

## EDITORIAL

# HYPOFRACTIONATION FOR PROSTATE CANCER RADIOTHERAPY—WHAT ARE THE ISSUES?

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You can't open a radiation journal these days without someone debating the  $\alpha/\beta$  ratio for prostate cancer (1–17). Another interesting contribution appears in this edition of the *IJROBP* (18). Why the debate? What are the issues? What might they mean for prostate cancer radiotherapy? In brief, the arguments have gone as follows:

1. One of the main motivations for delivering a treatment in many fractions is that late sequelae are generally more sensitive than early effects (such as tumor control) to changes in fractionation, so increasing the number of fractions generally spares late-responding tissues more than the tumor. This can be quantified in terms of the  $\alpha/\beta$  ratio:
  - A small  $\alpha/\beta$  ratio (2–4 Gy), typical of late sequelae, means large sensitivity to changes in fractionation.
  - A large  $\alpha/\beta$  ratio (> 8 Gy), typical of tumor control, means low sensitivity to changes in fractionation.
2. It is generally assumed that the mechanistic basis for the different fractionation response of tumors and late-responding normal tissues relates to the larger proportion of cycling cells in tumors. However, prostate tumors contain unusually small fractions of cycling cells (19), so back in 1999, Brenner and Hall (1) and Duchesne and Peters (2) reasoned that prostate tumors might not respond to changes in fractionation in the same way as other cancers. Both papers hypothesized that prostate tumors might respond to changes in fractionation more like a late-responding normal tissue. In mathematical terms, the suggestion was that the  $\alpha/\beta$  ratio for prostate cancer might be low, comparable to that for late sequelae. If so, much of the rationale for using many fractions, or using low dose rate, would disappear for prostate radiotherapy.
3. A first estimate of  $\alpha/\beta$  for prostate cancer was made in 1999 (1) by comparing results from external beam radiotherapy (EBRT) with those from brachytherapy (BT). Consistent with the theoretical hypotheses (see above), the estimated value of  $\alpha/\beta$  was 1.5 Gy (95% confidence interval: 0.8–2.2 Gy), comparable to  $\alpha/\beta$  values for late-responding normal tissues, and much smaller than those for most tumors.
4. The problem with this estimate (1) of the  $\alpha/\beta$  value for prostate, and almost all subsequent estimates (3–11, 13–18) is that they involve comparing or equating EBRT results with BT results. There are many pertinent differences between EBRT and BT (different dose distributions, different relative biological effectiveness, different overall times, different institutions, different PSA distributions, hypoxia), any or all of which could bias the  $\alpha/\beta$  estimate. Much of the debate has centered around the significance of these biases, and how to take them into account. Despite these problems, there does seem to be consensus among most of the analyses that have taken this approach, that the  $\alpha/\beta$  value for prostate cancer is indeed quite low, probably in the 1 to 4 Gy range (1, 2, 4–11, 13–16, 18), which is similar to the values for most late-responding tissues.
5. One analysis has also been performed (12) that avoided many, though not all, of the potential biases involved in comparing EBRT and BT. Here, EBRT + a 2-fraction high-dose-rate (HDR) BT boost was compared with EBRT + a 3-fraction HDR boost, all done with the same technique at the same institution. The resulting estimated  $\alpha/\beta$  ratio for prostate cancer was 1.2 Gy (95% confidence interval: 0.03–4.1 Gy), again comparable with  $\alpha/\beta$  values for late-responding normal tissues.
6. If the  $\alpha/\beta$  value for prostate cancer is indeed similar to that for the surrounding late-responding normal tissue, one could use fewer fractions (i.e., hypofractionate) or HDR and yet, by choosing the right dose, produce
  - Comparable tumor control and late sequelae to conventional fractionation/protraction
  - Reduced early urinary sequelae (5)
  - Patient convenience
  - Financial/resource advantages

- Potential for biologically based individualized treatments
7. The arguments presented above really relate to the  $\alpha/\beta$  value for prostate cancer *in relation to the  $\alpha/\beta$  value for the relevant late-responding normal tissue*. Just what is the appropriate  $\alpha/\beta$  value for late rectal complications? Extensive evidence from animal studies (20–26) suggests that for late rectal sequelae,  $\alpha/\beta$  is  $>4$  Gy—i.e., it is higher than for most other late sequelae. Although one must always be cautious of extrapolations from rodents to man, this higher value for late rectal damage is supported by clinical results that suggest that much late rectal injury is actually consequential of early effects (27–29), and thus a high  $\alpha/\beta$  value for late rectal damage is not unreasonable.
  8. The potentially high value of  $\alpha/\beta$  for late rectal complications (together with the low value of  $\alpha/\beta$  for prostate cancer) has two consequences:
    - It becomes less likely that the  $\alpha/\beta$  value for prostate cancer is greater than that for late rectal complications—the situation where hypofractionation or HDR would be suboptimal.
    - It becomes more likely that the  $\alpha/\beta$  value for prostate cancer is actually less than that for late rectal complications—the situation where hypofractionation or HDR would be optimal.
  9. If, then, the  $\alpha/\beta$  value for prostate cancer is actually less than that for the surrounding late-responding normal tissue, now hypofractionation or HDR, at the appropriate dose, would also yield
    - Increased tumor control for a given level of late complications, *or*
    - Decreased late complications for a given level of tumor control.

The implication of these considerations is that either hypofractionated EBRT or HDR BT, at the appropriate dose, has the potential to yield improved clinical results for prostate cancer compared with conventional fractionation or low dose rate.

Hypofractionation in a curative setting, even when the dose is appropriately lowered, is a *prima facie* unsettling idea, particularly because the literature has many examples of large dose per fraction resulting in unacceptable late effects (30–33). None of these reports are for prostate cancer, however. To the contrary, there is a report of 22 years' experience (1962–84)



Sir Laurence Olivier as Hamlet, 1948. Photo courtesy of the Everett Collection, Inc.

with 232 prostate cancer patients treated in London with a  $6 \times 6$  Gy protocol (34): Even with the much poorer dose distributions than are now routine, minimal long-term urologic or bowel morbidity was reported. There is also extensive experience from the Manchester school of treating prostate cancer with a  $15 \times 3.1$  Gy protocol, both before and since the era of conformal therapy, again with satisfactory results and without excess late sequelae (7). As an aside, Sir Laurence Olivier was treated in 1967 for prostate cancer with a hypofractionated 6-fraction protocol, reported no major sequelae, and lived a further 22 years (35).

For prostate cancer (and these considerations are unique to prostate cancer), hypofractionation or HDR deserves serious consideration. The London and Manchester experiences, together with the analyses summarized here, suggest that conservatively designed clinical trials (36), with a minimum of about 10 fractions, would be low-potential-risk/high-potential-gain studies.

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