Int. J. Radiation Oncology Biol. Phys., Vol. 56, No. 4, pp. 1093–1104, 2003

0360-3016/03/$–see front matter

ELSEVIER

doi:10.1016/S0360-3016(03)00132-9

CLINICAL INVESTIGATION **Prostate**

WHAT HYPOFRACTIONATED PROTOCOLS SHOULD BE TESTED FOR PROSTATE CANCER?

JACK F. FOWLER, D.SC., PH.D.,* MARK A. RITTER, M.D., PH.D.,* RICK J. CHAPPELL, PH.D.,† AND DAVID J. BRENNER, D.SC., PH.D.‡

Departments of *Human Oncology and †Biostatistics and Medical Informatics, University of Wisconsin-Madison, Madison, WI; ‡Center for Radiological Research, Columbia University, New York, NY

Purpose: Recent analyses of clinical results have suggested that the fractionation sensitivity of prostate tumors is remarkably high; corresponding point estimates of the α/β ratio for prostate cancer are around 1.5 Gy, much lower than the typical value of 10 Gy for many other tumors. This low α/β value is comparable to, and possibly even lower than, that of the surrounding late-responding normal tissue in rectal mucosa (α/β nominally 3 Gy, but also likely to be in the 4–5 Gy range). This lower α/β ratio for prostate cancer than for the surrounding late-responding normal tissue creates the potential for therapeutic gain. We analyze here possible high-gain/low-risk hypofractionated protocols for prostate cancer to test this suggestion.

Methods and Materials: Using standard linear-quadratic (LQ) modeling, a set of hypofractionated protocols can be designed in which a series of dose steps is given, each step of which keeps the late complications constant in rectal tissues. This is done by adjusting the dose per fraction and total dose to maintain a constant level of late effects. The effect on tumor control is then investigated. The resulting estimates are theoretical, although based on the best current modeling with α/β parameters, which are discussed thoroughly.

Results: If the α/β value for prostate is less than that for the surrounding late-responding normal tissue, the clinical gains can be rather large. Appropriately designed schedules using around ten large fractions can result in absolute increases of 15% to 20% in biochemical control with no evidence of disease (bNED), with no increase in late sequelae. Early sequelae are predicted to be decreased, provided that overall times are not shortened drastically because of a possible risk of acute or consequential late reactions in the rectum. An overall time not shorter than 5 weeks appears advisable for the hypofractionation schedules considered, pending further clinical trial results. Even if the prostate tumor α/β ratio turns out to be the same (or even slightly larger than) the surrounding late-responding normal tissue, these hypofractionated regimens are estimated to be very unlikely to result in significantly increased late effects.

Conclusions: The hypofractionated regimens that we suggest be tested for prostate-cancer radiotherapy show high potential therapeutic gain as well as economic and logistic advantages. They appear to have little potential risk as long as excessively short overall times (<5 weeks) and very small fraction numbers (<5) are avoided. The values of bNED and rectal complications presented are entirely theoretical, being related by LQ modeling to existing clinical data for approximately intermediate-risk prostate cancer patients as discussed in detail.

Hypofractionation, Prostate tumors, Approximately intermediate-risk, Reduced total doses.

INTRODUCTION

Brenner and Hall (1) suggested that in prostatic carcinomas the fractionation sensitivity (quantified by the α/β ratio) was comparable to that for late-responding normal tissue, for the biologic reason that prostate tumors have the slowest natural turnover rates of all tumors. The average T_{pot} (potential cell number doubling time, before any cell loss factor), measured before treatment is 40 days [range 15 to >60 days (2)], compared with about 5 days for many other types of tumor. Brenner and Hall's estimated value for α/β was 1.5 Gy (95% confidence interval [CI] = 0.8–2.2). For comparison, the "generic" α/β ratios for tumor and for late-responding normal tissue are usually assumed to be 10 Gy and 3 Gy, respectively. The initial estimate of 1.5 Gy for prostate was based on a modeling comparison of the doses of 65–80 Gy used for external beams and the higher doses used for permanent implants (100–160 Gy) (1). The challenge by King and Mayo (3) that α/β for prostate tumors was nearer to 5 Gy (higher than that of rectal complications) when estimated using a "heterogeneity model," has been dropped because of the problems with heterogeneity modeling (4, 5).

Reprint requests to: Dr. J. F. Fowler, Dept. of Human Oncology K4/316, 600 Highland Avenue, Madison, WI 53792. Tel: 608-265-0506; Fax: 608-263-9947; E-mail: jffowler@mail.humonc.wisc.edu

Funded in part by NIH grants CA-88960, CA-49062, and RR-11623.

Received May 28, 2002, and in revised form Jan 14, 2003. Accepted for publication Jan 21, 2003.

Table 1. Results of external-beam-only treatments of intermediate-risk prostatic cancer (6)

Center	Abbreviation	Dose per fraction (Gy)	Mean total dose (Gy)	Actuarial 5y bNED%	Number treated	Reference
Dothan	Alabama	1.9	66.0	50	16	Stokes (18)
Fox Chase	FCC1	2.1	72.78	70	42	Hanks (19)
	FCC2		76.84	82.5	36	
	FCC3		77.45	87	30	
Beaumont	Beau	1.9	66.6	45	142	Vicini (20)
Memorial Sloan-Kettering	MSK1	1.8	67.5	54	116	Zelefsky (21)
	MSK2		78.3	79	94	
M. D. Anderson, Houston	MDA1	2.0	66	44	124	Pollack (22, 23)
	MDA2		70	55	106	
	MDA3		78	86	29	
					Total 735	

Abbreviation: bNED = biochemical control with no evidence of disease.

A recent update and alternative analysis of the Brenner and Hall review, including 11 centers and 1471 patients (Table 1, Fig. 1), with 4- to 5-year no biochemical evidence of disease (bNED) results published between 1995 and 2000 (6), yielded an estimate of α/β for prostate tumors of 1.5 Gy (95% CI 1.2–1.8) (6). This is a close confirmation of Brenner and Hall's 1999 estimate (1). The narrower confidence interval is a consequence of more patients being included in the recent publications and the better fit of the model when incomplete repair is included in the implant dosimetry. Further, Dale and Jones (7) have pointed out that if allowance is made for an increased relative biologic effectiveness (RBE) for the nuclides I-125 and Pd-103, then the estimated α/β for prostate tumors is even lower, about 1.0 Gy.

Even more recently, Brenner *et al.* (8) have analyzed 3-year bNED results from a single-institute dose escalation study which yielded a value for α/β of 1.2 Gy (95% CI 0.03–4.1 Gy) (8). This latest analysis does not suffer from the potential problems of inter-institutional comparisons, nor does it suffer from the problems inherent in comparing brachytherapy with external-beam treatments. Further support for the concept of hypofractionation based on low values of α/β comes from the preliminary results of another institute's schedule using 2.5 Gy in 28 fractions to a total

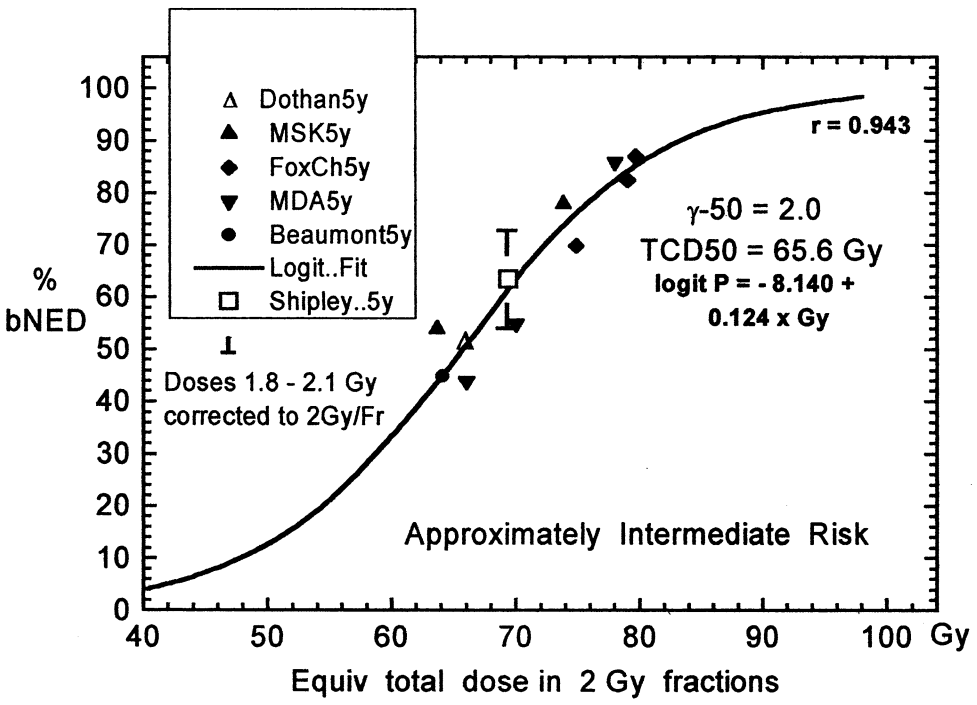

Fig. 1. Estimated probability of no evidence of disease at 5 years by PSA measurements (bNED) as a function of total dose in 2 Gy fractions (NTD) for approximately "intermediate-risk" patients especially 10–20 ng/mL pretreatment PSA. This curve was computed by logit regression of the reported actuarial results for the 10 dose-levels from five centers (Table 1) (18–23)), as in Fig. 1 of Ref. 6. The point for Shipley *et al.* was added subsequently, obtained by averaging the 5-year bNED results from their Figs. 1, 2, and 3 (24).

dose of 70 Gy, which showed strong trends of both increased bNED and decreased late complications in a randomized trial vs. 78 Gy in 39 fractions of 2 Gy (9, 10). Although follow-up for each of these studies is short, both provide additional evidence suggesting a low α/β ratio.

These low estimated values of α/β ratios give increasing credibility to an α/β for prostate tumors which is similar to that for late complications in surrounding tissues such as rectum. If this were the case, there would be little difference in "classic" late effects, for a given level of tumor control, for a wide variety of fractionation schedules, including hypofractionation. In particular, hypofractionated regimens for prostate cancer, in addition to their economic and logistic advantages, would be expected to result in less acute sequelae and less "consequential" late effects, for a given level of tumor control and "classic" late effects (11).

An even more advantageous scenario arises if the α/β ratio for prostate tumors was actually significantly less than that for late rectal complications (12). The nominal α/β value for "generic" late-responding tissue is generally taken to be around 3 to 4 Gy (13–17), although we consider in the "Discussion" section evidence that the α/β for rectal complications might actually be somewhat higher—perhaps in the 4 to 5 Gy range, due to contributions from "consequential" late effects which originate from tissue with α/β about 10 Gy. If the α/β value for prostate cancer is really less than for late-responding rectal damage, hypofractionated regimens could be designed with fewer but larger doses, to maintain equivalent late sequelae while yielding improved tumor control. Using such reductions of total dose, we should also expect less acute sequelae and less "consequential" late effects, provided that overall time is not shortened too drastically.

Using standard linear-quadratic (LQ) modeling (13), we have designed a set of protocols in which a series of dose steps is given, each step of which keeps the late complications constant in rectal tissues. This is done by adjusting the dose per fraction and total dose to maintain a constant biologically effective dose (BED) for late effects, assuming an α/β ratio of 3 Gy. The effect on tumor control is then investigated. We are asked by reviewers to emphasize that these results are purely theoretical and result from modeling using the LQ model, with the assumptions that α/β for prostate tumors is in the range of 1 to 2 Gy and is generally (but not always) lower than α/β for late rectal complications in the range 1 to 5 Gy.

METHODS AND MATERIALS

A dose–response curve for 5-year bNED of intermediate-risk prostate cancer, using external beam radiotherapy only, was constructed by logit regression from 10 dose points from five centers published in the period 1997–2000 (Table 1) (6, 18–23). "Intermediate-risk" patients were defined primarily as having prostate-specific antigen (PSA) between 10 and 20 ng/mL, and further in terms of *OR* Gleason score ≥ 7 *OR* stage $\geq$ T2b, as far as possible. Patients with lower PSA *and* Gleason score *and* stage would be considered favorable, whereas those with two or more of these high-risk characteristics would be classified as unfavorable. However, data corresponding to these criteria are difficult to isolate from the literature because of some variability in the boundaries of stage or of Gleason score between centers. Nevertheless the plotted data are judged by the original authors, and by our criteria as nearly as we could obtain them, as reasonable approximations to "intermediate risk." In our 2001 paper (6) we took account of this diversity by performing a sensitivity analysis "by removing each site [center] from the model, one at a time. Estimates of α and β in each case deviated by 20% or less [$\pm$ 0.3 Gy] from the overall estimate." No revision of that α/β value nor any revision of the external beam dose–response curve seems warranted. Figure 1 shows the same logit regression curve from Ref. 6 fitted to the same data, plotted against total dose in 2 Gy fractions. The small dose corrections from 1.8 or 2.1 dose per fraction were made assuming $\alpha/\beta = 1.5$ Gy for these prostate tumors. Retrospectively, we also compared this curve with the single dose point obtained from the large overview of pooled data from six institutes by Shipley *et al.* (24), with no conflict as shown in Fig. 1. The Shipley point plotted was obtained by calculating a weighted average of the 5-year bNED from the middle two of the four risk groups identified by Shipley *et al.* The dose–response curve in Fig. 1 passes through a TCD50 (dose for 50% tumor control) of about 66 Gy with a modest slope of γ-50 = 2.0% per percent of total dose. Sensitivity analyses are carried out (see "Results") to test the possibility that the slope of this dose–response curve might be found to be different when further data are analyzed in a few years' time

The second step was to calculate dose-per-fraction and total doses of a variety of regimens that would be predicted to give the same level of late effects as three current prostate cancer regimens, for a range of schedules currently regarded as ranging in aggressiveness from "conservative" to "highly dose escalated." Specifically, we chose 66, 72, and 78 Gy in 2 Gy fractions for starting dose regimens, as shown in Table 2, with the main results in the first five columns.

We have constructed a series of hypofractionated treatments which keep late complications constant, at the same physical dose plans as are currently used for the chosen 2 Gy fractionated schedules, but which cause more damage to the tumors as the dose fractions become fewer and larger. These are shown in Table 2 with three blocks of numbers, each representing a possible set of hypofractionated protocols for future prostate treatments. The standard nonhypofractionated treatment is assumed to consist of 33, 36, or 39 fractions of 2 Gy, given five times a week. The standard treatments of 2 Gy "daily" doses are shown in the first row of each of the three blocks in Table 2.

Each step (row in each block of Table 2) consists of an increasingly hypofractionated protocol where, typically, five fractions are subtracted from the row above (omitting the minimally hypofractionationed 30 fractions). All of the rows in a given block are designed to cause the same degree

Table 2. Future protocols for prostate cancer: iso-effective for late complications at α/β = 3 Gy

			With NTD and bNED for tumor α/β = 1.5 Gy		tumor α/β 1.0 Gy		tumor α/β 2.0 Gy	
No. Frs	Dose per Fr	Total dose (Gy)	NTD (Gy)	bNED (%)	NTD (Gy)	bNED (%)	NTD (Gy)	bNED (%)
33	2.00	66.00	66.0	51.6	66.0	52.8	66.0	50.9
25	2.43	60.77	68.3	58.5	69.5	62.8	68.3	58.3
20	2.83	56.60	70.2	64.4	72.3	70.0	68.4	58.4
15	3.42	51.37	72.3	69.9	75.7	77.9	69.4	62.3
10	4.44	44.37	75.3	77.1	80.4	86.0	71.4	67.4
5	6.76	33.81	79.8	85.5	87.5	94.0	74.0	74.4
36	2.00	72.00	72.0	69.2	72.0	69.4	72.0	69.1
25	2.58	64.51	75.2	77.0	77.0	80.3	73.9	73.9
20	3.00	60.00	77.1	81.0	80.0	85.4	75.0	76.7
15	3.62	54.35	79.5	85.2	83.7	90.1	76.4	79.7
10	4.69	46.85	82.8	89.6	88.8	94.3	78.3	83.4
5	7.12	35.58	87.6	94.0	96.3	97.6	81.1	87.8
39	2.00	78.00	78.0	82.6	78.0	82.5	78.0	82.2
25	2.73	68.13	82.2	88.9	84.6	90.9	80.6	86.9
20	3.16	63.28	84.3	91.2	87.8	93.6	81.7	88.6
15	3.82	57.23	86.9	93.5	91.8	95.9	83.2	90.4
10	4.92	49.23	90.3	95.7	97.2	97.8	85.2	92.4
5	7.46	37.29	95.4	97.6	105.1	99.1	88.2	94.7

Abbreviations: bNED = no biochemical evidence of disease; NTD = normalized total dose (to 2 Gy fractions).

of late damage in rectal tissue as either 33, 36, or 39 fractions of 2 Gy. This is done by assuming the α/β ratio for late damage is 3 Gy for all of the schedules, and adjusting the dose per fraction and total dose for each row so that the Biologically Effective Dose in Gy_3 is the same in every row within each of the three blocks in Table 2. (The BED is equal to the total dose multiplied by the relative effectiveness, which is defined as $1 + d/(\alpha/\beta)$, where d is the dose per fraction).

Thus, for example, in Block 2 of Table 2, in the first five columns the BED for the first row of 36 fractions of 2 Gy is 36×2 Gy $\times$ (1 + 2 Gy/3 Gy) = 120 Gy_3. By using the successive steps in the 36 Gy block, we reach five fractions of 7.12 Gy, for which the BED is 35.6 Gy $\times$ (1 + 7.18 Gy/3 Gy), which is also 120 Gy_3. In this way the late reactions in the rectal tissue are kept the same for each of the steps of the hypofractionation. The remaining columns in Table 2 illustrate sensitivity tests to test the LQ modeling, assuming different α/β ratios for the prostate, respectively 1 Gy and 2 Gy, but still keeping the late complications the same.

Having established fractionation regimens that would be expected, according to standard LQ modeling, to produce the same level of late effects, we now investigate what effect these more hypofractionated regimens would have on a prostate tumor with an α/β ratio that we initially assume to be 1.5 Gy (6). A convenient way to do this is to consider the Normalized Total Dose (NTD), which tells us the dose, given in 2 Gy fractions, that would give the equivalent biologic effect to the new hypofractionated dose (25, 26). The NTD (also called the LQED) is defined here as

$$NTD = D_{new}\left(1 + \frac{d_{new}}{\alpha/\beta}\right)\Big/\left(1 + \frac{2Gy}{\alpha/\beta}\right), \\ = \text{BED/(RE for 2 Gy fractions)}, \quad (1)$$

where D_{new} and d_{new} are respectively the total dose and dose per fraction for a suggested hypofractionation scheme. As we are trying to estimate the effect of these iso-late-effect schemes on tumor control, α/β = 1.5 Gy is the value appropriate here for the prostate.

For example, for a 3 Gy fraction size (as in the third row of the 36 Gy block in Table 2), the NTD for tumors with an α/β ratio of 1.5 Gy is:

$$60 \times (1 + 3 \text{ Gy}/1.5 \text{ Gy})/(1 + 2 \text{ Gy}/1.5 \text{ Gy}) = 77.1 \text{ Gy}. \quad (2)$$

This is the NTD—the dose in 2 Gy fractions that would give the equivalent biologic effect on prostate tumor to the lower hypofractionated dose of 20 $\times$ 3 Gy = 60 Gy. The late reactions in rectal tissue would of course be those corresponding to 36 F $\times$ 2 Gy = 72 Gy, whereas the effect on the prostate tumors would be larger with this hypofractionation scheme, corresponding to 77.1 Gy if given in 2 Gy fractions. Thus, there is a resultant therapeutic gain ratio of 77.1/72 = 1.07 in terms of equivalent doses. If we hypofractionated further to fewer and larger fractions, the therapeutic dose gains would become larger in principle. We caution below against excessive shortening of overall time.

If repair were the only factor affecting the consequences

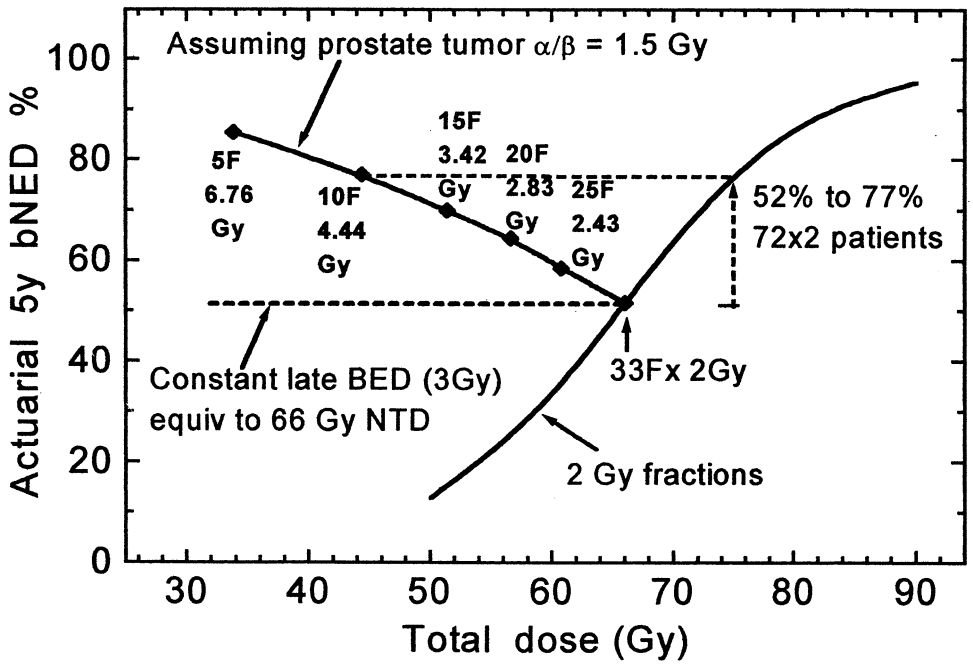

Fig. 2. Starting with 66 Gy in Fig. 1 (33 F × 2 Gy), the curve which rises to the left shows the estimated increase in bNED as total doses are reduced with fewer and larger fractions, calculated to keep late complications constant if α/β for the complications is 3 Gy.

of changes in fractionation, there would at first sight appear to be no apparent limit, except natural caution about the validity of the LQ model, to the reduction in number of dose fractions that should yield progressively improving therapeutic ratios. As we discuss later, however, there are other considerations. For example, we caution below against shortening to less than 5 weeks because of a possible risk of acute reactions in rectal tissue. This is especially true for the more modest hypofractions of 20 or 25 fractions (where total doses are still rather high) and for the highest range of 2 Gy starting doses in Block 3 of Table 2. We also warn against the use of too few fractions (<5) because this may limit the possibility of reoxygenation or redistribution of tumor cells into more sensitive phases of cell cycles.

A very practical question is how many patients would need to be enrolled in such clinical trials to obtain a significant difference in bNED. This consideration too is not favored in modest hypofractionation, where smaller gains in tumor control are predicted, as shown below.

RESULTS

The main results are shown in Table 2 in the first three columns, from which the following figures were constructed. Figure 2 shows the single curve for 2 Gy daily fractions, rising from left to right, with the proposed hypofractionated iso-late-effects schedules starting at 66 Gy and rising to the left toward lower total doses.

For example, it can be seen from Fig. 2 that 10 fractions, each of 4.4 Gy, should give about the same tumor control (measured, for example, by bNED) as 75 Gy in 2 Gy fractions, but with only the same late complications as 66

Table 3. Numbers of patients required to demonstrate the predicted differences at $p = 0.05$ and 90% power

Starting at conventional fractionation of:	66 Gy			72 Gy			78 Gy		
	33 × 2 Gy			36 × 2 Gy			39 × 2 Gy		
Using:	15 × 3.42 Gy			15 × 3.62			15 × 3.82		
	10 × 4.44			10 × 4.69			10 × 4.92		
	5 × 6.76			5 × 7.12			5 × 7.49		
Approx. no. of patients, total in 2 equal arms:									
Tumor α/β (Gy):	1.5	1	2	1.5	1	2	1.5	1	2
15 F	296	148	788	284	150	706	354	194	776
10 F	144	76	368	158	90	366	228	128	45
5 F	74	42	174	92	58	196	138	90	266

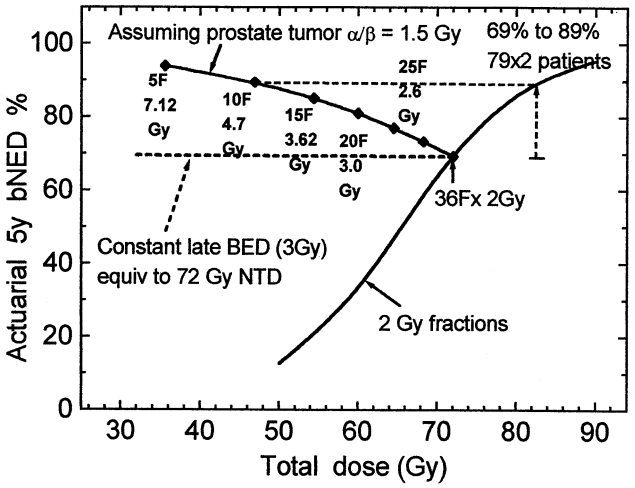

Fig. 3. As in Fig. 2, but starting at 72 Gy (36 F × 2 Gy).

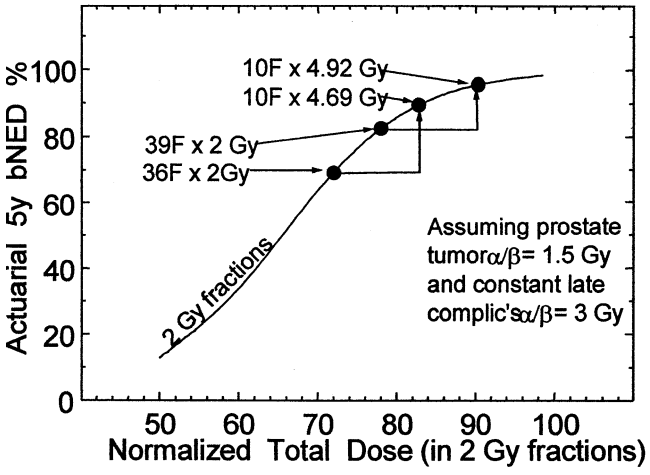

Fig. 5. Combination of Figs. 3 and 4 to illustrate the gains in bNED resulting for hypofractionation using 10 fractions instead of 36 or 39 fractions of 2 Gy.

Gy in 2 Gy fractions; in this case, the estimated bNED for tumors has increased from 51.6% (with 33 F × 2 Gy) to 77.1% (with 10 F × 4.44 Gy), so the therapeutic ratio has been increased substantially. This increase in bNED of 25% absolute would require a clinical trial with two arms of 72 patients in each, to have a 90% power of demonstrating the difference with a two-sided p value of 0.05 or less (Table 3). In this particular protocol, only one-third of the conventional number of fractions would have to be delivered, no increase in late complications would be expected to occur, and the early sequelae rate would be expected to decrease. These figures illustrate the major principle of the present strategy. They are based on the LQ modeling as described, with the essentially lower α/β ratio for prostate tumors than for late rectal complications.

Figures 3 and 4 show the corresponding results starting at 72 Gy and 78 Gy respectively in 2 Gy fractions. The gains in bNED (for iso-late-complications in rectum) are from 69.2% to 89.6% starting at 36 F × 2 Gy in Fig. 3 and hypofractionating to, say, 10 fractions of 4.7 Gy. This is an

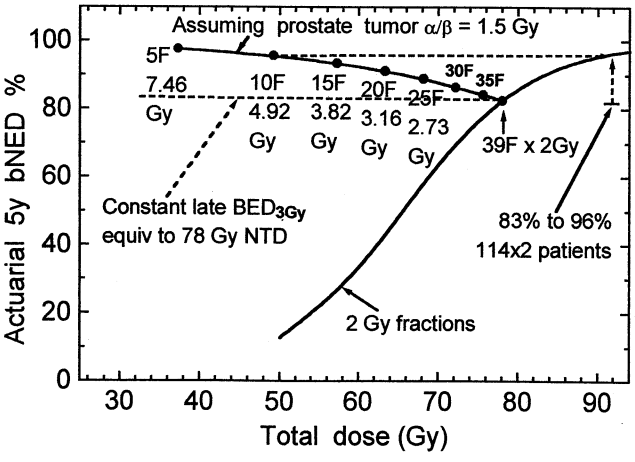

Fig. 4. As in Figs. 2 and 3, but starting with 78 Gy (39 F × 2 Gy).

estimated gain of 20.4% (absolute) in bNED, for our particular regression bNED vs. dose curve. It would require a clinical trial with two equal arms of about 79 patients in each (Table 3).

Figure 4 illustrates a situation of diminishing returns, where the highly escalated dose of 39 F × 2 Gy gives an estimated bNED of 82.6%, which is inflated to 95.7% if 10 external fractions of 4.9 Gy are used. This would require a clinical trial of 2 × 114 patients (Table 3). The obvious diminishing returns of a sigmoid curve are seen because the starting level is so high. The assumption is made that a sufficiently high dose could yield 100% bNED at 5 years, and this assumption is of course debatable, because of the risks, among others, of imperfect dose delivery or of occult metastatic disease at presentation.

Figure 5 illustrates some of the predicted bNED gains that might be seen with two of the 10-fraction hypofractionation schedules presented in Table 2, drawn to scale on the same graph as the bNED in Figs. 2 and 3. Late rectal effects are not increased within each escalation pair in Fig. 5, with no change in the physical dose distributions that were used in the present 2 Gy schedules of 72 or 78 Gy in 36 or 39 fractions. The small areas or volumes which receive specified high doses in rectal tissues in conformal or intensity-modulated radiotherapy (IMRT) techniques have to be maintained for each of the reduced-total-dose hypofractionation schedules: smaller, of course, if based on 78 Gy than on 72 Gy.

Sensitivity analyses for α/β of tumors

A sensitivity test was also carried out testing for the effect on bNED if the tumor α/β ratio was not 1.5 Gy but if iso-late-effect doses were still given assuming $\alpha/\beta = 3$ Gy (for constant late rectal complications) as in the first three columns of Table 2. We recalculated the estimated bNED values assuming that tumor α/β might be as low as 1.0 Gy (best case) or as high as 2 (worse than expected). This range

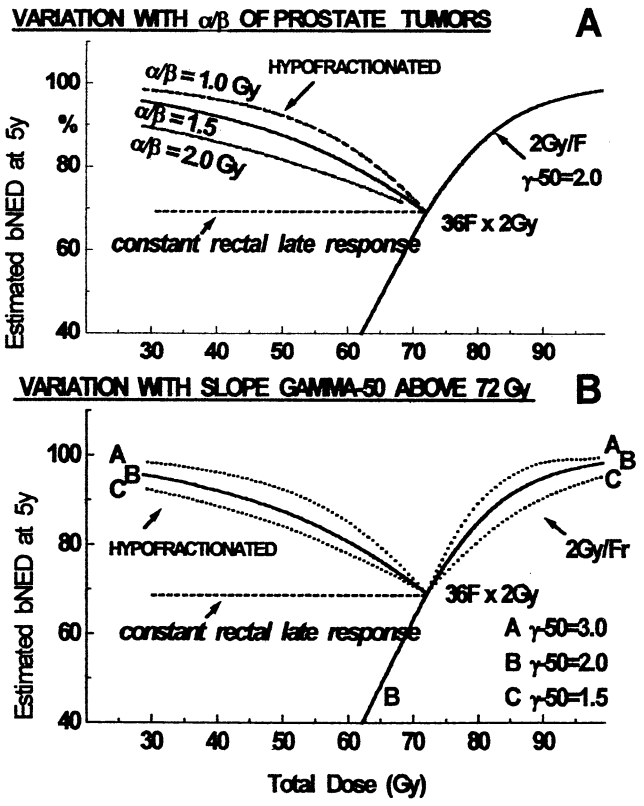

Fig. 6. Sensitivity testing: calculated effect on bNED for hypofractionated schedules (a) if prostate tumor α/β varies from 1.5 Gy to 1.0 or 2.0 Gy, dashed curves. (b) If slope of the basic dose–response curve for 2 Gy fractions varies from the γ-50 = 2.0 as in Fig. 1, to γ-50 = 1.5 or 3.0% bNED per percent increase in normalized total dose.

is twice as wide as the 95% confidence interval of the α/β = 1.5 (1.25 − 1.75) Gy value determined in our previous work (6). Fig. 6A depicts the central block of results from Table 2. It is clear that even if α/β varies from 1 to 2 Gy, there are substantial increases in gain for bNED predicted with hypofractionation which are not negated by this wide range of variation.

Sensitivity analyses for change of shape of the basic 2 Gy per fraction dose–response curve

We used the dose–response curve in Fig. 1 as a basis for the present modeling, but it can be criticized because of the inherent problems of identifying "intermediate-risk" patients from the published data reviewed. Fig. 6B therefore shows the effect of assuming drastic changes in shape of this basic dose–response curve if we are wrong in its γ-50 slope of 2.0 (B), and if subsequent clinical results suggest changes in slope to γ-50 = 1.5 (worst case (C)) or to 3.0 (an optimistically high slope [A]) for a clinical tumor-response curve. Both sensitivity-analysis curves are normalized to the same starting dose of 36 F × 2 Gy = 72 Gy as in Fig. 2. The results in Fig. 6B show somewhat similar alterations to the estimated bNEDs as the changes in α/β ratio in Fig. 6A. The "worst case" in Fig. 6B is not as low as the lowest curve in Fig. 6A by about 2% absolute, and the upper curves are within 1% agreement throughout. Again, these variations are not negligible quantitatively, but they do not cancel out the large gains predicted for hypofractionation.

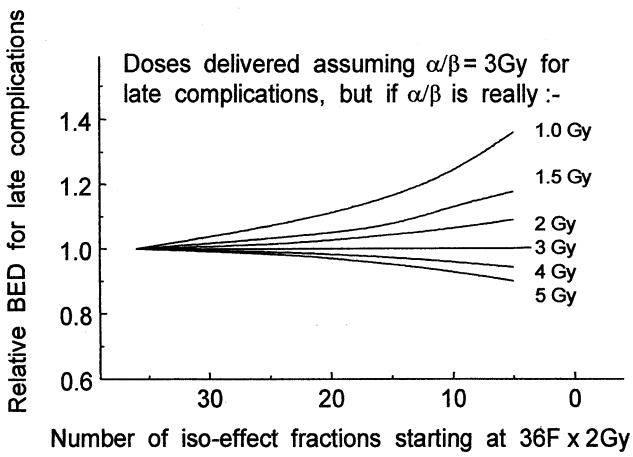

Fig. 7. Relative changes in late BED for rectal complications assuming a range of late-reaction α/β values in the range 1 to 5 Gy.

Sensitivity analyses for α/β of late complications

Figure 7 illustrates that the estimated increases in late complications are not larger than a few percent absolute, provided that the starting complication rates are less than about 10%. Figure 7 shows the results of testing the hypothesis that the α/β ratio of the critical late-responding tissue is not 3 Gy, as assumed in Table 2, but is some value between 1 and 5 Gy. Relative increases in late BED are shown for that range of α/β values. When the starting complication rate is low, the increase in complication rates is likely to be no steeper than approximately proportional to BED, although it would be steeper at incidences above about 15%.

If the late rectal α/β was exactly 3 Gy, the incidence of late complications in any of the suggested protocols would be constant for any number of fractions—this was how the suggested protocols were designed. If rectal α/β were larger than 3 Gy, the incidence of complications would be lower, which is desirable. If, however, the α/β of late rectal reactions were smaller than 3 Gy, say 1.0 Gy (which we argue below is most unlikely), the incidence of complications would be increased (in the absence of geometric dose–volume histogram changes), rising by factors of 1.15 or 1.25 at 15 or 5 fractions, respectively. Such low numbers of fractions is the "worst case" likely, meaning that if a given complication were normally 10% it could rise to 12.5%, or from 5% to 6.3%, when using only five fractions.

All the above considerations represent standard modeling around theoretically possible (but not necessarily expected) variations of the basic α/β = 3 Gy assumption for late effects. These hazards are ameliorated further by the developments of conformal and IMRT treatment planning within the last 10 years. Late rectal effects have been converted

from what used to be mostly stenosis (which is a "series tissue" problem, closing off the tube) to Grade 2 or 3 bleeding as rectal complications (a "parallel tissue" problem), amenable to controlling by restricting the area of rectal wall to less than 20% or 25% as described by Schwarchuk *et al.* (27) and Huang *et al.* (28), or less than 15 cm^3 by Kupelian *et al.* (29). It is only by those means that we have been able to escalate (in some countries) from the mid-60 Gy range a few years ago to the upper 70 Gy range in 2 Gy prostate treatments now. Dose–volume histograms showing high-dose regions of less than 15% rectum are not uncommon.

Evidence suggesting that late complications to the rectum tend to have higher values of α/β than the generic 3 Gy, thus permitting possibly larger gains than those illustrated above, will be discussed next. To be conservative, however, the main body of our tables and diagrams are based on a late complications value of $\alpha/\beta = 3$ Gy and standard LQ modeling.

DISCUSSION

How good are our assumptions?

The present estimates of doses and consequences have been made using the LQ formulation. The LQ formula, which is a mechanistically based approach, has been found to be robust for a well-spaced series of equal fractions of size between 1 and about 10 Gy (13, 30). Two very recent publications provide more evidence that the LQ formula continues to fit experimental cell survival data *in vitro* for single doses (31) and for multiple equal fractions (32). It is important to note, however, that this simple application of the model does not take into account other fractionation-related phenomena such as reoxygenation, redistribution, and repopulation, and we must consider how these might effect the conclusions of the current study. Repopulation has recently been invoked as a factor to consider in the permanent implant results (33). However, that modeling should take into account the factor Tk, the delay in days of the onset of "accelerated proliferation" after the beginning of irradiation (13). Because the distribution of dose throughout the implant volumes is nonuniform, rising to several times the prescribed dose of the periphery of the implant, it is assumed that it is adequate to stop proliferation and kill cells, as indeed the overall results demonstrate. Durations of Tk from 3 weeks to 5 weeks have been derived from clinical data in head-and-neck tumors (34–36), whose median pretreatment T_{pot} time is about 10 times shorter than the 40 days of prostate tumors. If the Tk value of prostate tumors is anywhere near to being proportional to T_{pot}, the effect of proliferation disappears from the estimation of α/β. The low value of $\alpha/\beta = 1.2$ Gy reported from clinical results of prostate treatments by Brenner *et al.* (8) supports this approach.

In terms of the parameters for the α/β value which we have considered here, the central issue is not just the value for prostate cancer, but the value for prostate compared with that for the surrounding late-responding normal tissue. Low α/β ratios of 3 to 4 Gy for late complications have generally been found in the slowly proliferating, late-reacting tissues, both in clinical and animal studies of rectal complications (13–17). Brain and spinal cord have lower values of α/β, of 1.5 or 2 Gy, but no other organs have been shown to have such low α/β values. No central nervous system is present close to prostate tumors, and we do not know the appropriate α/β values for the peripheral nerves present in the neurovascular bundles.

It was mentioned above that a generic value of 3 Gy is often assumed for late complications, including those in rectum. However, a study of animal experimental data reveals a more complicated picture. It should be borne in mind that if the α/β ratio for late rectal complications were higher than the value of 3 Gy that we have assumed up to now in this paper, then larger hypofractionated doses could be given with correspondingly larger clinical gains for the same constant late complication rates.

There is reasonable evidence that the α/β value for late-responding rectal complications is somewhat larger than this, typically around 4–6 Gy. For example, analyses of different experiments for late rectal damage in rodents by Brenner *et al.* (16) yielded 4.6 Gy (95% C.I. 4.0, 5.5). Van der Kogel *et al.* (37) reported 4.1 Gy (1.5, 7.7) and Dewit *et al.* (38) found 4.4 Gy (1.6, 7.7). Terry and Denekamp (39) reported a range of 3.1 to 5.1 Gy, while Dubray and Thames (17) found a range of 2.7 Gy (0.9, 4.8) to 6.7 Gy (2.2, 11.7). Gasinska *et al.* (40) found $\alpha/\beta = 6.4$ and 6.9 Gy for two different late rectal end points in mice.

Several authors have interpreted these somewhat high α/β values for late-responding rectal damage as indications that it is part "classical" late-responding damage, but in part "consequential" late damage, a conclusion also reached by other authors based on clinically observed correlations between early and late sequelae (16, 41–43). This would lead one to expect that the appropriate α/β value for late rectal sequelae would be somewhere between the value of 3 Gy for late effects and 10 Gy for classic early effects—and the animal data discussed above support this. We do not know exactly where rectal complications in humans would fall within this range—and it is possible that animal experiments might yield more consequential late sequelae than in the clinic, because the animal experiments are designed to yield a larger proportion of complications than in human patients. Nevertheless, these considerations suggest that it is very unlikely that the α/β value for late rectal complications would be significantly less than 3 Gy, with a range from 4–6 Gy being most plausible from the animal experiments listed above.

This somewhat larger-than-normal estimated α/β value for late-responding rectal damage makes it still more likely that the α/β for prostate tumors will not be larger than the α/β value for the relevant late-responding tissue—and increases the likelihood that the tumor α/β value will actually be less than the late-responding tissue α/β value.

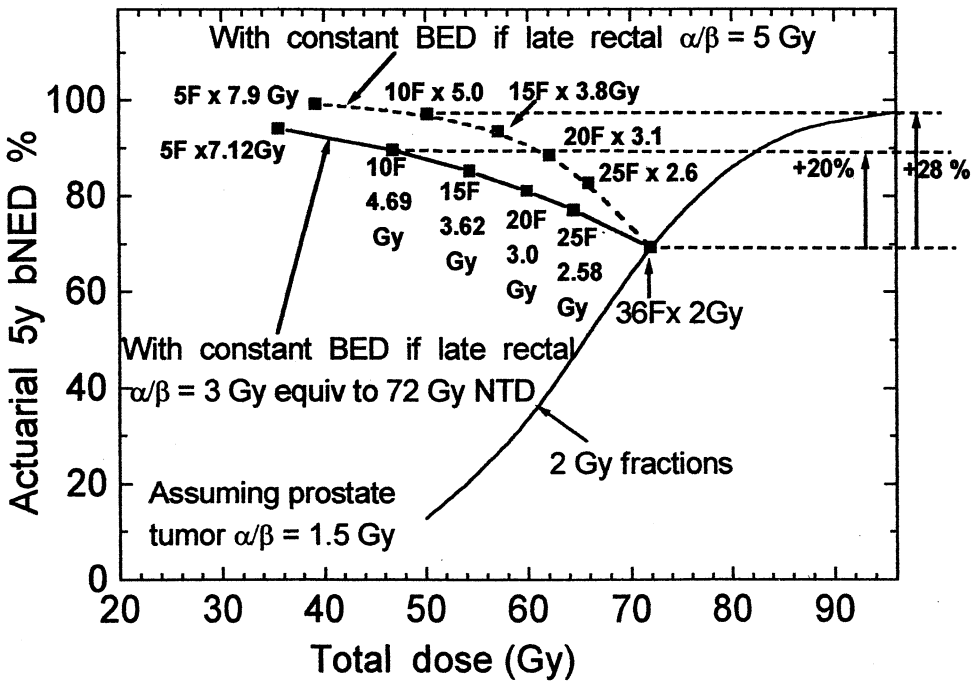

Fig. 8. As in Fig. 3, starting with 72 Gy in 2 Gy fractions, but with the constant late rectal complications calculated for α/β both 3 Gy (lower curve) and 5 Gy (upper curve). The upper curve shows a "best case" example.

The potential for improved outcome with hypofractionation

If the α/β value for prostate is reliably less than that for late-responding rectal damage, hypofractionated regimens could be designed with fewer but larger doses which maintain equivalent late sequelae while yielding improved tumor control. Again one would also expect less acute sequelae and thus, also, less "consequential" late effects, provided that overall time was not shortened unduly, for example to much less than about 5 weeks. For example, if the prostate α/β value is significantly less than the α/β for late complications, rather large increases in tumor control can be expected by changing from 30 or 40 fractions of 2 Gy to 20 or fewer larger fractions, without increasing the risk of late complications. There are already at least six clinical publications in evidence for some steps into hypofractionation for prostate cancer, at the rather modest end of hypofractionation with 28 fractions of 2.5 Gy (9, 10, 44) or 16 fractions of 3.13 Gy external beam (45).

Possible hypofractionation strategies

Table 2 presents protocols designed to keep the late complications as constant as possible, so there is no detriment to the patient in terms of late complications, and a likely advantage of increased tumor control.

This strategy requires a reduction in total dose with increasing fraction size as the number of fractions is decreased. Table 2 shows this reduction, as calculated with the LQ formula, initially assuming $\alpha/\beta = 3$ Gy for late effects. Using this value as a prior parameter in a Bayesian pattern of stopping-rules to govern dose-per-fraction escalation would enable improved estimates of α/β and consequently tolerance doses to be obtained in a properly designed Phase I–II clinical trial. We have however reported sensitivity tests which test the hypothesis that doses calculated to give constant rectal late effects assuming $\alpha/\beta = 3$ Gy actually encounter late-responding tissues with α/β ratios ranging from 1 to 5 Gy, and the results are not prohibitive (Fig. 7). Because α/β for acutely responding tissues is much higher, around 10 Gy, the proposed dose reductions should keep acute reactions safe, except in the case of excessively short overall times and very high total doses. The same is probably true of bladder reactions, based on the mouse bladder value of late $\alpha/\beta \sim 7$ Gy.

It is important to note that the relative gain from these strategies will be realized with or without high-tech conformal dose delivery, depending on the 2 Gy schedule used as the starting dose. The strategy depends only on the α/β ratio for prostate tumors being less than (or, at least, not being greater than) those for late complications. Should α/β be 4 or 5 Gy for late complications, as the animal data discussed above suggest, then we would be even safer using the doses in Table 2, or slightly higher doses could be recalculated as in Fig. 8 to generate the upper curve. If such higher doses per fraction could be used safely—which would require Phase I pilot studies—the numbers of patients required might become two equal arms of 62 patients (instead of 79 as in Fig. 3), to demonstrate a significant difference with $p = 0.05$ at the 90% power level using 10 fractions as in Fig. 8 in the upper hypofractionated arm.

Of course, using an IMRT technique, one could maintain the same high bNED as 78 Gy with 2 Gy fractions, but,

using say 20 F × 3.0 Gy, reduce complications to the same level as only 72 Gy NTD (compare Figs. 3 and 4 at 81–82% bNED). IMRT at 78 Gy or higher still does produce some rectal complications (bleeding), so there is room for improvement.

Overall treatment time

Because of the slow proliferation rate of prostate tumors, there is no biologic reason to shorten the overall schedules from the current 6 or 7 weeks. Shorter schedules, of course, have the potential to increase early sequelae (though probably not late rectal sequelae). In practice, departments might be tempted to explore much shorter overall times to save time, both for the patients and for the providers. At least initially we would caution against this, particularly for the very high total doses as in Block 3 of Table 2. Acute reactions diminish rapidly when overall time is expanded by only a few days, or by using 4 or 3 fractions per week.

Of course, as we have discussed, the hypofractionation regimens discussed here would, because of the lower total doses, result in decreased early sequelae, provided that overall time is not shortened too much. But this would be a consideration for the future, using clinical trials to address shortening specifically. At this time, therefore, we do not recommend shortening overall treatment times below, say, 5 weeks, pending appropriate Phase I clinical trials.

Minimum number of treatment fractions

We do not recommend a single fraction in any case. That would provide a very disadvantageous radiobiological option, because any tumor cells in a resistant state, whether because of cell cycle or because of physiologic milieu such as hypoxia, would have no chance of being sterilized by a subsequent fraction. We recommend, therefore that no less than five fractions are considered, to allow for possible reoxygenation or redistribution. We have therefore modeled expected tumor response for 5 to 25 fractions of external beam (or high-dose-rate) radiotherapy using the simplest LQ modeling.

It is not known how detailed factors of cell-cycle delay, progression, reoxygenation or other kinetic factors might play out in tumors when fewer and larger fractions are used; but within-tumor heterogeneity is likely to make any more detailed modeling difficult (30).

CONCLUSIONS

Hypofractionation will increase the therapeutic ratio between tumor control and late sequelae, provided that the α/β ratio for prostate tumors is lower than those for complications, including late rectal, late bladder, and any acute reactions. Considering both α/β values for prostate cancer and late rectal damage, the evidence is that the prostate α/β values are lower and it seems quite unlikely that they are higher than those for relevant sequelae. An apparently small difference of, say, between $\alpha/\beta = 1.5$ Gy for tumors and 3 Gy for late complications is quite large enough to allow clinically large increases in bNED (of 15% to 25% absolute).

The present modeling is based on the concept that no change in present treatment technique (of an institute) is required to achieve a good gain in bNED, with no increase in late or acute complications, using appropriate hypofractionation. Contrary to the expectation that these large fraction sizes require tighter fields, one could still achieve improved bNED while continuing to use low tech, less precise delivery, but with hypofractionation to lower total doses, provided that the limitation of high dose (~ 59–60 Gy NTD) to restricted rectal volumes is respected (27–29, 44). The increasing availability of IMRT and tomotherapy dose distributions makes the limiting of late complications even more feasible.

Equivalent bNEDs to the currently reported gains achieved using IMRT at high total doses of 2 Gy per fraction are predicted, at these lower hypofractionated doses (Figs. 2–4 and Table 2). This would be an inexpensive and efficient way of improving outcome, with no increase expected in late complications.

It is obvious that too-modest hypofractionation will not yield enough gain in bNED to be detectable with a practical number of patients in a clinical trial. Fewer than about 20 fractions will probably be necessary for a significant gain, and one purpose of this study is to guard against undue pessimism when the results of overcautious hypofractionation are considered. Other figures of patient numbers are given above with the results in Figs. 2 to 5. Multi-institutional trials would enable significant gains to be tested with quite short accrual times.

Finally, we caution again against the hasty adoption of extreme hypofractionation: using very small numbers of larger fractions, given in an unusually short overall time, without proper Phase I testing of the toxic effect of shortening or due allowance for rectal wall volume. We stress again that the new fraction-size regimens such as those described here must be used with appropriate reductions of the total dose. The present theoretical modeling provides some examples, but clinical pilot studies need to be carried out. None of these future schedules should be initiated without institutional review board approval.

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. Haustermans K, Fowler JF. A comment on proliferation rates in human prostate cancer [Letter]. *Int J Radiat Oncol Biol Phys* 2000;48:297.
3. King CR, Mayo CS. Is the prostate α/β ratio of 1.5 from Brenner and Hall a modeling artifact? *Int J Radiat Oncol Biol Phys* 2000;47:536–538.

4. Brenner DJ, Hall EJ. In response to Drs King and Mayo: Low α/β values for prostate appear to be independent of modeling details. *Int J Radiat Oncol Biol Phys* 2000;47: 538–539.
5. King CT, Fowler JF. A simple analytic derivation suggests that prostate cancer α/β ratio is low [Letter]. *Int J Radiat Oncol Biol Phys* 2001;51:213–214.
6. Fowler JF, Chappell RJ, Ritter MA. Is the α/β ratio for prostate tumors really low? *Int J Radiat Oncol Biol Phys* 2001;50:1021–1031.
7. Dale RG, Jones B. Is the α/β for prostate tumors really low? In regard to Fowler [RBE in] Fowler *et al.*, *IJROBP* 2001;50: 1021–1031. See also reply: Letter to the Editor. *Int J Radiat Oncol Biol Phys* 2002;52:1427–1428.
8. Brenner DJ, Martinez AA, Edmundson GK, Mitchell C, Thames HD, Armour EP. Direct evidence that prostate tumors show high sensitivity to fractionation (low α/β ratio) comparable to late-responding normal tissue. *Int J Radiat Oncol Biol Phys* 2002;52:6–13.
9. Kupelian PA, Reddy CA, Carlson TP, *et al.* Preliminary observations on biochemical relapse-free survival rates after short-course intensity-modulated radiotherapy (70 Gy at 2.5 Gy/fraction) for localized prostate cancer. *Int J Radiat Oncol Biol Phys* 2002;53:904–912.
10. Reuther AM, Willoughby TR, Kupelian PA. Toxicity after hypofractionated external beam radiotherapy (70 Gy at 2.5 Gy per fraction) versus standard fractionation radiotherapy (78 Gy at 2.0 Gy per fraction) for localized prostate cancer. Abstract # 1050. *Int J Radiat Oncol Biol Phys* 2002;54(Suppl. 2):187–188.
11. Brenner DJ. Towards optimal external-beam fractionation for prostate cancer [Editorial]. *Int J Radiat Oncol Biol Phys* 2000;48:315–316.
12. Fowler JF, Chappell R, Ritter MA. The prospects for new treatments for prostate cancer [Editorial]. *Int J Radiat Oncol Biol Phys* 2002;52:3–5.
13. Fowler JF. Review article: The linear-quadratic formula and progress in fractionated radiotherapy. *Br J Radiol* 1989;62: 679–694.
14. Leborgne F, Fowler JF, Leborgne JH, Zubizarreta E, Chappell R. Fractionation in medium dose rate brachytherapy of cancer of the cervix. *Int J Radiat Oncol Biol Phys* 1996;35:907–914.
15. Leborgne F, Fowler JF, Leborgne JH, Zubizaretta E, Chappell R. Biologically effective doses in medium dose-rate brachytherapy of cancer of the cervix. *Rad Onc Invest* 1997;5:289–299.
16. Brenner DJ, Armour E, Corry P, Hall E. Sublethal damage repair times for a late-responding normal tissue relevant to brachytherapy (and external-beam radiotherapy): Implications for new brachytherapy protocols. *Int J Radiat Oncol Biol Phys* 1998;41:135–138.
17. Dubray MB, Thames HD. Chronic radiation damage in the rat rectum: An analysis of the influences of fractionation, time and volume. *Radiother Oncol* 1994;33:41–47.
18. Stokes SH. Comparison of biochemical disease-free survival of patients with localized carcinoma of the prostate undergoing radical prostatectomy, transperineal ultrasound-guided radioactive seed implantation, or definitive external beam irradiation. *Int J Radiat Oncol Biol Phys* 2000;47:129–136.
19. Hanks GE, Hanlon AL, Pinover WH, Horwitz EM, Price RA, Schultheiss T. Dose selection for prostate cancer patients based on dose comparison and dose response studies. *Int J Radiat Oncol Biol Phys* 2000;46:823–832.
20. Vicini F, Kestin L, Martinez AA. The importance of adequate follow-up in defining treatment success after external beam irradiation for prostate cancer. *Int J Radiat Oncol Biol Phys* 1999;45:553–561.
21. 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.
22. Pollack A, Zagars GK, Smith LG, Antolak JA, Rosen II. Preliminary results of a randomized dose-escalation study comparing 70 Gy to 78 Gy for the treatment of prostate cancer (Abstr). *Int J Radiat Oncol Biol Phys* 1999;45(Suppl):146–147.
23. 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* 1999;45(Suppl.):507–512.
24. Shipley WU, Thames HD, Sandler JM, *et al.* Radiation therapy for clinically localized prostate cancer: A multi-institutional pooled analysis. *JAMA* 1999;281:1598–1604.
25. Yaes RJ, Patel P, Maruyama Y. On using the linear-quadratic model in daily clinical practice. *Int J Radiat Oncol Biol Phys* 1991;20:1353–1362.
26. Lebesque JV, Keus RB. The simultaneous boost technique: The concept of relative normalized total dose. *Radiother Oncol* 1991;22:45–55.
27. Schwarchuk MW, Jackson A, Zelefsky MJ, *et al.* Late rectal toxicity after conformal radiotherapy of prostate cancer (I): Multivariate analysis and dose–response. *Int J Radiat Oncol Biol Phys* 2000;47:103–113.
28. Huang E, Pollack A, Levy L, *et al.* Late rectal toxicity: Dose–volume effects of conformal radiotherapy for prostate cancer. *Int J Radiat Oncol Biol Phys* 2002;54:1314–1321.
29. Kupelian PA, Reddy CA, Carlson TP. Dose/volume relationship of late rectal bleeding after external beam radiotherapy for localized prostate cancer: Absolute or relative rectal volume? *Cancer Journal from American Express* 2002;8:62–66.
30. Brenner DJ, Hlatky LR, Hahnfeld 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.
31. Bartkowiak D, Hogner S, Nothdurft W, *et al.* Cell cycle and growth response of CHO cells to X-irradiation: Threshold-free repair at low doses. *Int J Radiat Oncol Biol Phys* 2001;50: 221–228.
32. Kummermehr J, Malinen E, Freykowski S, *et al.* The influence of autologous tumor fibroblasts on the radiosensitivity of squamous cell carcinoma megacolonies. *Int J Radiat Oncol Biol Phys* 2001;50:229–237.
33. Wang JZ, Guerrero M, Allen Li X. How low is the α/β ratio for prostate cancer? *Int J Radiat Oncol Biol Phys* 2003;55: 194–203.
34. Withers HR, Taylor JMG, Maciejewski B. The hazard of accelerated clonogen repopulation during radiotherapy. *Acta Oncol* 1988;27:131–146.
35. Brenner DJ. Accelerated repopulation during radiotherapy; quantitative evidence for delayed onset. *Radiat Oncol Invest* 1993;1:167–172.
36. Roberts SA, Hendry JH. The delay before onset of accelerated tumor cell repopulation during radiotherapy: A direct-maximum likelihood analysis of a collection of world-wide tumor-control data. *Radiother Oncol* 1993;29:69–74.
37. van der Kogel AJ, Jarrett KA, Paciotti MA, Raju MR. Radiation tolerance of the rat rectum to fractionated X-rays and pi-mesons. *Radiother Oncol* 1988;12:225–232.
38. Dewit L, Oussoren Y, Bartelink H, Thames HD. The effect of cis-diamminedichloroplatinum(II) on radiation damage in mouse rectum after fractionated irradiation. *Radiother Oncol* 1989;16:121–128.
39. Terry NAH, Denekamp J. RBE values and repair characteristics for colorectal injury after caesium 137 gamma ray and neutron irradiation. II Fractionation up to ten doses. *Br J Radiol* 1984;57:617–629.

40. Gasinska A, Dubray B, Hill SA, Denekamp J, Thames HD. Early and late injuries in mouse rectum after fractionated x-ray and neutron irradiation. *Radiother Oncol* 1993;26:244–253.
41. Jereczek-Fossa BA, Jassem J, Badzio A. Relationship between acute and late normal tissue injury after postoperative radiotherapy in endometrial cancer. *Int J Radiat Oncol Biol Phys* 2002;52:476–482.
42. Leung SW, *et al.* The corrrelation of acute toxicity and late rectal injury in radiotherapy for cervical carcinoma: Evidence suggestive of consequential late effect (CQLE). *Int J Radiat Oncol Biol Phys* 1998;40:85–91.
43. Dörr W, Hendry JH. Consequential late effects in normal tissues (Review). *Radiother Oncol* 2001;61:223–231.
44. Mohan DS, Kupelian PA, Willoughby TR. Short-course intensity-modulated radiotherapy for localized prostate cancer with daily transabdominal ultrasound localization of the prostate gland. *Int J Radiat Oncol Biol Phys* 2000;46: 575–580.
45. Logue JP, Livsey JE, Cowan RA, *et al.* Hypofractionated conformal radiotherapy of the prostate: 5-year outcome analysis [Abstract 1052]. *Int J Radiat Oncol Biol Phys* 2002;54(2S): 189.