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PULSED-DOSE-RATE BRACHYTHERAPY: DESIGN OF CONVENIENT (DAYTIME-ONLY) SCHEDULES

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Purpose: To design pulsed-brachytherapy (PDR) protocols that are expected to be at least as clinically efficacious (in terms of both tumor control and late sequelae) as continuous low-dose-rate (CLDR) regimens, but that involve irradiation only during extended office hours. Both interstitial and intracavitary brachytherapy protocols are considered.

Methods and Materials: The linear quadratic formalism was used in which the late normal tissue damage and tumor control for one protocol relative to another are assumed to be determined primarily by the level of cellular survival. PDR schedules were designed in which pulses are delivered during "extended office hours" (8 A.M. to 8 P.M.) with no irradiation overnight. Generally, the proposed PDR regimes last the same number of treatment days as the corresponding CLDR regimen, but the PDR treatment lasts longer on the final day (i.e., until 8 P.M.). PDR doses were calculated such as to produce a tumor control which is equivalent to standard CLDR protocols, and the corresponding predicted late complication rate was compared with that for CLDR. Ranges of plausible values for the half-times of sublethal damage repair for tumors and for late-responding normal tissues were considered.

Results: As has been previously shown, the efficacy of PDR relative to CLDR depends considerably on the repair rates for sublethal damage repair. Clinical and experimental evidence suggests that average repair half-times for early effects (e.g., tumor control) are less than about a half hour, and for late sequelae are more than about an hour. If these estimates are correct, daytime PDR regimes can usually be designed which take the same number of days as the corresponding CLDR regimen, but have comparable or better therapeutic ratios than CLDR.

Conclusion: Protocols for PDR can be designed to involve irradiation only during extended office hours, that are likely to result in clinical results comparable or better than CLDR, for any expected combination of the repair half-times of early- and late-responding tissues. The suggested protocols allow all of the advantages of a computerized remote-controlled afterloader while preserving the benefits of low dose rate. In addition, the protocols could allow the patient to go home overnight, or to stay overnight in an adjacent medical inn or hospital-associated hotel, rather than in a hospital bed—which could have major economic benefits. In such an economic situation, an extra treatment day for the daytime PDR could well be considered, which would virtually guarantee an improved clinical advantage relative to CLDR. © 1997 Elsevier Science Inc.

Pulsed brachytherapy, Daytime treatment, Linear quadratic.

INTRODUCTION

Because of its practicality, use of pulsed-dose-rate (PDR) brachytherapy is increasing. In PDR, a continuous low-dose-rate (CLDR) brachytherapy regimen is replaced with one involving a series of high-dose-rate pulses, typically (though not always) taking a few minutes each hour or two and typically (though not always) with the same overall dose and time as the corresponding CLDR regimen.

Pulsed-dose-rate brachytherapy is achieved with a remote afterloader containing a single high-activity source that is stepped through the catheters of an interstitial implant or intracavitary applicator, with dwell positions and times adjusted under computer control to achieve the required dose distribution.

In PDR, the advantages of computer-controlled remove afterloading can be exploited—namely good dose distributions and dose optimization made possible by a stepping source, as well as excellent radiation protection, since no source preparation is required and the single source is in the "safe" whenever the patient is nursed or visited. At the same time, all the benefits of low-dose-rate irradiation are maintained, since the intent of Brenner and Hall (2) in the introduction of PDR was to recommend a pulsing schedule that would maintain the same overall dose rate as CLDR, i.e., the same overall dose in the same overall

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time, delivered in 10-min pulses every hour throughout the treatment. This very conservative recommendation was primarily designed to be safe for almost any conceivable set of biological response parameters exhibited by the relevant target tissues.

Whilst PDR has prospered in Europe and elsewhere, in the US it has foundered on the Nuclear Regulatory Commission requirement that a physicist and/or radiotherapist (or some other suitably qualified person) be present throughout the treatment; that is, day and night, to deal with the possible, if unlikely, eventuality that the source becomes lodged inside the patient. An obvious way around this problem is to restrict treatment pulses to office hours, when the need for the presence of a physicist and/or radiation oncologist is not a problem. This can be done only by dropping the constraint that was considered prudent in the original paper on this topic (2)—that both the total dose and the overall treatment time must be the same as the conventional CLDR brachytherapy treatment—and instead allowing somewhat longer overall treatment times.

Such changes are easy to make with the great flexibility that PDR machines afford, and this approach has been used by the group in Rotterdam who went one step further and designed protocols with larger doses per pulse, longer separations per pulse, and significantly longer overall treatment times (17).

The purpose of the present article is to design PDR protocols for brachytherapy which exploit all of the technological advantages that accrue from a computer-controlled remote afterloader, maintain the biological properties of low dose rate, while confining treatment pulses to office hours—or at least, to extended office hours. Our initial goal is to investigate daytime PDR regimens which involve the same number of treatment days as the corresponding CLDR treatment. While our initial motivation was the based on regulatory considerations, "daytime" PDR could have further economic benefits, allowing, for example, patients to go home overnight between treatment sessions, or to spend nights in an adjacent medical inn or a hospital-associated hotel (12), rather than an inpatient hospital bed.

METHODS AND MATERIALS

General approach

The object of radiotherapy is to produce a larger response in the tumor than in surrounding normal tissues, particularly late-responding tissues. To some extent, this can be achieved by designing an appropriate dose distribution that confers a dose differential between tumor and normal tissue, an aim that can often be achieved in brachytherapy. A differential can also be achieved by the manipulation of biological parameters. Attention has focused in recent years on the α/β ratio as an important biological difference between early- and late-responding normal tissues (19). The fact that late-responding tissues tend to have smaller α/β ratios, and are therefore more sensitive to changes in fractionation, has been exploited in clinical trials of hyperfractionation with external beam radiation therapy.

There is, however, another important parameter that varies widely, namely, the rate of repair of sublethal radiation damage. There is much evidence from animal studies and from the clinic that sublethal damage repair rates are slower for late-responding normal tissue than for tumors or early-responding normal tissues; this was first suggested by Thames *et al.* (14), and has more recently been reviewed by Brenner *et al.* (4). Differences between repair rates between early- and late-responding tissues open up new possibilities for optimizing brachytherapy schedules. Essentially, differences in repair rates are for brachytherapy what differences in α/β are for external beam radiation therapy.

In this article, we address the problem of replacing doses given in various common CLDR brachytherapy exposures, with a series of pulses spread unevenly (i.e., during daytime hours only) over the same number of treatment days as the CLDR regimen. To maintain the therapeutic ratio (the ratio of complication rates for two regimens producing the same level of tumor control) of daytime PDR, which would otherwise suffer from the elimination of night-time irradiation, we allow the PDR regimes to be a few hours longer—specifically, to extend until 8 P.M. on the final treatment day.

Our approach is to calculate the daytime PDR dose regimen which would result in the same tumor control probability as the corresponding CLDR regimen—and then to compare the predicted normal-tissue complication probability (NTCP) of this PDR regime with that of the corresponding CLDR regimen. It is important to note that all the calculations are relative (PDR vs. CLDR), which makes the calculation rather less sensitive to parameter choice than would be the case for absolute calculations. Ranges of plausible values for the half-time of sublethal damage repair for tumors and for late-responding normal tissues were considered.

Assumptions

We use the linear quadratic formalism, in which late tissue damage and tumor control are assumed to be determined primarily by the level of cellular survival. For tumor control, we consider the initial number of tumorigenic cells, i.e., the number of cells that have the independent capability to initiate tumor regrowth. Let us denote this number by K. Let us suppose that a dose, D, delivered in a given fractionation pattern, produces a survival probability S for tumorigenic cells, i.e., the expected number of surviving tumorigenic cells is KS. Then, on the standard model, the tumor control probability (TCP) is given by the Poisson expression for no survivors, i.e.,

$$TCP = exp(-KS). \qquad \text{(Eq. 1)}$$

The underlying idea (13) is that Eq. 1 gives the fraction of cases in which all tumorigenic cells have been elimi-

nated when a radiotherapy regimen has reduced the cell survival probability S to a small number. Thus two regimens which produce the same predicted survival, S, would be predicted to produce the same TCP.

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

and combining Eqs. 1 and 2, the tumor control probability is

$$TCP = exp[-K\, exp(-\alpha D - G\beta D^2)]. \qquad \text{(Eq. 3)}$$

Here, D is the overall dose, and α and β are parameters that can be estimated from clinical and radiobiological data, as can the other parameters of the model. Mechanistically, the quantity G describes the interaction between sublethal damage produced by any portion of the radiation treatment with damage produced by any other portion. G is determined by the rate of sublethal damage repair (i.e., the repair half-time, $T_{1/2}$), and the particular fractionation pattern with which the dose D is delivered; given these, G can be readily calculated (3). It should be noted that because treatment times for brachytherapy are generally short, a term in Eq. 2 for time-dependent repopulation is not necessary.

Thus matching the exponent in Eq. 2 for two regimes would produce regimens with the same predicted TCP. Specifically,

$$\alpha D_{CLDR} + G_{CLDR}\beta D_{CLDR}^2 = \alpha D_{PDR} + G_{PDR}\beta D_{PDR}^2 \qquad \text{(Eq. 4)}$$

Similar methods can be used to calculate changes in normal-tissue complication probabilities (NTCP). Here, the complication probability can be written

$$NTCP = exp[-K_{late}\, exp(-\alpha_{late} D - G_{late}\beta_{late} D^2)]. \qquad \text{(Eq. 5)}$$

Here, K_{late} refers to the number of groups of cells in the normal tissue [''tissue-rescuing units'' (13)], whose destruction would result in the late complication.

The calculations in this article are based on the use of Eq. 4 to produce daytime PDR schemes with the same tumor control rate as a CLDR regimen, followed by use of Eq. 5 to calculate corresponding tissue complication rates.

Methodology

Having used Eq. 4 to estimate the doses of a daytime PDR regimen that would produce that same predicted tumor control rate as the corresponding CLDR regime, the next step is to investigate the predicted rate of late sequelae. In applications of Eq. 5 to estimates of late complication rates, a well-known problem has been that the results are very sensitive to the value of the parameter K_{late}, which is not known very accurately. Consequently, using Eq. 5 to predict the NTCP can easily give values which are uninformative. For our purposes, however, what are needed are estimates of the difference in NTCP for two closely related schemes, not estimates of absolute TCP. In this context, the problem of sensitivity to the value of K_{late} can be largely overcome.

To estimate changes in NTCP for a CLDR versus PDR regimen, we first assign a nominal NTCP value to the original CLDR regimen, typically of NTCP = 20%. Based on this NTCP value, K_{late} can be calculated from Eq. 5. This value of K_{late} is in turn used to calculate the NTCP for the corresponding PDR regimen, by substituting into Eq. 5 the new values of D and G. Thus, only changes of NTCP for the PDR regimen relative to the original CLDR regimen are calculated. Such differential values are far less sensitive to choices of parameters, especially to the choice of K_{late} than are absolute NTCP calculations (7). Making absolute predictions of the NTCP is, at the current time, not practical, and the method given here avoids the use of estimates of K_{late} from the literature.

In summary, our procedure for designing and comparing a daytime PDR regimen with a corresponding CLDR regime is:

1. Use Eq. 4 to calculate the total dose for the daytime PDR regime that would produce equal predicted tumor control compared with the CLDR regimen of interest. Use range of $T_{1/2}$ parameter values discussed below.
2. Assume the normal tissue complication probability (NTCP) for the CLDR regime of interest is, say, 0.2. Use this assumption to calculate K_{late} from Eq. 5. Use range of $T_{1/2}$ values discussed below.
3. Use Eq. 5 and calculated value of K_{late} to estimate NTCP for the PDR regime designed in (1). Compare with the assumed NTCP for CLDR regime. Use range of $T_{1/2}$ values discussed below.

Choice of parameters

As has been pointed out elsewhere (5, 9), the relative efficacy of PDR and CLDR regimens depends strongly on the half-times for sublethal damage repair ($T_{1/2}$) for early- and late-responding tissues. Here, we carry out calculations for a range of $T_{1/2}$ values that appear reasonable based on earlier analyses.

Repair rates for early- and late-responding tissue have been reviewed elsewhere (4). Following several suggestions from early hyperfractionation trials that 2-h to 4.5-h interfraction intervals were resulting in excessive late effects, Cox *et al.* (6) compared the results of hyperfractionated radiation therapy (for upper respiratory and digestive tracts) when the interfraction interval was either >4.5 h or ≤4.5 h; Cox *et al.* (6) clearly showed that although there was no difference in local control, late sequellae were significantly increased for the ≤4.5 interfraction interval arm. This suggests repair half-times of at

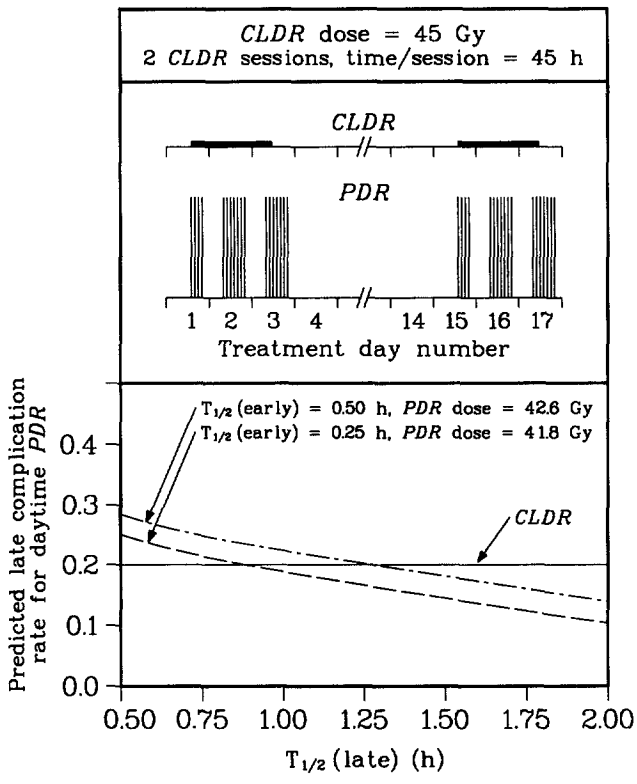

Fig. 1. (Top) Schematic of two 45-h CLDR insertions for cancer of the cervix, and the corresponding suggested daytime PDR regimen. Each treatment begins at 2 P.M. on the first day, and PDR treatments start on subsequent days at 8 A.M., with 2-hourly pulses until 8 P.M.. (Bottom) Predicted late complications of daytime PDR scheme with doses designed to produce the same tumor control rate as the corresponding CLDR regimen. Predicted PDR late-complication rates are based on an assumed rate of 0.2 for the corresponding CLDR regimen. Thus, curves above NTCP = 0.2 imply that the daytime PDR has a worse therapeutic ratio than the CLDR regimen, and curves below NTCP = 0.2 imply that the daytime PDR has a better therapeutic ratio than CLDR.

least ~200 min for late-responding tissues, and less than ~100 min for early-responding tissues.

Confirming evidence comes from the analysis of Turesson and Thames (15) of early- and late-responding skin damage after fractionated radiotherapy. For both early- and late-responding damage, they found a two-component repair process, with both early- and late-responding damage having an estimated fast repair time of ~25 min. However, the slow repair for early-responding damage had an estimated half-time of repair of ~75 min, whereas the corresponding estimated slow repair time for late-responding tissue was ~250 min, with confidence limits from 210 to 320 min. Recent rodent data on spinal cord (1), lung (16), kidney (11), and rectum (8) also support the suggestion of an average half-time of repair for late-responding damage of >1 h.

These considerations would suggest that early-responding tissues such as tumors have average half-times of repair of the order of tens of minutes; on the other hand, late-responding tissues have at least a component of repair with times of the order of a few hours. In this analysis, we present results for $T_{1/2}$ values for late-responding tissues ranging from 0.5 to 2 h, and for $T_{1/2}$ values for early responding tissues of 0.25 and 0.5 h.

In this analysis we have used α and β values (see Eqs. 3 and 4) of 0.1 Gy^{-1} and 0.01 Gy^{-2} for early-responding tissues (α/β = 10 Gy), and 0.07 Gy^{-1} and 0.0175 Gy^{-2} for late-responding tissues (α/β = 4 Gy). However, the results and conclusions are not very sensitive to changes in these values, and use, for example, of a range of [α,β] values as defined by Brenner and Hall (2) did not significantly effect our conclusions.

RESULTS

Although originally conceived as a substitute for interstitial brachytherapy (2), PDR has been used extensively for intracavitary brachytherapy for cancer of the uterine cervix. It is not possible here to consider all possible applications of brachytherapy, and so we consider here various representative CLDR brachytherapy regimens, and investigate possible replacement daytime PDR regimens. The CLDR regimes that we consider are (A) intracavitary brachytherapy, used in conjunction with external beam radiotherapy, for treating cancer of the uterine cervix (Fig. 1a): two CLDR insertions totaling 45 Gy, with each session taking 45 h (Fig. 1); and two CLDR insertions to-

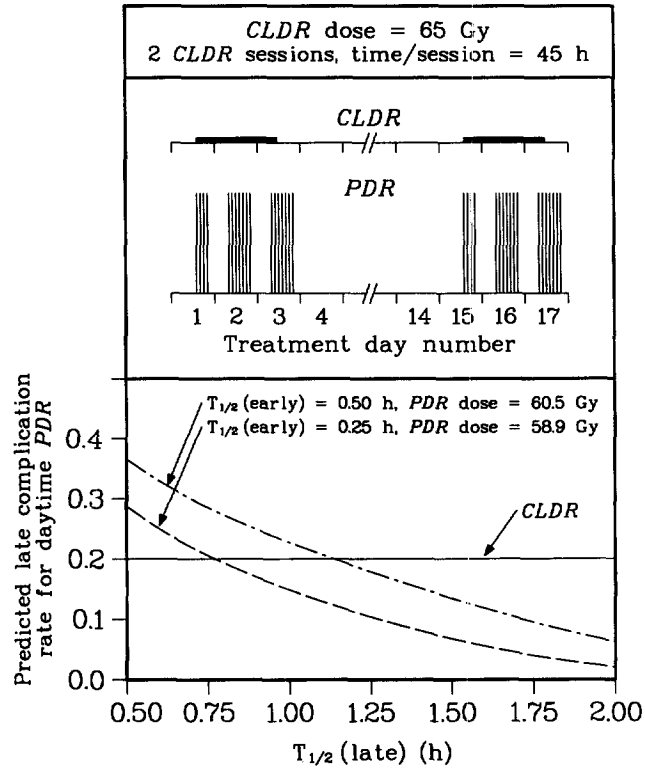

Fig. 2. As in Fig. 1 for two CLDR brachytherapy insertions totaling 65 Gy.

taling 65 Gy, with each session taking 45 h (Fig. 2); and (B) interstitial brachytherapy: 40 Gy delivered at a CLDR of 0.45 Gy/h (Fig. 3) [used, for example, in conjunction with external beam treatment (EBRT) in Stage I and II oral tongue cancers (18)]; and 70 Gy delivered at a CLDR of 0.51 Gy/h (Fig. 4) [used, for example, as a complete treatment for cancers of the mobile tongue and floor of mouth (10)].

For both CLDR and the corresponding daytime PDR regimen, we assume that the brachytherapy starts at 2 P.M. on the first day, to allow for prior planning and insertion. PDR pulses are delivered until 8 P.M. on each treatment day, and start at 8 A.M. on each treatment day except the first. The PDR regimes that we consider deliver a pulse every 2 h (at an assumed instantaneous dose rate of 1 Gy/min). Thus, four PDR pulses are delivered on the first day (2–8 P.M.), and seven on all subsequent days (8 A.M. to 8 P.M.). In all cases except the last (70 Gy CLDR), the PDR regime ends on the same day as the CLDR regime, i.e., the regimes take the same number of treatment days.

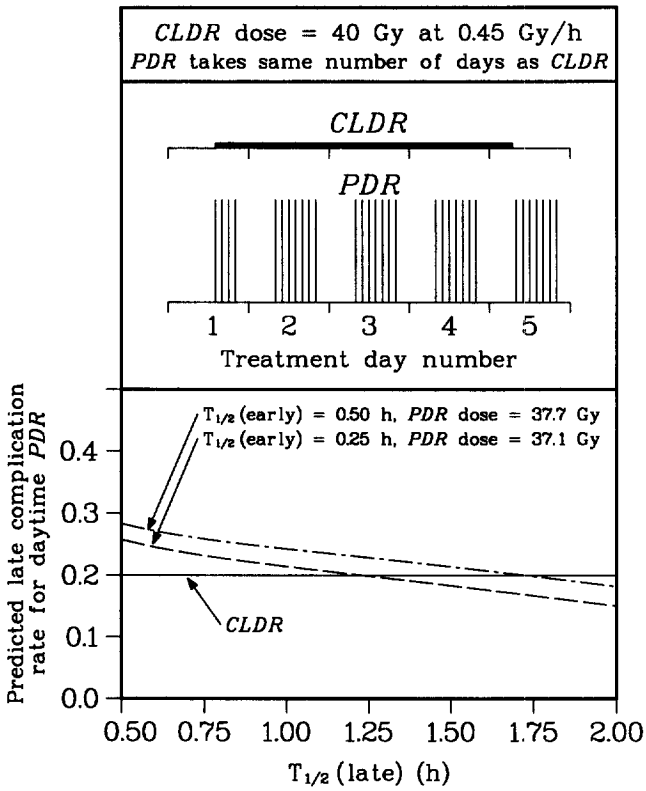

Fig. 3. (Top) Schematic of 40-Gy brachytherapy treatment, such as used in combination with EBRT for head and neck cancers (18), and the corresponding suggested daytime PDR regimen. (Bottom) Predicted late complications of daytime PDR scheme with doses designed to produce the same tumor control rate as the corresponding CLDR regimen. Predicted PDR late complication rates are based on an assumed rate of 0.2 for the corresponding CLDR regimen. Thus, curves above NTCP = 0.2 imply that the daytime PDR has a worse therapeutic ratio than the CLDR regimen, and curves below NTCP = 0.2 imply that the daytime PDR has a better therapeutic ratio than CLDR.

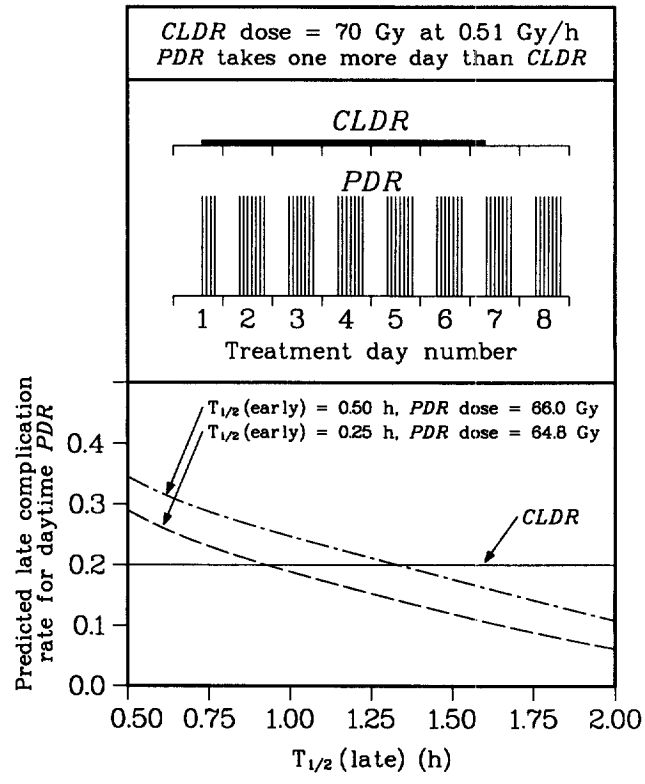

Fig. 4. (Top) Schematic of 70-Gy brachytherapy treatment, such as that used as sole treatment for head and neck cancers (10), and the corresponding suggested daytime PDR regimen. Note that in this case, the corresponding PDR treatment is scheduled for one more treatment day than the corresponding CLDR regimen. (Bottom) Predicted late complications of daytime PDR scheme with doses designed to produce the same tumor control rate as the corresponding CLDR regimen. Predicted PDR late complication rates are based on an assumed rate of 0.2 for the corresponding CLDR regimen. Thus, curves above NTCP = 0.2 imply that the daytime PDR has a worse therapeutic ratio than the CLDR regimen, and curves below NTCP = 0.2 imply that the daytime PDR has a better therapeutic ratio than CLDR.

In this case and in the Discussion, we also consider daytime PDR regimes which take 1 day longer than the corresponding PDR regimen.

Figures 1–4 show calculated NTCP for the daytime PDR schedules as a function of $T_{1/2}$ for late effects. Each daytime PDR regime dose was designed to give the same tumor control (TCP) value as the corresponding CLDR regime, and the curves give predicted NTCP values corresponding to different $T_{1/2}$ values for late-responding tissues. Calculations are shown for two plausible $T_{1/2}$ values (0.25 and 0.5 h) for early effects. As the NTCP calculations for the daytime PDR regimes are based on an assumed NTCP of 0.2 for the corresponding CLDR regime, predicted values for the PDR that are <0.2 imply an improvement in the therapeutic ratio compared with CLDR, and vice versa.

It should be noted that Fig. 4 (70 Gy interstitial brachytherapy), the corresponding daytime PDR regimen is designed to take one extra treatment day compared with the reference CLDR regimen. In con-

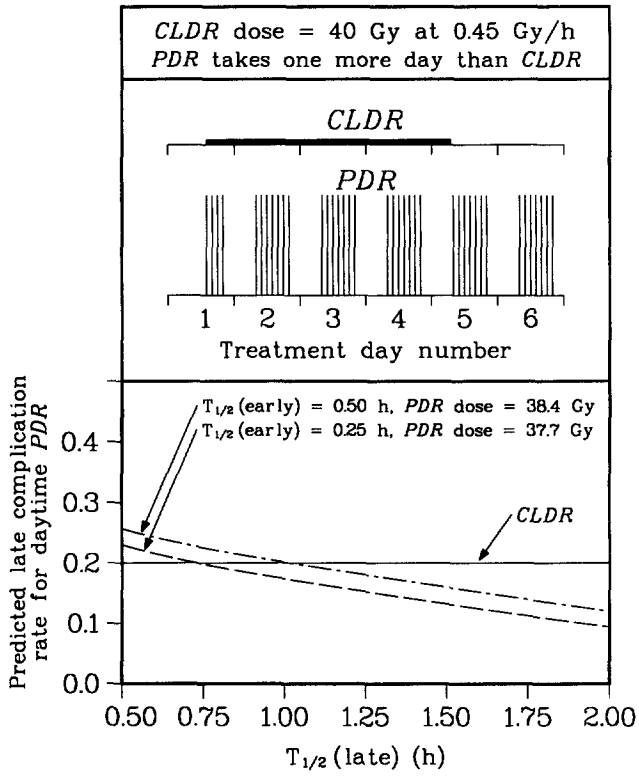

Fig. 5. (Top) Schematic of 40-Gy brachytherapy treatment, such as that used in combination with EBRT for head and neck cancers (17), and a corresponding suggested daytime PDR regimen taking 1 day longer than the corresponding CLDR regimen. (Bottom) Predicted late complications of daytime PDR scheme with doses designed to produce the same tumor control rate as the corresponding CLDR regimen. Predicted PDR late-complication rates are based on an assumed rate of 0.2 for the corresponding CLDR regimen. The curves should be compared with those in Fig. 3, which are matching the same CLDR regime, but in this case, an extra daytime PDR treatment day has been added.

trast to the more common lower brachytherapy doses (used in combination with EBRT), at this high brachytherapy dose, the daytime PDR regimen covering the same number of treatment days, as the corresponding CLDR treatment produces a significantly decreased therapeutic ratio.

DISCUSSION

In the first paper introducing PDR, we showed that a pulsed regimen results in essentially identical biological effects to CLDR so long as the pulses are small and frequent: for example, 0.6 Gy in 10-min pulses repeated every hour (2). However, if larger pulses are given, and separated by longer time intervals, biological equivalence can only be achieved if the overall time of the PDR schedule is somewhat longer than the CLDR regime it replaces. This idea was introduced by Visser *et al.* (17), and is evident again here where larger doses per pulse are necessary to allow for the relatively long overnight interval (12 h) when no radiation is given.

Examination of Figs. 1–4 suggests that if the average $T_{1/2}$ for early effects is less than about 0.5 h and the average $T_{1/2}$ for late effects is more than about 1 h, then practical daytime PDR regimens can be designed which have comparable or possibly better therapeutic advantage compared with a corresponding CLDR regime. There is persuasive evidence that $T_{1/2}$ values do follow this pattern, so it is not unlikely that daytime PDR would provide an improved therapeutic advantage compared to CLDR.

The daytime PDR schedules that we have investigated are quite convenient for the patient; there are 2-h gaps between pulses during the day, allowing meals to be served, visitors to be entertained, and general nursing care to be carried out, and there is no treatment at night. In fact the 12-h night-time gaps in treatment could, in principle, allow the patient to go home or to sleep in an adjacent medical inn or hospital-associated hotel (12) rather than occupying a hospital bed, which would significantly reduce the overall treatment cost.

In a situation where patients could avoid hospitalization, the financial benefits are likely to be sufficiently great that an extra day of PDR treatment could be economically possible, which would virtually guarantee an improved therapeutic advantage over the corresponding CLDR regimes. For example, Fig. 5 shows the case for a 40-Gy brachytherapy treatment (as in Fig. 3), but with an extra day of PDR treatment. It seems clear that this extra day will essentially ensure that the daytime PDR treatment will be more efficacious than the corresponding CLDR treatment—and avoiding hospitalization could still allow maintenance of a financial benefit relative to CLDR.

These calculations represent a first attempt to marry the evident benefits and convenience of PDR to the practical and logistical problems of treating common malignancies. It appears quite possible to use daytime PDR to combine the evident advantages of computer-controlled afterloaders and the desirability of excellent radiation protection, while preserving the radiobiological advantages of a low-dose-rate treatment.

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