Int. J. Radiation Oncology Biol. Phys., Vol. 52, No. 1, pp. 6–13, 2002

0360-3016/02/$–see front matter

ELSEVIER

PII S0360-3016(01)02664-5

RAPID COMMUNICATION

DIRECT EVIDENCE THAT PROSTATE TUMORS SHOW HIGH SENSITIVITY TO FRACTIONATION (LOW α/β RATIO), SIMILAR TO LATE-RESPONDING NORMAL TISSUE

DAVID J. BRENNER, PH.D., D.SC.,* ALVARO A. MARTINEZ, M.D., F.A.C.R.,†
GREGORY K. EDMUNDSON, M.SC.,† CHRISTINA MITCHELL, R.N., B.S.N.,† HOWARD D. THAMES, PH.D.,‡
AND ELWOOD P. ARMOUR, PH.D.†

*Center for Radiological Research, Department of Radiation Oncology, Columbia University, New York, NY; †Department of Radiation Oncology, William Beaumont Hospital, Royal Oak, MI; ‡Department of Biomathematics, M. D. Anderson Cancer Center, Houston, TX

Purpose: A direct approach to the question of whether prostate tumors have an atypically high sensitivity to fractionation (low α/β ratio), more typical of the surrounding late-responding normal tissue.
Methods and Materials: Earlier estimates of α/β for prostate cancer have relied on comparing results from external beam radiotherapy (EBRT) and brachytherapy, an approach with significant pitfalls due to the many differences between the treatments. To circumvent this, we analyze recent data from a single EBRT + high-dose-rate (HDR) brachytherapy protocol, in which the brachytherapy was given in either 2 or 3 implants, and at various doses. For the analysis, standard models of tumor cure based on Poisson statistics were used in conjunction with the linear-quadratic formalism. Biochemical control at 3 years was the clinical endpoint. Patients were matched between the 3 HDR vs. 2 HDR implants by clinical stage, pretreatment prostate-specific antigen (PSA), Gleason score, length of follow-up, and age.
Results: The estimated value of α/β from the current analysis of 1.2 Gy (95% CI: 0.03, 4.1 Gy) is consistent with previous estimates for prostate tumor control. This α/β value is considerably less than typical values for tumors (≥8 Gy), and more comparable to values in surrounding late-responding normal tissues.
Conclusions: This analysis provides strong supporting evidence that α/β values for prostate tumor control are atypically low, as indicated by previous analyses and radiobiological considerations. If true, hypofractionation or HDR regimens for prostate radiotherapy (with appropriate doses) should produce tumor control and late sequelae that are at least as good or even better than currently achieved, with the added possibility that early sequelae may be reduced. **© 2002 Elsevier Science Inc.**

Prostate cancer, Radiotherapy, HDR, Hypofractionation.

INTRODUCTION

There has been much recent discussion regarding the possibility that prostate tumors respond to changes in fractionation like a late-responding normal tissue, rather than like a typical tumor (1–6). The biologic rationale stems from the extremely slow average growth kinetics of prostate cancers (1–2, 7), more typical of late-responding normal tissues than of tumors.

Generally speaking, increased fractionation provides an increasing therapeutic advantage between tumor control and late sequelae, in that fractionation spares late-responding normal tissues more than tumors, because tumors normally respond as early-responding tissue (8). Sensitivity to change in fractionation can be quantified through the α/β ratio (8) in the linear-quadratic (LQ) formalism—in the language of the LQ 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). The suggestion for prostate cancers, however, is that the α/β ratio for tumor control is comparable to (or even possibly smaller than) that for the surrounding late-responding normal tissue (1–5).

If prostate tumors and the adjacent late-responding normal tissues do respond in essentially the same ways to changes in fractionation, the practical consequences would be profound (4). Hypofractionation schemes for prostate

Reprint requests to: D. J. Brenner, Ph.D., D.Sc., Center for Radiological Research, Columbia University, 630 West 168th Street, New York, NY 10032. Tel: (212) 305-9930; Fax: (212) 305-3229; E-mail: djb3@columbia.edu

This work was supported by NIH Grants CA-24232, CA-77285, and ES-07361.

Acknowledgments—Helpful discussions with Drs. Rainer Sachs, Eric Hall, Jack Fowler, and Rick Chappell are gratefully acknowledged. We also thank the members of the Departments of Urology and Radiation Oncology at William Beaumont Hospital who enrolled the patients in this trial.

Received Aug 15, 2001, and in revised form Aug 23, 2001. Accepted for publication Sep 4, 2001.

Table 1. Number of patients, median follow-up times, and prognostic indicators, stratified by number of implants, for the full patient population, and for the matched subgroups

	Number of cases	Median follow-up (years)	Mean clinical stage*	Mean pre-treatment PSA	Mean Gleason score	Mean age
2-implant group	134	3.0	$4.7 \pm 1.3^{\dagger}$	$8.9 \pm 5.2^{\dagger}$	6.8 ± 0.9	67.1 ± 7.9
3-implant group	58	6.6	$6.2 \pm 1.2^{\dagger}$	$17.7 \pm 13.4^{\dagger}$	7.1 ± 1.3	68.8 ± 6.6
2-implant subgroup	84	3.0	5.4 ± 1.0	9.2 ± 4.7	6.7 ± 0.8	66.9
3-implant subgroup	37	6.4	6.1 ± 1.3	10.9 ± 4.3	6.9 ± 1.1	68.8

* Using code T1c = 3, T2a = 4, T2b = 5, T2c = 6, T3a = 7, T3b = 8, T3c = 9.
† Significant difference ($p < 0.05$) between 2-implant group and the 3-implant group, using the Kolmogorov-Smirnov two-sample test (17).

radiotherapy (with appropriately modified doses) would be expected to produce tumor control and late sequelae that are at least as good as currently achieved with conventional fractionation, with the added possibility that early sequelae may be reduced (1, 4). Similarly, high-dose-rate (HDR) brachytherapy might be expected to produce results comparable to or better than those from low-dose-rate implants (1, 2).

Earlier attempts to estimate α/β values for prostate tumor control have relied on combining results from brachytherapy with results from external beam therapy (1, 3, 5). Essentially, analysis of brachytherapy results allows estimation of the parameter α and, given this parameter, analysis of external beam results allows estimation of α/β. Although this approach has generated consistent results using a variety of analysis techniques and with a variety of data sets (1, 3, 5), results from this approach need to be viewed with caution because of the inherent uncertainties in combining different data sets from brachytherapy and external beam therapy (6): First, the dose distributions and specifications from brachytherapy and external beam therapy are typically very different; and second, the data sets generally derive from different institutions, leading to potential differences in staging as well as scoring response (6). An additional issue is the possibility of a difference in biological effectiveness between the low-energy ^{125}I or ^{103}Pd photons most often used in prostate brachytherapy, and the high-energy X rays used in external beam irradiation (6, 9).

In this report we discuss some data and their analysis which, in large part, overcome these problems. Specifically, we report and analyze recent data from an external beam radiotherapy (EBRT) plus high-dose-rate (HDR) conformal brachytherapy boost protocol (10), in which the HDR treatment was given in either two or three implants, and at various different doses. This HDR dose escalation trial began in 1991 using the assumption that prostate cancer cells have an α/β of 10 Gy. These data are analyzed here either to confirm our original assumption, or to produce a revised estimated α/β value, the analysis being free of most of the uncertainties inherent in combining different types of data sets.

METHODS AND MATERIALS

Clinical studies

From November 1991 through June 2000, a total of 192 patients with unfavorable prostate cancer were prospectively treated in a dose-escalating trial with pelvic EBRT in combination with outpatient HDR brachytherapy, at William Beaumont Hospital. Patients with any of the following characteristics (or higher) were eligible: pretreatment prostate-specific antigen (PSA) 10.0 ng/mL, Gleason score 7, or clinical stage T2b. All patients received pelvic EBRT to a median total dose of 46.0 Gy in 1.8–2 Gy daily fractions (except for the days in which brachytherapy was delivered), for a total treatment time of 4.5 to 5 weeks.

The pelvic EBRT was integrated with ultrasound-guided transperineal conformal interstitial ^{192}Ir HDR brachytherapy, given in either two or three implants (10). From 1991 to 1995, 58 patients received three separate interstitial ^{192}Ir HDR implants during the first, second, and third weeks of pelvic EBRT. After October 1995, the remaining 134 patients received two interstitial ^{192}Ir implants during the first and third weeks of pelvic EBRT. The dose per HDR brachytherapy implant was escalated from 5.50 Gy to 6.50 Gy for those patients receiving three implants, and from 8.25 Gy to 10.50 Gy in those patients receiving two implants. Typical implant treatment times were less than 10 min, depending on source strength and dose.

Further details of the treatment technique, as well as early results, have been reported previously (10). A full analysis of treatment sequelae will be the subject of a separate publication (currently, there is no evidence of greater toxicities in the 2-implant group compared to the 3-implant group). No patient received hormonal therapy unless treatment failure was documented. Biochemical failure was defined according to the American Society for Therapeutic Radiology and Oncology Consensus Panel definition (11), although other definitions are possible, particularly for brachytherapy (12).

Follow-up and mean prognostic indicators (clinical stage, pretreatment PSA, Gleason score, age at treatment) of the 3-implant and 2-implant patient groups are given in Table 1. The median follow-up was 6.6 years (range: 1.9–8.9 years) for the 3-implant HDR treatments, and 3.0 years (range: 0.9

Table 2. Detail of prognostic indicators in the analyzed matched subgroups of patients*

Dose per implant (Gy), number of implants	Number of cases	Mean clinical stage†	Mean pre-treatment PSA	Mean Gleason score	Mean age
5.5 × 3	11	5.9	10.8	6.9	67.2
6.0 × 3	10	6.4	10.9	7.0	67.3
6.5 × 3	16	6.1	10.9	7.2	70.8
8.25 × 2	19	5.5	9.5	7.0	65.3
8.75 × 2	20	5.5	8.8	6.3	66.1
9.5 × 2	20	5.3	11.0	7.0	68.0
10.5 × 2	25	5.4	7.9	6.7	68.0

* No significant differences ($p > 0.05$) of the values of the prognostic indicators between any of the seven dose-per-implant categories, using the Kolmogorov-Smirnov test (17).
† Using code T1c = 3, T2a = 4, T2b = 5, T2c = 6, T3a = 7, T3b = 8, T3c = 9.

to 5.0 years) for the 2-implant HDR treatments. Of course it is important that our analyses be performed on different groups that are restricted to the same follow-up period (3 years, for this analysis), so bNED (biochemically, no evidence of disease) data for follow-up times above 3 years are not analyzed here, as discussed in detail below.

The data in Table 1 indicate that the distribution of values of the pretreatment PSA and of the clinical stage were significantly different in the 2-implant patient group compared to the 3-implant group. Pretreatment PSA, Gleason score, and probably clinical stage, are demonstrated prognostic indicators of clinical response (13–16). As it is our goal to fit all the data together to a common parametric model to estimate a value for the α/β ratio, it is essential that the 2- and 3-implant groups be matched with respect to these prognostic indicators—both overall and between each dose category. We therefore defined subgroups chosen from within the 2-implant group and subgroups chosen from within the 3-implant group, such that these subgroups are matched to each other, both overall and between each dose category, with respect to three prognostic indicators (pretreatment PSA, Gleason score, and clinical stage). Computer optimization based on random matching was used to ensure that both these subgroups excluded as few individuals as possible.

Specifically, from within the original groups (134 in the 2-implant group, 58 in the 3-implant group), we used computer optimization to identify matched subgroups; this yielded a total of 84 individuals in the 2-implant subgroup and 37 individuals in the 3-implant subgroup. Using the Kolmogorov-Smirnov test (17), the hypothesis could not be rejected that individuals from the matched subgroups come from the same distribution of pretreatment PSA, Gleason score, clinical stage, and age at treatment. Overall characteristics of the two subgroups are also given in Table 1, and details of the subgroups broken down by dose category are given in Table 2.

Formalism

We use standard models of tumor cure based on Poisson statistics (18). At a dose D, if the stem cell survival probability is S, the probability of avoiding biochemical failure after treatment (bNED) will be

$$\text{bNED} = (1 - S)^K \approx exp(-SK), \tag{1}$$

where K is related to the initial number of potential stem cells in the tumor, that is, cells that have the independent capacity to initiate tumor regrowth or biochemical failure. Here the survival probability, S, is given by the LQ formalism:

$$S = exp(-\alpha D - G\beta D^2). \tag{2}$$

Here α and β are the LQ parameters, and G is the Lea-Catcheside function describing the reduction in effect due to dose protraction (19). 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 (20).

For the combination of external beam and HDR treatments used here,

$$S = S_{\text{EBRT}} \times S_{\text{HDR}}, \tag{3}$$

where S_{EBRT} and S_{HDR} are, respectively, the survival probabilities from the external beam treatment, and the HDR treatment. In both cases, because the actual treatment times are much smaller than the estimated characteristic repair time [2.7 h (3)] for prostate cancer cells, the G function of Eq. 2 can be adequately described by

$$G = 1/N, \tag{4}$$

where N is the number of fractions (~24 for the EBRT, and either 2 or 3 for the HDR brachytherapy).

All the data (specifically, bNED frequency at 36 months) were fitted simultaneously to Eqs. 1–4 using a standard simulated annealing technique (21), with three free parameters (α, β, and K).

RESULTS

Biochemical outcome

Actuarial analysis of biochemical control for the matched subpopulations, calculated using the Kaplan–Meier method (22), is shown in Fig. 1a. As expected, the control rate after the 2-implant treatments was significantly larger than from the 3-implant treatments, using the log–rank test (23) to compare actuarial curves. The actuarial biochemical control rate after 36 months follow-up for the EBRT + 3-implant HDR subgroup varied from 64% to 75% (depending on dose), whereas the corresponding rate for the EBRT + 2-implant subgroup varied from 87% to 95%. Figure 1b shows the 2-implant vs. 3-implant results for all doses combined; the bNED rate at 3 years for the 2-implant group (mean total implant dose 18.7 Gy) was 94%, significantly higher ($p = 0.001$) than the corresponding rate of 70% for the 2-implant group (mean dose 18.2 Gy).

Estimation of α/β value

The best fit to all the bNED data, 36 months after treatment, using Eqs. 1–4 is shown in Fig. 2. The Pearson χ^2 goodness-of-fit statistic (24) indicates that the model provides an adequate fit to the data. The estimated parameter values were $\alpha = 0.026\ \text{Gy}^{-1}$, $\alpha/\beta = 1.2$ Gy, $K = 138$ cells. The 95% confidence interval (CI) for the α/β estimate, based on a Monte-Carlo normally distributed "synthetic data" simulation (21), was from 0.03 to 4.1 Gy, though the lower values in this confidence limit correspond to possibly unrealistically low values of the α parameter.

Also shown in Fig. 2 is a fit to the data in which α/β was constrained to be 10 Gy, a "nominal" value for most tumors (25, 26)—as well as the original assumption made at the outset of this trial. It is clear that this results in a poorer description of the data, with a much smaller separation between the two- and three-implant data than is seen clinically. For example at a total HDR dose of 16.5 Gy, the clinical data indicate a 23% difference (87% vs. 64%) in 3-year bNED rates for two vs. three implants. The best fit to the data with $\alpha/\beta = 1.2$ Gy does indeed predict a 23% difference, whereas an α/β value of 10 Gy predicts only half this difference (11.6%).

Potential effects of late failures

The follow-up time used in this analysis (3 years post-treatment for each group) is such that not all potential treatment failures in either the 2-implant or the 3-implant group would have yet occurred. For example, in the matched 3-implant group, where the mean follow-up time was actually 6 years, two additional late failures (at 3.1 and 3.3 years) were observed, though they were not included in the current analysis due to the necessity of using the same follow-up times as for the 2-implant group.

It is likely that the 2-implant group will show a lower incidence of late (>3-year) failures compared with the 3-implant group, because higher cure rates (or, equivalently, higher effective doses) are generally associated with early failure times—a trend established from external beam data (27, 28) (see Fig. 3). This trend is also visible in the current data within the 3-implant group: only in the lowest dose group of the 3-implant data are any failures observed after 3 years (Fig. 1a).

Based on these considerations, some sensitivity studies were performed to explore the possible effects of longer follow-up on the estimated α/β value. The matched data for the 3-implant groups with 6 years of follow-up were fitted to Eqs. 1–4, together with the matched data for the 2-implant group in which it was assumed that no further late failures will occur beyond the single case already observed in the 2-implant low-dose group (at 3.7 years); the estimated α/β value was 0.8 Gy, with a crude estimate of an upper limit (assuming two further late failures in the 2-implant low-dose group) of 1.7 Gy. A more conservative (though probably less realistic) assumption, that all the 2-implant patients will show the same pattern of late response as do the 3-implant patients, leads to an estimated α/β value of 2.9 Gy with a crude estimate of an upper limit of 6.9 Gy.

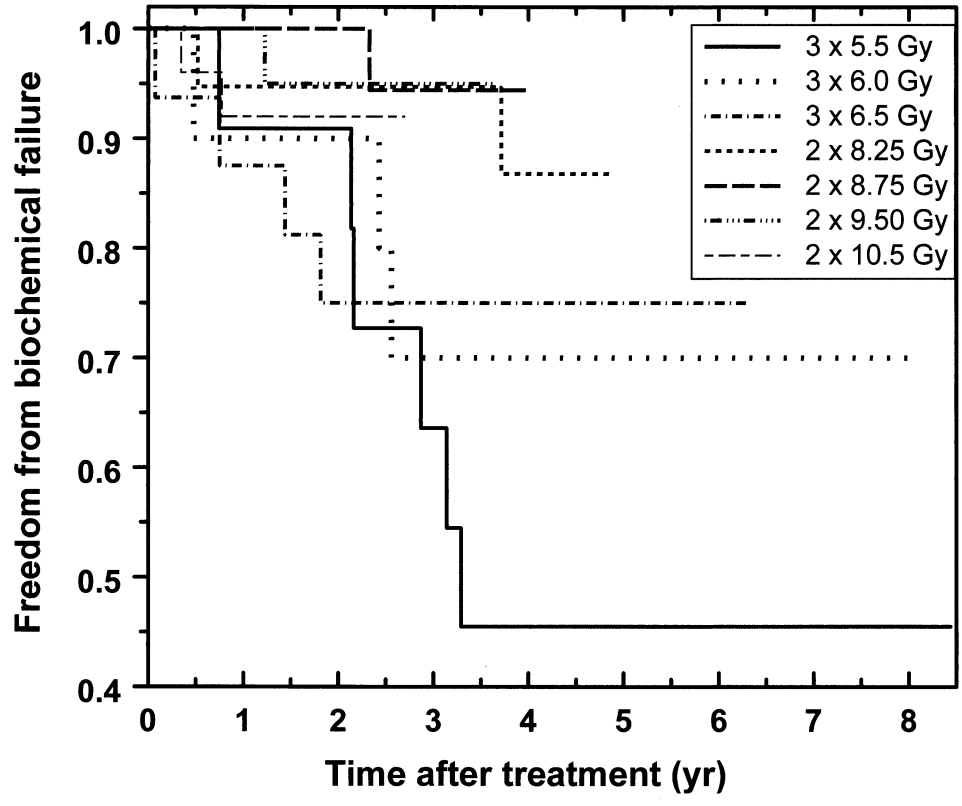
DISCUSSION

The estimated value of α/β from the current analysis of 1.2 Gy (95% CI: 0.03–4.1 Gy) is consistent with previous estimates for prostate tumor control. Specifically Brenner and Hall (1) estimated a value of 1.5 Gy (95% CI: 0.8–2.2 Gy), while Fowler *et al.* (3) estimated 1.49 Gy (95% CI: 1.25–1.76 Gy). Using a more generic comparison of EBRT and brachytherapy results, King and Fowler (5) estimated α/β values for prostate tumor control in the range from 1.8 to 2.8 Gy. All these values are considerably lower than typical value for other tumors ($\geq$8 Gy), and are comparable to typical values in the surrounding late-responding normal tissues (25, 26).

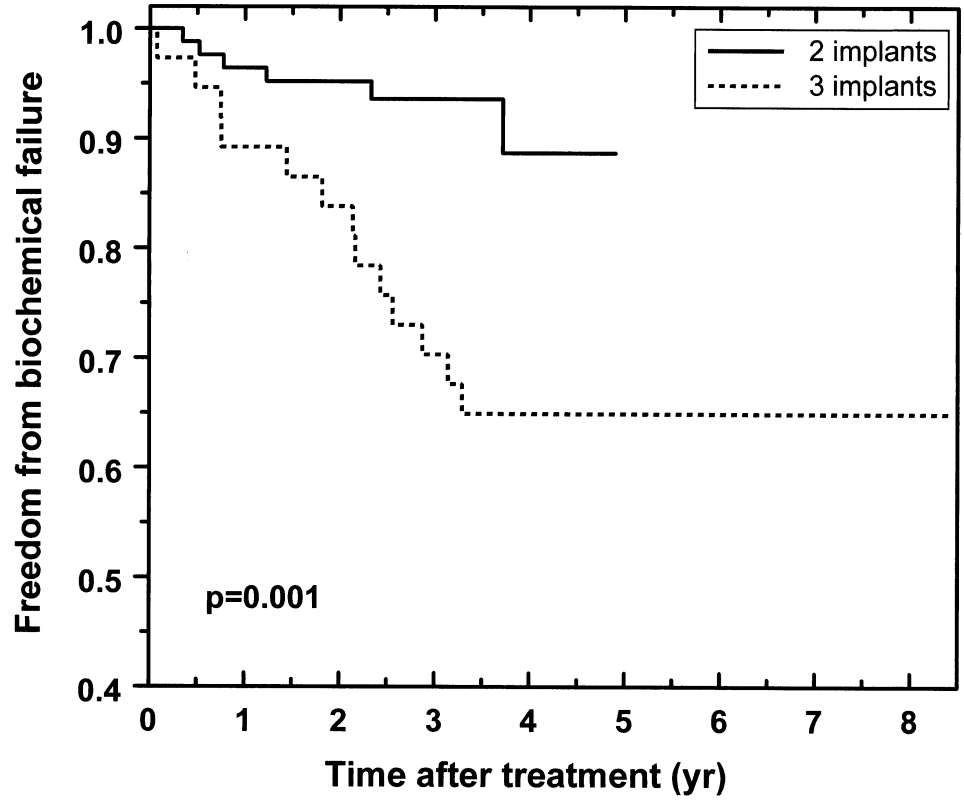
Necessarily crude projections of what the α/β ratio might be if a comparison of results was made after 6 years follow-up (rather than the 3-year analysis described here) suggest that the estimates would still be comparable to those for late-responding tissues, and lower than those for most other tumor types. A reanalysis after another, say, 2–3 years follow-up would, however, be useful.

All the earlier α/β values for prostate cancer relied on comparisons between independent EBRT and brachytherapy results; the problems associated with such comparisons have recently been discussed by D'Souza and Thames (6), who concluded that the uncertainties inherent in such comparisons (in particular relating to differences in dose distribution, dose rate, and radiation type) implied that a broad range of α/β values was possible. The technique used in generating the current estimate involves analysis of a single data set, within which there are differences only in the number of implants and the overall dose—thus avoiding the potential pitfalls (6) in EBRT–brachytherapy comparisons from different data sets.

An additional earlier analysis problem that the current approach largely overcomes is the potentially significant



(a)



(b)

Fig. 1. Actuarial plots of frequency of freedom from biochemical failure (bNED) in matched subgroups, as a function of time posttreatment, (a) stratified by number of HDR implants and dose per HDR implant, (b) stratified only by number of HDR implants. Further details are given in Tables 1 and 2.

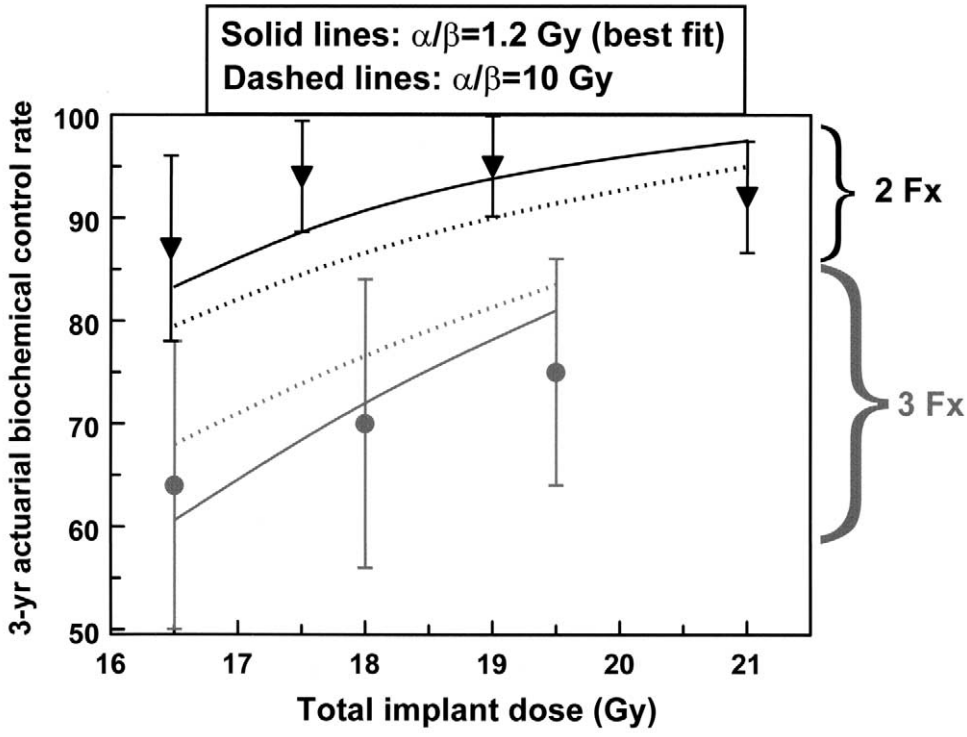


Fig. 2. Fits to Eqs. 1–4 of actuarial freedom from biochemical failure (bNED), analyzed at 3 years posttreatment, in matched subgroups who received either two or three implants of HDR brachytherapy. Triangles and upper curves refer to 2-implant brachytherapy. Circles and lower curves refer to 3-implant brachytherapy. Solid curves refer to the best fit to the data, with estimated α/β value of 1.2 Gy. Broken curves refer to a fit in which α/β was constrained to be 10 Gy.

difference in biological effectiveness between the low-energy ^{125}I or ^{103}Pd photons most often used in prostate brachytherapy, and the high-energy X rays used in EBRT (6, 9). In the protocol (10) analyzed here, a) the brachytherapy utilized higher-energy ^{192}Ir gamma rays, which have a biological effectiveness closer to that of high-energy photons (9), and b) the comparisons made here are essentially between different HDR brachytherapy dose/fractionation protocols, rather than between brachytherapy and EBRT protocols.

The disadvantage of the current analysis is the smaller number of patients analyzed (n = 121), compared with earlier α/β estimates (1, 3, 5) for which the various analyzed patient groups were more heterogeneous. Because the groups analyzed here are more homogeneous, both in regard to prognostic indicators and to treatment techniques, the statistical confidence limits of the current α/β estimate (95% CI: 0.03 to 4.1 Gy), though somewhat wider than quoted for earlier analyses, probably better reflect the true uncertainties than did those from previous studies. The good agreement, however, between the estimates from these different analyses, is encouraging.

The estimated α/β values for prostate tumor control appear clearly lower than for most other tumors, and are probably comparable to those of the adjacent late-responding normal tissues. Thus it appears that prostate tumors and the adjacent late-responding normal tissues respond in approximately the same ways to changes in fractionation. As pointed out previously (1, 2), this is not entirely unexpected because of the very slow average growth kinetics of prostate cancers (7), more typical of late-responding normal tissues than of tumors.

If the α/β value for prostate tumor control is typically low, the consequences for prostate cancer radiotherapy could be significant (4). For prostate cancer patients, appropriate hypofractionation schemes using EBRT with intensity-modulated beams, EBRT with an HDR boost, or monotherapy with HDR should produce tumor control and late sequelae that are as good, if not better, than currently achieved with conventional fractionation. The added possibility that early sequelae may be reduced (1, 4)* is, of course, attractive. In addition, the need for considerably fewer EBRT fractions would be a boon both for the patient and for resource-stretched radiotherapy centers. The need for fewer EBRT fractions could also be used as a rationale for the technically demanding intensity-modulated radiotherapy.

These considerations apply equally to EBRT and to

*Essentially the argument here (1, 4) is the correlate of the "standard" argument that if tumor control shows a large α/β and late sequelae a small α/β, then contracting the treatment will spare the tumor more than the late sequelae—an undesirable outcome. Here, early sequelae show a large α/β and prostate tumor control a small α/β, so contracting the treatment will spare early sequelae more than the tumor—a desirable outcome.

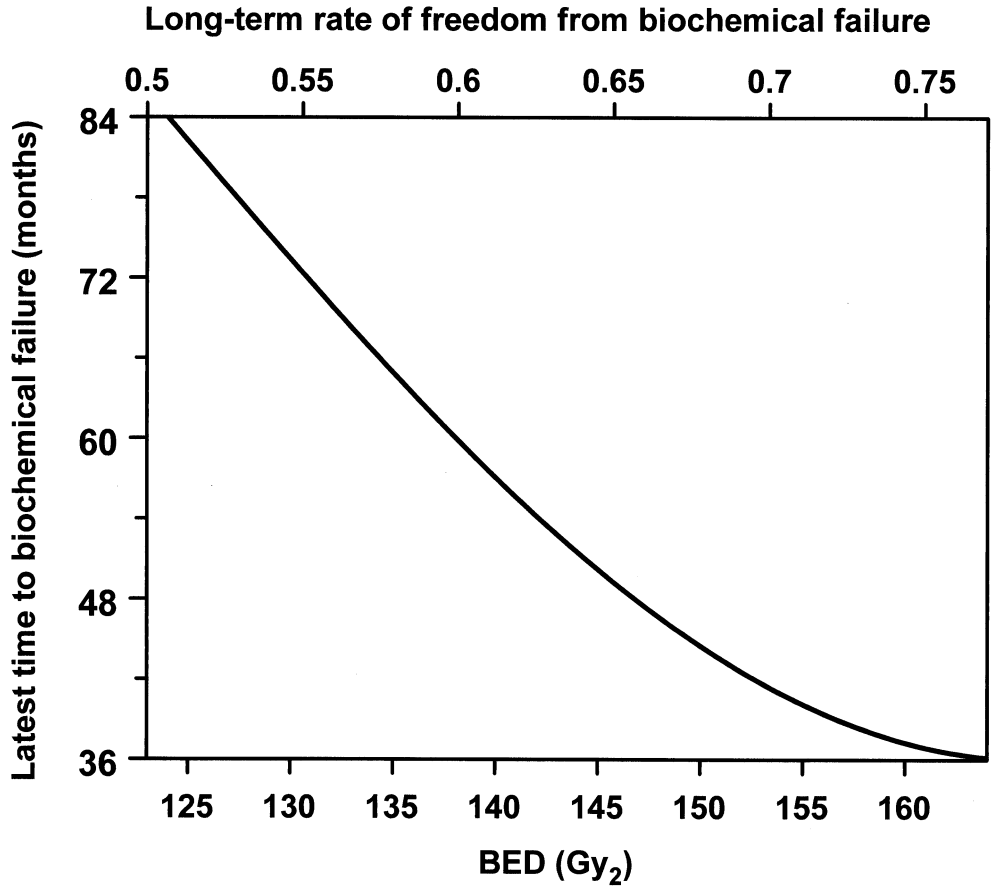


Fig. 3. For external-beam RT only, latest time to biochemical failure as a function of actuarial long-term disease-free rate (bNED, here at 57 months), and biologically equivalent dose, BED (Gy_2). For comparison, the BED values in the current study range from 131 to 173 Gy_2 in the 3-implant group, and from 175 to 220 Gy_2 in the 2-implant group. Data from recent analysis by Pollack *et al.* (27) on 1,127 stage T1–T4 prostate cancer patients treated in the PSA era.

HDR brachytherapy [as in this trial (10), as a boost, and also as a monotherapy (29, 30)]. In designing such treatments, however, it is important to estimate appropriate treatment doses using a suitably low α/β value, if equivalent tumor control to a conventionally fractionated regimen is desired. It is also important to point out that applying extreme fractionation regimens, such as delivering the total dose in 1 or 2 fractions, is almost certainly unwise, due to the likelihood of inadequate reoxygenation. In addition to these biologic considerations, due to current accuracy limitations in dose delivery by EBRT, the delivery of the entire treatment in as few as 1–2 fractions appears unwise; this dosimetric issue does not, however, necessarily apply to HDR monotherapy, where corrections can be made for organ motion and setup errors before treatment.

Since the 1960s, there has been a wealth of experience in Britain (31–35) and Canada (36) using large (2.5–3 Gy) EBRT fractions for treating prostate cancer. Given these, and the experimental and theoretical considerations discussed here suggesting that prostate cancers do respond to changes in fractionation like late-responding normal tissues, trials like those discussed by Logue *et al.* (35) using an EBRT dose of 60 Gy in 20 fractions, or the use of HDR brachytherapy (10, 29, 30), seem quite appropriate at this time.

REFERENCES

1. Brenner DJ, Hall EJ. Fractionation and protraction for radiotherapy of prostate carcinoma. *Int J Radiat Oncol Biol Phys* 1999;43:1095–1101.
2. Duchesne GM, Peters LJ. What is the α/β ratio for prostate cancer? Rationale for hypofractionated high-dose rate brachytherapy. *Int J Radiat Oncol Biol Phys* 1999;44:747–748.
3. Fowler J, Chappell R, Ritter M. Is alpha/beta for prostate tumors really low? *Int J Radiat Oncol Biol Phys* 2001;50: 1021–1031.
4. Brenner DJ. Toward optimal external-beam fractionation for prostate cancer. *Int J Radiat Oncol Biol Phys* 2000;48:315–316.
5. King CR, Fowler JF. A simple analytic derivation suggests that prostate cancer α/β ratio is low. *Int J Radiat Oncol Biol Phys.* 2001;51:213–214.
6. D'Souza WD, Thames HD. Is the α/β ratio for prostate cancer low? *Int J Radiat Oncol Biol Phys.* 2001;51:1–3.
7. Haustermans KM, Hofland I, Van Poppel H, *et al.* Cell kinetic

measurements in prostate cancer. *Int J Radiat Oncol Biol Phys* 1997;37:1067–1070.
8. Thames HD Jr, Withers HR, Peters LJ, *et al.* Changes in early and late radiation responses with altered dose fractionation: Implications for dose-survival relationships. *Int J Radiat Oncol Biol Phys* 1982;8:219–226.
9. Wuu CS, Kliauga P, Zaider M, *et al.* Microdosimetric evaluation of relative biological effectiveness for ^{103}Pd, ^{125}I, ^{241}Am, and ^{192}Ir brachytherapy sources. *Int J Radiat Oncol Biol Phys* 1996;36:689–697.
10. Martinez AA, Kestin LL, Stromberg JS, *et al.* Interim report of image-guided conformal high-dose-rate brachytherapy for patients with unfavorable prostate cancer: The William Beaumont phase II dose-escalating trial. *Int J Radiat Oncol Biol Phys* 2000;47:343–352.
11. Consensus statement: Guidelines for PSA following radiation therapy. American Society for Therapeutic Radiology and Oncology Consensus Panel. *Int J Radiat Oncol Biol Phys* 1997;37:1035.
12. Kattan MW, Fearn PA, Leibel S, Potters L. The definition of biochemical failure in patients treated with definitive radiotherapy. *Int J Radiat Oncol Biol Phys* 2000;48:1469–1474.
13. Corn BW, Hanks GE, Lee WR, *et al.* Prostate specific antigen density is not an independent predictor of response for prostate cancer treated by conformal radiotherapy. *J Urol* 1995;153: 1855–1859.
14. Pisansky TM, Kahn MJ, Bostwick DG. An enhanced prognostic system for clinically localized carcinoma of the prostate. *Cancer* 1997;79:2154–2161.
15. Zagars GK, Pollack A, von Eschenbach AC. Prognostic factors for clinically localized prostate carcinoma: Analysis of 938 patients irradiated in the prostate specific antigen era. *Cancer* 1997;79:1370–1380.
16. Vollmer RT, Montana GS. Predicting tumor failure in prostate carcinoma after definitive radiation therapy: Limitations of models based on prostate-specific antigen, clinical stage, and Gleason score. *Clin Cancer Res* 1999;5:2476–2484.
17. Gibbons JD. Nonparametric statistical inference. 2nd ed. New York: Marcel Dekker; 1985.
18. Tucker SL, Thames HD, Taylor JM. How well is the probability of tumor cure after fractionated irradiation described by Poisson statistics? *Radiat Res* 1990;124:273–282.
19. Lea DE, Catcheside DG. The mechanism of the induction by radiation of chromosome aberrations in Tradescantia. *J Genet* 1942;44:216–245.
20. Brenner DJ, Hlatky LR, Hahnfeldt PJ, *et al.* The Linear-Quadratic model and most other common radiobiological models result in similar predictions for time-dose relationships. *Radiat Res* 1998;150:1–9.
21. Press WH, Flanner BP, Teukolsky SA, *et al.* Numerical recipes. Cambridge: Cambridge University Press; 1986.
22. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958;53:457–481.
23. Mantel N. Evaluation of survival data and two new rank order statistics arising in its consideration. *Cancer Chemother Rep* 1966;50:163–170.
24. Pearson K. On the criterion that a given system of deviations from the probable in the case of a correlated system of variables is such that it can reasonably supposed to have arisen from random sampling. *Phil Mag Series 5* 1900;50:157–175.
25. Thames HD, Bentzen SM, Turesson I, *et al.* Time-dose factors in radiotherapy: A review of the human data. *Radiother Oncol* 1990;19:219–235.
26. Fowler JF. The linear-quadratic formula and progress in fractionated radiotherapy. *Br J Radiol* 1989;62:679–694.
27. Pollack A, Smith LG, von Eschenbach AC. External beam radiotherapy dose response characteristics of 1127 men with prostate cancer treated in the PSA era. *Int J Radiat Oncol Biol Phys* 2000;48:507–512.
28. Zelefsky MJ, Leibel SA, Gaudin PB, *et al.* Dose escalation with three-dimensional conformal radiation therapy affects the outcome in prostate cancer. *Int J Radiat Oncol Biol Phys* 1998;41:491–500.
29. Yoshioka Y, Nose T, Yoshida K, *et al.* High-dose-rate interstitial brachytherapy as a monotherapy for localized prostate cancer: Treatment description and preliminary results of a phase I/II clinical trial. *Int J Radiat Oncol Biol Phys* 2000;48: 675–681.
30. Martinez AA, Pataki I, Edmundson G, *et al.*, Phase II prospective study of the use of conformal high-dose-rate brachytherapy as monotherapy for the treatment of favorable stage prostate cancer: A feasibility report. *Int J Radiat Oncol Biol Phys* 2001;49:61–69.
31. Preston CI, Duncan W, Kerr GR. Radical treatment of prostatic carcinoma by megavoltage X-ray therapy. *Clin Radiol* 1986;37:473–477.
32. Hope-Stone H. External radiation therapy for prostatic carcinoma. In: Blandy JP, Lytton B, editors. The prostate. London: Butterworths; 1987. p. 173–187.
33. Read G, Pointon RC. Retrospective study of radiotherapy in early carcinoma of the prostate. *Br J Urol* 1989;63:191–195.
34. Lloyd-Davies RW, Collins CD, Swan AV. Carcinoma of prostate treated by radical external beam radiotherapy using hypofractionation: Twenty-two years' experience (1962–1984). *Urology* 1990;36:107–111.
35. Logue JP, Cowan RA, Hendry JH. Hypofractionation for prostate cancer. *Int J Radiat Oncol Biol Phys* 2001;49:1522–1523.
36. Duncan W, Warde P, Catton CN, *et al.* Carcinoma of the prostate: Results of radical radiotherapy (1970–1985). *Int J Radiat Oncol Biol Phys* 1993:26:203–210.