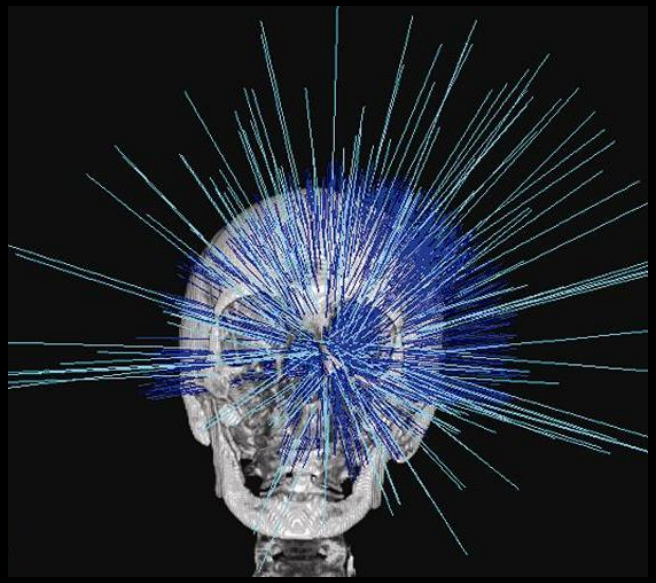
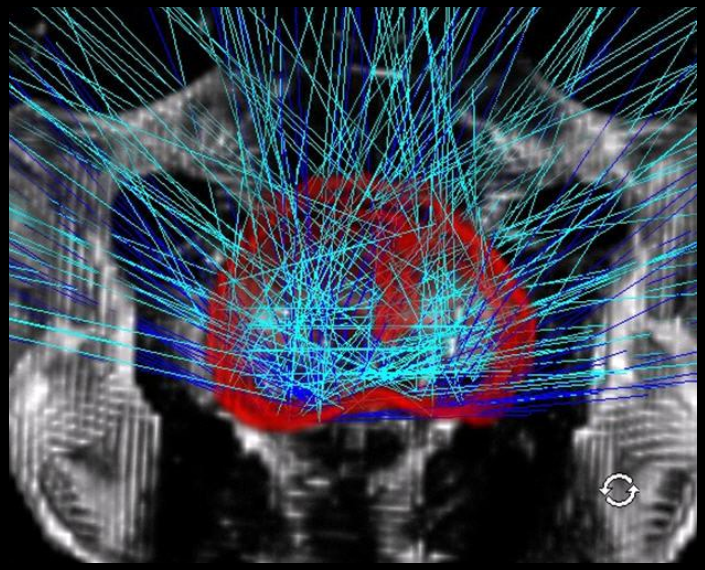
What are the Dominant Mechanisms at Play in Stereotactic Radiotherapy?





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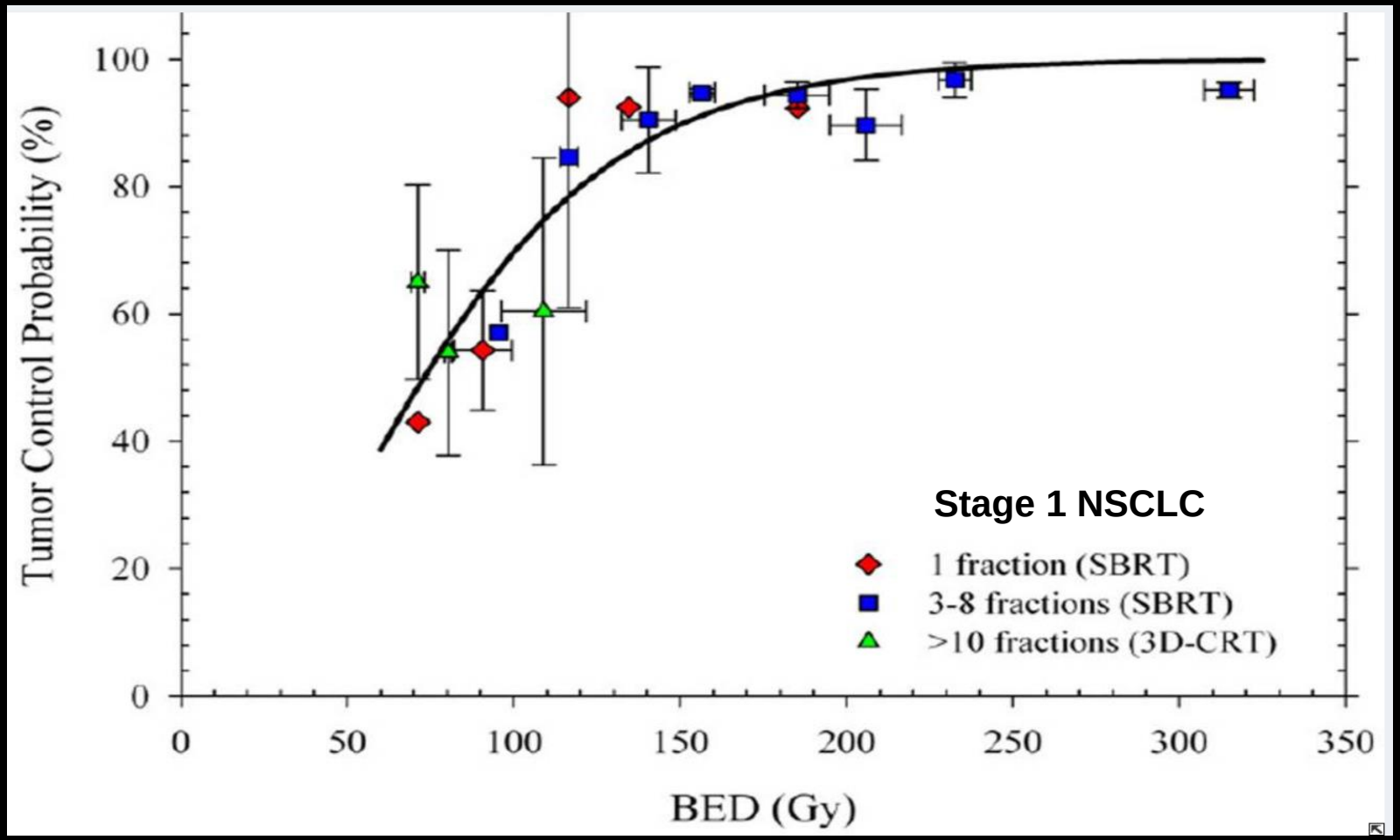
Stereotactic radiotherapy is producing excellent clinical results particularly for NSCLC and brain mets….



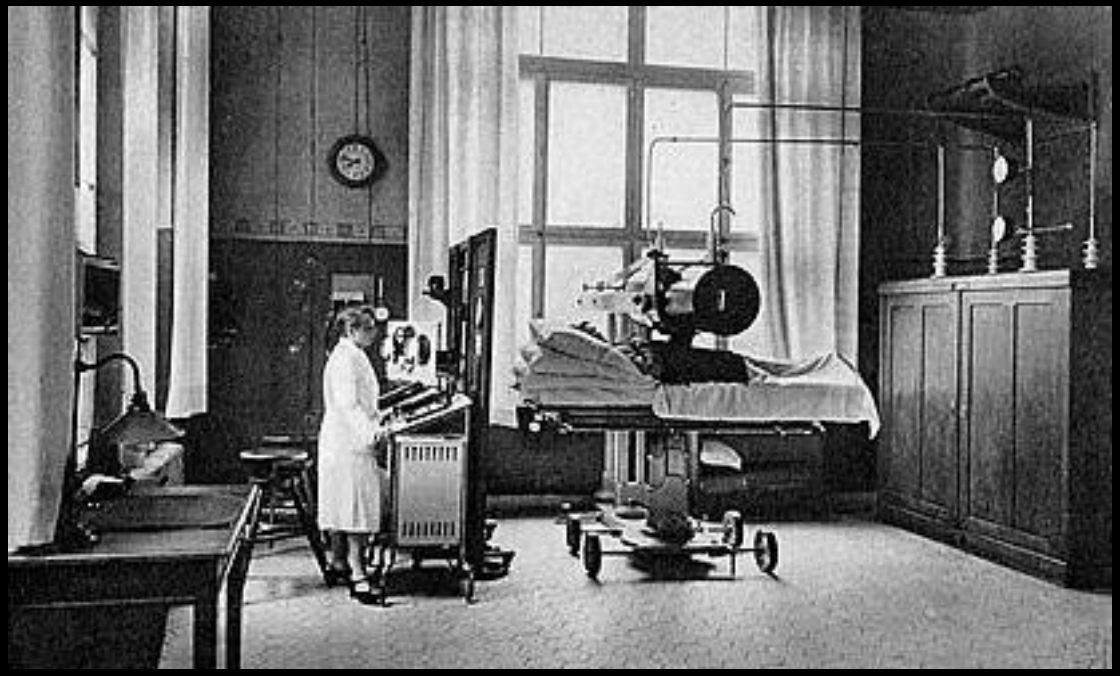
Brown, Brenner & Carlson, 2013

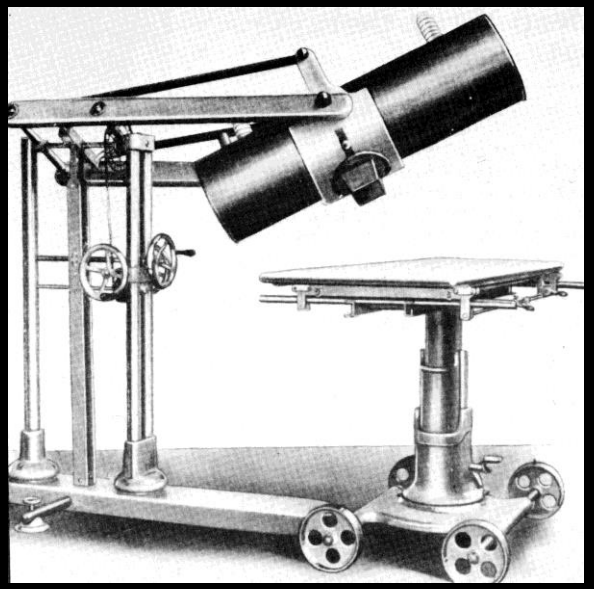
Stereotactic Radiotherapy

- To optimize SRT we need to understand how it is working….
- What are the biological principles underlying the clinical response to SRT?

What can we learn from history?

From 1900 to ~1920 radiotherapeutic practice was dominated by the German Erlangen School

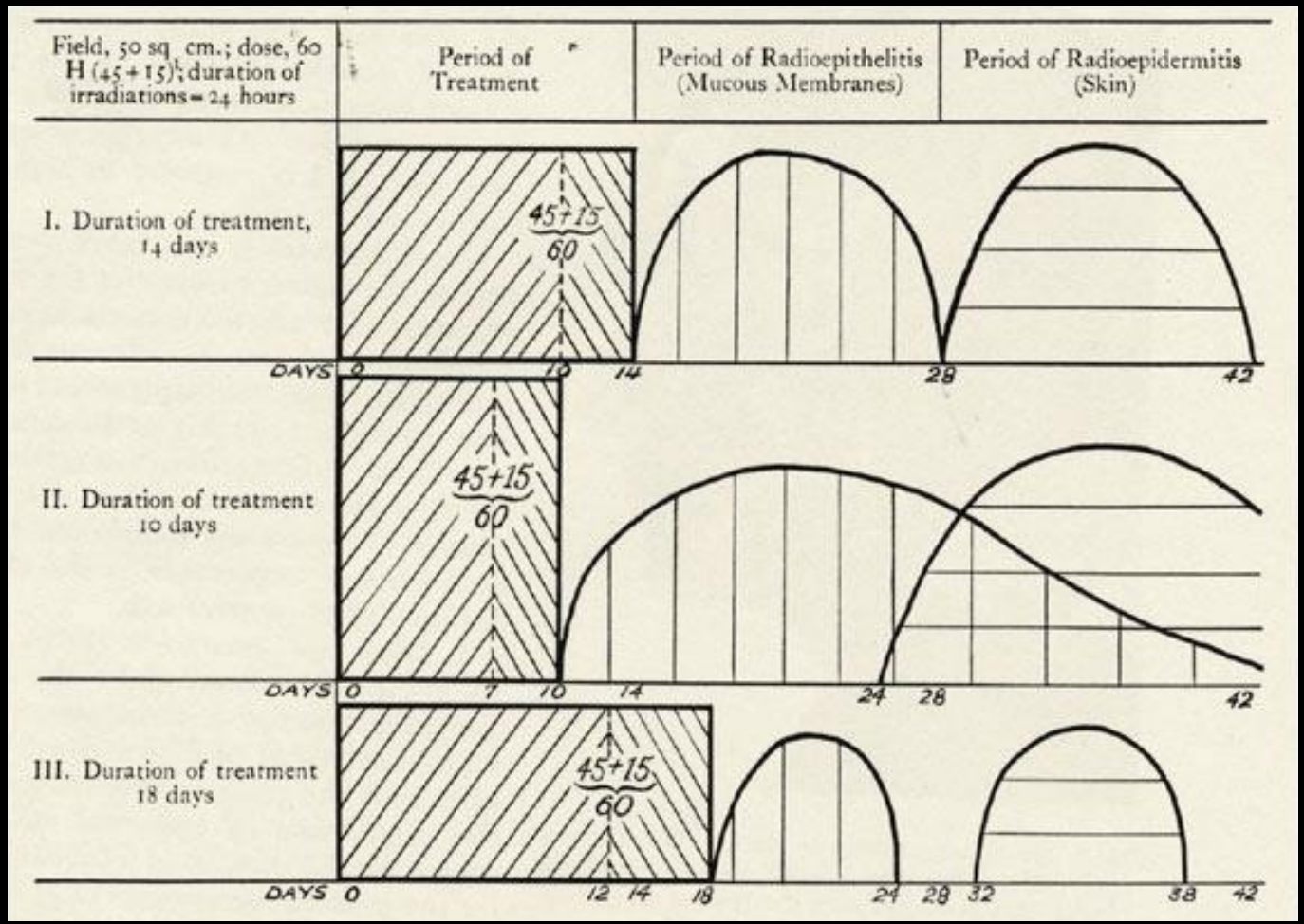




The Erlangen school advocated the use of a single large dose

1930s at the Institute Curie: The first systematic clinical studies on the effects of treatment duration

Henri Coutard



Coutard 1932

First long-term (5 year) follow-up of treatment outcome after fractionated RT

Henri Coutard

	5-Year Survival
Tonsillar region	18% (6 / 33)
Hypopharynx	10% (7 / 69)
Larynx	21% (13 / 60)

Far better than achieved by the German School!

Coutard 1932

Over the next 50 years, the use of fractionation in RT was axiomatic, and the question was how to optimize the fractionation…

What determines the optimal fractionation scheme for RT?

The Four R's

- ✓ **Repair**
- ✓ **Reoxygenation**
- ✓ **Repopulation**
- ✓ **Redistribution**

Predicting Radiotherapeutic Response….

The standard view around the year 2000…

1. Tumor control is related primarily to direct radiation killing of tumor clonogens
2. Radiation killing of tumor clonogens is reasonably well understood, and can be described by the mechanistically-based linear-quadratic (LQ) model
3. LQ models have been reasonably successful in designing new fractionation protocols

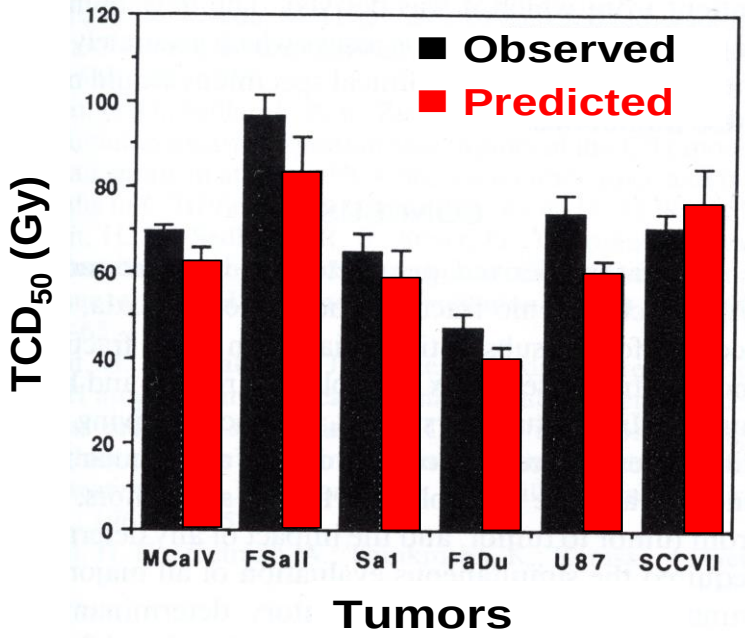
There have been many laboratory studies to test the standard model, that tumor control is related primarily to direct radiation killing of tumor clonogens

1. Measure radiation-induced tumor cell killing *in vitro*
2. Use the results to predict tumor control probability *in vivo*

Similar studies…

- ✓ Reinhold & De Bree 1968
- ✓ Barensen & Broerse 1969
- ✓ Rofstad 1989

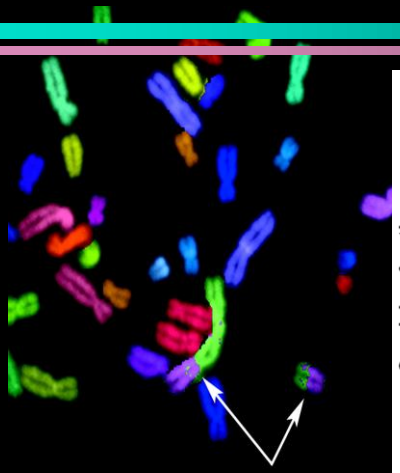
Predicted TCD_{50} based on in-vitro cell survival, vs. observed TCD_{50}

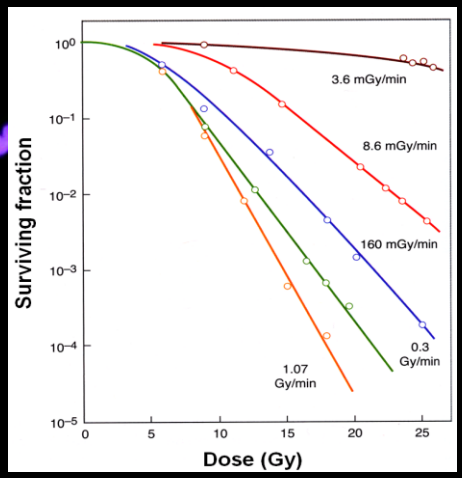


Gerweck, Zaidi & Zietman, 1994

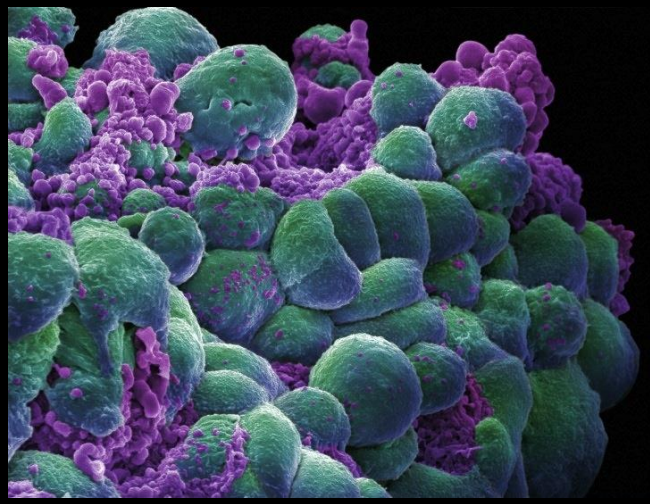
The Linear-Quadratic Model

- Started life as a mechanistic model of radiation-induced chromosome aberration and cell killing, at doses per fraction of a few Gy





- Its radiotherapeutic use was premised on the notion that tumor control is primarily determined by direct radiation-induced killing of tumor clonogens



The Linear-Quadratic Model

- Modern use of the LQ model includes heterogeneity - either intra-tumor or inter-tumor (or both)

Is the biology different at high doses per fraction?

Tumor Response to Radiotherapy Regulated by Endothelial Cell Apoptosis

Monica Garcia-Barros,[1] Francois Paris,[1] Carlos Cordon-Cardo,[2] David Lyden,[3] Shahin Rafii,[5] Adriana Haimovitz-Friedman,[4] Zvi Fuks,[4]* Richard Kolesnick[1]*†

About 50% of cancer patients receive radiation therapy. Here we investigated the hypothesis that tumor response to radiation is determined not only by tumor cell phenotype but also by microvascular sensitivity. MCA/129 fibrosarcomas and B16F1 melanomas grown in apoptosis-resistant *acid sphingomyelinase* (*asmase*)–deficient or *Bax*-deficient mice displayed markedly reduced baseline microvascular endothelial apoptosis and grew 200 to 400% faster than tumors on wild-type microvasculature. Thus, endothelial apoptosis is a homeostatic factor regulating angiogenesis-dependent tumor growth. Moreover, these tumors exhibited reduced endothelial apoptosis upon irradiation and, unlike tumors in wild-type mice, they were resistant to single-dose radiation up to 20 grays (Gy). These studies indicate that microvascular damage regulates tumor cell response to radiation at the clinically relevant dose range.

Ionizing radiation is a widely used therapy for solid tumors and is thought to act by directly targeting tumor clonogens, also known as stem cells (*1, 2*). Tumor curability is believed to be determined by the most resistant clonogen, because one surviving stem cell appears sufficient for reconstituting tumor growth (*3, 4*). This model appears relevant to several normal tissues, particularly those classified as rapid-turnover systems. For example, gastrointestinal (GI) damage is believed to result from direct interaction of radiation with the clonogenic compartment at the crypt of Lieberkühn base (*5, 6*). However, we recently reported that microvascular endothelial apoptosis is required for clonogenic cell dysfunction (*7*). GI damage was prevented when endothelial cell apoptosis was inhibited genetically by *asmase*$^{-/-}$ depletion or pharmacologically by intravenous basic fi-

"Very high doses per fraction of radiation might trigger an entirely different method of cell kill via an anti-angiogenic pathway involving endothelial apoptosis"

Do the same tumor control mechanisms apply at all doses per fraction?

- **Can we predict clinical results at very high doses per fraction based on clinical results at conventional doses per fraction, using standard well- established mechanistic models?**
- **Or do we need to add some special mechanism at high doses?**
- ***The standard mechanistic model – the linear quadratic model***

Several groups have extended the LQ model to account for "new" mechanisms at high doses / fraction

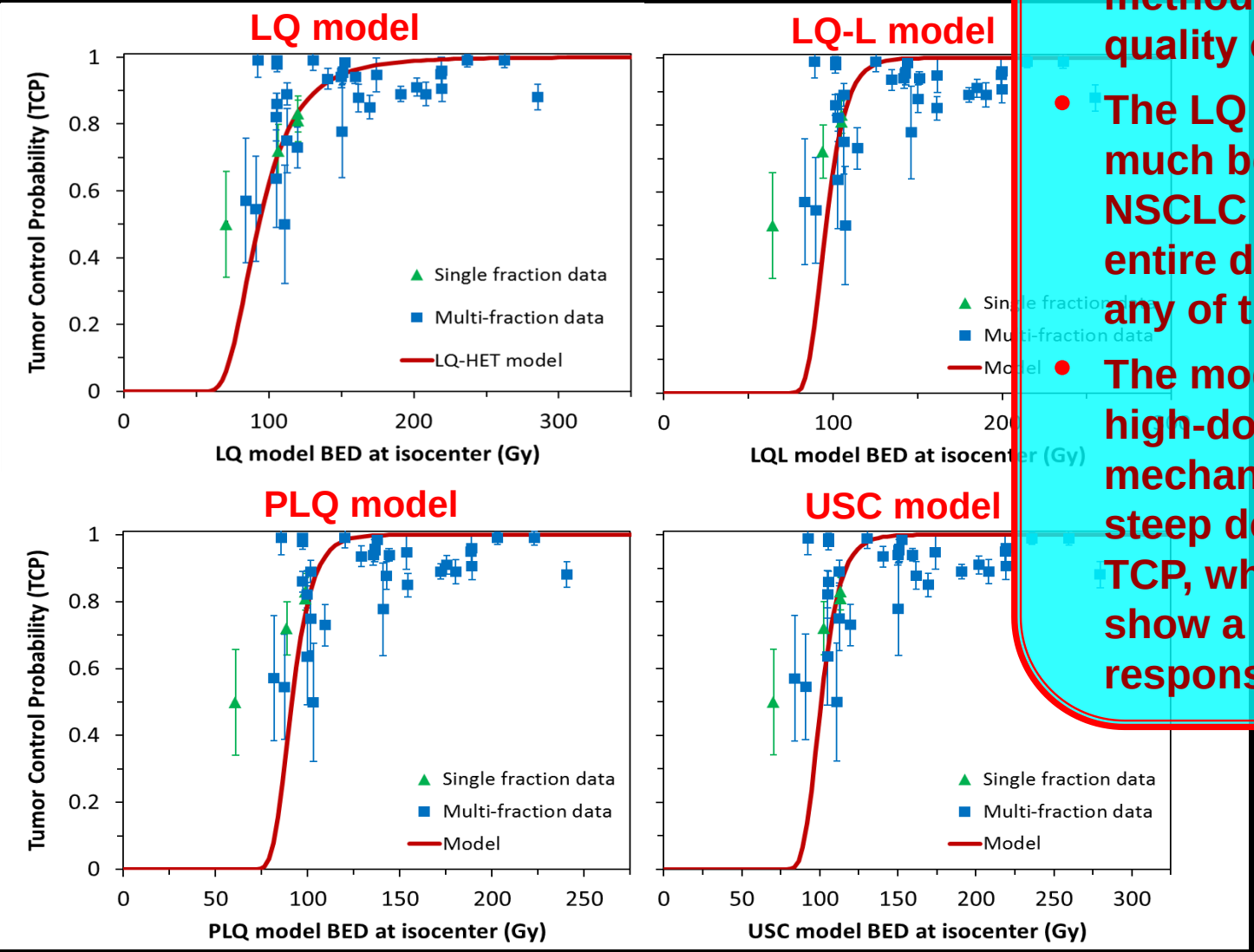
- **LQ-L model: straightens the dose response relation by adding a linear term at high doses per fraction**
- **PLQ model: gradually straightens the dose-response relation at high doses per fraction**
- **USC model: straightens the dose response relation starting at some high cutoff dose per fraction**

Let's test these models that have additional high dose / Fx terms, versus the standard LQ, using modern SRT clinical data

- SRT for NSCLC or brain metastases (Linac or Gamma Knife)
- Isocenter and peripheral tumor doses reported
- TCP reported for > 1 year follow-up
- Published SRT clinical data from last 15 years

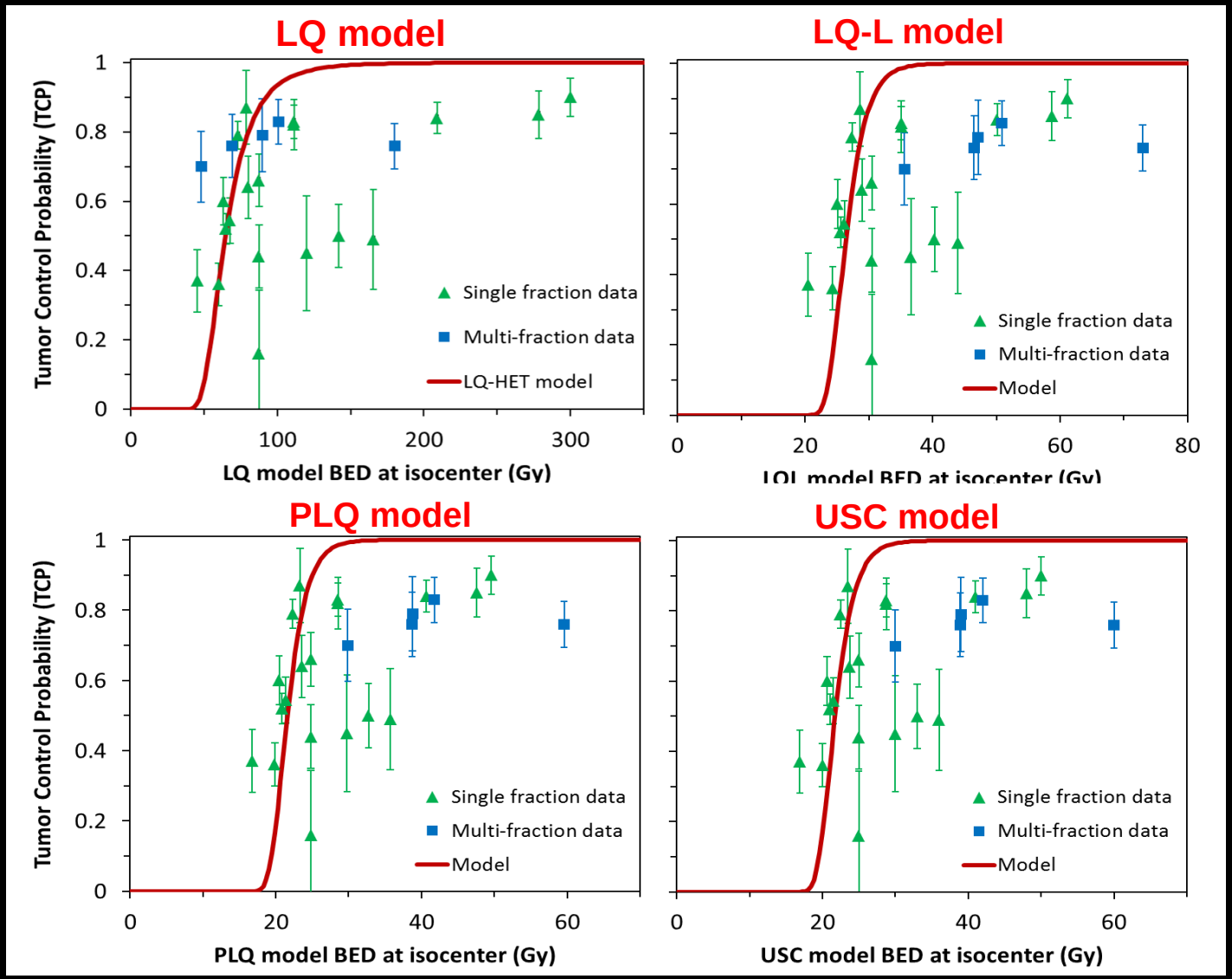
❖ 33 publications reporting on 2,965 patients

Model fits to early-stage NSCLC data

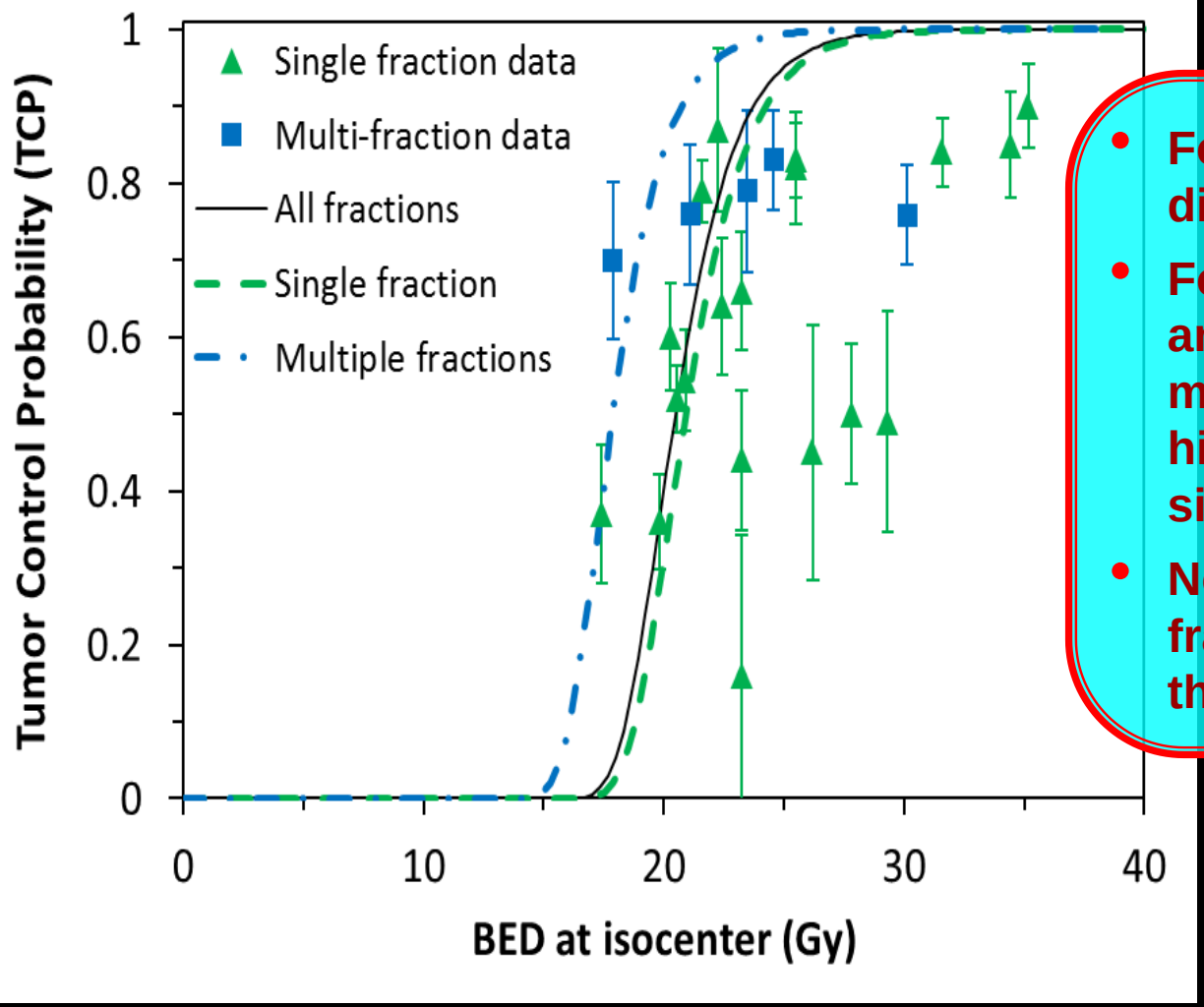


- Using the standard AICc method to compare quality of fit…
- The LQ model provided a much better fit to the NSCLC data over the entire dose range than did any of the other models
- The models that propose high-dose specific mechanisms predict a steep dose response for TCP, whereas the data show a quite shallow dose response

Model fits to brain metastases data

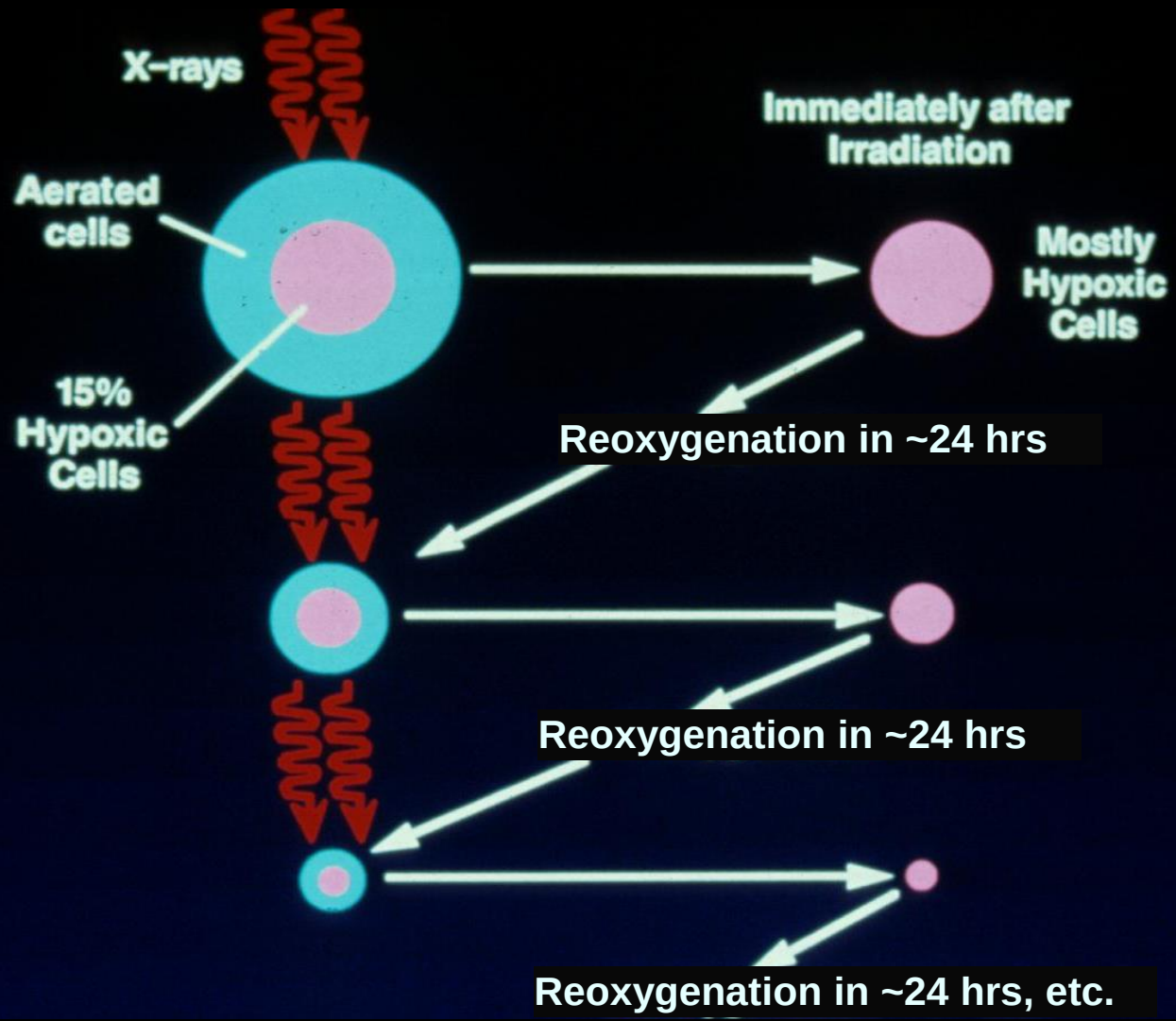


What about single-fractions vs. multiple fractions?

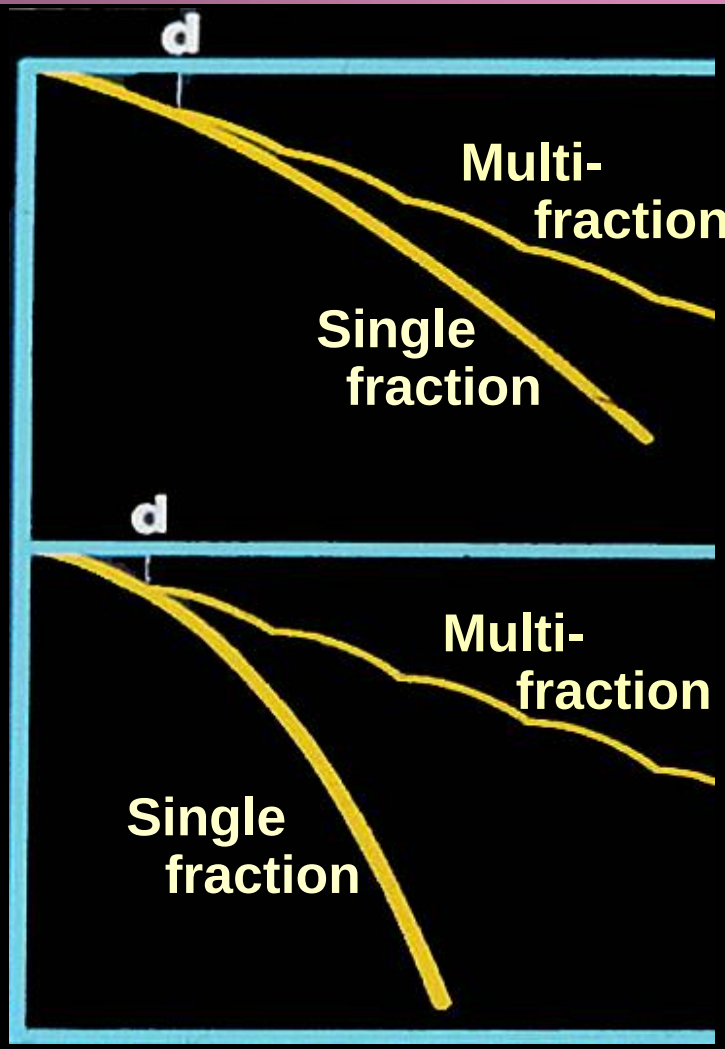


- For NSCLC we saw no discernable difference
- For brain metastases the analysis suggest that multiple fractions had higher effectiveness than single fractions
- No evidence that single fractions are more effective than multiple fractions

Hypoxia / Reoxygenation
One of the main reasons we fractionate



The other main reason we fractionate: Differential response of tumor control vs. late effects to changes in fractionation



TUMOR

- Less sensitive to changes in protraction
  - Quantified by large α/β ratio (≥10 Gy)

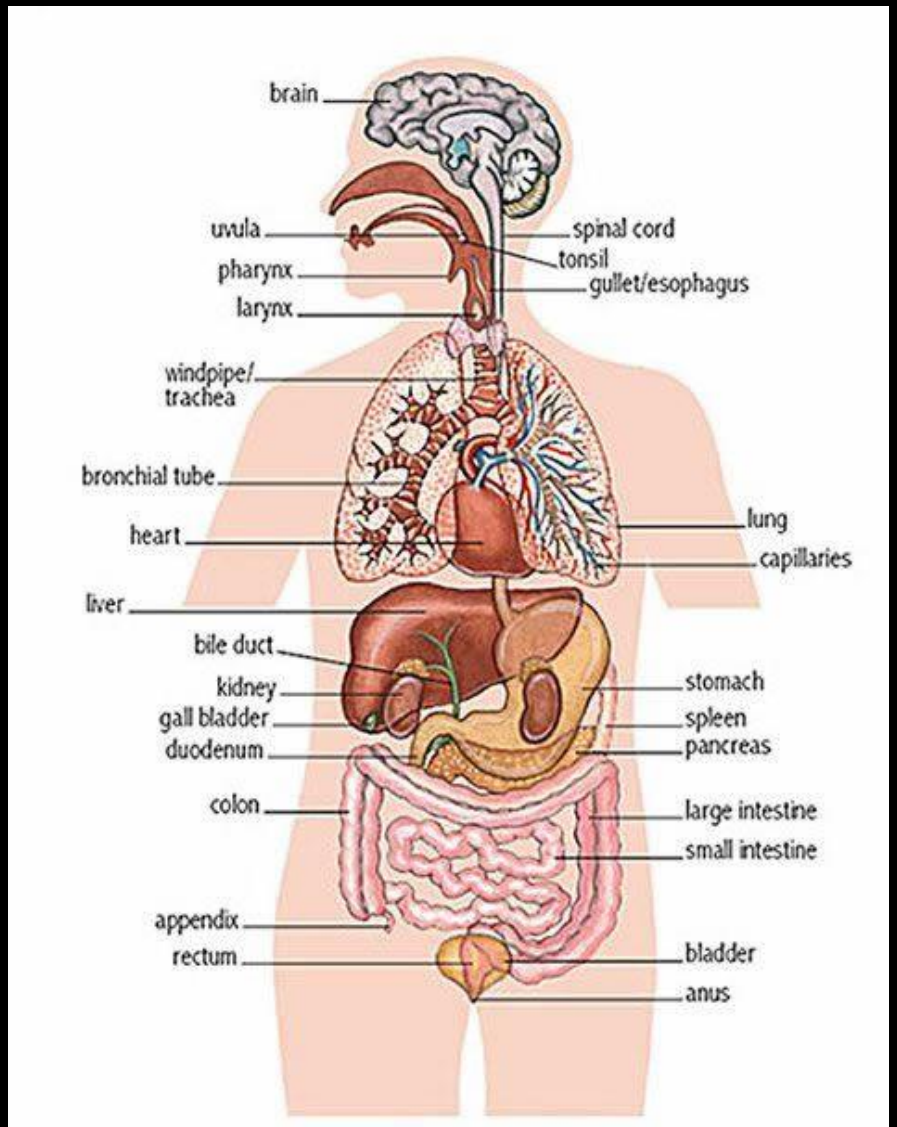
LATE-RESPONDING NORMAL TISSUE

- More sensitive to changes in protraction
  - Quantified by small α/β ratio (≤5 Gy)

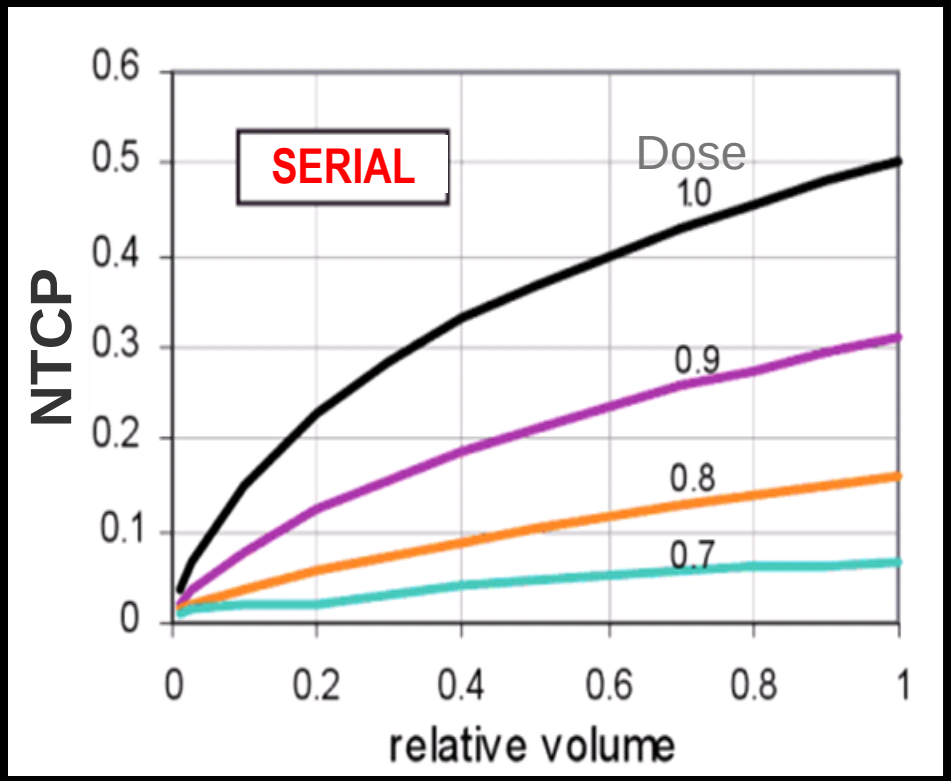
Stereotactic Radiotherapy: The Bottom Line

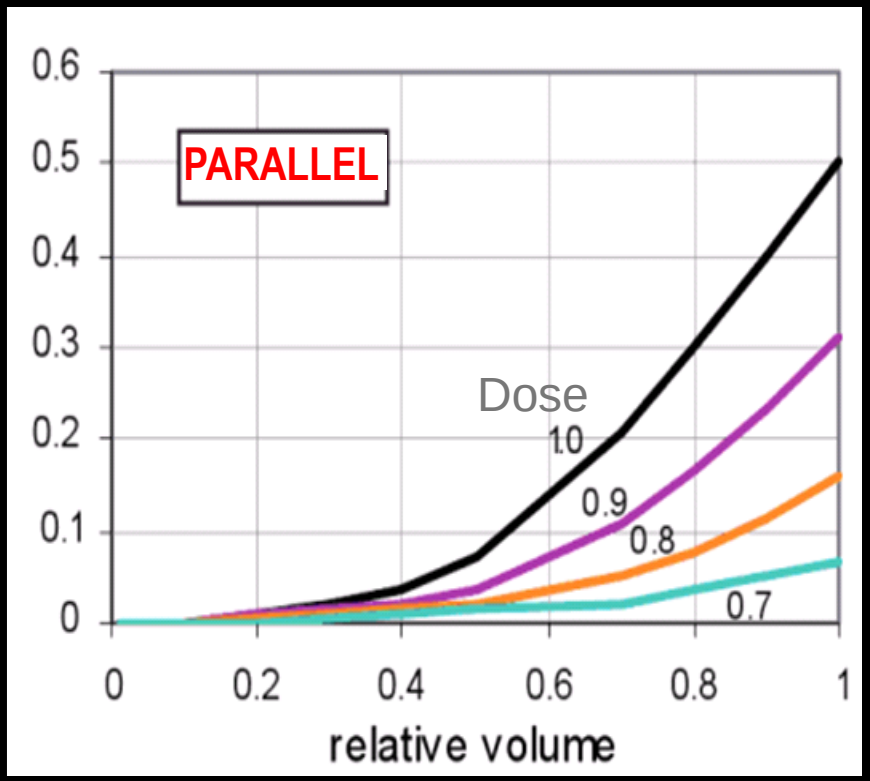
- SRT has had impressive success in treating some malignancies, particular in the lung and brain
  - The fundamental reason for these impressive results is that one can significantly increase the BED, because of the superb dose distributions that can be obtained with stereotactic RT
  - There is good evidence that the same mechanisms are producing tumor control at high doses per fraction as at conventional doses per fraction

SRT is successful for the lung and for brain mets – can we infer that it will be successful at other sites?



How much we need to worry about the effects of high doses per fraction on normal tissue will depend very much on whether the normal tissue is a serial or a parallel organ





e.g., Bladder, rectum, spinal cord

e.g., lung, brain, kidney

Goitein 2008

Conclusions (1)

- Formalisms introducing unique mechanisms at high doses, provide a worse fit to the clinical SRT data, compared with the LQ which assumes the same mechanisms at all doses

- There may be unique biological mechanisms at high doses, but even if there are, they do not significantly affect clinical tumor control at high doses / doses per fraction

- The reason SRT is so successful is that the great dose distributions allow significant dose escalation

Conclusions (2)

- We found no evidence that single-fraction SRT produces better tumor control that multiple fractions - and for brain mets fractionation is associated with improved tumor control

- Basic radiobiological principles tell us that we should always fractionate, though the parallel nature of lung and brain suggests that just a few fractions may be adequate for these sites

radiobiology radiobiology

Meet the new boss – same as the old boss!