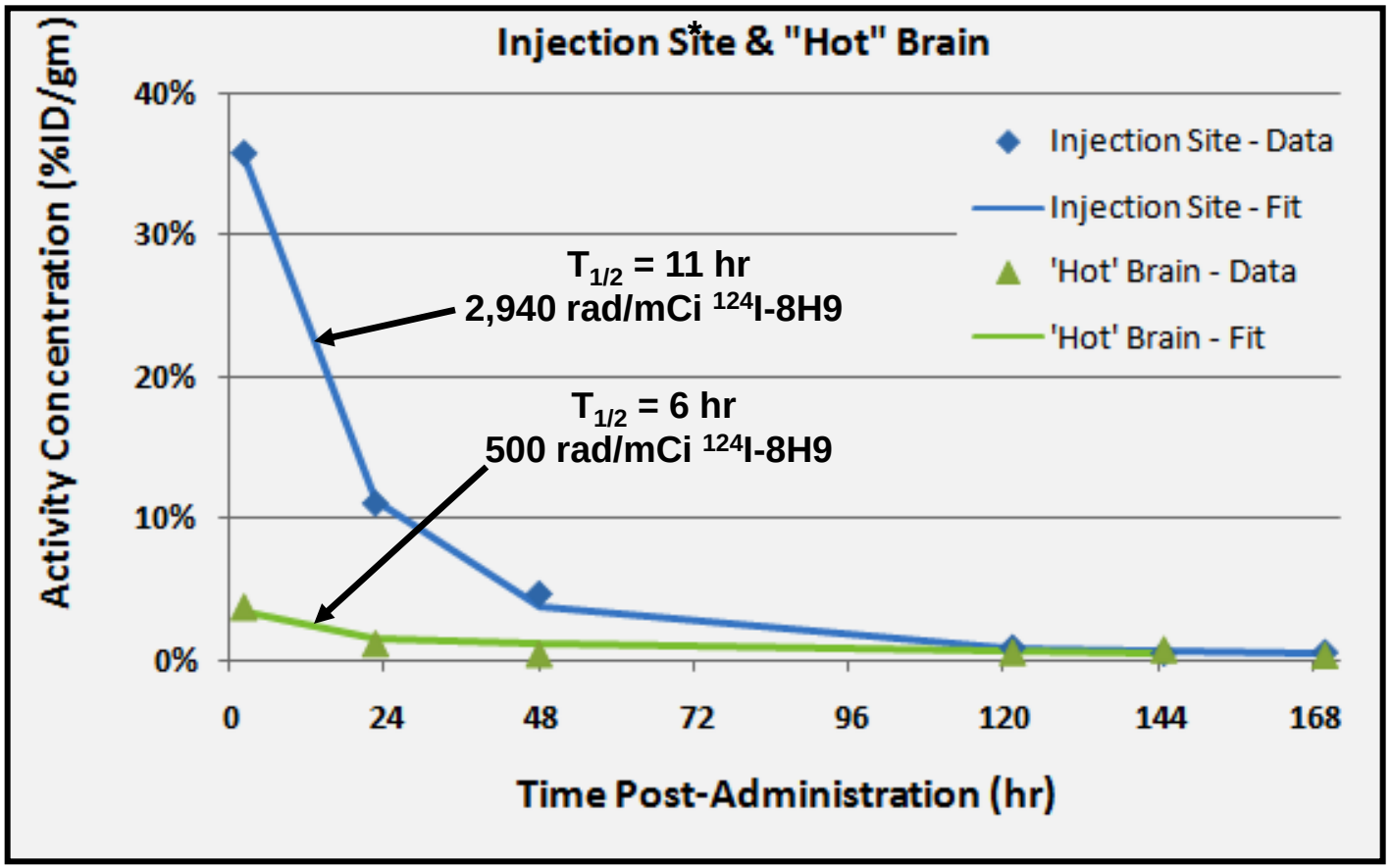
1st two of five serial images thru 7 d pi

A = Injection site, B CSF space, C = Thyroid*

* Thyroid not blocked with SSKI

Convection-Enhanced Delivery (CED) of Theranostic ^{124}I-8H9 Antibody
Pre-clinical Results

microPET-derived Kinetics and Dosimetry
following 10-μCi (10 μl) Infusion into Cerebellum of Normal Rat



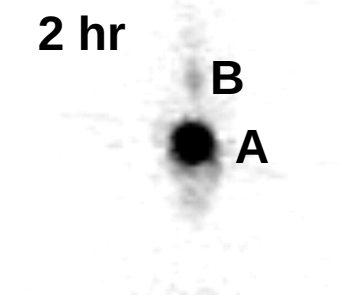
* The term, "'Hot' Brain," refers to CSF space remote from injection site.

Convection-Enhanced Delivery (CED) of Theranostic ^{124}I-8H9 Antibody
Pre-clinical vs Clinical Results

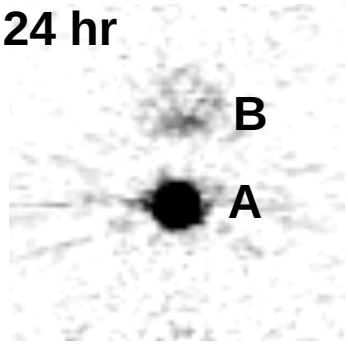
Serial PET Images (coronal) in Normal Rat (left) and Pontine Glioma Patient (right)

Time pi

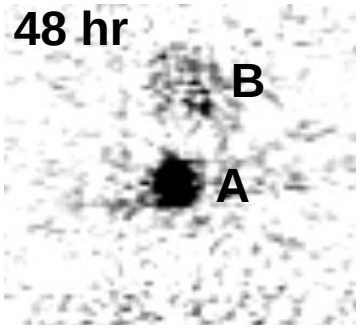
2 hr



24 hr



48 hr

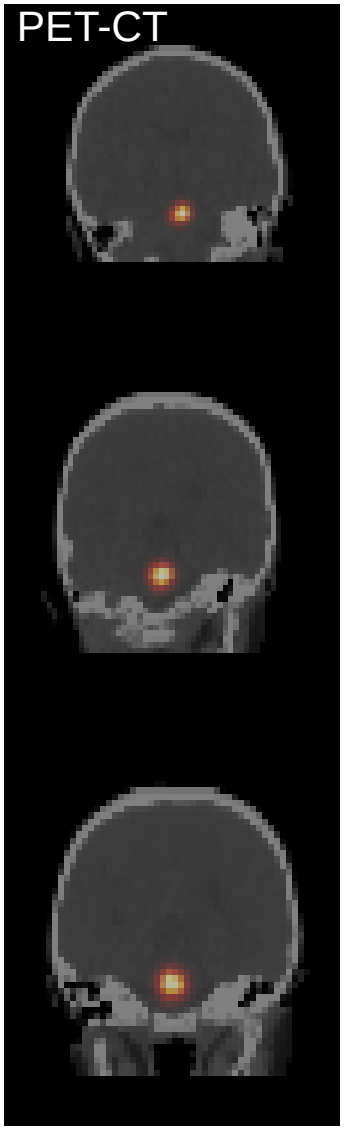


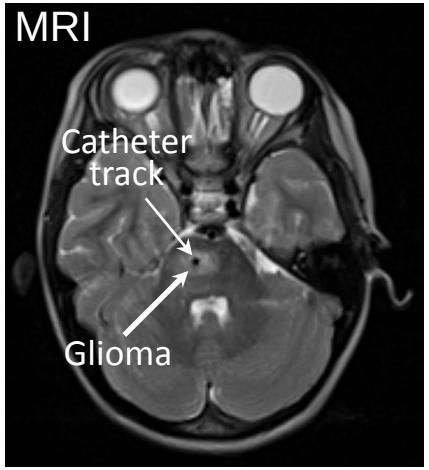
Time pi

3 hr

24 hr

72 hr



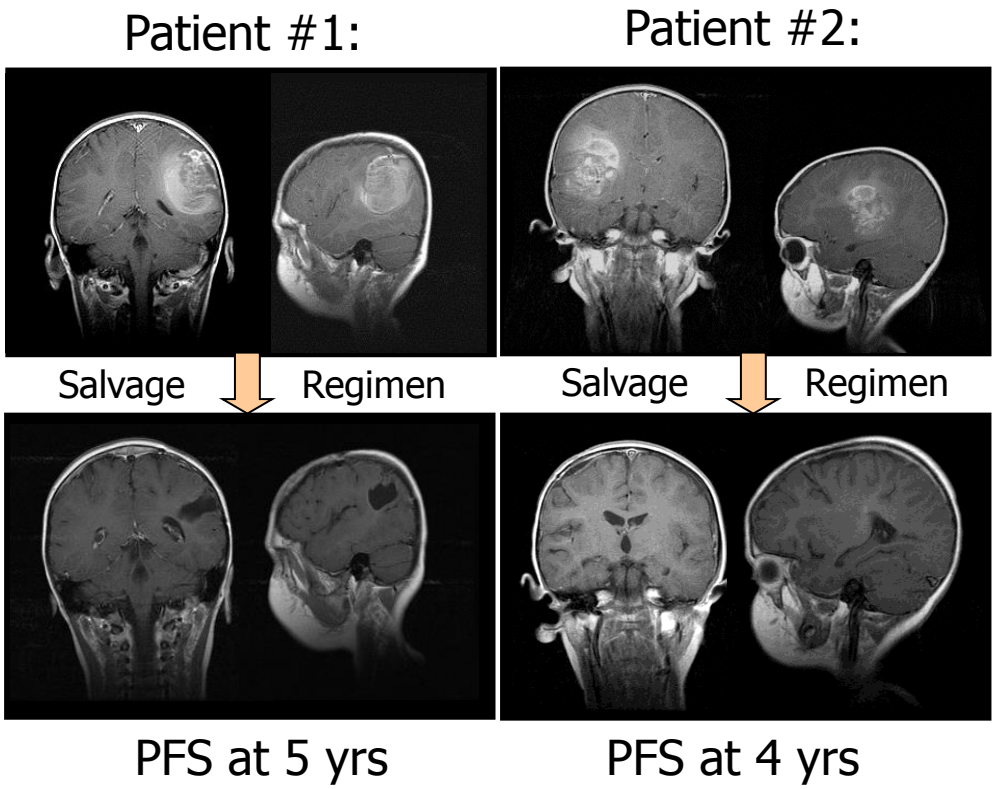


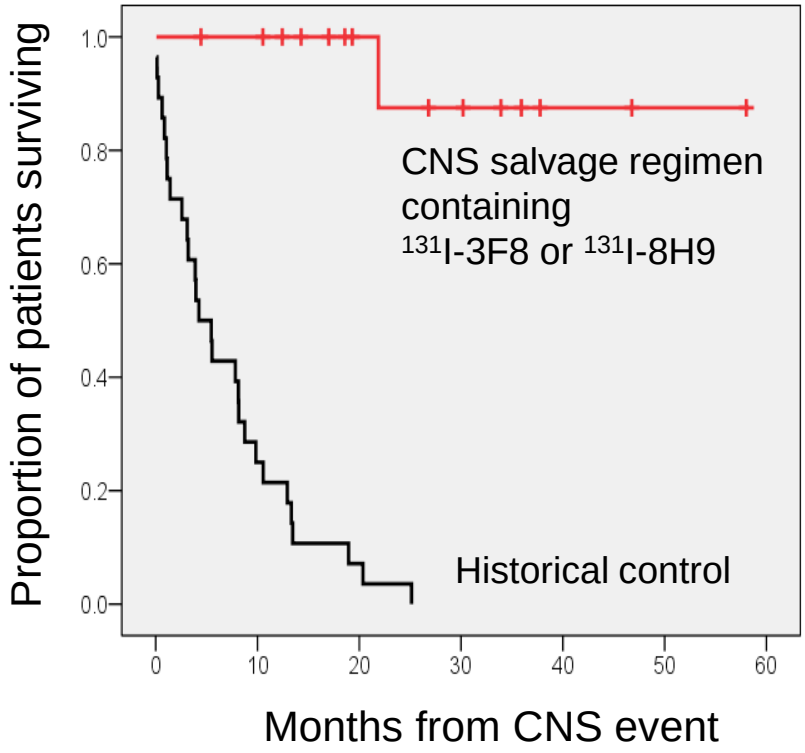
A: Injection site: Cerebellum
$T_{1/2}$ = 11 hr
D = 2,940 rad/mCi

B: CSF space
$T_{1/2}$ = 6 hr
D = 500 rad/mCi

Injection site
$T_{1/2}$ = 35 hr
D = 440 rad/mCi

Theranostic Approaches
CNS Cancers





EGFR inhibition

- **Cetuximab :**

- inhibition of EGFR kinase activity

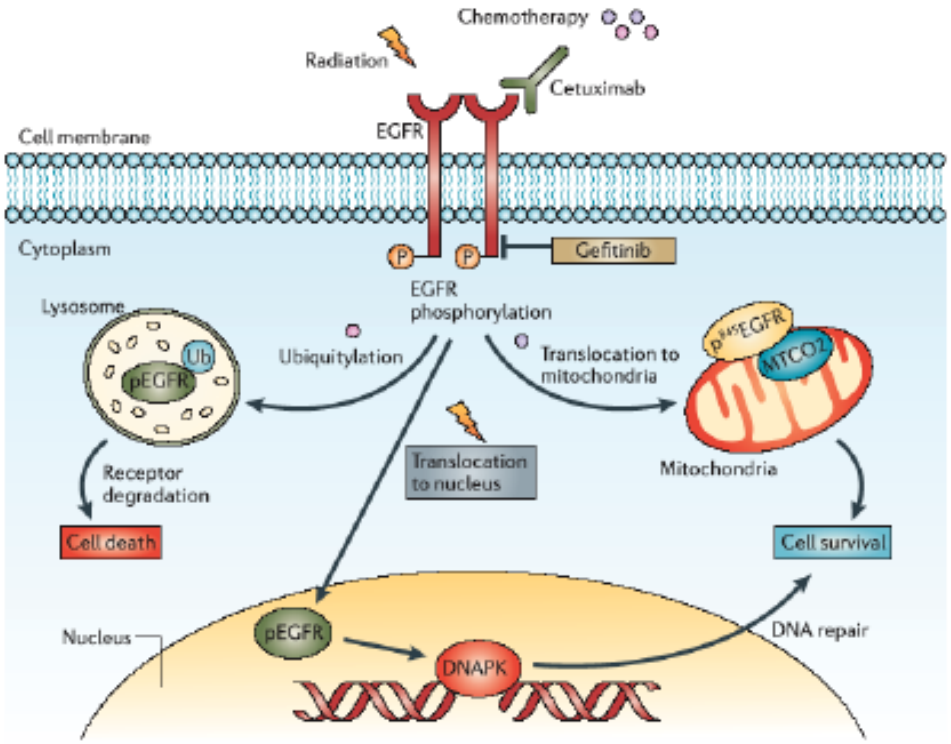
- inhibition of cell cycle progression

- increase of radio-induced apoptosis

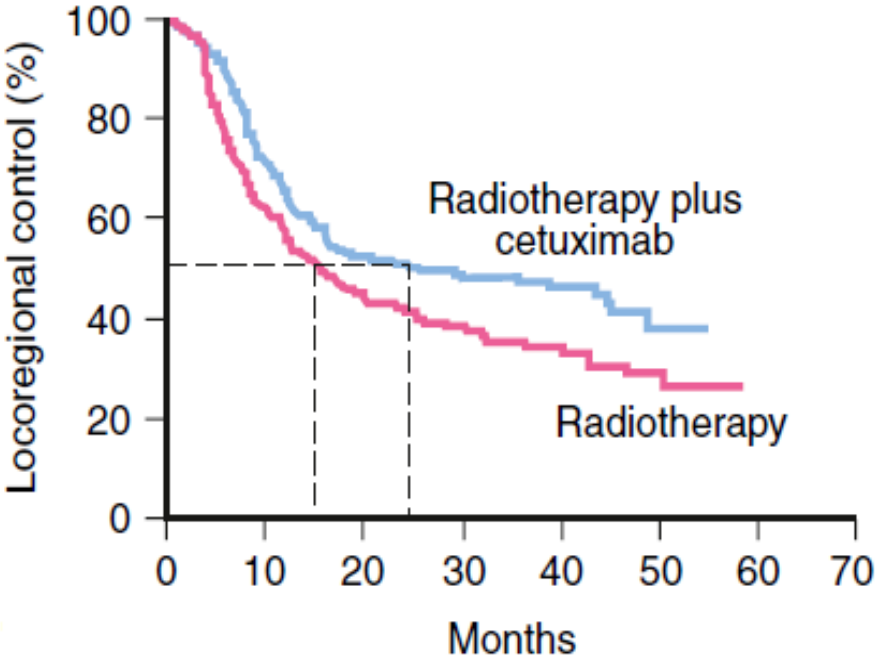
- anti-angiogenic effect

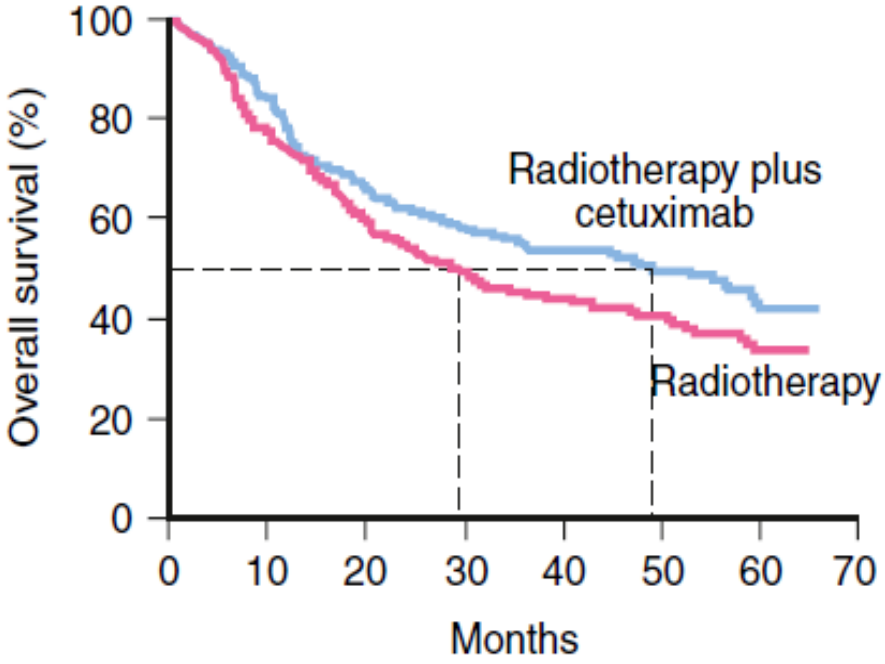
- ADCC (antibody dependent cellular toxicity)

- inhibition of DNA repair (via DNA-PKcs)

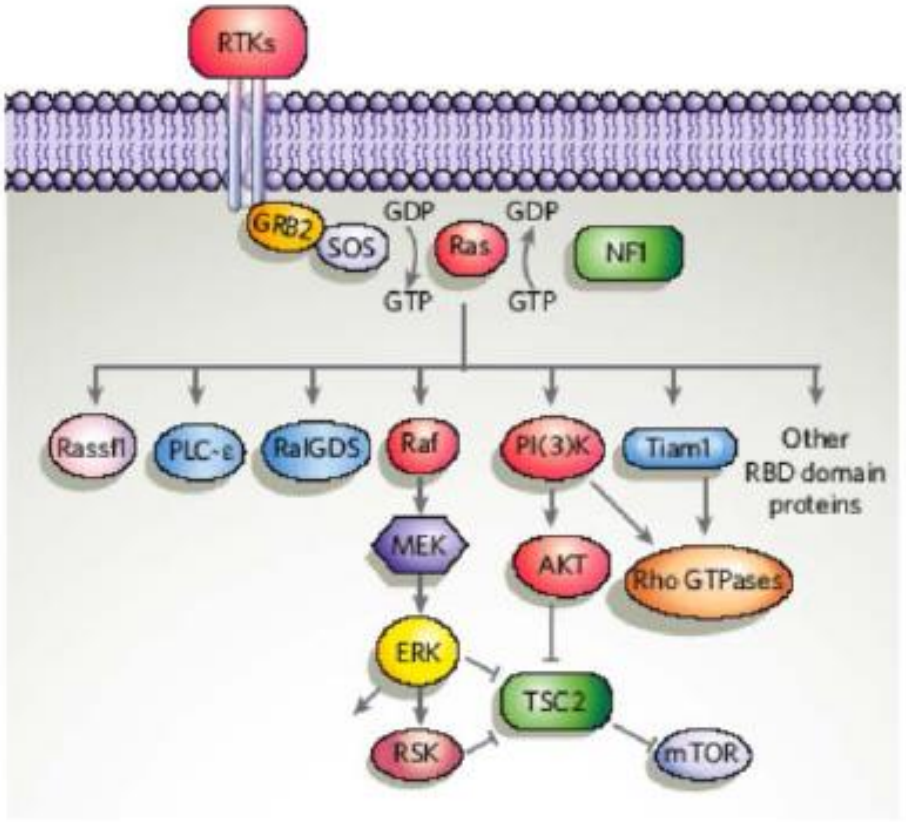


Targeting EGFR in Head and Neck Cancer





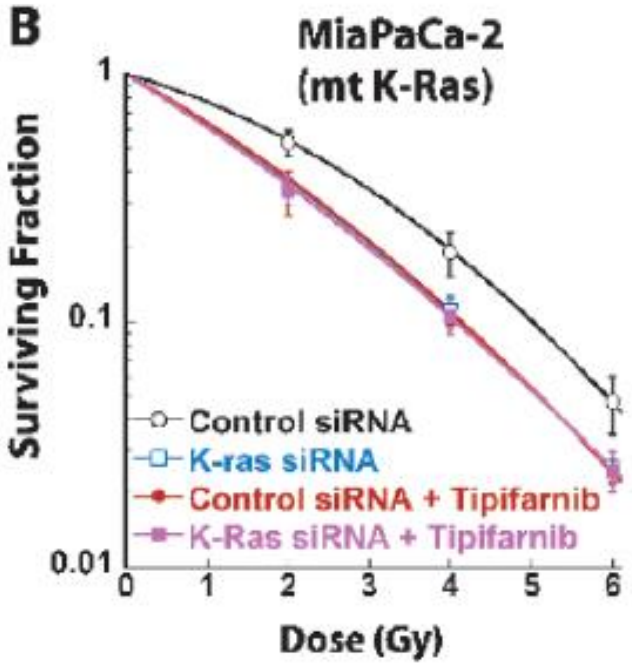
Ras inhibition



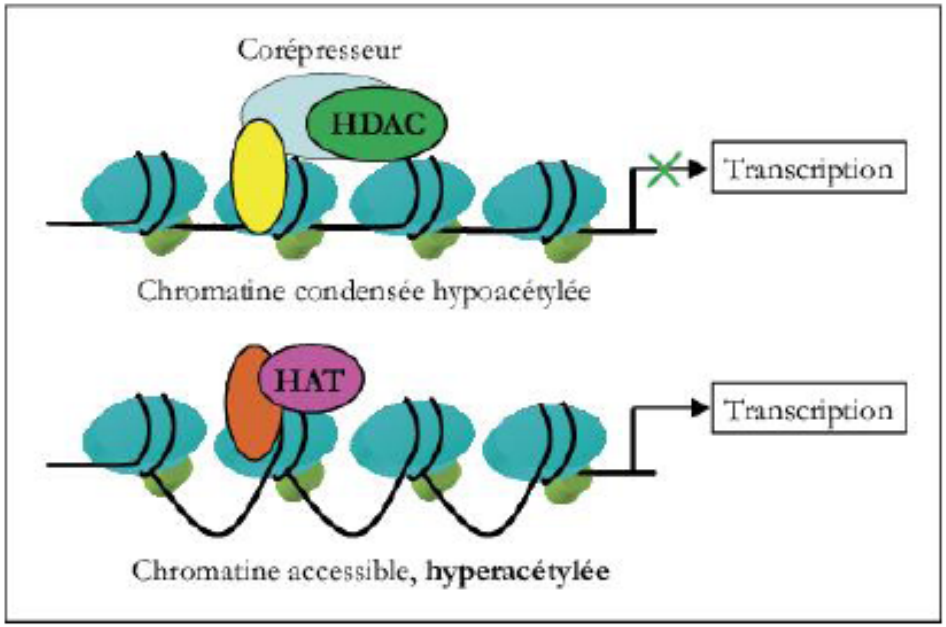
Oncogene RAS mutated in 20% of cancers

Ras controls proliferation, survival, differentiation, migration and angiogenesis

- Activation of Ras leads to radioresistance
- Inhibition of Ras activity by siRNA or farnesyl transferase inhibitor increases radiosensitivity



HDAC inhibitors



- 16 HDAC inhibitors
- radiosensitization *in vitro*
- not well known mechanisms
- differential effect tumor/normal tissues
- > 100 clinical trials on going
- one published trial with pelvic radiation therapy (PRAVO)

Histone deacetylase (HDAC)

regulation of chromatin structure, gene transcription, and radiosensitivity?

HDAC overexpression is oncogenic

→ 4 phase I trials on going (pancreas, lung, prostate, esophagus, HN) and 1 phase II/III trial (glioblastoma)

New Modalities

- Altered fractionation schemes tested in the clinic
- Intensity Modulated RT: dose-volume effects
- Radiosurgery: new biology?
- Charged Particles
- Radio-immunotherapy
- Targeted Radio-sensitization