AbstractID: 4400 Title: Optimizing Fractionation or Dose Rate for Prostate Cancer Radiotherapy

For most tumors, increasing the number of fractions / lowering the dose rate, results in an improved therapeutic ratio between tumor control and late sequelae. Why might this not be true for prostate cancer?

1. The basis for the difference in fractionation response of tumors and normal tissues is generally related to the fact that there is a larger proportion of cycling cells in tumors.
2. Back in 1999, various authors reasoned that prostate tumors might not respond to changes in fractionation in the same way as other cancers, as they contain smaller fractions of cycling cells – rather that they might respond like a late-responding normal tissue. If so, much of the rationale for using many fractions, or using LDR, would disappear.
3. A first estimate of α/β for prostate cancer was made in 1999, by comparing results from external beam RT (EBRT) with those from brachytherapy. The estimate was 1.5 Gy [0.8–2.2 Gy], similar to α/β values for late-responding normal tissues (~3 Gy).
4. If the α/β value for prostate cancer is indeed similar to that for the surrounding late-responding normal tissue, one could use many fewer fractions, or HDR, and yet, by choosing the right dose, have
   - ✓ Comparable tumor control and late sequelae to conventional fractionation
   - ✓ Reduced early urinary sequelae
   - ✓ Patient convenience
   - ✓ Financial / resource advantages
   - ✓ Potential for biologically-based individualized treatments
5. Various other groups used the same approach (comparing EBRT with brachytherapy) for estimating the α/β ratio, and got similar results. However the weakness inherent in this comparative approach (different dose distributions, different treatment times, different dose rates, different RBEs, etc) has led to much controversy.
6. Subsequently an analysis was performed which avoided many of these pitfalls, in which EBRT + a 2-fraction HDR boost was compared with EBRT + a 3-fraction boost, all done with the same technique at the same institution. The result was 1.2 Gy [0.03–4.1 Gy], again comparable with α/β values for late-responding normal tissues (~3 Gy), and confirming that hypo-fractionation or HDR are promising subjects for clinical trials of prostate cancer RT.
7. The arguments presented above really relate to the α/β value for prostate cancer *in relation to that for the relevant late-responding normal tissue.* Just what is the appropriate α/β value for late rectal complications? Evidence from animal studies is that $\alpha/\beta>4$ Gy for late rectal sequelae. This high value for late rectal damage is now supported by clinical results, which also suggest that much late rectal injury is actually consequential of early effects, and thus a high α/β value is not unreasonable.
8. If, then, the α/β value for prostate cancer is actually *less than* that for the surrounding late-responding normal tissue, now hypofractionation or LDR, at the appropriate dose, would yield
   - ✓ increased tumor control for a given level of late complications, *or*
   - ✓ decreased late complications for a given level of tumor control.

9. The 2005 bottom line is that the long-term clinical results to date for prostate hypofractionation do not give any indication of increased late sequelae compared with conventional fractionation – despite the fact that most of these results come from the pre-IMRT era.

Educational Objectives:

There is a great deal of controversy in the literature about the most appropriate value of the α/β ratio for prostate cancer. Hopefully the audience will leave with a better understanding of 1) why this is, and the 2) what is its significance in terms of optimizing prostate cancer radiotherapy?