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Biological equivalance of low dose rate to multifractionated high dose rate irradiations: investigations in mouse lip mucosa

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Abstract

Background and purpose: The aim of this study was to evaluate the biological equivalence of continuous low dose rate (LDR) irradiations to multifractionated high dose rate (HDR) regimes. The applicability of the LQ model was analysed for fraction sizes and dose rates relevant for the clinic.

Material and methods: Investigations were performed in mouse lip mucosa. HDR fractions were given in an overall treatment time ranging from 10 h to 3.5 days. The dose rate effect was analysed in the range of 84 to 0.76 Gy/h. For an assessment of biological equivalence in comparison to LDR, HDR irradiations have been performed in the same overall treatment time as the corresponding LDR regimes.

Results: Recovery leads to sparing of radiation damage as the dose rate is reduced from 84 to 0.76 Gy/h (20.0 versus 45.7 Gy ED_{50}). No significant additional sparing from 0.9 to 0.76 Gy/h could be demonstrated (44.9 versus 45.7 Gy ED_{50}). Even 30 HDR fractions in 24 h were not sufficient to match the effect of LDR over the same time period (38.2 versus 41.1 Gy ED_{50}). The present data give evidence for a bi-exponential repair process in mouse lip mucosa ($T_{1/2\ fast}$ 27 min, $T_{1/2\ slow}$ 150 min). Repair is dominated by the faster component (>80%).

Conclusions: LDR is the most efficient way to deliver radiation if recovery is to be maximised and the overall time kept as short as possible. When used with realistic parameters the LQ model is capable of providing quantitative guidelines in areas of clinical interest.

Keywords: Fractionation; Dose rate effect; Repair; Repair kinetics; Two components of repair kinetics; Linear-quadratic model; Brachytherapy

1. Introduction

The introduction of the pulsed dose-rate (PDR) technique into brachytherapy has several technical advantages. These include adaptable dose prescription and distribution and most of all significantly improved radiation safety for patient and staff.

In order to achieve a radiobiological response comparable to the experience of the routinely applied continuous low dose rate treatments the source scanning through the target volume is interrupted repeatedly. Despite the increasing use of PDR afterloading devices in clinical practice, experimental radiobiological data on biological equivalence of irradiations with different dose rates are scarce.

The present investigation dealt with the fractionation and dose rate effects in mouse lip mucosa, a typically early reacting tissue. The experiments were performed with dose-rates as low as 0.76 Gy/h and fraction sizes covered the clinically used range. The main topic addressed in the present experiments was to what extent a multifractionated high dose rate (HDR or PDR) regime can be equivalent in biological response to a continuous low dose rate (LDR) regime. In particular, the length of the overall treatment time in relation to the number of HDR fractions was investigated.

In addition, the applicability of the LQ concept for calculating isoeffective treatment regimes was validated with

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dose rates and fraction sizes relevant for the clinic.

2. Material and methods

2.1. Animals

Adult, female outbred NMRI mice with a body weight of 23–28 g were used for this study. Animals were kept in conventional housing during the experimental period and had unlimited access to water and food. Further details of the immobilisation set-up, which allowed the investigations of effects of irradiations lasting several hours were published previously [24]. A continuous flow of humidified air (>2.5 l/min) was given during irradiation to avoid an accumulation of carbon dioxide in the dead-air space of the anaesthesia circuit. No mice were lost due to the immobilisation procedure. Body weight loss was maximally 8% of the initial weight and was fully recovered by the time the radiation-induced damage of the oral mucosa impaired ingestion.

Prior to irradiation the mice were left for a period of 15 min to get accustomed to their position. The experiments have been carried out according to the 'Belgian Legislation on the Welfare of Laboratory Animals'.

2.2. Irradiations

Irradiations were performed with a Co^{60}-γ unit at a focus to skin distance of 140 cm for the LDR experiments and of 45 cm for the high dose-rate treatments. The dose-rate of the various LDR experiments was adjusted by the use of additional lead filters. The snouts of mice placed in a supine position were exposed to a single field irradiation, with the remaining part of the body shielded with 8 cm thick MCP alloy (Mining and Chemical Product, melting point 70°C, Metallurgie Hoboken, Belgium). A straightforward comparison of the LDR and fractionated HDR regimes could be performed, as equal volumes were treated and field geometry was comparable. No significant dose gradients, as usually present in low dose rate regimes with implanted radioactive sources, had to be taken into account. The homogeneity and accuracy of the dose distribution was checked repeatedly with TLD and film dosimetry. Six to 16 mice were used for each radiation dose point. In order to construct dose/response relationships five to nine dose levels were selected per experiment. Each experiment was repeated at least once.

2.3. Experimental design

Three different sets of experiments have been carried out. In the first series the fractionation effect was investigated with HDR irradiations at a constant dose rate of 84 Gy/h (see Fig. 1a). Single dose (SD), 2, 10 and 20 fractions were given in an overall treatment time ranging from 10 h to 3.5 days, ensuring that the interfraction intervals were always longer than 4 h. This duration of interval was known in lip mucosa to be sufficient for complete repair during the interfraction intervals [3,24]

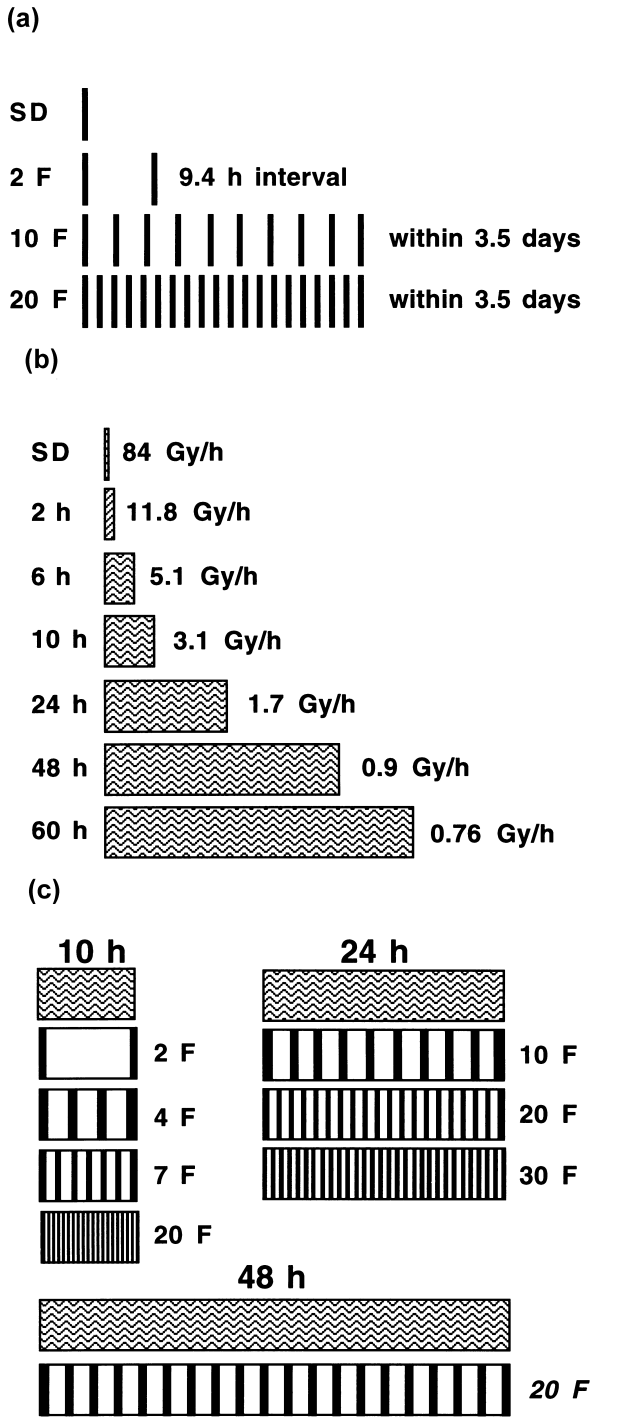

Fig. 1. (a) Experimental design of fractionated experiments with interfaction intervals >4 h (complete repair). (b) Experimental design of continuous low dose rate experiments. (c) Experimental design to compare continuous low dose rate to fractionated high dose rate irradiations (incomplete repair).

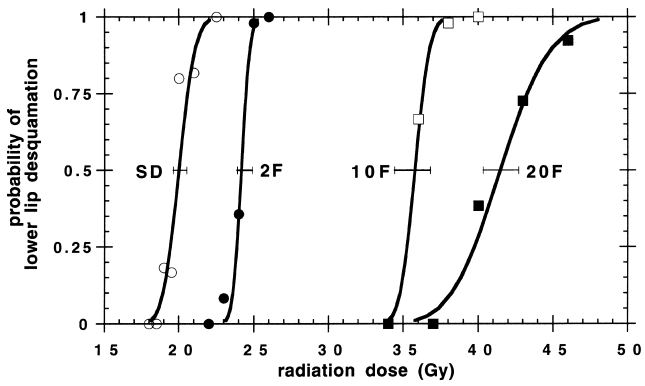

Fig. 2. Dose-incidence relationship for lower lip desquamation following HDR irradiations in complete repair conditions. Error bars represent 95% confidence limits of the ED_{50}.

The overall treatment time of the present investigations was always limited to 3.5 days. Therefore, significant effects of repopulation during the overall treatment time involved in the experiments can be excluded as previous investigations did not show any dose modification due to repopulation for overall treatment times shorter than 3.5 days [4,13].

The second set of experiments was aimed at elucidating the dose rate effects in mouse lip mucosa (see Fig. 1b). Overall treatment times were 0.2, 2, 6, 10, 24, 48 and 60 h. The corresponding dose-rates (at isoeffective dose levels) were in the range of 84 to 0.76 Gy/h.

For an assessment of biological equivalence in comparison to continuous irradiations, fractionated high dose rate irradiations have been performed in the same overall treatment time as the LDR regimes described above (see Fig. 1c). Two, 4, 7, 10 and 20 equally spread HDR fractions were given in a fixed overall treatment time of 10 h. Additionally, 10, 20 and 30 HDR irradiations were performed in 24 h. Finally, 20 HDR fractions were given in 48 h.

2.4. Assessment

Details of the scoring system for the acute mucosal reactions of the mouse lip mucosa were published previously [17,32]. The reactions of the lip mucosa were scored daily for a period of 3 weeks. As biological endpoint the incidence of lower lip mucosal desquamation in each group of mice was recorded, allowing a quantal analysis of the data.

2.5. Data analysis

ED_{50} values (radiation doses leading to lip mucosal desquamation in 50% of the animals) were determined by probit analysis [14] using the entire dose/response data. Estimation of α/β values and repair halftimes ($T_{1/2}$) was performed by use of a direct analysis computer program '$\alpha\beta$-est', which was kindly provided by the Dept. of Biomathematics of the M.D. Anderson Cancer Center, Houston, USA [6,26]. The values given in brackets represent 95% confidence limits. The analysis of the two-component model was performed by use of a custom written extension of '$\alpha\beta$-est' (Dept. of Biomathematics of the M.D. Anderson Cancer Center, Houston, USA).

3. Results

3.1. Fractionation in complete repair conditions

Fig. 2 illustrates the dose-response curves for lower lip desquamation fitted by probit methods to the data for each fractionation schedule. ED_{50} values are shown with 95% confidence intervals. A significant increase of isoeffect dose is achieved with increasing fraction number in conditions of complete repair (intervals >4 h). The single dose (SD) ED_{50} was 20 Gy (19.6–20.5), whereas 2 fractions in 10 h resulted in an isoeffective dose of 24.2 Gy (23.9–24.9). Ten and 20 fractions in 3.5 days lead to an ED_{50} of 35.8 Gy (34.4–36.8) and 41.5 Gy (40.3–42.7), respectively. Compared to the single dose treatment more than 20 Gy was spared due to fractionation. The data of all performed HDR-experiments are summarised in Table 1.

3.2. Dose rate effect

The dose rate effect reflects repair of sublethal damage during a continuous irradiation. In the present experiments this effect was investigated from 84 to 0.76 Gy/h, corresponding to overall treatment times ranging from 20 min to 60 h. Fig. 3 shows the dose-response curves for the LDR experiments. The data of all performed LDR-experiments are summarised in Table 2.

A significant increase in isoeffective dose (ED_{50}) occurred by lowering the dose rate (see Fig. 4 and Table 2). Single dose HDR (84 Gy/h) irradiation resulted in a ED_{50} of 20 Gy (19.6–20.5). A treatment lasting 2 h (11.95 Gy/h at isoeffect) increased the ED_{50} to 23.9 Gy (23.2–24.7). Compared to the acute HDR regime an increase of tolerance of more than 10 Gy was found for a continuous treatment of 6 h

Table 1

Multifractionated high dose rate: results of different regimes in complete and incomplete repair conditions (84 Gy/h)

No. of fractions/overall time	ED_{50} (Gy)
2/10	24.2 (23.9–24.9)
4/10	29.5 (28.8–30.1)
7/10	31.7 (30.7–32.5)
20/10	33.0 (32.0–34.1)
10/24	35.2 (34.1–36.3)
20/24	38.6 (37.8–39.4)
30/24	38.2 (36.9–38.9)
20/48	41.6 (39.9–43.7)
10/84	35.8 (34.4–36.8)
20/84	41.5 (40.3–42.7)

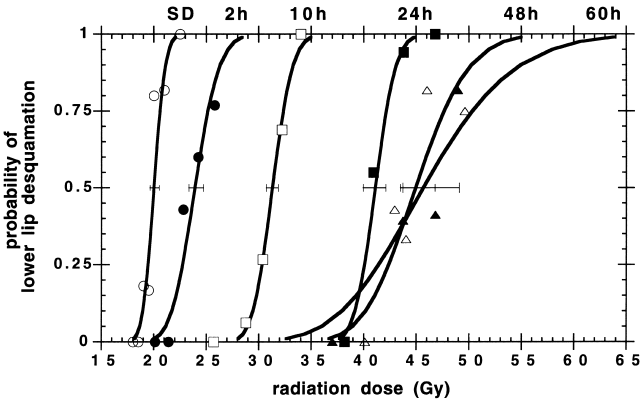

Fig. 3. Dose-incidence relationship for lower lip desquamation following LDR irradiations. Error bars represent 95% confidence limits of the ED_{50}.

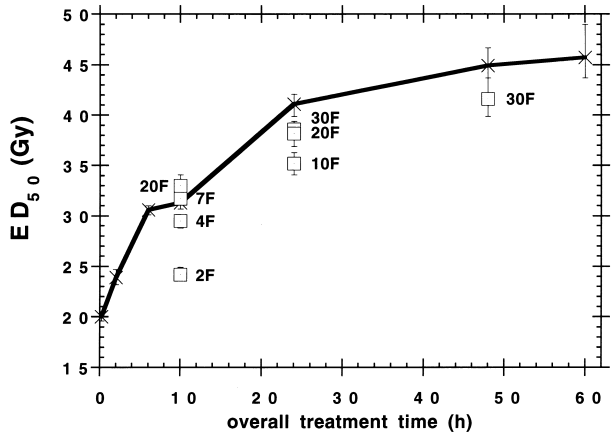

Fig. 4. Comparison of LDR and HDR experiments within identical overall treatment time. The bold curve shows the LDR data. The squares illustrate the corresponding HDR data.

(30.6 Gy versus 20 Gy). Additional sparing occurred with further lowering the dose rate to 0.9 Gy/h, with an increase in ED_{50} to 44.9 Gy (43.1–45.3). Lowering the dose rate below 0.9 Gy/h did not show a statistically significant further sparing (ED_{50} = 45.7 Gy).

3.3. Fractionation in conditions of incomplete repair

Multifractionated HDR irradiations were compared with continuous irradiations in three overall treatment times: 10 h, 24 h and 48 h (design shown in Fig. 1c). The results of these experiments are presented in Table 1 and summarised in Fig. 4 showing that for a 10-h treatment time, seven equally spaced fractions (1.6-h interval) are sufficient to achieve an effect equivalent to that obtained for a continuous irradiation. Only one schedule, 20 fractions in 10 h led to a slightly higher tolerance dose as compared to continuous low dose rate. For the longer times tested, 24 h and 48 h, the ED_{50} for fractionated irradiations never reached that obtained for a continuous irradiation.

4. Discussion

The sparing effect of fractionated or protracted irradiations is assumed to result from the same biological mechanism: cellular repair of sublethal radiation damage. In protracted regimes repair takes place during the irradiation, whereas in fractionated treatments repair occurs primarily during the intervals between fractions delivered acutely at high dose rates.

Table 2
Continuous low dose rate: results of different regimes

Irradiation time (h)	Dose rate[a] (Gy/h)	ED_{50} (Gy)
2	11.9	23.9 (23.2–24.7)
6	5.1	30.6 (30.1–31.0)
10	3.1	31.3 (30.6–31.9)
24	1.7	41.1 (39.9–42.1)
48	0.9	44.9 (43.7–46.7)
60	0.76	45.7 (43.7–49.0)

The data on the fractionation effect with interfraction intervals sufficient for complete repair (Fig. 1) reveal a relatively moderate increase of tissue tolerance with fractionation. The calculated α/β value of about 12 Gy (see Table 3a) is in good agreement with previous data on repair capacity of mouse lip and tongue, where α/β ratios for oral mucosal tissues in the range of 6 to 18 Gy were described [13,21,24]. The data are also comparable to published α/β ratios for human mucosa [10,12]. Similar values have been published for other early reacting tissues like skin [1] and jejunum [16].

Experimentally, the rate of sublethal damage repair can be estimated with fractionated HDR experiments with short interfraction intervals, insufficient for full repair. The effect of incomplete repair was assessed with twenty equally spaced HDR fractions given within different overall treatment times, lasting from 10 h to 3.5 days (see Fig. 5).

Twenty HDR fractions in 3.5 days lead to 41.5 Gy ED_{50}. The corresponding experiment with a shorter overall treatment time of 48 h resulted in virtually the same isoeffective dose (41.6 Gy ED_{50}). These results show that for a series of 20 fractions of approximately 2 Gy an interval of 2.4 h (as given in 48 h) is practically sufficient for complete repair in lip mucosa, as no increase in tolerance is observed when lengthening the overall time to 3.5 days, corresponding to inter-fraction intervals of 4.4 h. With shorter intervals but identical fraction number a significant loss of tolerance is seen due to incomplete repair (IR). The estimation of repair kinetics by direct analysis of all HDR experiments (Table 3a) resulted in a halftime of repair ($T_{1/2}$) of 40 min with confidence limits ranging from 36 to 44 min. This is in good agreement with data for other early reacting tissues. For tongue epithelium, Dörr et al. [13] estimated a half time of sublethal damage recovery for of 46 min (35–69 min). Denham et al. [12] estimated half-times in the range of 0.27–0.5 h for oral mucosa in 61 patients with advanced

Table 3

Repair parameters estimated with the incomplete repair model assuming mono- and bi-exponential repair kinetics, respectively

mono-exponential model data set	α/β (Gy)	$T_{1/2}$ (min)		
all data	12.2 (11.5, 13.0)	40 (36, 44)		
HDR data	12.8 (12.0, 13.6)	38 (34, 42)		
LDR data	12.4 (10.8, 14.5)	39 (38, 59)		
bi-exponential model data set	α/β (Gy)	$T_{1/2}$ slow (min)	$T_{1/2}$ fast (min)	$T_{1/2}$ slow/$T_{1/2}$ fast (%)
all data	11.1 (9.8, 12.5)	150 (12, 288)	27 (17, 37)	18 (–2, 37)
HDR data	12.1 (11.0, 13.4)	132 (–30, 300)	26 (12, 40)	13 (–9, 36)
LDR data	10.6 (7.3, 14.5)	198 (–132, 522)	30 (10, 50)	21 (–9, 52)

head and neck tumors.

The characteristics of both repair capacity and kinetics can also be determined with continuous irradiations using different dose rates. The present experiments were designed to include clinically used dose rates, by use of an immobilisation procedure described previously [24].

A significant dose rate effect was demonstrated in the range from 84 to 0.76 Gy/h as illustrated in Fig. 4. As long as the duration of treatment is short compared to the repair half-time the dose-rate effect is not pronounced. The increase in isoeffective dose is therefore relatively small in the range from 84 to 12 Gy/h (acute single dose versus 2 h LDR). In the range of 12 to 0.9 Gy/h (2 to 48 h irradiation time) a far more pronounced sparing of tolerance dose becomes evident, showing a gain of more than 20 Gy. No significant additional gain could be demonstrated while protracting the treatment from 48 to 60 h. Thus, no significant further dose sparing effect was observed while decreasing the dose rate further from 0.9 to 0.76 Gy/h. This confirms the LQ prediction that the biological consequences of changing dose rate follow a continuum, with the rate of change being greatest in an medium dose rate region. This is clinically important because some conventional definitions of dose rate erroneously imply that LDR, medium dose rate

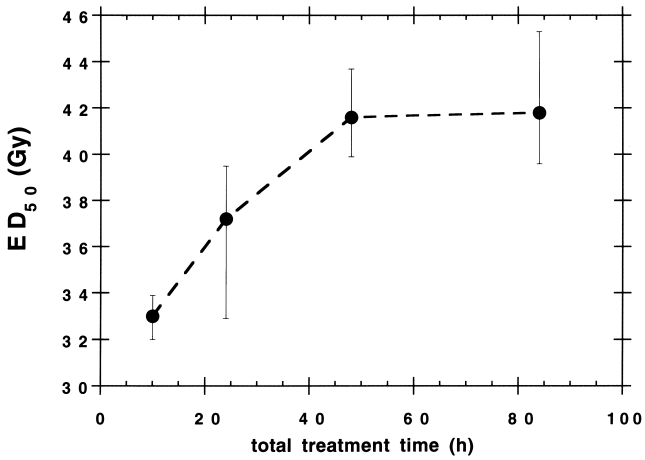

Fig. 5. Results of 20 HDR fractions given within different overall treatment times (10, 24, 48, 84 h).

(MDR) and HDR effects fall into discrete bands.

As previous HDR investigations in mouse lip mucosa did not reveal a dose modification due to repopulation for overall treatment times shorter than 3.5 days [4], these LDR-data confirm the absence of significant repopulation for irradiation times shorter than 60 h as necessary in the 0.76 Gy/h experiment.

Comparing fractionated HDR irradiations with intervals sufficient for complete repair with LDR regimes the following observations were made. The two fraction HDR irradiation resulted in an ED_{50} of 24.2 Gy. This corresponds approximately to the isoeffective dose obtained with 2 h continuous irradiation (23.9 Gy ED_{50}, 11.95 Gy/h). Twenty HDR fractions in 3.5 days is approximately equivalent with a continuous low dose rate regime lasting 24 h at a dose rate of 1.7 Gy/h.

In summary, fractionated HDR treatments with fraction sizes ranging from 12.1 to 2.1 Gy could mimic the effects of LDR regimes with dose rates ranging from 11.95 to 1.7 Gy/h. However, the overall treatment times for HDR treatments under complete repair conditions are far longer than the irradiation time of the LDR experiments, at isoeffective dose levels. The highest possible tolerance dose achieved with the 48 and 60 h LDR experiment (0.9 and 0.76 Gy/h, respectively) could not be mimicked by 20 fractions within 3.5 days, as the isoeffective doses differ significantly.

Low dose rate has similar biological advantages as hyperfractionation, maximising the differential between early and late responding tissues. To investigate whether a continuous low dose-rate treatment, as an irradiation with an infinite number of infinitely small doses, has an intrinsic repair advantage compared to fractionated high dose rate, the overall treatment time was kept constant in some of the experiments. For fixed overall treatment times increasing fractionation results in two counteracting phenomena: larger fraction numbers (and decreasing fraction sizes) increase the ED_{50}, however, due to the reduced interfraction intervals incomplete repair decreases isoeffect doses.

In the steep part of the dose rate effect curve the radiation response could be mimicked with fractionated HDR (see

Fig. 4). The effect of a 10 h continuous irradiation could be matched by a 7-fraction HDR regime, with an interfraction interval of 1.6 h (31.3 versus 31.7 Gy ED_{50}). In the flatter part of the dose rate curve, 20 or 30 fractions in 24 h or 20 fractions in 48 h were not sufficient to match the effect of continuous irradiation over the same time periods. Thus the effect of clinically used LDR schedules (>24 h) could not be matched with HDR fractionation with irradiations using practically applicable fraction numbers. Even with 10 fractions per day over 2 days or 30 fractions in a single day LDR-regimes could not be matched and isoeffective doses were about 10% below values obtained with LDR. In summary, a large number of small fractions is necessary to simulate low dose rate as used in brachytherapy. In agreement with the review of Turesson [28], we found that the short overall treatment time as applied with low dose rate methods can not be easily simulated with external beam therapy.

Accurate estimates of radiobiological effects of clinically applied dose rates, interfraction intervals and fraction sizes are necessary when switching from continuous low dose rate to fractionated high dose rate brachytherapy. Despite the increasing importance of such treatments little is known about the radiobiological characteristics of both early and late responding normal tissues at clinically used dose rates and especially on quantitative relationships between effects of protraction and fractionation. The magnitude of the dose rate and fractionation effect clearly depends on the repair half-time of tissues. For instance Turesson [28] showed in her review of published data on LDR a significantly stronger dose rate dependence for late, compared to acutely reacting tissues, typically characterised by fast repair kinetics.

The LQ concept, allowing the calculation of isoeffective treatments is increasingly used to quantify the effects of fractionation and dose rate. The inverse α/β-ratio of this model is a measure of the recovery capacity, $T_{1/2}$ describes the halftime for sublethal damage repair. Most tumurs respond comparably to acute reacting tissues with α/β-ratios usually larger than late reacting tissues.

The applicability of the LQ-concept was tested by calculating repair parameters for the two subsets of experiments (HDR versus LDR) separately. In order to estimate the kinetics and capacity of repair a direct analysis method [24,27] was applied, which incorporates the effects of incomplete repair due to short interfraction intervals or low dose rates. This method has the advantage of avoiding two step procedures (estimating isoeffective doses and performing a regression analysis on these data) and allows the calculation of confidence limits.

Based on a monoexponential repair model the analysis of the entire dose/response data (HDR and LDR) resulted in an α/β of 12.2 (11.5–13.0) Gy with a corresponding $T_{1/2}$ of 40 (36–44) min. A separate analysis of the HDR and LDR data set did not result in significant deviations from the results for the whole data set (Table 3a), demonstrating a consistent fit of the LQ model as applied to the fractionated HDR or continuous LDR conditions.

The results of these calculations are summarised in Table 3a. In summary, the estimated repair parameters are not significantly different for the subsets of data, indicating that repair characteristics estimated with HDR experiments adequately describe the increase in isoeffective dose, when the dose rate is lowered.

Based on in vitro experiments it was postulated that the experimental design for investigating repair kinetics may influence the estimation of this parameter [22]. In fractionated HDR experiments complex repair kinetics might be averaged in favour of a slower component. In contrast, low dose rate experiments may be dominated by an on average faster component [23]. Our results obtained in lip mucosa do not support this hypothesis, as the kinetics of repair estimated for the LDR experiments and the fractionated HDR experiments with fraction sizes as low as 1.28 Gy were not significantly different (Table 3a; $T_{1/2}$ 38 versus 39 min).

The original assumption of the LQ model was that repair follows first order kinetics, implying that one monoexponential parameter is sufficient to describe repair kinetics, both for fractionated and low dose rate regimes.

With the use of a direct analysis computer program incorporating all dose response data the fit of the data assuming more complex repair kinetics was estimated. Table 3b shows the results of calculations assuming a bi-exponential repair model. In summary, the data for the entire data set resulted in an α/β ratio of 11 Gy and corresponding two components of repair, about 18% of the damage being repaired with a halftime of 2.5 h and a second component repairing 82% with a halftime of about 0.5 h.

The likelihood-ratio test resulted in a significantly improved fit of the data compared to monoexponential repair kinetics ($P < 0.01$). This strongly suggests the existence of two components of repair in mouse lip mucosa.

Further experimental [2,30,31] and clinical data [29] also suggested the presence of two components of repair.

However, a single repair half-time satisfactorily describes the time effects for fractionated schedules and variations in dose rate in mouse lip mucosa. This becomes clear in Table 4, where the monoexponential repair parameters estimated

Table 4

Continuous low dose rate: comparison of experimental with predicted ED_{50} values based on repair parameters obtained with HDR — experiments

Irradiation time (h)	ED_{50} (Gy)		
	Experimental (95% CI)	Expected	Δ%
2	23.9 (23.2–24.7)	24.8	3.7
6	30.6 (30.1–31.0)	31.3	2.3
10	31.3 (30.7–31.9)	35.2	12.5
24	41.1 (39.9–42.1)	41.8	1.7
48	44.9 (43.7–46.7)	46.0	2.4
60	45.7 (43.7–49.0)	47.1	3.1

with the HDR experiments where used to calculate the expected increase in isoeffective dose for lowered dose rates. The good approximation of the data using a single $T_{1/2}$ using seems possible because the fast component is strongly predominant (>80%).

The comparison of calculated data with experimentally obtained isoeffective doses show a good fit of the data. The deviations of experimental data from predicted tolerance doses (Δ%) were, with the exception of the 10-h LDR experiment, less than 5%. This is probably not detectable in a clinical situation. The reason for the acceptable fit of the monoexponential repair model for our data might be the large proportion (>80%) of the damage being repaired by the fast component.

Already in 1969, Liversage [19] published theoretical considerations, meant as a basis for calculating equivalence between fractionated high dose rate and continuous low dose rate irradiations. Further mathematical approaches were developed in the following years [5,11,15,18,20]. However their applicability to experimental or clinical data had not been demonstrated for a well defined endpoint and a range of clinically relevant conditions.

Currently the LQ model provides an increasingly applied method of comparing the relative radiobiological efficacy of different time dose prescriptions to result in an equivalent biological endpoint. Although repair capacities and kinetics are known to vary greatly in different tissues some published equivalence calculations apply average values for repair parameters [7–9,28]. Based on α/β ratios and repair times of 36 sets of survival curves of human cells in vitro, Brenner and Hall [7] concluded that a 10-min pulse, repeated at hourly intervals, would produce a biological effect, virtually indistinguishable from LDR at 0.5 Gy/h.

As repair characteristics differ significantly among normal (acute and late reacting) and malignant tissues [25], the use of a general scaling factor for comparison of HDR/LDR cannot reflect the biological basis of radiation response. In addition, substantial uncertainties in the estimation of repair parameters are involved.

However, the choice of parameters can result in different conclusions. General equivalence is impossible to achieve where different repair characteristics are involved.

In principle, equivalence of various HDR and LDR schedules can be calculated easily with the LQ model including incomplete repair. These estimations are a useful guide, allowing the approximation of iso-effective dose.

Our data demonstrate that the LQ model adequately describes the fractionation and dose rate effect covering the clinically applied range in mouse lip mucosa, as a typical example for an acutely responding tissue. When used with realistic parameters the LQ model is capable of providing quantitative guidelines in areas of clinical interest.

Since the dose repair capacity for late reacting tissues is usually larger than for early responding tissues an increase of fraction number or a decrease in dose rate leads to more pronounced sparing effects for late than for early reacting tissues. Therefore, it is clearly also of importance to perform similar experiments in late reacting dose-limiting normal tissues in order to obtain quantitative information of biological effects of different dose rates and fractionation schedules.

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References

[1] Abe, Y. and Urano, M. Fraction size-dependent acute skin reaction of mice after multiple twice-a-day doses. Int. J. Radiat. Oncol. Biol. Phys. 18: 359–64, 1990.

[2] Ang, K.K., Jiang, G.L., Guttenberger, R., Thames, H.D., Stephens, L.C., Smith, C.D. and Feng, Y. Impact of spinal cord repair kinetics on the practice of altered fractionation schedules. Radiother. Oncol. 25: 287–94, 1992.

[3] Ang, K.K., Xu, F.X., Landuyt, W. and van der Schueren, E. The kinetics and capacity of repair of sublethal damage in mouse lip mucosa during fractionated irradiations. Int. J. Radiat. Oncol. Biol. Phys. 11: 1977–83, 1985.

[4] Ang, K.K., Xu, F.X., Vanuytsel, L. and van der Schueren, E. Repopulation kinetics in irradiated mouse lip mucosa: the relative importance of treatment protraction and time distribution of irradiations. Radiat. Res. 101: 162–9, 1985.

[5] Barendsen, G.W. Dose fractionation, dose rate and iso-effect relationships for normal tissue responses. Int. J. Radiat. Oncol. Biol. Phys. 8: 1981–97, 1982.

[6] Bentzen, S.M., Thames, H.D., Tucker, S.L. and Smith, C. New options in direct analysis of dose-response data. Int. J. Radiat. Biol. 57: 221–225, 1990.

[7] Brenner, D.J. and Hall, E.J. Conditions for the equivalence of continuous to pulsed low dose rate brachytherapy. Int. J. Radiat. Oncol. Biol. Phys. 20: 181–90, 1991.

[8] Brenner, D.J. and Hall, E.J. Fractionated high dose rate versus low dose rate regimens for intracavitary brachytherapy of the cervix. I. General considerations based on radiobiology. Br. J. Radiol. 64: 133–41, 1991.

[9] Brenner, D.J., Martel, M.K. and Hall, E.J. Fractionated regimens for stereotactic radiotherapy of recurrent tumors in the brain. Int. J. Radiat. Oncol. Biol. Phys. 21: 819–24, 1991.

[10] Chougule, A. and Supe, S.J.T.I. Linear quadratic model-estimation of alpha/beta ratio for mucosal reaction. Strahlenther.-Onkol. 169: 427–30, 1993.

[11] Dale, R.G. The application of the linear-quadratic model to fractionated radiotherapy when there is incomplete normal tissue recovery between fractions, and possible implications for treatments involving multiple fractions per day. Br. J. Radiol. 59: 919–927, 1986.

[12] Denham, J.W., Hamilton, C.S., Simpson, S.A., O'Brien, M.Y. and Ostwald, P.M. Acute reaction parameters for human oropharyngeal mucosa. Radiother. Oncol. 35: 129–137, 1995.

[13] Dörr, W., Breitner, A. and Kummermehr, J. Capacity and kinetics of SLD repair in mouse tongue epithelium. Radiother. Oncol. 27: 36–45, 1993.
[14] Finney, D.J. and Marcus, P.I. Probit Analysis. A Statistical Treatment of the Sigmoid Response Curve. Cambridge University Press, Cambridge, 1952.
[15] Fowler, J.F. The linear-quadratic formula and progress in fractionated radiotherapy. Br. J. Radiol. 62: 679–694, 1989.
[16] Huczkowski, J. and Trott, K.R. Jejunal crypt stem-cell survival after fractionated gamma-irradiation performed at different dose rates. Int. J. Radiat. Biol. Relat. Stud. Phys. Chem. Med. 51: 131–7, 1987.
[17] Landuyt, W., Keizer, J., Chin, A. and van der Schueren, E. Evaluation of mouse lip mucosa reactions after combinations of *cis*-diammine-1,1-cyclobutanedicarboxylate platinum (II) (CBDCA) and irradiation: single and fractionated treatments. Int. J. Radiat. Oncol. Biol. Phys. 13: 1367–1370, 1987.
[18] Ling, C.C. Permanent implants using Au-198, Pd-103 and I-125: radiobiological considerations based on the linear quadratic model. Int. J. Radiat. Oncol. Biol. Phys. 23: 81–87, 1992.
[19] Liversage, W.E. A general formula for equating protracted and acute regimes of radiation. Br. J. Radiol. 42: 432–440, 1969.
[20] O'Donoghue, J.A. Comparison of the predictions of the LQ and CRE models for normal tissue damage due to biologically targeted radiotherapy with exponentially decaying dose rates. Radiother. Oncol. 15: 359–362, 1989.
[21] Scalliet, P., Landuyt, W. and van der Schueren, E. Effect of decreasing the dose rate of irradiation on the mouse lip mucosa. Comparison with fractionated irradiations. Radiother. Oncol. 10: 39–47, 1987.
[22] Steel, G.G. Recovery kinetics deduced from continuous low dose-rate experiments. Radiother. Oncol. 14: 337–343, 1989.
[23] Steel, G.G., Deacon, J.M., Duchesne, G.M., Horwich, A., Kelland, L.R. and Peacock, J.H. The dose-rate effect in human tumour cells. Radiother. Oncol. 9: 299–310, 1987.
[24] Stüben, G., Landuyt, W., van der Schueren, E., van der Kogel, A.J. and Reijnders, A. Estimation of repair parameters in mouse lip mucosa during continuous and fractionated low dose-rate irradiation. Radiother. Oncol. 20: 38–45, 1991.
[25] Thames, H.D., Bentzen, S.M., Turesson, I., Overgaard, M. and van den Bogaert, W. Time-dose factors in radiotherapy: a review of the human data. Radiother. Oncol. 19: 219–235, 1990.
[26] Thames, H.J., Rozell, M.E., Tucker, S.L., Ang, K.K., Fisher, D.R. and Travis, E.L. Direct analysis of quantal radiation response data. Int. J. Radiat. Biol. Relat. Stud. Phys. Chem. Med. 49: 999–1009, 1986.
[27] Tucker, S.L., Thames, H.D., Brown, B.W., Mason, K.A., Hunter, N.R. and Withers, H.R. Direct analyses of in vivo colony survival after single and fractionated doses of radiation. Int. J. Radiat. Biol. 59: 777–795, 1991.
[28] Turesson, I. Radiobiological aspects of continuous low dose-rate irradiation and fractionated high dose-rate irradiation. Radiother. Oncol. 19: 1–15, 1990.
[29] Turesson, I. and Thames, H.D. Repair capacity and kinetics of human skin during fractionated radiotherapy: erythema, desquamation, and telangiectasia after 3 and 5 years' follow-up. Radiother. Oncol. 15: 169–188, 1989.
[30] van den Aardweg, G. and Hopewell, J.W. The kinetics of repair for sublethal radiation-induced damage in the pig epidermis: an interpretation based on a fast and a slow component of repair. Radiother. Oncol. 23: 94–104, 1992.
[31] van Rongen, E., Thames, H.J. and Travis, E.L. Recovery from radiation damage in mouse lung: interpretation in terms of two rates of repair. Radiat. Res. 133: 225–233, 1993.
[32] Xu, F.X., van der Schueren, E. and Ang, K.K. Acute reactions of the lip mucosa of mice to fractionated irradiations. Radiother. Oncol. 1: 369–374, 1984.