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REVIEW ARTICLE

The radiobiology of prostate cancer including new aspects of fractionated radiotherapy

JACK F. FOWLER

Emeritus of Medical School of Wisconsin University, Department of Human Oncology, University of Wisconsin-Madison, USA

Abstract

Total radiation dose is not a reliable measure of biological effect when dose-per-fraction or dose-rate is changed. Large differences in biological effectiveness (per gray) are seen between the 2 Gy doses of external beam radiotherapy and the large boost doses given at high dose-rate from afterloading sources. The effects are profoundly different in rapidly or slowly proliferating tissues, that is for most tumors versus late complications. These differences work the opposite way round for prostate tumors versus late complications compared with most other types of tumor. Using the Linear-Quadratic formula it is aimed to explain these differences, especially for treatments of prostate cancer. The unusually slow growth rate of prostate cancers is associated with their high sensitivity to increased fraction size, so a large number of small fractions, such as 35 or 40 "daily" doses of 2 Gy, is not an optimum treatment. Theoretical modeling shows a stronger enhancement of tumor effect than of late complications for larger (and fewer) fractions, in prostate tumors uniquely. Biologically Effective Doses and Normalized Total Doses (in 2 Gy fraction equivalents) are given for prostate tumor, late rectal reactions, and—a new development—acute rectal mucosa. Tables showing the change of fraction-size sensitivity (the alpha/beta ratio) with proliferation rates of tissues lead to the association of slow cell doubling times in prostate tumors with small α/β ratios. Clinical evidence to confirm this biological expectation is reviewed. The α/β ratios of prostate tumors appear to be as low as 1.5 Gy (95% confidence interval 1.3–1.8 Gy), in contrast with the value of about 10 Gy for most other types of tumor. The important point is that $\alpha/\beta = 1.5$ Gy appears to be significantly less than the $\alpha/\beta = 3$ Gy for late complications in rectal tissues. Such differences are also emerging from recent clinical results. From this important difference stems the superior schedules of, for example, 20 fractions of 3 Gy, or 10 fractions of 4.7 Gy, or 5 fractions of 7 Gy, which can all give tumor results equivalent to 80–90 Gy in 2 Gy fractions, while keeping late complications equivalent to only 72 Gy in 2 Gy fractions. Combination treatments of external beam (EBRT) and brachytherapy boost doses (25F $\times$ 2 Gy plus 2 $\times$ 10 Gy) can give higher biological tumor effects than any EBRT using daily 2 Gy doses, and with acceptable late complications. Monotherapy by brachytherapy for low-risk cancer prostate using two to four fractions in a few days can give even higher biological effects on the tumors.

Introduction

Readers who are familiar with the Linear Quadratic formulations in radiotherapy may wish to skip to the end of the Introduction. New readers will find the ESTRO course book "Basic Clinical Radiobiology" [1] clear and concise.

It is common practice to deliver radiotherapy to patients in a schedule of 5 fractions per week of 2 grays (Gy), up to 33 to 39 factions and a total of 66 to 78 Gy in 7 to 8 weeks. This is not necessarily the optimum schedule for all types of tumor, but if dose-per-fraction is altered, the biological effect is no longer proportional simply to total dose. A correction must be made for the size of each dose-per-fraction, or for different dose-rates. This correction depends on the type of tissue being irradiated, especially on its proliferation rate, and can be adequately described by the Linear-Quadratic formula, which defines the shape of cell survival curves as a function of radiation dose.

The *initial slope* of a cell survival curve (alpha or α) represents the *intrinsic radiosensitivity* of the cell, and is a non-repairable type of damage. It is linearly dependent on dose. The *curvature* of the cell survival curve (beta or β) represents a repairable type of injury with time, responsible for the dose-per-fraction and dose-rate variations in radiobiology. It is proportional to the square of the dose, hence the quadratic term.

Correspondence: Prof. J.F. Fowler, DSc, PhD, 150, Lambeth Rd, London SE1 7DF, UK. Tel: +44-207-207-7997. E-mail: jackfowler@btinternet.com

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The shape of the cell survival curve depends on those two factors, initial slope and curvature; these are called the alpha and beta coefficients respectively. The sum of their effects represents the overall radiosensitivity of any type of cell that is irradiated. The dependence of radiosensitivity of cells on natural, unirradiated, proliferation rate is due to the relative size of the two factors. With a slow cell proliferation rate the long cell cycle times allow plenty of time for intracellular repair between successive fractions. The ratio of the alpha to the beta term is then naturally low. By contrast, rapidly proliferating cells have little time for repair, so that the ratio of alpha to beta is large.

The ratio of a to b then determines the sensitivity of a particular type of cell to alterations in radiation fraction size [2]. Rapidly proliferating cells, with high α/β ratios, are not very sensitive to alterations in fraction size or dose-rate. This is true of most types of tumor [3] but not of prostate tumors. Slowly proliferating cells however, with low α/β ratios (that is with plenty of repair, and misrepair, capability) are very sensitive to increase in fraction size or dose-rate. Thus late-responding normal tissues, in which the late complications occur, are unfortunately sensitive to large doses per fraction. Thus hypofractionation is avoided for most types of tumor, and correctly so.

Table I illustrates the difference in α/β ratios between normal tissues, in the absence of any treatment [3]. The difference between the high α/β ratios of around 10 Gy for rapidly proliferating tissues and the lower ratios $\sim$2 to 4 Gy for slowly proliferating tissues is clear. This difference is correlated with cell proliferation rate.

Proliferation rate is described in terms of a population doubling time, the Potential Doubling Time (Tpot), which can be measured from biopsies after administration in situ to the patient of a DNA thymidine tracer. Table II lists some Tpot ratios determined for human tumors. There are a few types of tumor with untypically low ratios of α/β, of which prostate tumors show the lowest α/β ratio, because they have the longest Tpots of any human tumors, from 15 to more than 70 days [4]. Incidentally, the next longest Tpot in human tumors is for breast carcinoma, with a median Tpot of 14 days but a range extending to rapid growth (3–70 days). Most carcinomas, however, have median Tpot values of 4–9 days, and each type ranges from about 2 to 20 or 30 days [5].

Table I. Ratios of α/β for early and late radiation reactions in normal tissues, determined from laboratory animal and clinical data [1,3].

Early reactions	α/β (Gy)	Late reactions	α/β (Gy)
Skin	9–12	Kidney	2–2.4
Jejunum	6–10	Rectum	2.5–5
Colon	9–11	Lung	2.7–4
Testis	12–13	Bladder	3–7
Mucosa	9–10	CNS: brain,spinal cord	1.8–2.2

Table II. Pretreatment potential doubling times (Tpot) measured in human tumor biopsies by flow cytometry [3,4].

	Median	Range
Larynx	4 days	2–19 days
Tongue	4–6	2–16
Mouth, cheek	3.4	2–15
Esophagus	5	2.5–20
Ca. cervix	5	3–20
Rectum	5	3–18
Prostate	42	15–>70
Breast	14	3–70

Because they are mostly rapidly proliferating, many types of tumor—especially carcinomas—have high ratios of α/β, from 10 Gy up to infinity. It is logical therefore to use a large number of small doses to treat them by radiotherapy, so as keep damage to late-reacting normal tissues relatively low. However, the very long turnover times in prostate tumors are associated with the low ratio of α/β for those tumors (Table III). Optimum fractionation for prostate tumors is therefore more likely to involve fewer and larger fraction than 2 Gy up to 78 Gy in 39 fractions, which is a recent "conventional" proposal to treat prostate tumors in the USA. The case for hypofractionation specifically for prostate cancer is a biologically logical one [6,7].

Why do we think α/β is small in prostate tumors?

Brenner and Hall [8] were the first to point out (in 1999) that there is clinical evidence supporting the idea that prostate tumors have exceptionally low values of α/β. They used the documented result that similar biochemical long-term control is achieved using external beam doses of about 70 Gy in 1.8–2.0

Table III. Ratios of α/β for human tumors, derived from clinical data where different doses per fraction were used [1].

Vocal cord	$\sim$9.9 Gy	Harrison et al. 1988
Oropharynx	13–19	Rezvani et al. 1993
Larynx	25–35	Maciejewski et al 1988
Larynx	50–infinity	Chappell & Fowler 1995
Larynx	50–infinity	Roberts & Hendry 1998
Only a few types of tumor have low values of α/β:		
Malig. melanoma	0.6 Gy	Bentzen et al. 1989
Prostate Ca.	1.5	Brenner & Hall 1999
Prostate Ca.	1.49	Fowler et al. 2001
Prostate Ca.	1.2	Brenner ... Martinez 2002
Rhabdomyosarcoma	2.8	Timmerman 2002

Gy fractions but using 145 Gy from permanent Iodine-125 low-dose-rate irradiation. They derived an α/β ratio of 1.5 Gy with a 95% confidence interval of 0.8 to 2.2 Gy, based on 367 patients from two treatment centers. Two years later our group in Wisconsin updated this analysis (9) with 1020 patients from 11 centers, and came to the same result of $\alpha/\beta = 1.5$ Gy, with a narrower confidence interval of 1.25 to 1.75 Gy (ref. 9 and the present Figure 1). Much discussion has followed these results [10] but 5-year clinical results continue to accrue that support the low values of α/β between 1 and 2 Gy [11–13] and our group has no reason to alter our expectation that α/β is approximately 1.5 Gy or even slightly below that value.

A particular criticism that has aroused discussion is that neither Brenner and Hall nor Fowler et al. assumed that repopulation in the tumors was significant during low dose-rate treatment with I^{125} [8,9]. Wang et al. [14] and Kal and Van Gellekom [15] preferred to assume that repopulation in the tumors started at a time T_k (or T_{onset}) of 0 or 28 days after starting treatment. This assumption of short onset time caused a 23% reduction of I^{125} dose from 145 to 112 Gy, and resulted in an estimate of $\alpha/\beta =$ 3–4 Gy instead of the previously derived 1.5 Gy. Apart from this point about early onset of repopulation, it should be noted that all four of the above calculations agreed on a small value of α/β [8,9,14,15]. The half-time of repair makes a relatively small difference. It is emphasized that the difference between those proposing $\alpha/\beta = 1.2$–1.5 Gy [8,9] and those proposing 3–4 Gy [14,15] is entirely dependent on the assumption of the onset time of tumor repopulation.

In rebutting the assumption of an early start of repopulation, Fowler et al. [10] quoted well-established clinical data, which showed that the median delay times of reappearance of PSA were 10 months for patients who relapse clinically and 16 months for those who do not [16]. They pointed out that these long reappearance times are not consistent with a Tk as short in prostate tumors (where median Tpot = 42 days), as it is in the much more rapidly proliferating head and neck tumors (Tpot = 3 to 6 days). They propose that an assumption of Tk as short as 0 to 28 days [14,15] is not biologically reasonable for prostate tumors, so that the α/β ratio is most likely to remain at or close to 1.5 Gy. There are no clinical results that contradict this conclusion. Two new clinical reports suggesting that α/β about 1.5 Gy are analysed below [12,13].

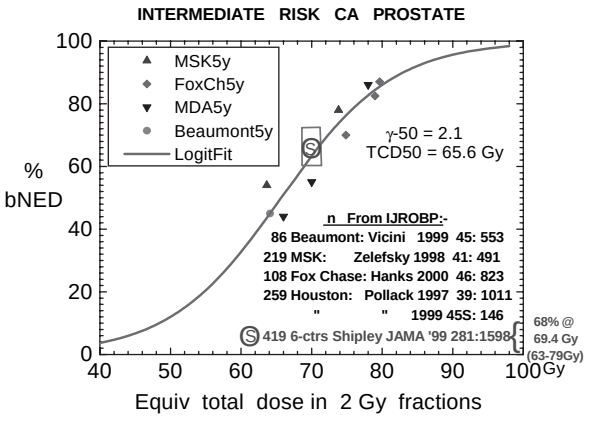

Figure 1. Logit plot of 5-year biochemical non-recurrence versus total dose in 2 Gy fractions from four centers as listed for intermediate risk prostate cancer, with the summary result of Shipley et al. (the two central categories) as a vertical rectangle. The references are given in full in Fowler et al. [9,19].

The observation that hypoxic cells can be identified by DNA labeling in prostate tumors [17] is interesting but their significance in relation to α/β values is unknown. It might be speculated that hypoxia, usually due to poor blood supplies in tumors, might slow down proliferation and thus help to diminish the value of the ratio α/β.

Material and methods

Because prostate tumors have exceptionally long turnover times, it is logical to expect that their α/β ratios might be small, more typical of late than of early-reacting normal tissues. Then hypofractionation would be a better strategy for radiation treatment than the many small fractions used for other tumors [6,7], as is also the case with malignant melanoma [18]. Provided that the α/β ratio for prostate tumors *is significantly below that for late rectal complications* [9], then hypofractionated schedules can be designed which will keep late reactions constant and also give greater tumor cell kill. These possibilities are fully explored by Fowler et al. [19] for three levels of rectal late complications, and some of those theoretical results are reproduced below.

A Biologically Effective Dose (BED) can be calculated for any dose per faction d (and for a total dose nd when n equal fractions are given), if a value for the appropriate tissue α/β ratio is assumed [3]:

$$BED = nd(1 + d/[\alpha/\beta]) \qquad (1)$$

Calculations are carried out most easily as BED in Gy_{10} or Gy_3 (for rapidly or slowly reacting tissues respectively), or $Gy_{1.5}$ for prostate tumors. The subscript shows the α/β ratio that was assumed. However, they are not immediately familiar units unless the reader uses them regularly, so it is also common to convert a BED to the LQ equivalent dose in 2 Gy fractions, called Normalised Total Dose or NTD_{2Gy}. We shall often give both here. Table IV explains the link for conversion between them.

To calculate a series of schedules that should give equal late complications, for example in rectal tissue, a calculation must be made of the various schedules that would give constant late rectal reactions using fewer and larger fractions. For example, if we accept the level of rectal reactions given by 74 Gy = 37F × 2 Gy, then use of the standard linear quadratic formula:

$$BED = 74(1 + 2/3) = nd(1 + d/3) \qquad (1a)$$

enables different values of d and n to be calculated, all with the same late-reaction BED in Gy_3. These are converted to NTD_{2Gy} by dividing each BED by 1.667, as described in Table IV. The results are shown in Table V for n = 25, 20, 15, and some smaller numbers of fractions to tabulate possible hypofractionation schedules that would keep late rectal complications constant. The constancy of the BED in Gy_3 and the NTD_{2Gy} in Gy in the third and fourth columns is the justification for this set of calculations. The final two columns give the NTD_{2Gy} for tumor cell kill assuming $\alpha/\beta = 1.5$ Gy for prostate tumors, and the corresponding estimated 5y bNEDs from Figure 1. The escalation of tumor effect with increasing dose per fraction, in spite of reduced total doses and constant late complications, can be seen by comparing columns four and five in Table V. This demonstrates the principle of the hypofractionation method, provided that the α/β ratio for prostate tumors is significantly less than for the rectal complications.

Results and discussion: External beam radiotherapy

First a calculation must be made, similar to Table V, for constant late rectal BEDs for fewer (and therefore larger) fractions. This was done by Fowler et al. [19] for three levels of total dose: 66, 72, and 78 Gy in 2 Gy fractions, all for intermediate risk prostate tumors. This risk category was defined as "Stage 1 or 2, pretreatment PSA 10–20 ng/ml, with at least one other risk factor, Gleason stage = >7, OR Stage 2b". It was for this subset of patients that we constructed Figure 1 from the literature [9,19]. The results are shown in Figures 2a, b and c, reproduced with permission from our reference [19]. The original curve for 2 Gy per fraction schedules rises to the right, and the hypofractionated schedules to the left, because total doses are reduced as in Table V. It can be seen that, as the total doses decrease with fewer but larger fractions, the tumor effect rises appreciably, although the late rectal complications should remain constant. At the level of 66 Gy for late rectal complications respectively (Figure 2a), the estimated bNED values rise from 52 to 78% with 10 fractions of hypofractionation [19]. This is a large enough change to be detected with a modestly sized clinical trial, about 150 patients, whilst larger numbers of more modestly hypofractionated fractions will require many more patients. Fowler et al. discuss those schedules, with estimated confidence limits [19]. They also discuss in detail the possibility that the α/β ratio for late rectal complications might possibly be somewhat higher than 3 Gy, which would make the hypofractionation strategy even safer. It makes the modeled value of $\alpha/\beta = 1.5$ Gy for tumors less likely to overlap.

All those schedules assume that the area of rectal wall irradiated to the tumor-prescribed dose is restricted to what it would be for respectively 66 Gy, 72 Gy, and 78 Gy in 2 Gy fractions. These rectal surface areas naturally become smaller through the sequence of three dose levels just described. Huang et al. [20] and Vargas & Martinez [21] have suggested limited areas of rectal wall for a range of maximum doses to any point in the rectal wall (Table VI and Figure 3). It is emphasized that the reliable limitation of rectal wall high-dose area is as important as the accuracy of maximum rectal dose itself in achieving safe treatments.

Clinical confirmation that some of these hypofractionated doses work in practice have come from Toronto [22] where they have been using 20F × 3.0 Gy for over two years now, without either late or early rectal or bladder problems. This schedule is equivalent to only 72 Gy in 2 Gy fractions for late

Table IV. The link between BED and NTD_{2Gy} is simply proportional to the relative effectiveness (RE) of a 2 Gy fraction, which is $(1+2/[\alpha/\beta])$.

Tissue	Assumed α/β Ratio (Gy)	RE for 2Gy fractions	Divide BED by this RE to get NTD_{2Gy}
Prostate tumor	1.5 Gy	1+2/1.5 = 2.333	2.333
Late complications (rectum)	3.0 Gy	1+2/3 = 1.667	1.667
Acute complications (mucosa)	10.0 Gy	1+2/10 = 1.2	1.2
Converting BED to NTD_{2Gy} requires dividing the appropriate BED by the figure in the final column			

RE = (1 + d/[α/β]), where BED = total dose × RE. [1,2]; NTD_{2Gy} is the normalized total dose in 2 Gy fractions that would give the same log cell kill as the schedule being analyzed.

Table V. Hypofractionated schedules calculated for external beam radiotherapy for constant late rectal complications assuming $\alpha/\beta = 3$ Gy.

		Rectal		Tumor	
Hypofractionated Schedule	Total Dose (Gy)	BED Gy3 for $\alpha/\beta = 3$Gy	Late rectal Complications NTD $_{2Gy}$ ($\alpha/\beta = 3$Gy)	Calculated NTD_{2Gy} ($\alpha/\beta = 1.5$Gy)	Estimated bNED (from Figure 1)
37F $\times$2.00	74.0	123.3	74.0 Gy	74.0 Gy	75.5%
25F $\times$2.69	65.73	123.3	74.0	78.7	82.8
20F $\times$3.06	61.11	123.3	74.0	79.6	84.0
15F $\times$3.69	55.33	123.3	74.0	82.0	87.3
10F $\times$4.77	47.65	123.3	74.0	85.4	90.0
5F $\times$7.73	36.16	123.3	74.0	90.2	94.0
3F $\times$9.70	29.10	123.3	74.0	93.1	95.8

New total dose $= 74 \times (1 + 2/3)/(1 + d/3)$ for the constant late BED of 123.3 Gy_3. NTD_{2Gy} = normalized total dose, the schedule using 2 Gy fractions that would give the same log cell kill. The final two columns also present the consequent prostate tumor effects, as normalized total dose (NTD2Gy in 2 Gy fractions) assuming $\alpha/\beta = 1.5$ Gy; and the estimated 5 year percentage bNED (from Figure 1).

complications, but to a prostate tumor of NTD_{2Gy} of 78 Gy.

Analyses of recently published results of hypofractionation

An interesting confirmation that α/β may be as low as 1.0 Gy comes from a Canadian randomized trial in which 20 hypofractionated doses totaling only 52.5 Gy were compared with 66 Gy in 2 Gy fractions, with 936 prostate patients of intermediate risk analyzed [12]. Figure 4 shows that when Lukka et al's data [12] were analyzed by the present LQ method, assuming $\alpha/\beta = 1.5$ Gy, the point was above the generic curve from Figure 1 although the 66 Gy control arm point was correctly on it. This meant that their hypofractionated arm did better than expected from the modeling point of view, although the total hypofractionated dose was too low to give equality with the control arm. When however the Lukka et al. data were reanalyzed by the present author assuming $\alpha/\beta = 1.0$ Gy instead, the point then fell right on the generic curve (Figure 5). Thus their trial should not be interpreted as a failure, because it indicated clearly that α/β was indeed as low as 1 to 1.5 Gy, although the proportion of bNED could not be as high as the control arm because of the choice of the low total dose. Hypofractionation with somewhat higher, carefully modeled, total doses would give much better tumor results.

In Manchester, UK, they have been using the total dose that the Canadians used in Lukka's trial, but in only 16 fractions of 3.125 Gy instead of 20 fractions of 2.625 Gy. Livesy et al. recently reported Manchester's hypofractionated results, and showed results that they state are consistent with 66 Gy in 2 Gy fractions and indicative of an α/β ratio of approximately 1.5 Gy [13]. Simple modeling using our Equation (1) confirms this. In all these examples of hypofractionated treatment of prostate cancer the number of fractions can be greatly reduced, with no additional late complications and with improvement in tumor effect.

Kupelian et al. report safe experience with 28 fractions of 2.5 Gy [22], and Ritter et al (personal communication, 2002) have planned a dose-per-fraction escalation trial starting with 22 $\times$ 2.94 Gy, then moving to 16 $\times$ 3.63 Gy and eventually to 12F $\times$ 4.29 Gy. The first step has recently been successfully completed.

A Phase III clinical trial is being proposed in Sweden [24]. It aims to demonstrate a 10% increase (from 70% to 80% from a slightly less optimistic estimate than our Figure 1) in freedom from failure in the hypofractionated arm at 5 years. This would require a total of 600 patients in the two arms combined, (80% power, $p = 0.05$). The control arm will consist of 35F $\times$ 2 Gy = 70 Gy plus a boost dose of 4F $\times$ 2 Gy, totaling 78 Gy in real 2Gy fractions. The hypofractionated arm will consist of 7F $\times$ 6.1 Gy to a total of 42.7 Gy in 4 weeks. The BEDs, however, show that the hypofractionated arm has a tumor-equivalent dose of 92.7 Gy NTD_{2Gy} (assuming $\alpha/\beta = 1.5$ Gy) but a rectal-equivalent late NTD_{2Gy} of 78 Gy (assuming $\alpha/\beta = 3$ Gy). All fractions will be localized by marker guidance. The constraints on rectal wall area were mentioned above [20,21], and in Table VI.

Practical alternatives to 2 Gy fraction schedules in postoperative or combined external-beam and brachytherapy treatments

For surgical patients where the margins of the excised tumor were either not clear or were suspect, a postoperative schedule of 35F $\times$ 2Gy = 70 Gy has sometimes been used. Such a schedule could be converted, by using a formula similar to Equation (1), to 25 or 20 or 15 larger fractions, all totaling the same late BED in Gy_3 and therefore the same

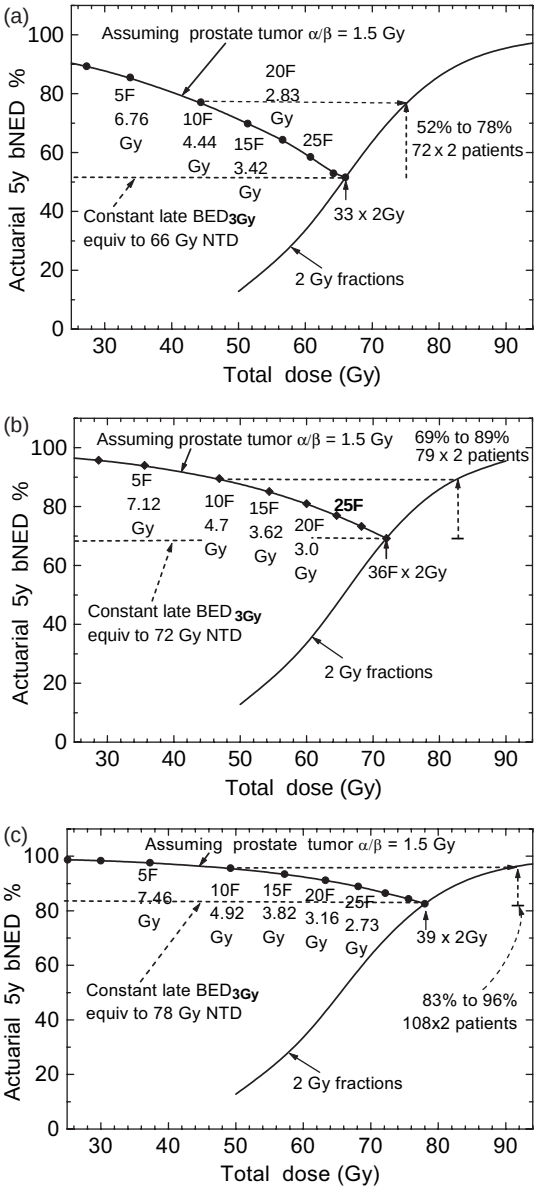

Figure 2. These three figures show the same curve for 2 Gy fractions as in Figure 1, rising to the right, and a curve rising to the left for hypofractionated, reduced, total doses calculated to keep the late rectal complications constant at (a) 66 Gy, (b) 72 Gy, and (c) 78 Gy NTD_{2Gy} respectively. Each point is designated with the number of fractions and the size of each. Reproduced with permission of Elsevier Scientific from Ref. [19].

Table VI. Rectal volume or surface area vs. tolerated maximum dose, for external beam conformal treatment of prostate Ca.

Dose (Gy)	Area or volume (%)
60	35–41
70	22–26
75.6	11–13
78	3–4
80	~2

From Huang et al. [20], with the 80 Gy point from N. Dogan (personal communication).

NTD_{2Gy} (with $\alpha/\beta = 3$Gy) as 35 fractions of 2 Gy. The risk of incidence of late complications would of course remain the same as from the standard 2 Gy schedule totaling 70 Gy. Table VII lists these schedules, together with the expected prostate tumor results, which can be seen to be slightly better, in Table VIIA. Alternatively, lower hypofractionated doses could be used, calculated instead for the *same risk of non-recurrence* as the 70 Gy NTD but *less risk of late complications,* as in Table VIIB.

A further saving in fraction numbers in combined external beam and HDR brachytherapy boost treatments could be achieved by using hypofractionation instead of 2Gy given 5 times a week for the external beam segment. Table VIII illustrates how this could be done by reducing the 25 fractions of 2 Gy to 20, 15, or even 10 larger fractions, all giving the same late-complication BED in Gy_3, with the same NTD_{2Gy} of 50 Gy in 2 Gy fractions.

It is clear that both better tumor response and better economy of resource utilization can be achieved by hypofractionation, in prostate tumors specifically. The prediction of acute rectal mucosal reactions is described below. We shall look at brachytherapy in the next section.

Brachytherapy and hypofractionation

Until recently the main use of hypofractionation in prostate cancer has been as brachytherapy high-dose-rate boost doses. The story of Alvaro Martinez's careful dose escalation studies, with 46 Gy in 2 Gy fractions to whole prostate, added to three HDR boost doses of 5.5 Gy, escalating through 3×6 and 6.5 Gy, then to two HDR boost doses of 8.25, 8.75, 9.5 and now to 2×10.5 Gy is well known [11; & many presentations by Martinez]. Its remarkably good tumor results have given us the first direct clinical evidence that α/β really is as low as 1.5 or even 1.2 Gy [11]. Martinez et al. have avoided rectal complications by limiting the dose to any part of the rectum to 70% or 75% of the prescribed tumor dose. The tumor NTD_{2Gy} for their combination schedule (external beam plus brachytherapy of 46 Gy$+2 \times$ 10.5 Gy 20 [11,25]) is 118 Gy (assuming $\alpha/\beta = 1.5$ Gy), see Table IX. The strict limitation of dose to the rectum means that its NTD_{2Gy} is no higher than 80 Gy (in 2 Gy fraction equivalents assuming $\alpha/\beta = 3$ Gy). The tumor effect, however, is significantly above the highest NTD_{2Gy} achieved by any purely external beam treatment (which is currently approximately 78 Gy in a number of US centers and 95 Gy at the Sloan Kettering Institute escalation trial (personal communication) in 2 Gy fraction equivalents assuming $\alpha/\beta = 1.5$Gy. Martinez is also collaborating with Gustafson, Demanes et al. with

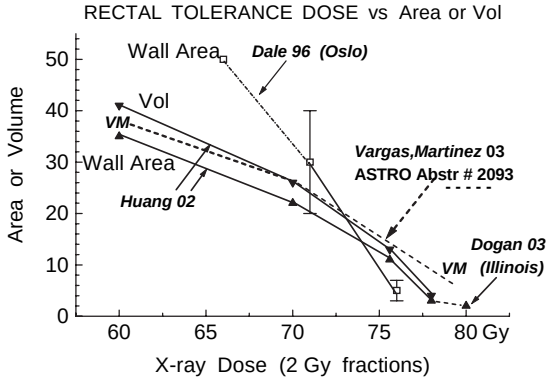

Figure 3. Rectal maximum dose (in 2 Gy fractions) vs. irradiated volume or wall area, from clinical data of prostate treatments. The data from Huang et al. [20] and Vargas et al. [21] agree, except at the highest doses and smallest volumes. The point at 80 Gy and 2 cm^2 is from Dr Nesrin Dogan (personal communication).

another monotherapy consisting of 6F $\times$ 7 Gy of HDR [26]. A schedule that is nearly equal to that of Martinez (116 Gy NTD_{2Gy} to tumors) has been in regular use for over six years in Kiel, Germany by Kovacs et al. and in Uppsala and then in the Karolinska Hospital, Stockholm by Nilssen et al., using 25F $\times$ 2 Gy plus two brachytherapy boost doses of 10 Gy [27 & Nilsson et al., personal communication]. This schedule is the equivalent of $NTD_{2Gy} = 116$ Gy to tumors but only 71 Gy to the rectum, because their brachytherapy dose to rectal wall does not exceed 60% of the tumor-prescribed dose. Table IX summarizes these "strong" brachytherapy schedules—strong in terms of tumor Gy_{10} or NTD_{2Gy} values. A recent review presents long-term results from Martinez et al. and Kovacs

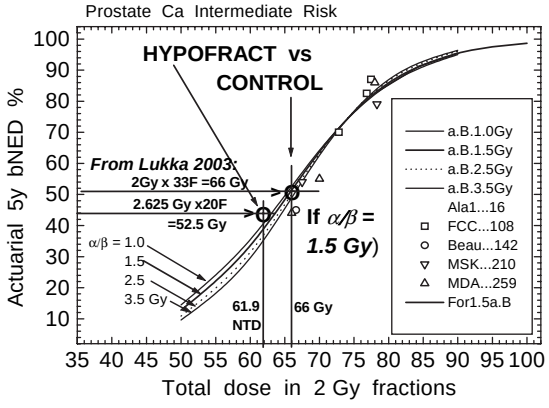

Figure 4. The same curve as in Figure 1, modeled for four different values of prostate tumor α/β, to allow for the range of dose per fraction from 1.8 to 2 Gy. The open circles record results for the two arms of the Canadian trial [12] of a hypofractionated low total dose schedule (44% bNED) versus a control arm of 66 Gy in 2 Gy fractions (51% bNED). In this figure the α/β ratio for the prostate tumor schedule was assumed to be 1.5 Gy and the hypofractionated schedule does not fit, although the 33F $\times$ 2 Gy = 66 Gy schedule does.

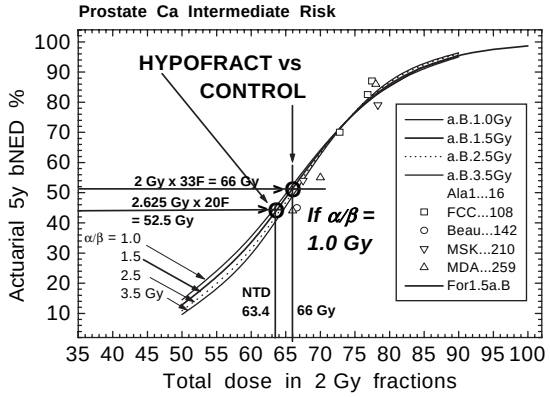

Figure 5. As Figure 3 but assuming $\alpha/\beta = 1.0$ Gy for the prostate tumor schedule [12]. This assumption shows a better fit for the hypofractionated tumor result.

et al., together with Gustafson et al. [26] who used 6F $\times$ 7 Gy. It is remarkable that these experienced groups have developed schedules that are closely similar in tumor BED or NTD_{2Gy}. The relatively low rectal doses of the Swedish groups are achieved with urethral catheter localization and a gradually increased number of HDR cannulae, typically between 12 and 20, to give well-controlled doses to anterior rectal wall.

Monotherapy by brachytherapy

Finally, there are several brachytherapy schedules in use as monotherapy for earlier stage prostate tumors, not outside the prostate capsule [25–28]. It is interesting to look at how this modeling compares them with the other schedules, as summarized in Table X. The schedule of Yoshioka et al. [28] uses nine HDR insertions of 6 Gy each, giving all nine fractions in 5 days at 2F per day.

Martinez et al. are using four HDR fractions of 10 Gy each (escalated from 9.5 Gy), given in two successive days with a single insertion of the cannulae, the doses being at least 6 hours apart (Lecture at ACRO Annual Meeting, Orlando, February 2004). This schedule delivers an NTD_{2Gy} of 131 Gy to prostate tumors (assuming $\alpha/\beta = 1.5$ Gy). This NTD_{2Gy} exceeds the combination schedules in Table IX and is in turn exceeded by the two-fraction monotherapy 2F $\times$ 15 Gy two weeks apart, for the same early stage prostate tumors, being developed by S. Nilsson et al. at the Karolinska Institute, Stockholm and B. Lennernas et al. at the Sahlgrenska Hospital, Göteborg. This delivers a tumor NTD_{2Gy} of 141 Gy, but because all of the rectal wall can be kept below 60% of the prescribed tumor dose, the rectal BED is a modest 98 Gy_3 and its NTD_{2Gy} is only 59 Gy.

Table VII. Hypofractionation to save resources: replacing a postoperative 35F × 2 Gy with 20 or 15 F; with (A) constant late complications and enhanced tumor effect; or (B) with constant tumor effect but reduced late complications.

Postop schedule	Total dose Gy	Late rectal BED Gy3	Late rectal NTD_{2Gy} α/β 3 Gy	Tumor NTD_{2Gy} $\alpha/\beta = Gy_{1.5}$	Tumor BED $Gy_{1.5}$
A: Constant late complications in rectum; with enhanced tumor effect:					
35F × 2Gy	70 Gy	116.67	70 Gy	70 Gy	163
20F × 2.94	58.8	116.67	70 Gy	74.5 Gy	174
15F × 3.56	53.7	116.7	70 Gy	77.6 Gy	181
B: Alternatively, equal tumor effects; fewer rectal complications:					
35F × 2Gy	70 Gy	116.67	70 Gy	70 Gy	163
20F × 2.83	56.6	110	66	70 Gy	163
15F × 3.36	50.4	107	64.2	70 Gy	163

The late rectal damage would, theoretically, probably be acceptable up to 2F × 17 or 18 Gy (see below), but the incidence of late urethral complications is more problematic. Little is known about urethral complications with these good brachytherapy distributions, but neither early nor late serious urethral complications are currently being reported from these strong schedules [25–28].

A new aspect of modeling is to include some prediction of acute mucosal reactions, both in the rectum and in the urethra. Since this is a new and relatively unconfirmed method of prediction, it is presented here as preliminary modeling that requires further clinical data.

The question of acute mucosal reactions in short overall times

We have described the modeling of BED for late rectal complications and for prostate tumor cell kill, and these are standard linear quadratic calculations using formula [1]. There is one more type of modeling that has been proposed recently: the prediction of acute reactions. It is of course biologically likely that if hypofractionated doses were administered in too short overall times, such as daily intervals or shorter, the acute reactions might become intolerable. A longer schedule spaced over several weeks would have allowed repopulation to spare acute reactions. Late complications in contrast have little or no overall-time factors, but acute oral mucosal reactions begin their compensatory proliferation at about 7 days (with small daily fractions) and have an average doubling time of about 2 or 3 days [30,31]. They might start sooner if very large fractions were used [29].

The prediction of acute reactions has been analyzed by our group in terms of BED only for oral or pharyngeal mucosa in head and neck radiotherapy [30], so its use to predict acute rectal mucosa is speculative and requires relevant clinical evidence for validation. But, for oral mucosa, a "critical tolerance zone" of BED = 59–63 Gy_{10} was found, when calculated by certain criteria described below A simple LQ formula including cell proliferation [3] was used:

$$\mathrm{BED} = \mathrm{nd}\left(1 + \frac{\mathrm{d}}{\alpha/\beta}\right) - \frac{\log_e 2}{\alpha T_p}(T - T_k) \qquad (2)$$

Table VIII. Hypofractionation to save resources: using fewer and larger external beam fractions than the 25F × 2 Gy = 50 Gy in the combination with brachytherapy boost doses of 2F × 10 Gy HDR [25,27].

		Ext. Beam NTD_{2Gy}			Combined Tumor $\alpha/\beta = 1.5$		Combined Acute Mucos. BED
Schedule	Total Dose (Gy)	if $\alpha/\beta = 3$Gy	if $\alpha/\beta = 1.5$Gy	if $\alpha/\beta = 10$Gy	NTD_{2Gy}	bNED	$\alpha/\beta = 10$Gy, Tk = 7 days, $\alpha = 0.35$/Gy, Tp = 2.5 days
25 × 2Gy	50	50	50	50	116	~100%	48.3 Gy_{10} if OvT = 46 days
20 × 2.34	46.8	50	51.3	48.1	117	~100	51.6 Gy_{10} if 39 days
15 × 2.85	42.7	50	53.1	45	119	~100	54.3 Gy_{10} if 32 days
10 × 3.72	37.7	50	55.5	42.5	121	~100	56.0 Gy_{10} if 25 days

OvT = Overall time for the combined treatment. All these acute mucosal BEDs are less than 60 Gy_{10} and are therefore considered safe. The first five columns summarize the normalized total doses (in 2 Gy fractions equivalent by LQ modeling) for three types of tissue for the external beam treatments, demonstrating the equivalence for late rectal reactions. The final four columns show the combined tumor effects and acute mucosal BEDs from both external beam and brachytherapy components, assuming that rectal mucosa receives less than 60% of the prescribed dose to tumor.

Table IX. Analyses of the several strongest schedules presently used (as defined by tumor BED) to treat intermediate risk prostate cancer; assuming $\alpha/\beta = 1.5$ Gy for tumor and $\alpha/\beta = 3$ Gy for late rectal reactions (they are combination schedules of EB plus 2F of HDR $\times 10$ or 10.5 Gy).

Reference	Tumor		Late rectal reactions		
Schedule	BED $Gy_{1.5}$	NTD_{2Gy}	Rectal dose as % of tumor dose	BED Gy_3	NTD_{2Gy}
	α/β=1.5Gy			$\alpha/\beta = 3$Gy	
Martinez et al. [11,25]					
Combin 46 Gy EB+2 $\times$10.5	275	118 Gy	75%	133	80 Gy
Galalae et al. [25]					
Combin 50 Gy EB+2 $\times$10Gy	271	116 Gy	100%	170	102 Gy
			70%	130	78 Gy
Nilsson et al., Lennernas et al. [27]					
Combin 50Gy EB+2 $\times$10Gy	271	116 Gy	60%	119	71 Gy

Overall time was represented by T, with the first day designated Day 0, not Day 1. The parameters were selected with a comprehensive review of clinical results from several dozen published schedules used for treating head and neck cancer [30]. They included $\alpha/\beta = 10$ Gy; alpha $= 0.35$ Gy^{-1}; an onset time for repopulation in human oral mucosa of $T_k =$ 7 days [31]; and an average doubling time of $T_p =$ 2.5 days thereafter, as described in detail by Fowler et al. [30]. Although this formula is likely to be too simple in its representation of only two repopulation rates, zero and T_p, it has served well in comparing tumor BEDs in the head and neck schedules studied [30].

What is not yet clear is the level of critical Gy_{10} applying to acute rectal mucosa reactions, because no external prostate schedules have yet given more than 63 Gy_{10} (for 20F $\times$ 3 Gy given at 5F per week, as at Toronto since two years ago [21]. They report no clinical problems.) Figure 6 shows the schematic relationship between overall time and acute mucosal BED in Gy_{10} as defined above.

An important conclusion from Figure 6 and from the calculations in Table XI is that all the acute BEDs in Gy_{10} diminish rapidly, at the rate of about 0.8 Gy per day in this modeling. A schedule could therefore easily be lengthened by a few days to bring its acute mucosal BED down if necessary. The use of only 3 or 4 fractions per week instead of 5 may be needed for this purpose, if acute mucosal problems in the rectum are seen. It is interesting that fewer problems of acute reactions are predicted for the really few (and largest) fractions than in the middle range of external beam hypofractionation, because then the total doses have been reduced more, to keep late complications safe.

As a footnote, the acute mucosal Gy_{10} calculated for the proposed Swedish Phase III clinical trial using the 7F $\times$ 6.1 Gy schedule [24] yields Gy_{10} values of less than 60 Gy_{10} if the treatments are given no faster than two per week, so that should be an acceptable risk. Table XI summarizes some Acute Gy_{10} values for various schedules. It is emphasized that we do not know an upper limit for a "tolerance Gy_{10}" for rectal mucosa; nevertheless if a value below 63Gy_{10} is predicted for a given schedule, or even 63.7 because of Toronto's experience, we can be reasonably sure that it is safe.

Table X. Brachytherapy as monotherapy for early stage carcinoma of prostate.

Reference	Tumor		Late rectal reactions		
Schedule	BED $Gy_{1.5}$	NTD_{2Gy}	Rectal dose as % of tumor dose	BED Gy_3	NTD_{2Gy}
	α/β=1.5Gy			$\alpha/\beta = 3$Gy	
Martinez et al. [25]					
Monotherapy 4F $\times$9.5 y	278	119 Gy	75%	128	77 Gy
Monotherapy 4F $\times$10 Gy	306	131	75%	140	84
Gustafson et al. [26]					
Monotherapy 6F $\times$7 Gy	238	102	if 100%	140	84
			if 70%	80	49
Yoshioka et al. [28]					
Monotherapy 9F $\times$6 Gy	271	116	70%	96	61
Nilsson et al., Lennernas et al. [27]					
Monotherapy 2F $\times$15 Gy	330	141	60%	72	43

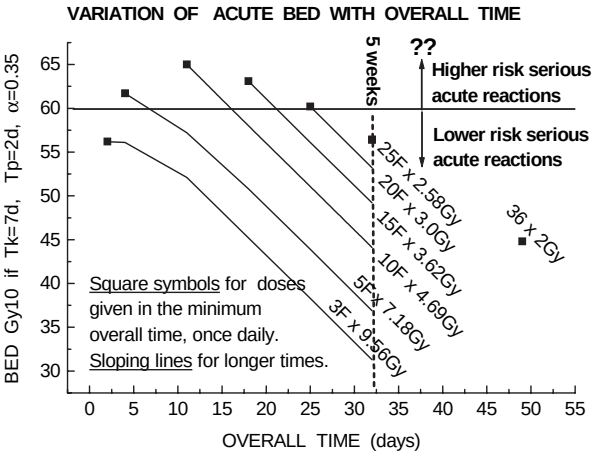

Figure 6. Acute mucosal BED in Gy_{10} [30] versus overall time of a schedule. The BED for 5 fractions a week is shown by the solid square symbols. The rate of decrease of BED with increasing overall time in this theoretical modeling [30] is shown by the falling straight lines. The horizontal "lower risk" border is from oral and pharyngeal radiotherapy only, with larger mucosal areas treated than in the rectum at prostate cancer treatment doses (see text).

There is some evidence that the upper limit of the acute rectal Gy_{10} band might be higher in prostate treatments than 63 Gy_{10}. The monotherapy schedules described in Table IX yield Gy_{10} values as large as 70–80 Gy or more because their overall times are even less than the 7-day onset time T_k in mucosa. However, all these brachytherapy schedules are careful to irradiate only a few square centimeters of anterior rectal wall. Such small areas are likely to permit the higher BEDs to be given, in a way consistent with late rectal tolerance restraints [20,21], and in contrast with oral mucosa where much larger areas of mucosa are generally involved, even with IMRT. More detailed rectal (and urethral) data on this point are required.

Discussion and conclusions

In the search for optimum treatments there are two main questions. One is how high do we *need* to go, in tumor dose, BED or NTD_{2Gy}, for patients of various risk categories? Do we need to go much above 100 Gy NTD_{2Gy}? We have seen that this is feasible, especially with brachytherapy. However, it will be several more years before tumor non-recurrence results at 5 or 7 years make plain the answer in prostate cancer. In the meantime, if we do not wish to stop short of adequate doses we should continue to escalate dose for those patients judged to require treatment. This brings us to the second question: Can we achieve such high doses without unacceptable risks of complications? It is for this second question that definitive answers may be found first, because of the long timescale for obtaining prostate tumor outcome clinically.

Table XI. Summary of acute mucosal BEDs in Gy_{10}, assuming $\alpha/\beta = 10$ Gy; alpha = 0.35 Gy^{-1}; Tk = 7 days; Tp = 2.5 days (30). First day is Day 0, not Day 1.

		Acute BED (Gy_{10})	
Schedule	Overall time (days)	Predicted safe	No data, but query high
7F × 6.1 Gy given at 5 F per week (Sweden)	8	–	68.0
7F given at 3 F per week + 1 day	14	63.2*	–
7F given at 2 F per week + 1 day	21	57.7	–
5F × 6.7 Gy (Dr Berit Madsen, Seattle) 5F/wk	4	56.0	–
From Figure 2b 20F ×: 3.0 Gy at 5F per week	25	63.7*	–
15F × 3.62 Gy at 5F per week	18	–	65.2
15F × 3.62 Gy at 3F per week	32	54.2	
10F × 4.69 Gy at 5F per week	11	–	65.7
10F × 4.69 Gy at 3Fper week	21	57.8	–
5F × 7.12 Gy at 5F per week	4	61.0	
From Figure 2c 20F × 3.16 Gy at 5F per week	25	–	68.9
20F × 3.16 Gy at 3F per week	44	53.9	–
15F × 3.82 Gy at 5F per week	18	–	70.5
15F × 3.82 Gy at 3F per week	32	59.4	–
10F × 4.92 Gy at 5F per week	11	70.2	–
10F × 4.92 Gy at 3F per week	21	62.3	–
5F × 7.46 Gy at 5F per week	4	–	?65.1
5F × 7.46 Gy at 3F per week	9	63.5*	–

If the acute Gy_{10} is less than 60 Gy, the schedule is probably safe from acute complications. BEDs above 60 Gy_{10} have yet to be evaluated for acute rectal reactions. *From Toronto using 20F × 3.0 Gy, given 5F per week in 25 days, no acute problems are reported clinically [22]. It is emphasized that a reliable upper limit for these rectal acute BEDs has not yet been established. Further data on them are required, especially in relation to area of rectal wall irradiated.

Table XII. Summary of NTD_{2Gy}s for two-dose brachytherapy monotherapy.

Schedule Dose Gy prescribed	Tumor NTD_{2Gy} dose (Gy)	Rectal late NTD_{2Gy} if 60% of prescribed tumor dose	Acute mucosal Gy_{10} rectal 60% ureth 100% of tumor dose		Late ureth. NTD_{2Gy} if 100% of prescr. tumor dose
$\alpha/\beta = 3$Gy	$\alpha/\beta = 1.5$Gy	$\alpha/\beta = 3$Gy	$\alpha/\beta = 10$Gy	$\alpha/\beta = 10$Gy	dose; $\alpha/\beta = 3$Gy
2×13.0	108 Gy	34 Gy	39	50	83.4 Gy
2×13.5	116 Gy	36 Gy	42	53	89.3 Gy
2×14.0	124 Gy	38 Gy	44	56	95.4 Gy
2×14.5	132 Gy	40 Gy	46	59	101.4 Gy
2×15.0	141 Gy	42 Gy	48	63	108.0 Gy
2×15.5	151 Gy	46 Gy	51	66	114.6 Gy
2×16.0	160 Gy	48 Gy	53	69	121.8 Gy
2×16.5	170 Gy	51 Gy	55	73	129.0 Gy ?
2×17.0	180 Gy	54 Gy	58	77 ?	136.2 Gy ??
2×17.5	191 Gy	57 Gy	61	80 ?	143.4 Gy ??
2×18.0	201 Gy	60 Gy	64 ?	84 ??	151.0 Gy ??

*Given in combined schedule. All doses in last column would be too high unless less than about 2–5 cm of urethral length is irradiated. This uncertainty to be determined by future data. Mucosal BEDs and NTDs with query marks appear likely to be dangerous, until further data become available. "?" suggests this dose is *possibly* too high; "??" suggests *likely to be* too high.

Radiobiological modeling can certainly help, first by explaining the effective BEDs and NTDs of tumor doses from the various modalities with different doses per fraction; simple total dose is not adequate; second, by analyzing BEDs and NTD_{2Gy}s for tissues at risk. This second question can only be settled by clinical data, after further appropriate analysis to check the parameters. During the process of dose escalation, however, indications of tissues that might be more at risk can be provided, however speculatively. Potential complications in these tissues can then be approached ethically by designing appropriate dose escalation trials, instead of choosing some favorite level of dose for a new trial. Statisticians call this progressive upgrading of basic assumptions after an eighteenth-century mathematician, Thomas Bayes, but its use is modern and relatively new in clinical trials.

In this spirit of careful dose escalation to high BEDs, we have modeled the radiobiological effects of two large brachytherapy doses for monotherapy of prostate cancer. Some of the results are listed in Table XII. We emphasize that these are theoretically obtained BEDs and NTD_{2Gy}s, and it is only from clinical experience that we can obtain an idea of what might be the highest "tolerable" doses. They will be higher for smaller high-dose volumes, down to a few cm^2 of rectal wall, and we are only beginning to learn them. The dependence on volume (or mucosal area) will also apply to the acute mucosal reactions listed in Table XII.

Such modeling of LQ BEDs and NTD_{2Gy}s enables us to compare various schedules quantitatively. It has shown clearly the potential advantages of hypofractionation that are (unfortunately) specific for only prostate tumors, as far as we know yet. It does not predict specific upper dose limits to normal tissues, largely because new methods of dose delivery such as IMRT and tomotherapy can reduce the volumes of normal tissues irradiated much more stringently than earlier. But, by comparison with known schedules, relative improvements in therapeutic ratio can be evaluated, even to the extent of predicting how many patients would be needed for clinical trials to test less recurrence. One of the useful functions of modeling is to suggest in which tissues, in what dose ranges, problems of complications might be expected to arise, so that ethical dose-escalation trials can be organized.

By keeping strictly to clearly defined parameters, such as the linear-quadratic ones used here instead of "elegant variations", and by using simple LQ equations, consistent results can be obtained, for example the remarkable agreement for tumor effects of some of the best schedules in regular use.

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