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EDITORIAL

TOWARD OPTIMAL EXTERNAL-BEAM FRACTIONATION FOR PROSTATE CANCER

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As an increasing number of men are undergoing radiotherapy for prostate cancer, and at younger ages, it is becoming more and more important to define optimal radiotherapeutic regimens to treat the disease. A great deal of effort has rightly been put into improving dose distributions, through three-dimensional conformal radiotherapy and intensity-modulated radiotherapy (1), as well as through brachytherapy (2).

Less attention has, however, been paid to fraction size. By and large, most protocols for external-beam treatment of prostate cancer have adhered to 1.8–2 Gy fractions, although results with hyperfractionation (3) and hypofractionation (4) have recently been reported. In part, this lack of attention to fraction size can be attributed to the comparatively slow-growing nature of prostate tumors (5), implying that overall treatment time is unlikely to be a critical factor.

Fractionation plays another key role in radiotherapy, however, typically providing a therapeutic advantage between tumor control and late sequelae. Generally speaking, this therapeutic advantage comes by fractionating as much as possible, in that fractionation spares late-responding normal tissues more than tumors, because tumors normally respond as early-responding tissue (6)—in the language of the linear–quadratic model, fractionation spares tissues with a low α/β ratio (late-responding tissues) more than it does tissues with a high α/β ratio (early-responding tissues typical of most tumors).

As we have known for many years, however, prostate tumors are highly atypical of most malignancies. Most prostate tumors consist of an extremely low proportion of cycling cells (5, 7), but with many dormant cells waiting to be recruited into cycle if stimulated. So, from the perspective of radiation sterilization, our major task is probably to sterilize noncycling, as well as cycling, prostate cells. In such a situation, the prostate would be expected to respond to changes in fractionation as a late-responding tissue, in which case the rationale for increased fractionation would disappear.

In fact, a recent editorial by Duchesne and Peters (8) suggested just this in the context of brachytherapy—that high-dose-rate (HDR) brachytherapy of the prostate might be as efficacious as low-dose-rate, because the tumor and the surrounding late-responding tissue would respond in the same way to changes in fractionation. These concepts have recently been quantified by estimating an average α/β value for prostate tumors directly from clinical data, and the value obtained was indeed typical of a late-responding tissue, about 1.5 Gy (9, 10).

The same conclusion can be drawn from a recent report by Martinez *et al.* (11) on HDR brachytherapy boosts after external-beam treatment for unfavorable prostate cancers. HDR brachytherapy was given either as three 6-Gy treatments or two 9-Gy treatments. An α/β value of 10 Gy for the prostate tumors would result in essentially identical tumor control for these two treatments, whereas an α/β value of 1.5 Gy would result in significantly increased tumor control for the 2×9 Gy compared to the 3×6 Gy boost. In fact, a significantly increased tumor control was seen with the 2×9 Gy boost (96% vs. 70% at 3 years, $p = 0.002$), consistent with a low α/β value.

What does this mean for external-beam radiotherapy of the prostate? Essentially what we have is a late-responding target tissue (the prostate tumor), adjacent to which are the bladder and rectum, both of which can exhibit early and late morbidity. Thus, moving to a smaller number of larger fractions (hypofractionation) should affect tumor control and late morbidity in the same way, so, assuming the prescribed dose is decreased appropriately, no change in tumor control or late sequelae rates would be expected. In other word, more convenient schedules, consisting of fewer larger fractions, should achieve equal tumor control with no increase in late effects.

As an added bonus, because early sequelae are less responsive to changes in fractionation, for a given level of tumor control and late sequelae, one would expect less early morbidity from a hypofractionated regimen. Although early sequelae are not generally dose limiting, a

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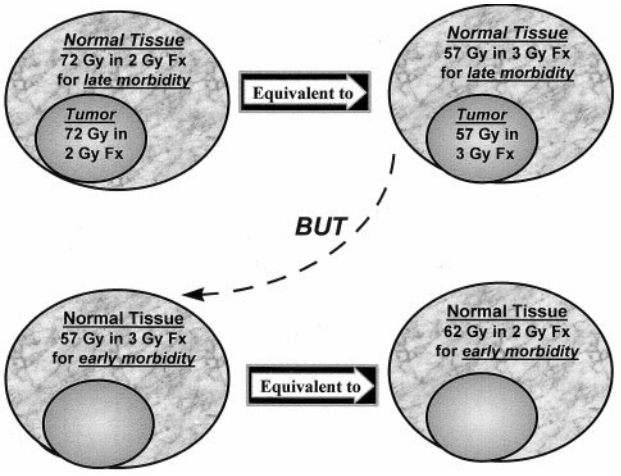

Fig. 1. Schematic of estimated equivalence between a "standard" 36 × 2 Gy (72 Gy) external-beam prostate cancer treatment, and a hypofractionated 19 × 3 Gy (57 Gy) treatment for a prostate tumor and adjacent normal tissue. Equivalency is expected both for tumor control and for late sequelae. However for early sequelae, the hypofractionated treatment is equivalent to 62 Gy in 2-Gy fractions which, compared to the original 72 Gy in 2-Gy fractions, means that the hypofractionated schedule should result in considerable sparing of early morbidity. Calculations were performed with α/β values of 1.5 Gy (prostate tumor), 1.5 Gy (late-responding normal tissue), and 10 Gy (early-responding normal tissue), though the principles would remain valid as long as the prostate tumor has an α/β value comparable to late-responding normal tissue (9, 10).

significant reduction in early genitourinary and gastrointestinal complications would certainly be welcome.

These notions are illustrated in Fig. 1 for a "standard" prostate cancer external-beam regimen of 72 Gy in 36 2-Gy fractions. We assume typical α/β values for late-responding tissues (i.e., for the prostate, and for late morbidity) and a typical α/β value for early morbidity. Then 72 Gy in 2-Gy fractions would be equivalent, both in tumor control and late morbidity, to about 57 Gy given in 3-Gy fractions. However, if we did give 57 Gy in 3-Gy fractions, this would be equivalent, in terms of early morbidity, to 62 Gy in 2-Gy fractions. So the net result of moving from 72 Gy in 2-Gy fractions to 54 Gy in 3-Gy fractions would be an unchanged level of tumor control and late sequelae, but a considerable reduction in early sequelae—as well as a treatment regimen that is more convenient for the patient, and less resource intensive for the clinic.

While a move to larger fractions may initially appear contrarian, in fact highly hypofractionated schemes (such as 6 × 6 Gy—equivalent, using the parameters in Fig. 1, to about 78 Gy in 2-Gy fractions) have been used in Britain for many years to treat prostate cancer, without excessive late sequelae (12). Early results from a hypofractionated intensity-modulated radiotherapy regimen for prostate cancer (mean dose, 75.3 Gy in 2.7-Gy fractions) were reported from the Cleveland Clinic in a recent issue of the Journal (4). Converted to 2-Gy fractions (using the parameters in Fig. 1), this regimen corresponds to about 90 Gy for tumor control and for late sequelae, and about 80 Gy for early sequelae; early results for acute toxicity were encouraging (4).

In summary while the advances made in the dose delivery of radiotherapy of prostate cancer have been very encouraging, improving treatments by tailoring site-specific fractionation patterns to the basic radiobiology also looks promising. Hypofractionation for prostate cancer appears to be (*1*) as efficacious as standard fractionation, (*2*) more convenient for the patient, both in terms of logistics and acute morbidity, as well as being (*3*) less resource intensive than standard fractionation.

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