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BIOLOGY CONTRIBUTION

FRACTIONATION AND PROTRACTION FOR RADIOTHERAPY OF PROSTATE CARCINOMA

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Purpose: To investigate whether current fractionation and brachytherapy protraction schemes for the treatment of prostatic cancer with radiation are optimal, or could be improved.
Methods and Materials: We analyzed two mature data sets on radiotherapeutic tumor control for prostate cancer, one using EBRT and the other permanent seed implants, to extract the sensitivity to changes in fractionation of prostatic tumors. The standard linear-quadratic model was used for the analysis.
Results: Prostatic cancers appear significantly more sensitive to changes in fractionation than most other cancers. The estimated α/β value is 1.5 Gy [0.8, 2.2]. This result is not too surprising as there is a documented relationship between cellular proliferative status and sensitivity to changes in fractionation, and prostatic tumors contain exceptionally low proportions of proliferating cells.
Conclusions: High dose rate (HDR) brachytherapy would be a highly appropriate modality for treating prostate cancer. Appropriately designed HDR brachytherapy regimens would be expected to be as efficacious as low dose rate, but with added advantages of logistic convenience and more reliable dose distributions. Similarly, external beam treatments for prostate cancer can be designed using larger doses per fraction; appropriately designed hypofractionation schemes would be expected to maintain current levels of tumor control and late sequelae, but with reduced acute morbidity, together with the logistic and financial advantages of fewer numbers of fractions.

Prostate cancer, Radiotherapy, HDR, Hypofractionation.

INTRODUCTION

Radiotherapy is one of the primary modalities for treating cancer of the prostate. About 30% of all prostate cancer patients who are treated with curative intent receive radiotherapy, amounting to about 80,000 individuals per year in the United States (1).

The most common radiotherapy technique for treating prostatic cancer is external beam radiotherapy (EBRT), now often delivered conformally to spare as much normal tissue as possible (2). In addition, with improved technology, there is renewed interest in brachytherapy treatments of prostatic cancer, using either temporary or permanent implants, and using either low or high dose rate (3).

While there has been considerable interest in optimizing the treatment dose through dose escalation studies (2, 4–8), rather less attention has been paid to optimizing the fractionation pattern (for EBRT) or the dose rate (for brachytherapy). In large part this is because, until now, the radiobiological parameters describing the response of the prostatic tumor to changes in fractionation have not been evaluated.

In order to estimate radiobiological parameters describing the response of the tumor to changes in fractionation, it is generally necessary to analyze clinical dose–response data involving a variety of different fractionation/protraction patterns. As we shall discuss, the patterns of current EBRT treatments for prostatic cancer do not allow such analyses, because the existing dose escalation studies have typically involved an almost uniform fractionation regimen. In addition, the extensive brachytherapy experience obtained over many years with ^{125}I permanent implants also does not permit quantitative studies of the effects of fractionation, because the dose rates are sufficiently low that the dose–effect relations reflect essentially complete repair of sublethal damage.

We suggest here that it is possible to extract the radiobiological parameters describing the response of the tumor to changes in fractionation (specifically, the α/β ratio in the linear-quadratic formalism), by analyzing both EBRT *and* brachytherapy data, even though neither singly can yield the appropriate information.

Interestingly, the value of the α/β parameter which is

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obtained from the current analysis of dose–prostate-specific antigen (PSA) failure relations is low, indicating a high sensitivity to fractionation, consistent with that of a late-responding normal tissue. This result is not entirely unexpected, in that it has long been conjectured that the difference in fractionation response between late-responding normal tissues and tumors is related to the proportion of target cells that are cycling (or, perhaps equivalently, the average cell-cycle time (9)), and prostatic tumors typically contain very low proportions of cycling cells.

If prostatic tumor cells do respond to fractionation as would a late-responding normal tissue, this would have important implications for treatment design. For example, the use of many (typically 35–40) small dose fractions in EBRT of the prostate would not be necessary, in that this is predicated on an expected differential response to fractionation between the tumor and the adjacent late-responding normal tissue; if the fractionation sensitivity is the same for the tumor and the surrounding late-responding normal tissue, much smaller numbers of fractions (with an appropriately reduced dose) would be expected to be at least as efficacious, but logistically and financially advantageous. Similarly for brachytherapy, high dose rate would be expected to be as efficacious as low dose rate, but with the added advantages of logistic convenience and potentially more reliable dose distributions.

METHODS AND MATERIALS

Formalism

We use standard models of tumor cure based on Poisson statistics (10). We define K to be the initial number of potential stem cells in the tumor, that is, cells that have the independent capacity to initiate tumor regrowth and, thus, biochemical failure. At a dose D, if the stem cell survival probability is S, the probability of avoiding biochemical failure (sometimes called freedom from biochemical failure [*FFBF*]) will be

$$FFBF = (1 - S)^K \approx exp(-SK), \quad (1)$$

where the survival probability is given by the linear-quadratic (LQ) formalism:

$$S = exp(-\alpha D - G\beta D^2). \quad (2)$$

Here α and β are the linear-quadratic parameters, and G is the Lea-Catcheside function describing the reduction in effect due to dose protraction (11). This factor G depends on the details of the temporal distribution of dose, as well as the rate of repair of sublethal damage. The mechanistic underpinning of the LQ formalism has been discussed elsewhere (12).

In Eq. 2, the linear (α) term is dose-protraction independent, while the quadratic (β) term in dose does depend on the protraction regime, through the Lea-Catcheside function, G. Consequently, the ratio α/β is a measure of the response of the system to changes in protraction. A large value of α/β, in which $\alpha \gg \beta$, would imply a small sensitivity to changes in fractionation. By contrast, a smaller value of α/β would imply a larger sensitivity to changes in fractionation. Consequently, the value of the ratio α/β, sometimes called the repair capacity, is a key determinant of fractionation sensitivity.

Formulae for the Lea-Catcheside function, G, are available for many dose rate/fractionation schemes (9, 11, 13), and a methodology for calculating G for any dose protraction distribution has also been described (14). The two cases of interest here are i) a permanent brachytherapy implant, and ii) EBRT consisting of n well-separated acute fractions, each of dose d. For a permanent brachytherapy implant, G is (13):

$$G = T_{1/2}{}^{biol}/(T_{1/2}{}^{biol} + T_{1/2}{}^{phys}),$$

where $T_{1/2}{}^{phys}$ is the physical half-life of the implant isotope, and $T_{1/2}{}^{biol}$ is the half-time for sublethal damage repair of the target prostatic cancer cells. Typical values of $T_{1/2}{}^{biol}$ are less than a few hours, so for a long-lived isotope like ^{125}I ($T_{1/2}{}^{phys} = 60$ days),

$$G \approx 0, \Rightarrow S = exp(-\alpha D). \quad (\textit{permanent brachytherapy implant}) \quad (3)$$

For n identical well-separated EBRT fractions each of dose d,

$$G = 1/n \Rightarrow S = exp(-\alpha D - \beta D^2/n = exp[-D(\alpha + \beta d)]. \quad (\textit{EBRT, n fractions each of dose d}) \quad (4)$$

Tumor repopulation

It should be noted that Eqs. 2–4 do not include a term to take into account the effects of prostate tumor repopulation during the treatment (15). This was done because prostate tumors are generally growing with an effective rate which is too small for tumor repopulation over the treatment time to be significant. Probably the best estimate of effective tumor repopulation rates comes from PSA doubling times in patients with local failure (16). Such PSA doubling times vary from <12 months to >5 yr (17), with recent systematic studies showing mean PSA doubling times of 12.6 months (18) and 11.4 months (19) for radiotherapy patients with local failure. These effective doubling times are much longer than prostate cancer radiotherapy treatment times, either for EBRT, or for the effective treatment time (20) of ^{125}I permanent implants. Based on these considerations, and the known lack of effect of overall treatment time in EBRT for prostate cancer (21), tumor repopulation is expected to have a negligible impact on the current analysis.

Estimation of α/β from clinical dose–response data

In general, given some clinical dose–response data such as dose vs. *FFBF*, it is in principle possible to fit the data to Eqs. 1 and 2 and thus estimate the parameters α and β and hence α/β. However there are two very common situations, one in brachytherapy, and one in EBRT, where, even if

dose–response data are available, this approach does not work. First, in brachytherapy, if the dose rate is sufficiently low such that the quadratic term in Eq. 2 becomes negligible compared to the linear term (*i.e.*, $G \approx 0$), then (see Eq. 3) nothing can be learned about the quadratic parameter, β. The second situation is in EBRT, when an essentially uniform fractionation scheme (well-separated fractions of dose d) is used: in this case, as can be seen from Eq. 4, only information about the sum, $\alpha + \beta d$, can be obtained.

Unfortunately, these two situations are just those for which mature clinical dose–response data are available for tumor response (or biochemical response) after radiotherapy of prostatic cancer. In particular, several groups have published data for tumor response vs. dose for permanent implants of ^{125}I seeds, and several groups have also published dose–response data for EBRT, where increasing doses correspond to the addition of further similar fractions to those delivered at lower doses.

In principle, however, it is possible to use both data sets to estimate α/β. Specifically, from low dose rate brachytherapy studies, it is possible to estimate the linear parameter, α (see Eq. 3). Given an estimated value of α, EBRT data can then be used to generate the parameter β (see Eq. 4), and hence the α/β ratio.

Clinical data

For permanent ^{125}I implants, a recent study reported dose–response relationships based on 134 individuals who received permanent ^{125}I implants, with a median follow-up time of 32 months (8). The endpoint was freedom from biochemical failure (*FFBF*, i.e., PSA nadir above 1 ng/ml or two consecutive PSA increases). The quoted doses were D90, the dose delivered to 90% of the prostate volume, as assessed using computed tomography (CT)-based dose–volume histograms. The reported dose–response relations are for a distribution of initial PSA values (10% <4, 68% <10, 87% <20, and 13% >20 ng/ml). The subjects were stratified by dose into five groups (<100 Gy, 100–119.9 Gy, 120–139.9 Gy, 140–159.9 Gy, and ≥160 Gy). *FFBF* rates at 3 years for the five dose groups were, respectively, 0.53, 0.82, 0.80, 0.95, and 0.89.

For EBRT, several groups have reported dose–response relationships (2, 5–7). The report with the most extensive dose stratification is by Hanks *et al.* (7) who presented data from 233 individuals who received conformal EBRT. The endpoint is freedom from biochemical failure at 3 years. The results are divided into 5 dose groups (65–69.9 Gy, 70–72.4 Gy, 72.5–74.9 Gy, 75–77.4 Gy, 77.5–80 Gy), and stratified into 3 groups by initial PSA (<10, 10–19.9, and >20 ng/ml). Over the given dose range, *FFBF* increased significantly with dose for the two higher PSA groups, with the lowest PSA group showing a dose-independent *FFBF* averaging 0.88.

Effect of initial PSA

In our modeling of the clinical data, we have made the assumption that the initial PSA is determined primarily by the volume of the tumor, i.e., by the initial number of clonogens (i.e., K in Eq. 1, see Ref. 22), and consequently that the *cellular* radiation response, S, of the tumor cells (α and β in Eq. 2) does not depend on the initial PSA. This assumption will allow us to estimate the α and β parameters from a combination of the brachytherapy and EBRT data sets. In the Results section, we will discuss evidence from the current analysis that this assumption is reasonable—in brief that the clinical data, when stratified by PSA, can be well described with the same α and β values, but simply varying the number of clonogens, K; this was true both for the EBRT and the brachytherapy data sets.

From prior clinical data (23, 24) it is clear that serum PSA is primarily determined by the number of target cells (i.e., the prostate tumor volume). Whether PSA is also, in lesser part, determined by the Gleason or clinical stage of the tumor is less clear (23, 24), though the most recent evidence suggests that "Gleason grade and clinical stage are excellent predictors of stage pT3 disease but not of serum PSA . . ." (25).

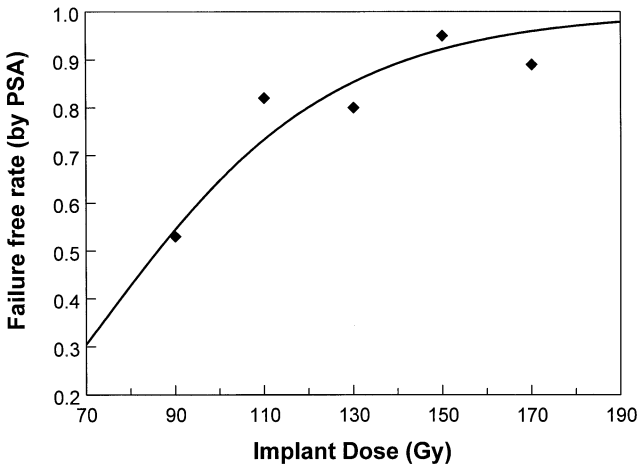

Fig. 1. Failure-free (assessed by PSA) rate at 3 years as a function of permanent implant (^{125}I) dose. Data points are from Stock *et al.* (8); the curve shows a fit to the data using Eqs. 1 and 3 with two free parameters, α and K.

RESULTS

Brachytherapy data

The ^{125}I permanent implant data described above, from Stock *et al.* (8), were fitted to Eqs. 1 and 3, with two free parameters, α and K. The standard simulated annealing technique was used for the fit (26). The data and the fit are shown in Fig. 1. Based on a chi-square goodness of fit test (26), the hypothesis that the data follow Eqs. 1 and 3 could not be rejected at the 0.05 level of significance. The estimated value of α was 0.036 Gy^{-1}, with 95% confidence limits, derived using the Monte-Carlo based synthetic data generation technique (26), of [0.026, 0.045].

Stock *et al.* (8) also stratified the data into two PSA groups and two dose groups. In order to investigate our

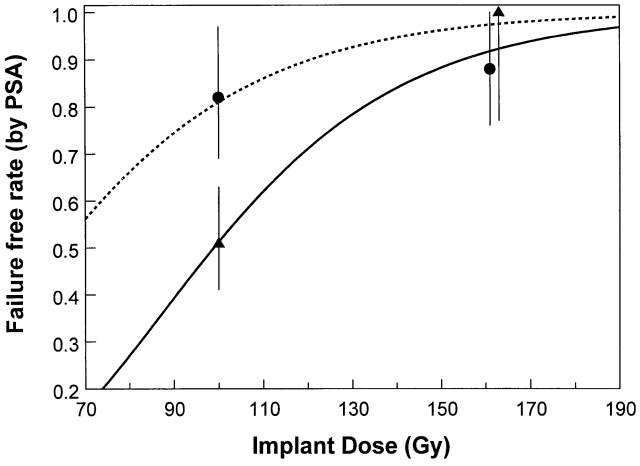

Fig. 2. Points show failure-free (assessed by PSA) rate as a function of permanent implant (^{125}I) dose, reported by Stock *et al.* (8). Data are stratified by initial PSA (●: ≤10 ng/ml, ▲: >10 ng/ml), and subdivided into two dose groups (<140 Gy [mean ~100 Gy] and ≥140 Gy [mean ~160 Gy]). Curves show fit to the data using Eqs. 1 and 3), but with α fixed from the fit shown in Fig. 1, and allowing only *K*, relating to the number of clonogens, to vary between the high and low PSA data sets.

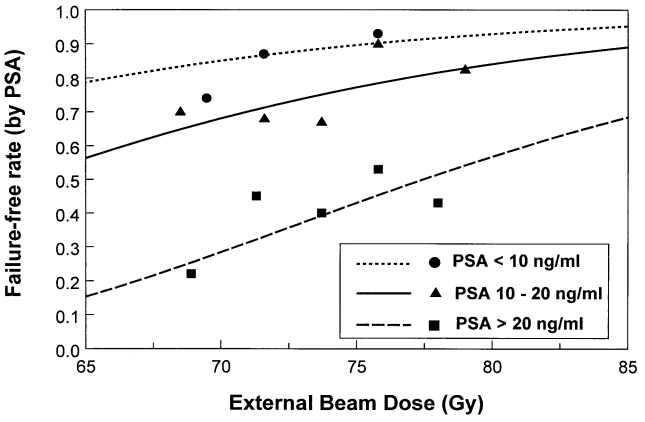

Fig. 3. Points show failure-free (assessed by PSA) rate at 3 years as a function of fractionated external-beam radiotherapy dose, reported by the Fox Chase Cancer Center [Hanks *et al.* (7) and Pinover *et al.* (27)]. Data points are stratified by initial PSA level. Lines show fits to the data (bottom curve: >20 ng/ml; middle curve: 10–19.9 ng/ml; top curve: <10 ng/ml), which are based on Eqs. 1 and 4), with α fixed from the fit to the brachytherapy data shown in Fig. 1; the four free parameters in the fit were thus β and *K*, the number of clonogens, the latter being allowed to vary between the three PSA data sets.

assumption that changes in radiation response with PSA are controlled by the tumor volume, rather than the radiobiological parameters (here, α), we used the same value α as obtained when fitting all the data, and attempted to fit the PSA-stratified data by allowing only *K*, the number of clonogens, to vary. The results, shown in Fig. 2, do indeed suggest that the changes in response with PSA can be predicted solely by changing the initial number of clonogens.

External beam data

The conformal external beam radiotherapy data described above, from Hanks *et al.* (7) were fitted to Eqs. 1 and 4. The data, which are stratified into three PSA groups, were fitted with four free parameters (K_1, K_2, K_3, corresponding to the three PSA groups, and β); as discussed above, the parameter α was fixed at 0.036 Gy^{-1}, based on the brachytherapy analysis above. The results are shown in Fig. 3. Based on a chi-square goodness of fit test (26), the hypothesis that the data follow Eqs. 1 and 4 could not be rejected at the 0.05 level of significance. The value of β obtained in this analysis was 0.024 Gy^{-2}, with 95% confidence limits of [0.019, 0.029].

The results in Fig. 3 also add support to our assumption that changes in response with PSA can be predicted solely by changing the initial number of clonogens, in that the same radiobiological parameters (α and β) were used for all three curves, only the number of clonogens *K* (proportional to the tumor volume), being allowed to vary.

Estimation of α/β

Based on the α and β estimates described above, the estimated value of α/β was 1.5 Gy, with 95% confidence limits of [0.8, 2.2]. As a test of the sensitivity of the analysis, we progressively fixed α/β at increasing values, and refit the EBRT data, to see where the fit no longer adequately described the data. At values of α/β above 2.8 Gy, using the chi-square test, we could reject the hypothesis, at the 0.05 significance level, that the data follow Eqs. 1 and 4 with these α/β values.

DISCUSSION

Understanding the sensitivity to fractionation of prostate tumors is important on several levels. First and foremost, it should allow significant improvements in treatment protocols for the large population who undergo radiotherapy for prostate cancer—about 80,000 individuals per year in the U.S. Second, being a very slow growing tumor containing a low proportion of proliferating cells, it may allow conclusions to be drawn about the overall relationship between fractionation sensitivity and cellular proliferation.

Fractionation sensitivity and cellular proliferation

While it is generally accepted (28) that most tumors show a lower sensitivity to fractionation (typical α/β values of 10–12 Gy) than most late-responding normal tissues (typical α/β values of 2–4 Gy), it has long been known that there are exceptions to this general trend. For example, malignant melanoma (29) and some sarcomas (30) have been shown to exhibit large sensitivities to fractionation (α/β values respectively of 0.57 and 0.4 Gy). What appears common to these two tumor types is that they are slow growing and/or have low labeling indices (LI, a measure of the proportion of cells undergoing DNA synthesis). For example, mesenchymal sarcomas (31) and human soft tissue sarcomas (32)

have respectively been reported to have geometric mean potential doubling times (T_{pot}) of 26 and 13 days, and geometric mean LIs of 2% and 5%. For malignant melanoma, an estimated mean T_{pot} is 11 days, with a mean LI of 5% (31).

Prostate cancers show both extremely large T_{pot} values [measured mean of $>$ 34 days (17)], and very low LIs, typically less than 1% (17, 33). Thus, given the pattern suggested here, it is not, *a posteriori*, surprising, that prostate tumors would show a large sensitivity to fractionation, as demonstrated in this analysis, with $\alpha/\beta = 1.5$ Gy.

There is a good deal of independent evidence suggesting that a decreasing proportion of cycling cells in an irradiated population results in a greater sensitivity to fractionation (i.e., low α/β). The primary evidence comes, as we have discussed, from comparing the fractionation response of late-responding normal tissues with that of tumors (28). Late-responding normal tissues, which generally contain a far smaller proportion of cycling cells, generally show much smaller α/β values than do most tumors.

Further evidence for a relationship between proliferative status and fractionation sensitivity comes from *in vitro* cell survival data. Deschavanne and Malaise (34), analyzing cell survival data, compared α/β ratios for 41 different cell lines of human origin, in plateau phase (i.e., nonproliferating) vs. exponential (i.e., proliferating) growth. They found that the mean α/β ratio for exponentially growing cells was 1.7 times larger than for plateau-phase cells. Other, smaller-scale studies support these results, such as that of Suit *et al.* (35) with human glioma cells, where the estimated α/β value for exponentially growing cells was 2.9 times larger than for plateau-phase cells.

Finally, an *in vitro* endpoint in which proliferating and resting cells can be directly compared is cellular survival in murine hair follicles, where the cells are either in anogen (proliferating) or telogen (resting) phase. Two analyses (36, 37) both concluded that the α/β ratio for the resting-phase cells was significantly smaller than that for proliferating cells.

On the basis of this body of evidence, it seems likely that the low α/β value that we have estimated for prostate tumors can be directly linked to the very low proportion of proliferating cells in these tumors.

Implication for radiotherapy of prostate cancer

If prostatic tumor cells do respond to fractionation as would a late-responding normal tissue, this would have important implications for treatment design. In a "classical" radiotherapy situation, α/β is large for tumor control and for early-responding sequelae, and small for late-responding sequelae; in this situation, where late-responding tissues respond more to changes in fractionation, use of many fractions produces a differential sparing of late-responding tissues, and hence an improved therapeutic ratio.

For prostate cancer, however, based on the current analysis, the tumor and the surrounding late-responding tissues are likely to have similar α/β values, and thus similar sensitivities to changes in fractionation. Consequently, fractionation will neither significantly increase nor decrease the therapeutic advantage between tumor control and late sequelae. It is still likely, however, that the relevant early-responding tissue responsible for acute toxicity will have a low sensitivity to changes in fractionation (high α/β), and so large fraction sizes (hypofractionation) would be expected to differentially reduce acute toxicity, assuming enough overall time is allowed for regenerative cellular proliferation.

As an example, we assume that both the prostatic tumor and the surrounding late-responding normal tissue have an α/β of 1.5 Gy (as estimated here for the tumor), and that the surrounding acutely-responding normal tissue has an α/β of 10 Gy. Then a "conventional" treatment of 36 2-Gy fractions (72 Gy) would be equivalent, in terms of tumor control and late sequelae, to twelve 4-Gy (48 Gy) or six 6-Gy fractions (36 Gy). However, considerably reduced acute sequelae would be expected—for the 12×4 Gy case, the early sequelae would be equivalent to those from 56 Gy given in 2-Gy fractions. In addition, of course, delivering fewer fractions would have considerable implications, both logistic and financial.

In fact, the use of a 6×6-Gy fractionation scheme for treating localized prostate cancer has been reported by Collins *et al.* (38). They report on 232 patients treated using this technique, over a 22-year period from 1962 to 1984. In comparison to contemporary "conventional" fractionation schemes, they report comparable local response and minimal late morbidity—a result in accord with the current considerations, and generally inconsistent with α/β values for prostate cancer of $\sim$10 Gy.

These considerations are quite similar to those for the treatment of malignant melanoma. In this case the best estimate of α/β is 0.57 Gy (29), which is likely to be comparable, if not smaller than that for the dose-limiting late subcutaneous fibrosis (39). Applying the same logic as discussed above, various investigators (40, 41) suggested use of hypofractionation for treating malignant melanoma, and this technique, with doses per fraction up to 9 Gy, has turned out to be a safe and effective treatment (29).

Similar considerations hold for prostate cancer brachytherapy, where high dose rate (HDR) applications, at the appropriately reduced dose, would be expected to be as efficacious as low dose rate in terms of tumor control and late sequelae, but might be expected to give less acute toxicity. In addition, of course, HDR has the added advantages of logistic convenience and potentially more reliable dose distributions. As an example, and under the same assumptions for α/β as made above for EBRT, a standard 10×2 Gy conformal EBRT boost might be replaced with 2 HDR brachytherapy treatment of 5.25 Gy each, resulting in similar tumor control and comparable or less late sequelae—even apart from any improvements in late sequelae due to the improved dose distribution.

A final practical consideration relates to currently used alternative fractionation schemes for prostate cancer. For

example both hyperfractionation (42) and HDR brachytherapy (43) are currently being investigated. In the case of hyperfractionation, as we have discussed, if α/β values for prostate cancer are comparable to those for surrounding late-responding normal tissue, nothing would be gained by using larger numbers of smaller fractions. In the case of HDR brachytherapy, while we have argued that this technique might be ideal for treating prostate cancers, it would be important to use doses based on isoeffect calculations using appropriate values of α/β.

SUMMARY

We have analyzed two mature data sets on radiotherapeutic tumor control for prostate cancer, one using EBRT and the other using permanent implants, to extract the sensitivity to changes in fractionation of prostatic tumors. We were able to compare directly these two data sets because the effects of initial PSA can be accounted for based on the tumor volume (number of target cells). It appears that prostatic cancers are significantly more sensitive to changes in fractionation than most other cancers. In retrospect this result is not too surprising as there is a documented relationship between proportion of proliferating cells and sensitivity to changes in fractionation, and prostatic tumors contain exceptionally low proportions of proliferating cells.

If this result is generally valid, external beam treatments for prostate cancer can be designed that utilize large doses per fraction; appropriately designed hypofractionation schemes would be expected to maintain current levels of tumor control and late sequelae, but with reduced acute morbidity, together with the logistical and financial advantages of fewer numbers of fractions.

Similarly, HDR brachytherapy would be a highly appropriate modality for treating prostate cancer. Appropriately designed HDR brachytherapy regimens would be expected to be as efficacious as low dose rate, but with the added advantages of logistic convenience and potentially more reliable dose distributions.

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