The Radiobiology of Small Fraction Numbers

What determines optimal fractionation for conventional radiotherapy?

The Four R’s

- Repair
- Reoxygenation
- Repopulation
- Redistribution
DNA repair results in reduced cell killing when a treatment is fractionated.

Different types of tissue respond quantitatively differently to changes in fractionation.

So why do we fractionate?

- Late-responding normal tissues are more sensitive to changes in fractionation (small $\alpha/\beta$) than are early-responding tissues such as tumors (large $\alpha/\beta$).
- So fractionation spares late-responding tissues compared to most tumors.
A basis for these $\alpha/\beta$ differences

- *In vitro:*
  - non-cycling cells are associated with low $\alpha/\beta$
  - cycling cells are associated with high $\alpha/\beta$

Tumor:
Cycling cells: High $\alpha/\beta$

Late-responding normal tissue:
Few cycling cells: Low $\alpha/\beta$

Hypoxia / Reoxygenation: The other reason we fractionate

Fractionation results in *reoxygenation*

Reoxygenation in ~24 hrs, etc.
Hypoxia and malignancies

- Almost all malignant tumors, even a few mm in diameter, contain hypoxic cells
- A malignant tumor containing even a small hypoxic fraction would require an exceedingly high single-fraction dose for sterilization
- Therefore fractionation appears highly advantageous when attempting to cure malignant tumors

Accelerated Repopulation

As a tumor shrinks, surviving clonogens proliferate at an accelerated rate

So... for external beam RT of tumors...

- Must fractionate treatment
  - to overcome hypoxia
  - for differential response with late effects
- Must prolong treatment
  - to limit early sequellae
- Would like to shorten treatment
  - to prevent accelerated repopulation
For stereotactic RT of malignant tumors:

- Must fractionate treatment
  - to overcome hypoxia
  - for differential response with late effects
- Must prolong treatment
  - to limit early sequelae
- Would like to shorten treatment
  - to prevent accelerated repopulation

Is the biology different at high doses per fraction?

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

Is the standard model (tumor control related primarily to radiation killing of tumor clonogens) inapplicable at high doses?

“The single-fraction dose to inactivate experimental tumors is well predicted by measured clonogenic fraction and in-vitro radiation-induced cell survival”
Other papers showing correlations between in vitro tumor-cell radiosensitivity and in vivo tumor control at high single doses / fraction

“Ablative” Radiotherapy:
A different dominant mechanism for tumor control at high doses per fraction?

- The LQ model fails to predict high dose / Fx tumor control … “so some new biology must be going on”
- The LQ model will certainly fail at very high single doses
- But this doesn’t imply that the standard model (tumor control related primarily to radiation killing of tumor clonogens) is wrong
- Nor does it contradict the rationale that fractionation will improve outcome after RT for tumors

Fractionation for malignant tumors

All malignant tumors, small or large, slow or fast growing, sensitive or resistant, will be more effectively treated with fractionation than with a single fraction
Stereotactic radiosurgery / ablative RT

The Bottom Line

- Stereotactic radiosurgery and SABR have had impressive success in treating some malignancies, particularly in the brain and lung
  - But, for any given malignancy, better results should be obtained with fractionation
  - There is no need for conventional fractionation, 5-10 fractions is optimal
- For vascular disease and benign tumors, fractionation may only be needed if the lesions are large

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2. Hypofractionated radiotherapy

In most RT scenarios, we fractionate to take advantage of the differential $\alpha/\beta$ ratio between tumor and late responding normal tissue

- non-cycling cells are associated with low $\alpha/\beta$
- cycling cells are associated with high $\alpha/\beta$
Prostate Cancer

- Prostate tumors are not typical of most tumors, containing far fewer cycling cells
- Do prostate tumors have the typical differential response to fractionation for tumor control relative to late-responding tissues?
- What is an appropriate $\alpha/\beta$ value for prostate tumors?

Based on clinical data from implant and external beam data:

$\alpha/\beta$ for prostate cancer

= 1.5 Gy  [95% CI: 0.8 - 2.2]

“comparable with typical $\alpha/\beta$ for late-responding normal tissues”

Brenner and Hall 1999

If the $\alpha/\beta$ ratio for prostate cancer is comparable to that for normal tissue:

- We lose one of the fundamental rationales for using many fractions or using low dose rate
- So hypo-fractionation or HDR rather than conventional fractionation or LDR become potential options for prostate RT
Since the 1999 estimate of $\alpha/\beta$, there have been more than 70 further papers in the literature relating to $\alpha/\beta$ values for prostate.

Two recent large studies of $\alpha/\beta$ for prostate:

- 5,969 patients: $\alpha/\beta = 1.4$ Gy (95% CI 0.9-2.2)
- 5,093 patients: $\alpha/\beta = 1.55$ Gy (95% CI 0.46-4.52)

If $\alpha/\beta$ for prostate cancer is about the same as for surrounding late-responding normal tissue,

- Less rationale for using many fractions or LDR
- Fewer fractions at the right dose would give
  1. The same tumor control and late sequelae as current regimens
  2. Patient convenience
  3. Financial / resource advantages
Our findings suggest that late toxicity is equivalent between the two treatment groups, and that the hypofractionated schedule used in this trial is superior to the conventional fractionation in terms of FFBF.

A therapeutic advantage of the hypofractionated compared to the conventional dose schedule for RT of prostate cancer was evident at 90 months in the present study.

Is this mechanistically-based argument for hypofractionation unique to prostate?

"Prostate tumors are not typical of most tumors, containing far fewer cycling cells"

- This does not apply to most other tumor types
- Perhaps it applies to melanoma?
Melanoma is a slow-growing tumor with few dividing cells

Clinical radiotherapy of malignant melanoma
Department: Radiation Oncology, Mayo Clinic, Arizona, Arizona, Arizona, Arizona, Arizona, Arizona, Arizona
Upon submission: 14 March 2007

α/β = 0.57 (95% CI: 1.07 – 2.5)

Successful hypofractionation for choroidal melanoma

Is this mechanistically-based argument for hypofractionation unique to prostate?

"Prostate tumors are not typical of most tumors, containing far fewer cycling cells"

- This does not apply to most other tumor types
- Perhaps it applies to melanoma?
- Perhaps it applies to some other early-stage tumors?
What about early-stage breast cancer?

Much interest in accelerated partial breast irradiation for early-stage breast cancer

NSABP B-39/RTSG 0413: 3.4 or 3.85 x 10 fractions BID

2,236 patients α/β = 4.6 Gy (95% CI 1.1-8.1)

What about lung?

α/β = 8.2 Gy (95% CI 7.0-9.4)

How much you need to worry about the effects of hypofractionation on normal tissue will depend very much on whether the normal tissue is a serial or a parallel organ

e.g., lungs, kidneys

e.g., brain, bladder, rectum, spinal cord

Goitein 2008
When the goal is to optimize the therapeutic ratio between tumor control and late complications, basic radiobiological principles tell us that we should fractionate.

- Prostate is a mechanistically understood exception.
- Melanoma and possibly early breast cancer may likewise be exceptions.
- No such radiobiological rationale appears to exist for lung hypofractionation, but the parallel nature of normal lung tissue may well permit less fractionation than at other sites, when the irradiated volume is small.

This speaker does not think there is persuasive evidence for “new radiobiology” at high doses per fraction.