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FULL PAPER

Biphasic and monophasic repair: comparative implications for biologically equivalent dose calculations in pulsed dose rate brachytherapy of cervical carcinoma

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Objective: To consider the implications of the use of biphasic rather than monophasic repair in calculations of biologically-equivalent doses for pulsed-dose-rate brachytherapy of cervix carcinoma.

Methods: Calculations are presented of pulsed-dose-rate (PDR) doses equivalent to former low-dose-rate (LDR) doses, using biphasic vs monophasic repair kinetics, both for cervical carcinoma and for the organ at risk (OAR), namely the rectum. The linear-quadratic modelling calculations included effects due to varying the dose per PDR cycle, the dose reduction factor for the OAR compared with Point A, the repair kinetics and the source strength.

Results: When using the recommended 1 Gy per hourly PDR cycle, different LDR-equivalent PDR rectal doses were calculated depending on the choice of monophasic or biphasic repair kinetics pertaining to the rodent central nervous and skin systems. These differences virtually

disappeared when the dose per hourly cycle was increased to 1.7 Gy. This made the LDR-equivalent PDR doses more robust and independent of the choice of repair kinetics and α/β ratios as a consequence of the described concept of extended equivalence.

Conclusion: The use of biphasic and monophasic repair kinetics for optimised modelling of the effects on the OAR in PDR brachytherapy suggests that an optimised PDR protocol with the dose per hourly cycle nearest to 1.7 Gy could be used. Hence, the durations of the new PDR treatments would be similar to those of the former LDR treatments and not longer as currently prescribed.

Advances in knowledge: Modelling calculations indicate that equivalent PDR protocols can be developed which are less dependent on the different α/β ratios and monophasic/biphasic kinetics usually attributed to normal and tumour tissues for treatment of cervical carcinoma.

The use of low-dose-rate (LDR) brachytherapy (BT) for cervical cancer is being phased out and replaced by either high-dose-rate (HDR) or pulsed-dose-rate (PDR) BT [1–4]. At the Christie Hospital in Manchester, UK, PDR has been implemented in place of LDR for the BT component of a combined external beam (EB) and BT treatment of cervical carcinoma [4]. The Groupe Européen de Curietherapie–European Society for Radiotherapy & Oncology (GEC-ESTRO) recommendations [5] were used to calculate the equivalent prescribed doses of PDR BT compared with those of the formerly used LDR-BT protocol [6]. Those guidelines use generic values of linear-quadratic parameters and monophasic repair kinetics. For the organs at risk (OARs), biphasic repair has become a more accurate characterisation of the repair kinetics. This is based on clinical evidence of a slow repair component for skin telangiectasia [7], oral mucosa [8] and subcutaneous fibrosis [9]. There is also more detailed knowledge of the two fast

and slow components for clonogenic cells in mouse kidney [10], rat spinal cord paralysis [11], mouse pneumonitis [12,13] and pig skin early reactions [14].

PDR BT uses cycles (or pulses) of 0.5–1.0 Gy given usually at 1–1.5-h intervals, and dose distributions using PDR or LDR can be made virtually identical [15]. It was shown that 1 Gy cycles at intervals of 1–3 h (varied among animal studies) resulted in similar biological effects from the same total doses delivered continuously at 0.50–0.75 Gy per hour. Higher doses per cycle and different cycle intervals resulted in deviations from equivalence because of biphasic repair, in particular for late-reacting tissues [16,17]. The therapeutic ratio of PDR vs LDR depends on cycle dose size and interval and tissue repair characteristics [α/β ratios and repair half-times ($T_{1/2}$)]. In normal tissues with a $T_{1/2} < 0.5$ -h component, PDR may be more damaging than LDR [18], but the effect should be reduced if the dose per cycle is < 1 Gy [16,19].

The present study reports calculations of LDR-equivalent PDR doses using biphasic *vs* monophasic repair kinetics for both the tumour and for the OAR, and the consequent implications.

MATERIALS AND METHODS

Clinical background

When there are negative nodes, cervical carcinoma treatments at the Christie Hospital comprise 45-Gy EB in 20 daily fractions over 4 weeks using a small 4-field conformal plan, plus 2 fractions (1 week apart) each of 13-Gy PDR using a 1-Gy/1-h cycle (instead of 22.5-Gy LDR delivered at 1.55 Gy h⁻¹) to Point A. For positive nodes, 40-Gy EB covers the whole pelvis, plus 2 fractions of 19 Gy PDR BT, again using 1-Gy/1-h cycles (instead of 32.5 Gy LDR) at Point A. In both cases, the EB component remains the same for PDR as for LDR [20]. The equivalent PDR doses were calculated [6] using generic values of the relevant parameters, *i.e.* $\alpha/\beta=10$ Gy (Point A) and 3 Gy (OAR), $T_{1/2}=1.5$ h, dose reduction factor (DRF) at the OAR=0.7, as in the GEC-ESTRO recommendations [5].

Modelling methods

The equations describe protocols where the exposure time, dose rate and interfraction time may differ within the schedule, and they incorporate biphasic repair. Biologically effective dose (BED) is defined as follows:

$$\text{BED} = D_T + \frac{1}{\alpha/\beta} \frac{[\phi(\Xi, \mu_1) + c\phi(\Xi, \mu_2)]}{[1+c]} \sum_{i=1}^{i=N} d_i^2 \quad (1)$$

and surviving fraction (SF of cells or structural/functional units) is given by

$$\text{SF} = e^{-\alpha \cdot \text{BED}} \quad (2)$$

where α , β and α/β are the conventional linear-quadratic parameters, μ_1 and μ_2 are the rates of the two repair processes (where $\mu_1 > \mu_2$), Ξ denotes the start time, exposure time and dose rate of every fraction, c is the partition coefficient between the two repair processes and $\phi(\Xi, \mu)$ is a complex function of the protocol and the repair rate μ [equation (21) in [21]; [22]]. D_T is the total dose, and d_i is the dose for the i th fraction of N total fractions. If the tissue repair is monophasic, $c=0$. For PDR, there will be N_d dwell positions, N_c cycles and hence $N=N_d \times N_c$ fractions in total. The absolute partitioning between the two repair processes “ μ_1 ” and “ μ_2 ” is $1.0/(1+c)$ and $c/[1+c]$, respectively.

In order to obtain biological equivalence between two protocols, the total dose in the protocol to be equivalenced (*vs* a reference protocol) was assumed and modulated using a mathematical convergence algorithm until the required BED equivalence was achieved, using fixed dose rates and interfraction times of the estimated protocol. An α/β of 10 Gy was assumed for tumour (Point A). A dose rate of 3 Gy h⁻¹ was assumed during the exposure portion of the 1-h cycle, corresponding to the lowest activity sources available, and 6 Gy h⁻¹ was also investigated. For the OAR, an α/β of 4 Gy was used for the rectum, being the mean of values calculated from clinical and rodent data [23],

Table 1. Linear-quadratic model parameters

Location	Standard α/β ratios used
Point A	10 Gy
Rectum	4 Gy

and DRF=0.7. The biphasic repair kinetic models used were based on the analysis of data from early skin reactions in pigs [4] and late central nervous system (CNS) paralysis [11]. The numerical values used are listed in Tables 1 and 2.

RESULTS

Biologically effective dose calculation methodology for pulsed-dose-rate protocols: validation

PDR BT is based on positioning a radiation source along one or more catheters at various predefined dwell locations. An in-house PDR BT computer program was used to calculate the dose/dose rate distributions for a hypothetical catheter assembly, giving the BED at a specified point. The rectangular assembly had two planes (1 cm apart), each consisting of three catheters (4 cm long, 1 cm apart) and the ¹⁹²Ir dose distribution was determined from distribution tables [24]. The intercycle time was 1 h, and the exposure time was 20 or 6 min delivering 1 Gy on average within the assembly and set to 30 cycles.

Two different protocols were compared. The reference protocol was a full explicit protocol (EPDR) at a selected point in space based on the total number of fractions from every dwell position ($N_d \times N_c$), whereas the concise PDR protocol simply used the average exposure dose, dose rate for every cycle (N_c fractions). Points receiving 1.0, 0.5 and 0.2 Gy per cycle were chosen and equivalenced against the appropriate 30-cycle EPDR protocol. Monophasic $T_{1/2}$ of 1.5 h and skin biphasic repair kinetics were used. There was almost perfect agreement (<0.5% maximum difference) between the full EPDR and the simpler concise PDR protocol (Table 3). Consequently, this simpler PDR method was used for all further calculations.

Pulsed-dose-rate protocol analyses and the influence of repair kinetics

The replacement PDR protocol was initially required to deliver a 1-Gy/1-h cycle with 6- to 20-min exposure (dependent on source strength) to Point A. The optimum PDR protocol was determined by equivalencing the concise PDR protocol to the negative nodes or positive nodes LDR protocols. Because the number of PDR cycles has to be an integer, *i.e.* no partial cycles, the “best fit” (BF) protocol was achieved by specifying a number of cycles and determining the BED-equivalent PDR protocol dose. The fraction number was then iterated until the dose per cycle of the PDR protocol was closest to 1 Gy. The required dose for equivalence differed by 1.54 and 2.32 Gy for 22.5- and 32.5-Gy LDR, respectively (Table 4, column 4). There was an effect of dose per cycle on the equivalent dose, and the dose discrepancy for the different repair kinetics was minimal when the BFPDR dose per cycle was nearest to 1.7 Gy [Table 4 and Supplementary Table 1 (see Appendix)].

Table 2. Repair kinetics used in analyses

Repair kinetics	Repair halftimes (h)		Coefficient c
Monophasic	1.500	—	0.000
Biphasic, central nervous system	0.190	2.16	0.980
Normalised partition coefficients	0.510	0.49	
Biphasic, skin	0.103	2.97	0.375
Normalised partition coefficients	0.730	0.27	

Since the actual repair kinetics at Point A are unknown, this protocol would lead to minimal difference in the biological effect between the LDR and the equivalent PDR protocols, providing that one of the repair models is a reasonable representation. This minimisation effect applies to protocols where the average dose rate during the exposure part of the cycle is either 3 Gy h^{-1} or 6 Gy h^{-1} (Supplementary Table 1).

Normal tissue effects using “best-fit” pulsed-dose-rate protocols

The DRF for the rectum, a major OAR, is commonly taken to be 0.7 [5]—here assumed the same for both LDR and PDR protocols. The selected therapeutic PDR dose per cycle and the exposure dose rate components were modulated by the DRF to create the rectal PDR protocol. Again, the actual rectal repair kinetics are not known and so the three different repair models were used with $\alpha/\beta = 4 \text{ Gy}$.

The BED induced by the above DRF-modulated PDR reference protocol to the OAR was then determined. This was related to the original therapeutic LDR protocol for the rectum used to deliver the therapeutic dose at Point A except that the LDR dose (to the OAR) was now modulated for equivalence to the above reference protocol. If this equivalenced LDR dose is less than the original DRF-modulated therapeutic LDR dose, then the BF equivalenced PDR protocol would be less damaging to the rectum compared with the therapeutic LDR protocol. The equivalent LDR dose to the DRF-modulated BFPDR protocol for the OAR will not necessarily be the same as the therapeutic LDR (DRF-modified) protocol because:

- the BFPDR protocols equivalenced to the therapeutic LDR protocols used Point A repair kinetics and α/β ratios
- calculating the LDR dose equivalent to the DRF-modified BFPDR protocol at the OAR used the OAR repair kinetics and α/β ratios.

These results are shown in Table 5 and Supplementary Tables 2–5, columns 7, 8, 9. Note that when using BFPDR

equivalencing, the “actual” dose per cycle is the BFPDR total dose per cycle and not the “nearest-to” dose per cycle.

Modelling implications

There is potentially a large dosage variation for the equivalent PDR protocols (relative to the appropriate fixed LDR protocols) owing to the assumed repair kinetics, especially at small fractional doses. This is reflected by the different calculated number of PDR cycles and the dose per cycle. However, the discrepancy is virtually eliminated when using nearest-to 1.7 Gy per cycle equivalence (Table 4, column 4; Supplementary Table 2, columns 10–12).

A therapeutic LDR dose of 22.5 Gy at Point A was equivalent to 25.2 Gy delivered in 25 cycles BFPDR using nearest-to 1 Gy per cycle, calculated using a single repair halftime of 1.5 h at Point A (Table 4, column 1). Using a DRF of 0.7, the rectal wall would receive a therapeutic LDR dose of 15.75 Gy delivered at 1.085 Gy h^{-1} (Supplementary Table 2, column 2). For 25 cycles BFPDR, the equivalent total rectal PDR dose (column 5) would be 17.64 Gy using monophasic repair kinetics, 17.03 Gy using CNS repair parameters or 16.56 Gy using skin repair parameters (see nearest-to 1 Gy per cycle—top, middle and lower panels, respectively). Assuming monophasic repair kinetics for the tumour, the BFPDR doses (Supplementary Table 3, column 5) were converted back to an equivalent LDR dose at the rectal wall of 15.10 Gy assuming monophasic repair kinetics for the rectum (column 7), or 15.73 Gy using CNS repair kinetics (column 8) or 16.41 Gy using skin repair kinetics (column 9). These latter three doses differ from each other by a maximum of 8.7% and differ from the starting LDR dose of 15.75 Gy by a maximum of 4.2%, indicating the small differences as a result of the different choices of repair kinetics for the rectum vs the tumour.

For the higher LDR dose of 32.5 Gy (Supplementary Table 3), when using nearest-to 1 Gy per cycle and monophasic repair at Point A, the equivalent BFPDR dose was 36.9 Gy delivered in 37 cycles. With a DRF of 0.7, the rectal wall would receive an equivalent LDR dose of 22.75 Gy delivered at 1.085 Gy h^{-1} . For

Table 3. Comparison of total doses using the full explicit pulsed dose rate (EPDR) protocol and the concise PDR protocol

PDR total dose (Gy)	EPDR total dose (Gy)			
	20-min exposure time per cycle		6-min exposure time per cycle	
	Repair halftime (1.5 h)	Skin repair kinetics	Repair halftime (1.5 h)	Skin repair kinetics
30.00	30.00	30.15	30.01	30.07
15.00	15.01	15.04	15.00	15.02
6.00	6.00	6.00	6.00	6.00

Table 4. Maximum difference in total pulsed dose rate dose at Point A using different repair kinetics

Monophasic	Biphasic	Biphasic	Maximum difference in total dose (Gy)
Best fit to required dose per cycle=1.0 Gy			
Reference protocol: negative nodes LDR dose=22.5 Gy, dose rate=1.55 Gy h ⁻¹ , α/β ratio=10 Gy			
Repair $T_{1/2}$ =1.5 h	CNS repair kinetics	Skin repair kinetics	
Number of cycles=25	Number of cycles=24	Number of cycles=24	
Total dose=25.20 Gy	Total dose=24.33 Gy	Total dose=23.66 Gy	1.54
Reference protocol: positive nodes LDR dose=32.5 Gy, dose rate=1.55 Gy h ⁻¹ , α/β ratio=10 Gy			
Repair $T_{1/2}$ =1.5 h	CNS repair kinetics	Skin repair kinetics	
Number of cycles=37	Number of cycles=36	Number of cycles=35	
Total dose=36.91 Gy	Total dose=35.72 Gy	Total dose=34.59 Gy	2.32
Best fit to required dose per cycle=1.7 Gy			
Reference protocol: negative nodes LDR dose=22.5 Gy, dose rate=1.55 Gy h ⁻¹ , α/β ratio=10 Gy			
Repair $T_{1/2}$ =1.5 h	CNS repair kinetics	Skin repair kinetics	
Number of cycles=13	Number of cycles=13	Number of cycles=13	
Total dose=21.92 Gy	Total dose=21.96 Gy	Total dose=22.0 Gy	-0.08
Reference protocol: positive nodes LDR dose=32.5 Gy, dose rate=1.55 Gy h ⁻¹ , α/β ratio=10 Gy			
Repair $T_{1/2}$ =1.5 h	CNS repair kinetics	Skin repair kinetics	
Number of cycles=19	Number of cycles=19	Number of cycles=19	
Total dose=31.68 Gy	Total dose=31.71 Gy	Total dose=31.76 Gy	-0.08

CNS, central nervous system; LDR, low dose rate.

37 cycles of BFPDR, the equivalent total rectal PDR dose (column 5) would be 25.84 Gy using monophasic repair kinetics, 25.00 Gy using CNS repair parameters or 24.21 Gy using skin repair parameters (see nearest-to 1 Gy per cycle—top, middle and lower panels, respectively). Assuming monophasic repair kinetics for the tumour, the BFPDR doses (column 5) were converted back to an equivalent LDR dose at the rectal wall of 21.69 Gy assuming monophasic repair kinetics for the rectum (column 7), 22.60 Gy using CNS repair kinetics (column 8) or 23.57 Gy using skin repair kinetics (column 9). These latter three doses differ from each other by $\leq 9\%$ and differ from the starting LDR dose of 22.75 Gy by $\leq 5\%$.

Increasing the source strength (*i.e.* exposure dose rate) by a factor of 2, when using nearest-to 1 Gy per cycle, was found to change equivalent doses by $\leq 2\%$ (Table 4; Supplementary Tables 4 and 5).

The effect of changing the nearest-to dose per cycle was also explored. Using 3 Gy h⁻¹ exposure dose rate (Supplementary Table 2), an increase in dose per cycle decreased the number of cycles required and decreased the total rectal PDR dose for equivalence. When using monophasic repair kinetics at Point A and nearest-to 1 Gy per cycle, the equivalent rectal LDR dose was slightly less than the rectal BFPDR dose, whichever repair kinetics were chosen, but the reverse was the case using 2 Gy per cycle. Also, the changes in the equivalent rectal LDR dose, as the dose per cycle was increased from nearest-to 1.0 to 1.7 Gy, were least (within 2%: 15.86/15.73 and 15.83/16.41, respectively) in

the case of assumed CNS or skin repair kinetics for the rectum compared with monophasic kinetics (5%: 15.89/15.10). In addition, the variation in the equivalent rectal LDR dose caused by the use of the different repair kinetics was least (within 2%) when using nearest-to 1.7 Gy per cycle (Supplementary Table 2, columns 10–12) compared with 7% for 1 Gy per cycle and 16% for 0.5 Gy per cycle. The results were virtually the same for the higher BT dose of 32.5 Gy at Point A (Supplementary Table 3) and for the higher (source strength) exposure dose rate (Supplementary Tables 4 and 5). Hence, the uncertainties associated with the choice of repair kinetics for the rectum (either conventional 1.5-h monophasic or skin or CNS biphasic) would be minimised to very low levels using 1.7 Gy per cycle.

Nevertheless, the formal equivalent LDR dose to the rectal wall may well be greater or lesser than the therapeutic LDR protocols (Supplementary Tables 4 and 5). Again, there are obvious differences depending on the chosen repair kinetics, and even some low doses per cycle gave an increased rectal dose for the BFPDR equivalent protocol compared with the LDR protocol. This variation is relatively small for DRF=0.7 with the nearest-to 1.7 Gy per cycle PDR protocol, where the maximum increase in the equivalent LDR dose relative to the LDR protocol (22.5 Gy) was $\leq 1.4\%$ (0.22 Gy) for 3 Gy h⁻¹, $\leq 2.67\%$ (0.42 Gy) for 6 Gy h⁻¹ and 0.31 Gy and 0.57 Gy, respectively, for the 32.5 Gy LDR protocol. The rectal doses for the BFPDR protocols using nearest-to 1.6 and 1.8 Gy per cycle were similar to those for the nearest-to 1.7 Gy per cycle protocol (Supplementary Tables 6 and 7).

Table 5. Optimised pulsed dose rate (PDR) for nearest-to 1.7 Gy per cycle vs LDR 22.5 Gy and 32.5 Gy at Point A with DRF=1.0 or 0.7 at the rectum

Repair kinetics for Point A: monophasic $T_{1/2} = 1.5$ h, α/β ratio = 10 Gy						Rectal repair kinetics α/β ratio = 4 Gy				
DRF	Rectal LDR dose (Gy)	Rectal LDR dose rate (Gy h^{-1})	Number of PDR cycles	Rectal PDR dose (Gy)	Rectal PDR dose rate (Gy h^{-1})	$T_{1/2} = 1.5$ h	Biphasic CNS	Biphasic skin	$T_{1/2} = 1.5$ h	Biphasic CNS
						Equivalent rectal LDR dose (Gy) delivered from point A			% change in LDR to the rectum (equivalent to PDR) compared with the therapeutic dose (column 2)	
0.70	15.75	1.09	13.00	15.34	2.10	15.89	15.86	15.83	0.89	0.70
1.00	22.50	1.55	13.00	21.92	3.00	22.83	22.80	22.77	1.47	1.33
0.70	22.75	1.09	19.00	22.18	2.10	22.95	22.93	22.91	0.88	0.79
1.00	32.50	1.55	19.00	31.68	3.00	32.96	32.96	32.96	1.42	1.42
Repair kinetics for Point A: biphasic CNS, α/β ratio = 10 Gy						Rectal repair kinetics α/β ratio = 4 Gy				
DRF	Rectal LDR dose (Gy)	Rectal LDR dose rate (Gy h^{-1})	Number of PDR cycles	Rectal PDR dose (Gy)	Rectal PDR dose rate (Gy h^{-1})	$T_{1/2} = 1.5$ h	Biphasic CNS	Biphasic skin	$T_{1/2} = 1.5$ h	Biphasic CNS
						Equivalent rectal LDR dose (Gy) delivered from Point A			% change in LDR to the rectum (equivalent to PDR) compared with the therapeutic dose (column 2)	
0.70	15.75	1.09	13.00	15.37	2.10	15.93	15.90	15.87	1.14	0.95
1.00	22.50	1.55	13.00	21.96	3.00	22.89	22.85	22.82	1.73	1.56
0.70	22.75	1.09	19.00	22.20	2.10	22.98	22.96	22.94	1.01	0.92
1.00	32.50	1.55	19.00	31.71	3.00	33.00	33.01	33.00	1.54	1.57
Repair kinetics for Point A: biphasic CNS, α/β ratio = 10 Gy						Rectal repair kinetics α/β ratio = 4 Gy				
DRF	Rectal LDR dose (Gy)	Rectal LDR dose rate (Gy h^{-1})	Number of PDR cycles	Rectal PDR dose (Gy)	Rectal PDR dose rate (Gy h^{-1})	$T_{1/2} = 1.5$ h	Biphasic CNS	Biphasic skin	$T_{1/2} = 1.5$ h	Biphasic CNS
						Equivalent rectal LDR dose (Gy) delivered from Point A			% change in LDR to the rectum (equivalent to PDR) compared with the therapeutic dose (column 2)	
0.70	15.75	1.09	13.00	15.40	2.10	15.97	15.94	15.90	1.40	1.21
1.00	22.50	1.55	13.00	22.00	3.00	22.95	22.91	22.87	2.00	1.82
0.70	22.75	1.09	19.00	22.23	2.10	23.03	23.01	22.98	1.23	1.14
1.00	32.50	1.55	19.00	31.76	3.00	33.08	33.08	33.07	1.78	1.75

CNS, central nervous system; DRF, dose reduction factor; LDR, low dose rate.

α/β ratio sensitivity analysis

The above results listed in Supplementary Tables 2–5 all depend on the α/β ratios applied to Point A and the rectum as well as the repair kinetics. The effects of changing the α/β ratio for Point A to 20 Gy and to 5 Gy were investigated (Supplementary Tables 8 and 9), and large differences were obtained for nearest-to 0.5 Gy per cycle. For monophasic kinetics, the total BFPDR dose ranged from 26.16 Gy in 52 cycles to 33.87 Gy in 68 cycles for equivalencing to 22.5-Gy LDR and 38.19 Gy in 76 cycles to 50.09 Gy in 100 cycles for 32.5-Gy LDR, with similar variations between the different repair kinetics. The maximum dose difference between repair kinetics using 3 Gy h^{-1} BFPDR for an α/β of 5 Gy was 5.79 Gy for 22.5-Gy LDR and 8.15 Gy for 32.5 Gy. When the nearest-to dose per cycle = 1.7 Gy was used (Supplementary Tables 8 and 9), the BFPDR total dose for monophasic kinetics ranged from 22.1 Gy in 13 cycles to 21.75 Gy in 13 cycles for 22.5-Gy LDR and 31.93 Gy in 19 cycles to 30.93 Gy in 18 cycles for 32.5 Gy. Also, the maximum BFPDR dose difference between repair kinetics at 3 Gy h^{-1} was 0.1 Gy for 22.5-Gy LDR and 0.36 Gy at 6 Gy h^{-1} . Using a BFPDR cycle dose nearest-to 1.7 Gy and an exposure dose rate between 3 and 6 Gy h^{-1} minimised any difference in equivalencing BFPDR to the LDR protocols.

The Appendix indicates that if the equivalencing process between two protocols gives rise to equality between the BEDs and also the total dose for both protocols, then the equivalencing is independent of α/β (Supplementary Tables 8 and 10). The temporal repair kinetics used in the present analyses do not seem to infer any significant differences between the BFPDR results for the 1.7 Gy per cycle protocol—although they most certainly do for some other BFPDR protocols when the concept of near-extended equivalence (Appendix) is not attained.

Regarding the choice of α/β for the rectum, when using the nearest-to 1.7 Gy per cycle BFPDR protocol, the difference between the equivalent LDR to the PDR protocol and the therapeutic LDR protocol (DRF=0.7) was $\leq 1.9\%$ for $\alpha/\beta = 2 \text{ Gy}$ and $\leq 0.25\%$ for $\alpha/\beta = 6 \text{ Gy}$ (Supplementary Table 10). Although the rectal results for BFPDR are not themselves formally equivalenced, they do depend upon near-extended equivalence protocols derived for Point A. The use of such protocols for the rectum (which could receive a different dose at a different dose rate from Point A) reduces the variation between rectal doses for different α/β values and repair kinetics.

Total radiotherapy protocol

It is also important to address the total protocol, *i.e.* by including the EB component (Table 6). The Christie Hospital previously used a two-fraction LDR protocol at a dose rate of 1.55 Gy h^{-1} separated by 7–10 days, and this was equivalenced for BED using dose modulation against (1) the standard therapeutic LDR protocol+EB, and (2) BFPDR nearest-to 1.7 Gy per cycle+EB. For the negative-node scenario, the 2-fraction LDR equivalent protocol for BFPDR nearest-to 1.7 Gy per cycle at DRF=1.0, the % difference in equivalent doses was $\leq 0.87\%$, whilst for DRF = 0.7, the increase was $\leq 0.45\%$. The results for the positive-node case were similar at ≤ 1.02 and $\leq 0.54\%$, respectively. The minimal variation between equivalences for Point A is owing to the prior near-extended equivalence which defined

the protocols being used. No relative biological effectiveness correction owing to different radiation energy spectra of external and BT fields was invoked, in line with current BT practice.

Further implications of extended equivalence

The PDR dose at different DRFs was determined by taking the BFPDR dose at DRF=1.0 (Point A), and modifying it by the appropriate DRF. An alternative approach was investigated using the number of cycles specified by the BFPDR (DRF=1.0) protocol for nearest-to 1.7 Gy per cycle, but equivalencing the protocol directly against an LDR protocol where the dose and dose rate were modified by the DRF *a priori*. These additional results for monophasic, CNS and skin repair kinetics (Supplementary Table 2) were for DRF=0.5, 0.7, respectively (11.05, 15.41; 11.07, 15.44; 11.10, 15.48) Gy compared with the values of (10.96, 15.34; 10.98, 15.37; 11.0, 15.4) Gy, indicating effectively a 1:1 scalability between the two methods (Supplementary Table 11). Extended equivalence between two protocols is therefore propagated under DRF modulation for the repair kinetics and protocol investigated and applies only to the nearest-to 1.7 Gy per cycle PDR protocol in this study. Given that there is very little difference between these results under extended equivalence, any calculations based on the LDR dose gradients *e.g.* [25], would apply equally to the appropriately DRF-modulated BFPDR equivalent dose distribution.

In the above analyses, the reference protocol comprised the PDR or LDR protocol plus the EB component of 20 daily fractions (45 Gy or 40 Gy depending upon the presence of nodes), and the protocol to be equivalenced was an LDR treatment with 2 fractions separated by 48 h (from the end of 1 fraction to the start of the next) at $\text{DRF} \times 1.55 \text{ Gy h}^{-1}$. The biphasic-repair skin data for the PDR protocol were chosen because they gave the highest dose for the nearest-to 1.7 Gy per cycle for BFPDR at Point A.

DISCUSSION

Using Point A as reference with $\alpha/\beta = 10 \text{ Gy}$, monophasic repair ($T_{1/2} = 1.5 \text{ h}$) and DRF=0.7, 25 (nearest-to 1.0 Gy) BFPDR cycles to Point A were calculated as equivalent to 22.5 Gy LDR and 37 cycles for 32.5-Gy LDR. These PDR cycle numbers are consistent with those of 26 and 38 cycles (of exactly 1 Gy), respectively, calculated using the GEC-ESTRO recommendations [6].

The present calculations are internally consistent, but it is stressed that the calculated equivalent PDR doses at Point A and at the rectal wall are only best estimates. The estimated doses depend on the actual α/β ratios, DRF at the rectal wall and repair kinetics, applicable in this scenario. An α/β of 10 Gy for tumours is a generic value, assumed here to apply to cervical carcinoma. We used an α/β of 4 Gy for the rectum in an attempt to use a more tissue-specific value rather than a conventional generic value of 3 Gy for late reactions. A DRF of 0.7 is recommended [5] although 0.6 was used in an earlier study [26,27]. Even higher values are reported in the literature, and the actual value may well vary among patients. Further, it is assumed that the same DRF applies to the therapeutic LDR and PDR protocols, and violation of this could lead to a significantly different interpretation of the results. The monophasic repair halftime of 1.5 h is again generic for both tumours and normal tissues.

Table 6. A two-fraction low-dose-rate (LDR) protocol equivalence [at biologically effective dose (BED)] using dose modulation against (1) the standard therapeutic LDR protocol + external beam (EB) and (2) "best fit" pulsed-dose-rate nearest-to 1.7 Gy per cycle + EB

EB: 20 fractions, 45 Gy+PDR/LDR 22.5 Gy or EB: 20 fractions, 40 Gy+32.5 Gy PDR/LDR									
Repair kinetics used for Point A: Biphasic skin									
α/β ratio = 10 Gy									
Dose reduction factor	Point A LDR dose (Gy)	Point A LDR dose rate (Gy h^{-1})	Number of cycles	Point A PDR dose (Gy)	Rectal PDR dose (Gy)	Rectal PDR dose rate (Gy h^{-1})	Rectal LDR dose (Gy)	Rectal LDR dose rate (Gy h^{-1})	
1.00	PDR equivalent to LDR 22.5 $\rightarrow$		13.00	22.00	22.00	3.000		NA	
1.00	22.5:1 fraction	1.55			NA		22.5	1.55	
% Difference between PDR and LDR equivalences using equivalencing to 2 fraction LDR protocol, 1.55 Gy h^{-1} at the rectum and 48 h between fractions $\rightarrow$									
0.70	PDR equivalent to LDR 22.5 Gy $\rightarrow$		13.00	22.00	15.40	2.100		NA	
0.70	22.5:1 fraction	1.55			NA		15.75	1.085	
% Difference between PDR and LDR equivalences using equivalencing to 2 fraction LDR protocol, $\text{DRF} \times 1.55 \text{ Gy h}^{-1}$ at the rectum and 48 h between fractions $\rightarrow$									
1.00	PDR equivalent to LDR 32.5 Gy $\rightarrow$		19.00	31.76	31.76	3.000	NA	NA	
1.00	32.5:1 fraction	1.55			NA		32.5	1.55	
% Difference between PDR and LDR equivalences using equivalencing to 2 fraction LDR protocol, 1.55 Gy h^{-1} at the rectum and 48 h between fractions $\rightarrow$									
0.70	PDR equivalent to LDR 32.5 Gy $\rightarrow$		19.00	31.76	22.23	21.00	NA	NA	
0.70	32.5:1 fraction	1.55			NA		22.75	1.085	
% Difference between PDR and LDR equivalences using equivalencing to 2 fraction LDR protocol, $\text{DRF} \times 1.55 \text{ Gy h}^{-1}$ at the rectum and 48 h between fractions $\rightarrow$									
Reference: PDR or LDR+EB; equivalenced to 2 fraction LDR $\text{DRF} \times 1.55 \text{ Gy h}^{-1}$ for 48-h gap									
Point A repair kinetics, α/β ratio = 10 Gy				Rectal repair kinetics, α/β ratio = 4 Gy			Rectal dose rate for equivalent protocol (Gy h^{-1})		
$T_{1/2} = 1.5 \text{ h}$	Biphasic CNS	Biphasic skin		$T_{1/2} = 1.5 \text{ h}$	Biphasic CNS	Biphasic skin			
Equivalenced 2 fraction total LDR dose at Point A (Gy) for LDR or PDR + EB dose protocol				For LDR or PDR + EB dose protocol					
56.93	60.28	63.61		51.29	55.89	61.05		1.550	
56.83	60.23	63.62		50.85	55.48	60.68		1.550	
0.18	0.08	-0.02		0.87	0.74	0.61		NA	
	NA			49.56	54.11	58.97		1.085	
				49.34	53.93	58.82		1.085	
				0.45	0.33	0.26		NA	
62.67	65.61	68.52		57.58	61.60	66.08		1.550	

(Continued)

Table 6. (Continued)

Reference: PDR or LDR+EB; equivalenced to 2 fraction LDR DRF×1.55 Gy h ⁻¹ for 48-h gap						Rectal dose rate for equivalent protocol (Gy h ⁻¹)
Point A repair kinetics, α/β ratio=10 Gy			Rectal repair kinetics, α/β ratio=4 Gy			
T _{1/2} =1.5 h	Biphasic CNS	Biphasic skin	T _{1/2} =1.5 h	Biphasic CNS	Biphasic skin	
Equivalenced 2 fraction total LDR dose at Point A (Gy) for LDR or PDR+EB dose protocol			For LDR or PDR+EB dose protocol			
62.67	65.55	68.52	57.00	61.02	65.51	
0.16	0.09	0.00	1.02	0.95	0.87	
NA			51.88	55.81	59.99	
			51.60	55.55	59.76	
			0.54	0.47	0.38	
						NA

CNS, central nervous system; DRF, dose reduction factor; NA, not applicable.

Repair halftimes have been discussed extensively with respect to PDR BT, *e.g.* [28], but without definitive conclusions. We have used what we consider to be more appropriate biphasic repair kinetics, in particular for the OAR, albeit examples of CNS in rodents and skin in pigs because the actual values for human rectum are not known.

An important feature of the results is that the dose per cycle can be increased above 1 Gy, so decreasing the number of cycles, and the equivalent PDR doses become more robust when expressed in terms of LDR doses, *i.e.* they are less dependent on the choice of repair kinetics. A dose per cycle of nearest-to 1.7 Gy at Point A appears about optimum, and in that case, the rectal PDR dose and its equivalent LDR dose are independent of choice of repair kinetics used here. Further, a BFPDR protocol consisting of nearest-to 1.7 Gy per cycle displays near isoeffect responses for all the repair kinetics and α/β ratios used here (Supplementary Tables 2–5). This minimises any uncertainties owing to inappropriate selection of modelling parameters. Also, the nearest-to 1.7 Gy per cycle BFPDR protocol even minimises uncertainties related to the use of inappropriate α/β ratios for the Point A and the rectum.

If equivalence at the rectal wall is not achieved exactly, because of other factors not taken into account, one question is “what difference is acceptable?” This can be estimated using the steepness of the dose-response curve. In the trials of LDR alone conducted previously, there were $\sim 10\%$ major complications produced by 65 Gy (1.55 Gy h^{-1} at Point A) and $\sim 20\%$ by 75 Gy [26]. This corresponds to a local- γ -factor at the (mid) 15% response level (γ_{15}) of 0.67% extra (absolute percentage points) complications per 1% more dose (and a γ_{50} value of ~ 2 , which is near the low end of the range of 1 (low) to 6 (high) dose-response slopes for late normal tissue reactions) [29]. As the BT component forms only a part of the total treatment, dose changes in the former are somewhat diluted in the total dose, indicating that the equivalent LDR doses to the rectum in the PDR scenario of up to a few percent above the actual LDR doses used previously, would produce very few extra complications and in some cases, the doses would be less. Indeed, for monophasic repair at Point A, but biphasic repair in the rectum, BFPDR could deliver an increased rectal dose even at 0.5 and 1.0 Gy per cycle compared with the LDR protocols. However, for monophasic repair in both tissues, there would be a reduction in the total rectal dose for nearest-to $\leq 1.0 \text{ Gy}$ BFPDR protocols at 3 and 6 Gy h^{-1} exposure dose rates (Table 5).

Based on monophasic repair, it was noted previously that the EQD2 to the OAR may be less for PDR than for LDR, *e.g.* by an average of 5.8% for these cervical treatments [6]. This implied a small therapeutic advantage of PDR vs LDR owing to lowering the average dose rate from around 1.5 to 1 Gy h^{-1} . This was also observed in the present study, using monophasic repair for both the Point A and the rectum, 1 Gy per pulse and $\text{DRF} = 0.7$, where the rectal equivalent LDR dose of 15.10 Gy (Supplementary Table 2, column 10) in the PDR scenario was less by 4.13% than the LDR dose of 15.75 Gy estimated in column 2 and 4.66% in the case of the higher BT dose (Supplementary Table 3, column 10). However, this suggested benefit disappeared when biphasic rectal repair was used [corresponding values were -0.13% (CNS

kinetics) and +4.19% (skin kinetics); Supplementary Table 2, columns 10 and 11] or when the dose per cycle was increased from 1 Gy to 1.7 Gy in which case the monophasic/biphasic rectal equivalent LDR dose results were all about the same (the differences in columns 10–12 were only +0.89%, +0.70%, +0.51% from the dose of 15.75 Gy estimated in column 2). These changes by <1% in equivalent LDR doses would be expected to produce negligible changes in complication rates.

CONCLUSIONS

It is concluded that the use of both biphasic and monophasic repair for modelling the effects on the OAR in PDR BT suggests that the dose per cycle could be increased from 1 Gy to the BFPDR dose per cycle nearest to 1.6–1.7 Gy. In this case, the differences in equivalent doses dependent on the choice of repair kinetics virtually disappeared. This would greatly minimise any

prescription dosage changes owing to the use of inappropriate repair kinetics and α/β ratios. Also, in this case, the treatment times for the therapeutic LDR and equivalenced BFPDR protocols would be very similar, not longer for PDR as is currently the case, and this would help in maximising the patient throughput per PDR machine.

These particular equivalenced protocols above conform to the concept of extended equivalence where the obtained equivalence is simultaneously achieved for the total dose and the BED. Further, it has been shown that for DRFs in the range 0.5–1.0, the equivalencing process between the LDR and BFPDR protocols achieving extended equivalence has to be undertaken only for the DRF=1.0. The equivalence for any other DRF between 0.5 and 1.0 is obtained simply by modulating the dose and dose rate of the equivalenced protocol (DRF=1.0) by the required DRF.

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APPENDIX

Extended equivalence

The biologically effective dose (BED) Equation (1) may be written

$$\text{BED} = D_T + \frac{1}{\alpha/\beta} \Phi(\Xi, \mu) \sum_{i=1}^{i=N} d_i^2 \quad (1)$$

where $\Phi(\Xi, \mu)$ is the composite repair function for the protocol Ξ . For the same tissue, the BED is constant between equivalent protocols. If it is also imposed that the total dose D_T is constant between the equivalenced protocols, then from Equation (1), equivalence requires that

$$\Phi(\Xi_{\text{ref}}, \mu) \sum_{i=1}^{i=N} d_{\text{ref},i}^2 = \Phi(\Xi_{\text{equiv}}, \mu) \sum_{i=1}^{i=N_{\text{equiv}}} d_{\text{equiv},i}^2 \quad (2)$$

for the reference (ref) and equivalent (equiv) protocols, respectively. Hence, from Equation (2), the extended equivalence is independent of α , β and the α/β ratio when using the same radiation quality for the specified tissue. Thus, if equivalence protocols can be found which satisfy the above conditions, they will be more resilient when calculating equivalence protocols in situations where the α/β ratio is not accurately known. Even if absolute equality is not found for the total dose, it is likely that the effect of varying the α/β ratio will be greatly reduced when equality is almost achieved.

Supplementary material

The supplementary tables can be found at <http://bjr.birjournals.org/site/supplmaterial/20130288supplementarytables.pdf>