Time-dose factors in radiotherapy: a review of the human data

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(Received 12 June 1989, revision received 26 April 1990, accepted 10 May 1990)

Key words: Time-dose factors; Human data

Summary

The values for α/β (fractionation sensitivity, or recovery capacity) for early and late reactions in human normal tissues are consistent with results from experimental animals. For breast treatments direct analysis indicates that for early reactions α/β is in the range 7 to 11 Gy, while for late effects it is in the range 2 to 4 Gy. Data on recovery kinetics in human tissues is limited but these indicate that recovery may be slower in humans than in rodents. For early skin reactions the halftime of recovery is about 1 h, while for late telangiectasia it is more than 3 h. α/β values for human tumors are more variable than in rodents: some are high (head and neck, lung, skin, cervix) and similar to those for early reacting normal tissues. Others are low, including melanomas, where α/β was estimated at 0.6 (−1.1, 2.5) Gy, and liposarcomas, where direct analysis of cases surveyed from the literature suggested that α/β = 0.4 (−1.4, 5.4) Gy. Repopulation kinetics is faster in the mucosa of the soft palate and faucial pillars (1.8 Gy/day) than in head and neck tumors (up to 1 Gy/day).

Introduction

The use of alternative fractionation strategies such as treatment acceleration requires some means of predicting changes in tolerance. Lately, the linear-quadratic (LQ) formulation has made up for some of the shortcomings of earlier formulae, by permitting extrapolation to wider ranges of fractionation parameters such as dose per fraction (but not treatment time). The parameters of the LQ model (e.g. α/β) have been investigated extensively in animals, but uncertainties in their values, coupled with the problematic mouse-to-man extrapolation, have limited their use. LQ parameters (including some means to account for proliferation) for human normal tissues and tumors would of course be preferable, and the purpose of this paper is to review the pertinent data.
Materials and methods

In this section we summarize the ways in which repair and repopulation are quantified in this review. An abbreviated version has been published elsewhere [62].

**Data selection.** Clinical studies were included in the analysis when tumor control or normal-tissue complications had been assessed in the presence of fairly wide variation in dose per fraction and total dose, or overall treatment time. The raw data were available for a few studies, but in most cases data were extracted from reports in the literature. For the most part, therefore, no attempt could be made to control for patient selection or other factors that may have confounded the analysis.

**Repair capacity.** Repair capacity refers to sparing that occurs from the use of smaller fraction sizes, presumably as a result of intracellular repair in the target-cell population; this sparing is independent of that attributable to repopulation of survivors. Repair capacity is (inversely) quantified by the ratio of LQ parameters $\alpha/\beta$ [57], and is also referred to as “fractionation sensitivity”. The preferred method of estimating $\alpha/\beta$ is the so-called “direct” or maximum likelihood technique [58]. Here the raw data are available and the response is known for each patient, for a variety of doses and doses per fraction. Responses are dichotomous and include time to recurrence of primary tumor or presentation with late injury, whether or not confluent mucositis occurred, etc. Such data are rarely available for humans, and often the only information available is that the level of complications was more severe in one fractionation regimen than in another, where the dose per fraction and total dose were different. This is usually the case for results taken from the literature, and for these a second approach is employed, which we will term the “two-regimen” method. Suppose that in the first regimen the total dose $D_1$ is given in fractions of size $d_1$, and in the second the corresponding doses are $D_2$ and $d_2$. Suppose further (and this is an important restriction) that clonogen regeneration is approximately the same in the two regimens. Then if the reaction (or tumor control) is higher in the second regimen, it can be shown that [60, Eqn. (3.8)].

\[
\alpha/\beta < (d_2D_2 - d_1D_1)/(D_1 - D_2)
\]

while the opposite inequality holds if the reaction (or tumor cure) is higher in the first regimen. Approximate equality holds if there is fair certainty of equivalent effect.

**Repair kinetics.** In experimental animals repair kinetics has been quantified in terms of the halftime for repair, $t_{1/2}$, and in the models usually employed [54,56] to describe the data this time corresponds to the time required for the repair of half the remaining damage. Again the preferred method of estimating $t_{1/2}$ is direct analysis, i.e. where the data are scores of yes or no for each patient according to whether a threshold was reached.

**Repopulation.** The introduction of a term for exponential repopulation into the LQ model for cell killing has been considered recently by many authors [17,18,20,29,30,41,42,53,63,74,77,78], so many, in fact, that it would seem like an idea whose “time has come”, even though the proliferation rate is known to change during treatment (e.g. [77]) and so exponential regeneration at a constant rate can only be a rough approximation.

The dose equivalent of regeneration per day ($D_{\text{prolif}}$) will be used to quantify repopulation. This is measured by determining differences between isoeffective doses in fractionation regimens characterized by different weekly dose rates or overall times, or by calculating dose increments required to offset splits in a course of radiotherapy [34]. However, it has also been estimated from dose-effect models with the LQ model plus a linear time term such as “$yT$” (e.g. [20,63,72]). To avoid confusion in defining $D_{\text{prolif}}$, it is worthwhile to contrast these approaches:
(1) With wide variability in dose per fraction \(d\), total dose \(D\), and time \(T\), the biological effect can be taken as \(E = \alpha D + \beta DD - \gamma T\), with parameters obtained from likelihood estimation. Here \(T\) is the time during which proliferation occurs at the (assumed fixed) rate \(\gamma\), after any initial time lag. The dose equivalent of proliferation per day, for fraction size \(d\), would then be \(D_{\text{prolif}} = \gamma/(\alpha + \beta d)\). The total effect \(TE = E/\beta\) [60] can then be written:

\[
TE = (\alpha/\beta + d)D - (\gamma/\beta)T = (\alpha/\beta + d)D - (\alpha/\beta + d)D_{\text{prolif}}T. \tag{2}
\]

(2) When there is little variation in dose per fraction (as with many clinical studies), the total doses are normalized to doses in 2-Gy fractions and \(E = \alpha D/(\alpha/\beta + 2) - \gamma T\) [76], where \(\alpha\) is effective initial slope for fractions of size \(d\). In this case \(D_{\text{prolif}} = \gamma/\alpha\). Assuming that \(\alpha_{\text{eff}} = \alpha + \beta d\), which is the correct theoretical interpretation, we are led to the same result [Eqn. (2)].

(3) When \(D_{\text{prolif}}\) is estimated empirically, e.g. from dose increments required to offset splits in a treatment [35], then even though the analysis cannot be done for lack of raw data, presumably \(D_{\text{prolif}} = \gamma/\alpha_{\text{eff}}\). Assuming that \(\alpha_{\text{eff}} = \alpha + \beta d\), which is the correct theoretical interpretation, we are led to the same result [Eqn. (2)].

Finally, with more than one treatment per day, the quantities \(\alpha/\beta\), \(t_{1/2}\), and \(D_{\text{prolif}}\) may be used to quantify changes in tolerance. From the arguments given above, the total effect \(TE\) of a dose \(D\), given in fractions of size \(d\) \(m\) times per day, is

\[
TE = [\alpha/\beta + d(1 + h_m)] [D - D_{\text{prolif}} T] \tag{3}
\]

where accelerated clonogen proliferation (equivalent to \(D_{\text{prolif}}\) Gy/day) is assumed to occur for \(T\) days, after a lag at the inception of treatment. The incomplete-repair factors \(h_m\) are tabulated for different interfraction intervals and assumed repair halftimes ([60], Table 6.3).

**Results**

*Head and neck treatments*

**Acute effects – repair capacity.** The most significant dose-limiting acute reactions in modern radiotherapy for head and neck tumors are mucosal reactions. Because they are very sensitive to the weekly dose rate [10,22,61], two-regimen comparisons may be questionable. Thus, mucositis has been observed to be more severe with accelerated fractionation [49] and hyperfractionation [48]; each involves a higher weekly dose than conventional fractionation. Because of this confounding factor, no estimate of \(\alpha/\beta\) for mucosal reactions is available.

**Acute effects – repair kinetics.** From 1979 to 1983, the RTOG conducted a prospective phase III study of hyperfractionation of advanced head and neck tumors that compared a standard schedule of 66–74 Gy/7–8 weeks with \(2 \times 1.2\) Gy/day to give 60 Gy/5 weeks [43]. The interfraction interval in the twice-a-day regimen ranged from 3 to 7 h, and further analysis showed that acute reactions were significantly worse when the interval was 4.5 h or less. This yields no definite statement about \(t_{1/2}\). For the sake of comparison with animal results ([60], Table 3.6), however, suppose that a significant effect was noticed only if the amount of unrepaired damage was 20% or more; the \(t_{1/2}\) was then at least 2 h for repair in the mucosa. In contrast, halftimes measured in rodent tissues range from 0.5 to 1.5 h. It must be noted that Karim et al. [38] reached the opposite conclusion, and this is discussed below under “Late effects”.

**Acute effects – repopulation.** Mucosal reactions are determined by the rate of dose accumulation, i.e. the weekly dose rate. This is illustrated in Fig. 1, which shows reactions during and after treatment of the membranes of the soft palate and faucial pillars; treatments were done with two parallel opposed portals of a cobalt-60 unit. Figure 1a shows the mucosal reactions of patients
Fig. 1. Mucositis (solid curves) in the soft palate and faucial pillars and tumor regression (dashed curves) for patients treated with (a) 55 Gy in 4-4.5 weeks, (b) 55 Gy in 5-5.5 weeks, (c) 55 Gy in 6-6.5 weeks (from Fletcher et al. [22], with permission of the author and Charles C. Thomas Publishers).
exposed to 55 Gy in 4 to 4.5 weeks, with fraction sizes of 2.45–2.75 Gy (5 days/week). Of 20 patients, 3 showed signs of healing during the last week of treatment. When the daily dose was 2–2.2 Gy (Fig. 1b), 2/11 patients had begun healing during the last week of treatment. Figure 1c shows the mucosal reactions when the daily dose was 1.83–2 Gy, and it appears that in 6/8 patients healing of these reactions occurred during the final stages of treatment.

The data shown in Fig. 1 suggest that human oral mucosa is capable of regenerating under the pressure of cell killing induced by daily doses of 1.8 Gy, i.e. $D_{\text{p}}$ is around 1.8 Gy/day toward the end (but probably not the beginning) of a 6-week course of radiotherapy. There is clearly variation between patients, and in some individuals this value will be somewhat higher or lower. The sharp rise of reactions early on suggest that the unperturbed rate of regeneration is slower. This rate of regeneration is consistent with the data of Van den Bogaert [9].

It is also evident from Fig. 1 that the timing of the onset of reactions depends on the rate of dose accumulation. At 2.45–2.75 Gy/day the mucous membrane of the soft palate produces a confluent mucositis, which starts at the end of the second week, reaches its peak in the middle of the third and on average begins to regress at the fifth week [22]. Healing was complete at the first return appointment 6 weeks after the end of treatment. After 2–2.2 Gy/day patients experienced either a studded mucositis or in a few cases, confluent mucositis at 2.5–3 weeks. The time of onset was even later for 1.83–2 Gy/day; the usual healing time was 8–10 weeks from the beginning of treatment.

These results are consistent with other studies. Maciejewski et al. [41] reported a 52% incidence of severe mucositis in patients treated with daily doses primarily in the range 1.3 to 2.7 Gy, and interpreted this as a result of the rapid rate of dose accumulation. Radiotherapy experience (reviewed in [61]) suggests that acute effects from treatment regimens protracted over several weeks are governed more by rate of dose accumulation than
by fraction size. Van den Bogaert [9] reported on mucosal reactions scored during multiple-fractions-per-day (MFD) trials of the EORTC. The results may be summarized as follows: (1) the time of appearance of mucosal reactions is independent of the total dose given; (2) there is a direct relationship between the total dose given and the duration of the reaction; (3) the total dose necessary to induce confluent mucositis is about 20 Gy when the fraction size is 2 Gy or higher in once-per-day treatments, or when higher daily doses are given in smaller fraction sizes in MFD treatments; and (4) the delay between the moment a dose of about 20 Gy has been given and the time of appearance of confluent mucositis is about 9 days. However, Turesson et al. (abstract, 6th Annual ESTRO Meeting, Lisbon 1987) observed that 9/30 experienced confluent mucositis after treatment with 33 Gy in 2 weeks with 2 x 2.1 Gy/day. There is at present no explanation for this inconsistency.

Late effects – repair capacity. $\alpha/\beta$ for late complications in the supraglottic larynx was estimated using direct analysis from a group of 155 cases [40]. With a 3-year follow-up after radiotherapy, 21 late complications were noted, 9 cases of cartilage necrosis and 12 cases of severe edema. Total doses of 49–65 Gy were given in 21–35 fractions in 32–65 days. $\alpha/\beta$ was 3.8 Gy, with 95% confidence limits of 0.8–14.0 Gy.

The incidence of severe late effects (mucosal or skin fibrosis, mucosal or bone necrosis) was scored in 268 patients who survived at least 18 months after treatment of cancer of the oral cavity or oropharynx [41]. Total doses ranged from 30 to 72 Gy in 35–60 days; doses per fraction varied from 1.8 to 6 Gy, with 70% of the patients receiving fractions of 2.3–2.7 Gy. Non-parametric and parametric (direct) analyses indicated a low value of $\alpha/\beta$, and by the latter method the estimate 0.8 (−0.6, 2.5) Gy was obtained. Severe late responses were associated with severe acute responses independently of dose per fraction, suggesting that some late effects were consequences of severe acute injury.

The results of two-regimen comparisons yield upper limits on $\alpha/\beta$ when complications are deemed worse with larger dose fractions ([60], Table 3.7). For late cartilage necrosis after treatment of larynx tumors $\alpha/\beta < 4.4$ Gy [36] and $\alpha/\beta < 4.2$ Gy [26,52]. Approximate equivalence of effect yields the estimate 3.4 Gy [33]. Finally, for late complications after treatment of oropharynx tumors there was equivalence between conventional (70 Gy/7 weeks, 2 Gy/fraction) and hyperfractionated (80.5 Gy/7 weeks, 1.15 Gy/fraction) treatments [37], yielding the estimate 4.5 Gy.

Late effects – repair kinetics. In the trial of hyperfractionation [43] alluded to above in the discussion of repair kinetics for acute effects, it was noted that late effects were also worse with short intervals. Fibrosis was reported in 40% (16/40) of the complete responders treated at intervals of 4.5 h or less vs. 27% (3/11) with longer intervals. Necrosis was reported in 7% (3/41) of the complete responders treated at short intervals and none of the 11 complete responders treated at longer intervals. Therefore, as argued above, it is possible that the halftime for repair of late injury was 2 h or longer.

It should be noted that the opposite finding was made by Karim et al. [38]. These authors treated advanced laryngeal carcinoma by either conventional fractionation (72–78 Gy, 2 Gy per fraction) or MFD (67.5–72.5 Gy, 2 x 1.25 Gy per day). The interval between fractions has been gradually reduced from 6 to 1.5 h, and the latter is being followed routinely at present without, according to the authors, any significant enhancement of severe radiation complications. There is no obvious explanation of this discrepancy, except to note that only 52 patients had MFD treatments and if these are subdivided on the basis of interfraction intervals between 6 and 1.5 h very small strata result, with low strength for testing the hypothesis of no difference in complication frequency. Moreover, more than 50% of the MFD patients had recurrences, which would complicate the evaluation of late sequelae.
To illustrate the importance of the interfraction interval for MFD radiotherapy, the situation was modeled with the incomplete-repair (IR) model [54], assuming the correctness of the picture emerging from the data of Marcial et al. [43]. It was assumed that the repair halftime was 2 h, and in accordance with Marcial et al. that 40% complications occurred with 3.5-h intervals, as opposed to 27% with 5.5-h intervals (these being the weighted averages of short and long intervals). Parameters of the IR model were chosen to match these data, and the hypothetical dependence of incidence of late complications on interfraction interval is shown in Fig. 2. These calculations are purely illustrative, since the raw data were not available (i.e. the actual intervals and incidence of complications), and Fig. 2 would look somewhat different with other choices of times, parameters, etc. The steep dependence on interval would remain, however, and it may be appreciated that much of the advantage of using small dose fractions in MFD radiotherapy might be lost with intervals of 4 h or less between two doses given each day, and that 6 h or longer would be preferable.

Late effects were analyzed [44] in a series of 39 head and neck patients with 2-year minimum follow-up who had been treated by rapid hyperfractionation using 6–8 fractions per day with a 2-h interfraction interval. Seventy percent of the patients experienced late complications (cervical fibrosis, necrosis, edema), and in 54% these were severe. This result is consistent with the graph shown in Fig. 2 and illustrates the sensitivity of late tolerance to the interval between two or more doses given each day.

**Late effects – repopulation.** There are conflicting data regarding the importance of regeneration for late-responding normal tissues of the head and neck region. Overgaard et al. [46] observed that introduction of a 3-week split in the treatment of larynx cancer had no effect on the incidence of late edema and laryngeal fistula after laryngectomy. On the other hand, Maciejewski et al. [41] reported that each day’s extension of treatment beyond 21 days was associated with an increase of 0.25 Gy in the dose necessary for a certain level of injury (0.29 Gy if a 2-Gy per fraction regimen had been used).

**Tumors – repair capacity.** The two-regimen comparisons for repair capacity in tumors are usually based on comparisons between 5 fractions/week and fewer than 5 fractions/week. Even though the overall time may be the same in the two regimens, the different rates of dose accumulation may cause regeneration of tumor clonogens to be different. If the regenerative response of tumor clonogens (see below) to radiation injury is assumed similar to that of the mucosa of origin and the earlier onset of reactions in the mucosa after higher weekly dose rates reflects a higher level of proliferative response, then more regeneration in tumors would be expected after 5/week than after 2/week treatments. Based on these considerations it can be shown that Eqn. (1) above would be modified to

\[
\frac{\alpha}{\beta} > \frac{(d_2 - d_1)}{(D_1 - D_2) + \text{regen}_1 - \text{regen}_2}
\]  

(4)
where dose $D_i$ is given in fractions of size $d_i$, and is the relative amount of proliferative recovery for regimen $i$ ($D_{prolif} \times$ treatment time).

Harrison et al. [32] reported that hypofractionation reduced the therapeutic ratio for Tis, T1, and T2 squamous cell carcinoma of the vocal cord. One hundred and thirty one patients were treated with conventional daily 2 Gy fractions, and 66 patients were treated once per week with large (5.5–6.5 Gy) fractions; both groups were treated over a period of approximately 6 weeks. In the Tis and T1 patients the failure rate was worse in the once/week group ($p = 0.06$); in the smaller T2 group no significant difference was found. These results indicate that for Tis and T1 vocal cord cancers $\alpha/\beta > 9.9$ Gy.

Byhardt et al. [12,14] reported on the treatment of 94 patients with carcinomas of the oral cavity and oropharynx with 3 or 5 fractions/week. Total dose for the 5-fraction per week schedules ranged from 60 Gy/30 fractions per 46 days to 72 Gy/36 fractions per 51 days. The 3-fraction per week schedules ranged from 54 Gy/18 fractions per 42 days to 72 Gy/24 fractions per 51–77 days (only 3 patients in latter group). Local control was 59% (31/63) for 5/week and 12% (4/31) for 3/week treatment. Since there was some variation in doses no precise lower limit of $\alpha/\beta$ can be calculated. Assuming, however, that 55.5 Gy was given in 6 weeks in the 3/week treatments and 60–62 Gy was given in 6 weeks in 5/week treatment, for oral cavity and oropharynx tumors $\alpha/\beta > 6.5$–10.3 Gy. Handa et al. [31] conducted a randomized trial of 2 and 5 fractions per week in the treatment of cancer of the oral cavity. Patients received 60–65 Gy/6–6.5 weeks (5/week), or 50–53 Gy (2/week) in the same time. Local control was 71% (5/week) vs. 57% (2/week), a difference considered to be significant, suggesting that for carcinoma of the oral cavity $\alpha/\beta > 7$ Gy.

Tumors – repair kinetics. There are no data on repair kinetics.

Tumors – repopulation. Withers et al. [77] analyzed literature data on tumor control doses for various head and neck cancers treated with different fractionation regimens. Results that permitted a reasonably accurate assessment of local control rate, dose per fraction, total dose, and overall treatment duration were used in a direct analysis to estimate 50% control doses, and the dependence of these on treatment time was analyzed. These analyses suggested that clonogen repopulation in squamous cell carcinomas of the head and neck accelerates after a lag period of 4 ± 1 weeks from the inception of therapy, and that $D_{prolif}$ was about 0.6 Gy/day after rapid regeneration had begun. These results agreed with those obtained from an analysis of the results of treatment of carcinoma of the larynx [39]. Other estimates for this tumor are $D_{prolif} = 0.4$ Gy/day [11], 0.3 Gy/day [35], and 0.5 Gy/day [46].

Taylor et al. [53] analyzed dose-time factors in the external-beam treatment of 473 patients with squamous cell carcinoma of the pharyngeal wall, vocal cord, pyriform sinus, and supraglottic larynx. The estimate of $D_{prolif}$ varied between sites, but estimates were in general larger than 1 Gy per day. Bentzen et al. [4] presented a reanalysis of the results of treatment of 181 patients with oropharynx tumors, and estimated $D_{prolif}$ at 0.68 Gy/day, with 95% confidence interval (0.1, 1.3) Gy/day.

These results for head and neck treatments (and for other sites) are summarized in Tables I and II.

Breast treatments

Acute effects – repair capacity. Acute effects of postmastectomy irradiation of parasternal fields have been assessed in prospective clinical fractionation studies at Gothenburg since 1972 [66,67], and these have recently been reanalyzed using the direct method [72]. Schedules with 1, 2, or 5 fractions per week and 2 or 3 fractions per
### TABLE I
Recovery capacity of human tissues and tumors.

<table>
<thead>
<tr>
<th>Tissue/tumor</th>
<th>Analysis</th>
<th>$\alpha/\beta$ (Gy)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Early reactions</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin (erythema)</td>
<td>D</td>
<td>8.8 (6.9, 11.6)</td>
<td>[72]</td>
</tr>
<tr>
<td>(desquamation) ($t \leq 29$ days)</td>
<td>D</td>
<td>12.3 (2, 23)</td>
<td>[5]</td>
</tr>
<tr>
<td>(t &gt; 29 days)</td>
<td>D</td>
<td>11.2 (8.5, 17.6)</td>
<td>[72]</td>
</tr>
<tr>
<td>Lung (acute)</td>
<td>TR</td>
<td>&gt; 8.8</td>
<td>[16]</td>
</tr>
<tr>
<td><strong>Late reactions</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supraglottic larynx (late sequela)</td>
<td>D</td>
<td>3.8 (0.8, 14)</td>
<td>[40]</td>
</tr>
<tr>
<td>Larynx (cartilage necrosis)</td>
<td>TR</td>
<td>3.8 (0.8, 14)</td>
<td>[33]</td>
</tr>
<tr>
<td></td>
<td>TR</td>
<td>&lt; 4.4</td>
<td>[36]</td>
</tr>
<tr>
<td></td>
<td>IR</td>
<td>&lt; 4.2</td>
<td>[26,32]</td>
</tr>
<tr>
<td>Oropharynx (late sequelae)</td>
<td>TR</td>
<td>~3.8</td>
<td>[37]</td>
</tr>
<tr>
<td>Skin (Telangiectasia)</td>
<td>D</td>
<td>3.9 (2.7, 4.8)</td>
<td>[72]</td>
</tr>
<tr>
<td>Skin</td>
<td>D</td>
<td>3.7 (0.2, 4.7)</td>
<td>[8]</td>
</tr>
<tr>
<td>Skin (subcutaneous fibrosis)</td>
<td>D</td>
<td>1.9 (0.8, 3)</td>
<td>[8]</td>
</tr>
<tr>
<td>Shoulder (impaired movement)</td>
<td>D</td>
<td>3.5 (0.7, 6.2)</td>
<td>[7]</td>
</tr>
<tr>
<td>Lung</td>
<td>D</td>
<td>3.3 ± 1.5</td>
<td>[20]</td>
</tr>
<tr>
<td>Lung (pneumonitis)</td>
<td>TR</td>
<td>&lt; 3.8</td>
<td>[16]</td>
</tr>
<tr>
<td>Cord (myelopathy)</td>
<td>TR</td>
<td>&lt; 3.3</td>
<td>[19]</td>
</tr>
<tr>
<td>Brachial plexus (plexopathy)</td>
<td>TR</td>
<td>&lt; 5.3</td>
<td>[50]</td>
</tr>
<tr>
<td>Bowel (stricture/perforation)</td>
<td>TR</td>
<td>2.2 &lt; $\alpha/\beta$ &lt; 8</td>
<td>[3,21]</td>
</tr>
<tr>
<td><strong>Tumors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vocal cord</td>
<td>TR</td>
<td>&gt; 9.9</td>
<td>[32]</td>
</tr>
<tr>
<td>Oral cavity/oropharynx</td>
<td>TR</td>
<td>&gt; 6.5, 10.3</td>
<td>[12,14]</td>
</tr>
<tr>
<td></td>
<td>TR</td>
<td>&gt; 7</td>
<td>[31]</td>
</tr>
<tr>
<td>Lung (squamous cell, large cell, adenoc.)</td>
<td>D</td>
<td>~50–90</td>
<td>[14]</td>
</tr>
<tr>
<td>Cervix</td>
<td>TR</td>
<td>&gt; 13.9</td>
<td>[73]</td>
</tr>
<tr>
<td>Skin</td>
<td>D</td>
<td>8.5 (4.5, 11.3)</td>
<td>[63]</td>
</tr>
<tr>
<td>Melanoma</td>
<td>D</td>
<td>0.6 (–1.1, 2.5)</td>
<td>[6]</td>
</tr>
<tr>
<td>Liposarcoma</td>
<td>D</td>
<td>0.4 (–1.4, 5.4)</td>
<td>[59]</td>
</tr>
</tbody>
</table>

D = Direct analysis; TR = two-regimen analysis.
Parentheses enclosed 95% confidence interval; ± S.E.
Reanalysis of published raw data.

Day were used on 750 fields in 450 patients. When treatment times were between 11 and 29 days the repair capacity was similar for erythema and desquamation: for erythema $\alpha/\beta = 8.8$ (6.9, 11.6) Gy (95% confidence limits in parentheses), and for desquamation $\alpha/\beta = 11.2$ (8.5, 17.6) Gy. There was no significant influence of time, but for times longer than 29 days the repair capacity was much reduced, with $\alpha/\beta$ being between 18 and 35 Gy. Bentzen et al. [4] have estimated $\alpha/\beta = 12.3$ (2, 23) Gy for erythema resulting from postmastectomy treatments.

**Acute effects – repair kinetics.** Short interfraction intervals (0.25 and 4 h) were sometimes used in the studies of Turesson and Notter [66,67,70,71], permitting use of the IR model to estimate the repair halftime [72]. There were insufficient data to obtain precise estimates, but an interesting feature was the existence of two identically valued
TABLE II
Repopulation in human tissues and tumors.

<table>
<thead>
<tr>
<th>Tissue/tumor</th>
<th>Analysis</th>
<th>$D_{0.200}$ (Gy/d)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral mucosa</td>
<td>TR</td>
<td>~1.8</td>
<td>[22]</td>
</tr>
<tr>
<td>Skin (telangiectasia)</td>
<td>D</td>
<td>0.29</td>
<td>[72]</td>
</tr>
<tr>
<td>Lung (pneumonitis)</td>
<td>D</td>
<td>0.45</td>
<td>[20]</td>
</tr>
<tr>
<td>Various head and neck cancers</td>
<td>D</td>
<td>0.6, 1</td>
<td>[53] [77]</td>
</tr>
<tr>
<td>Oropharynx cancer</td>
<td>D</td>
<td>0.68</td>
<td>[4]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0.1, 1.3)*</td>
<td></td>
</tr>
<tr>
<td>Larynx cancer</td>
<td>D</td>
<td>0.6</td>
<td>[39]</td>
</tr>
<tr>
<td></td>
<td>TR</td>
<td>0.4</td>
<td>[11]</td>
</tr>
<tr>
<td></td>
<td>TR</td>
<td>0.3</td>
<td>[35]</td>
</tr>
<tr>
<td></td>
<td>TR</td>
<td>0.5</td>
<td>[46]</td>
</tr>
</tbody>
</table>

D = direct analysis; TR = two-regimen analysis.

*a 95% confidence limits.

maxima of log likelihood with nearly the same estimates of all parameters except for the repair halftime. Although this does not necessarily imply the existence of two components, one maximum corresponded to a short repair halftime of about 0.3-0.4 h and the other to a slower halftime of 1.1-1.3 h.

**Acute effects – repopulation.** In the skin reaction studies of Turesson and Notter [67] there was no significant time factor up to 6 weeks. However, as noted above the repair capacity was reduced after 4 weeks.

**Late effects – repair capacity.** Turesson and Notter [68,69] assessed the degree of late telangiectasia resulting from daily and once- or twice-weekly postmastectomy irradiation of parasternal fields, and the results have been reanalyzed using direct analysis [72]. The repair capacity for late telangiectasia differed significantly from those for erythema and desquamation: $\alpha/\beta = 2.8$ (1.7, 3.8) Gy for 5-year follow-up. The effect of treatment time was significant (see below), however, and when this was included in the analysis $\alpha/\beta = 3.9$ (2.7, 4.8) Gy.

Bentzen et al. [8] used direct analysis to assess the repair capacity for late subcutaneous fibrosis and telangiectasia in 229 breast cancer patients who had received postmastectomy irradiation in either 2/week or 5/week treatment [47]. The $\alpha/\beta$ ratios were 1.9 (0.8, 3.0) Gy for fibrosis, and 3.7 (0.2, 4.7) Gy for telangiectasia. In addition to repair capacity, latency was also estimated: the time to expression of 90% of the ultimate frequency of moderate or severe complications was 3.2 (2.3, 3.9) years for fibrosis and 4.7 (4.0, 4.8) years for telangiectasia. Notably, for subcutaneous fibrosis the time to reach a specific grade of reaction increased with the grade, consistent with the clinical impression that fibrosis progresses in severity over time (Fletcher, private communication, 1988). Treatment times ranged from 29 to 35 days in the 22-fraction group, and from 37 to 46 days in the 12-fraction group; there was no significant influence of time for either endpoint.

In the same breast cancer patients Bentzen et al. [7] used direct analysis to estimate the repair capacity for impaired shoulder movement after postmastectomy radiotherapy [47]. Maximal flexion and abduction of the arm were measured with unfixed scapula using a score determined relative to the contralateral arm. $\alpha/\beta$ was 4.4 (-1.6, 9.6) Gy, and 3.5 (0.7, 6.2) Gy when corrected for age of the patient. The latency until expression of 90% of the ultimate frequency of moderate and severe shoulder impairment was 3.9 (3.1, 4.6) years.

Powell et al. ([50] and private communication) studied brachial plexus injury in breast cancer patients treated with breast and lymphatic irradiation in two different fractionation regimens: 54 Gy in 30 fractions over 6 weeks, and 45.9 Gy in 15 fractions over 6 weeks. Actuarial analysis showed that the incidence of brachial plexopathy at 5.5 years was higher (5.9%) with the larger fraction sizes than with the small (1%); $p = 0.07$. Two-regimen analysis leads to the upper bound $\alpha/\beta < 5.34$ Gy.

Atkins [1] found that frozen shoulder and other complications were much more severe after treatment with 2 fractions of 12.5 Gy than after treatment with 20 fractions of 2.5 Gy, indicating that $\alpha/\beta < 7.5$ Gy.
Late effects — repair kinetics. From the Gothenburg series [70,71] the repair halftime for late telangiectasia (with time correction) was 3.4 (2.8, 4.2) h for 5-year follow-up, as estimated by direct analysis [72]. As was seen for acute reactions (above), there were two identical maxima in the log likelihood, and these might be indicative of a fast repair halftime of about 0.4 h and a slow halftime of 3–4 h; the other parameters were the same in the two analyses.

Late effects — repopulation. For late telangiectasia [71] $D_{prolif}$ was 0.29 Gy/day for 2-Gy fractions. As mentioned above, a time dependence was looked for in the Aarhus data [7,8] and was not found. It must be noted that the interpretation in terms of repopulation of the added 0.29 Gy/day is problematic, and the possibility of a slow (intracellular) repair process cannot be excluded.

Tumor — repair capacity. Although there have been several reports of poor results with large-fraction treatments of breast cancer, most two-regimen comparisons relate to repair capacity for late effects.

Tumor — repair kinetics. There are no data on repair kinetics.

Tumor — repopulation. Fletcher [24] has reviewed the history of treatment of non-deseminated breast cancer by radiation with and without surgery. The qualitative conclusion is that overall time was not as important as in the treatment of squamous cell tumors of the head and neck region. Baclesse reported on a series of 145 patients treated with radiation alone at the 51st Congress of the French Surgical Association in 1948 (cited in ref. [24]). Large masses in the breast received 7000–9000 R in 16 weeks; the supraclavicular area received 5000 R skin dose in 12 weeks if there were no palpable nodes, and higher doses were given to axillary nodes. Doses as low as 4100 R produced control in relatively small tumors, while in large tumors higher doses and a minimum of 3 months treatment time were necessary.

Clarke et al. [13] retrospectively analyzed the results of conservation treatment of breast cancer at the Institut Gustave-Roussy between 1970 and 1981. The difference between local-regional recurrences was significant for patients treated less than 7 weeks following biopsy as opposed to 7 weeks or longer after biopsy (the difference was marginally significant when two additional prognostically significant variables were included in the fit). The time to local recurrences was longer than has been observed following mastectomy only: these were observed gradually over 5 years and appeared as late as 11 years after treatment (the recurrences matched the primaries in histology and Bloom grade). In distinction to recurrences of head and neck tumors, where for most sites over 90% are apparent before 2 years, breast recurrences were uncommon in the first 2–3 years of follow-up.

As in the discussion of repair capacity of breast tumors, no definitive conclusions can be drawn, but the impression gained is of a reduced influence of time. These remarks do not apply to inflammatory breast tumors, where accelerated treatment has been shown to be beneficial [2].

Lung treatments

Acute effects — repair capacity. The RTOG has conducted a series of trials of hyperfractionation for treatment of lung cancer [16]. The available data come from randomized Phase I/II trials, where total doses were 60 Gy in 2-Gy fractions, and 64.8, 69.6, 74.4, and 79.2 Gy in 2 x 1.2 Gy per day. The acute effects were classified as any toxicity experienced within 90 days from the start of treatment, and this included acute pulmonary reactions and esophagitis or esophageal stricture. Severe acute reactions were higher in the hyperfractionation arm with total dose 64.8 Gy, indicating (assuming equivalent or higher level of regeneration in the hyperfractionation arm) that $\alpha/\beta > 8.8$ Gy for acute reactions. If incomplete repair were a factor during the short (4 h) interfraction intervals in the hyperfractionation arm, the estimate of the lower bound would be even higher.
Acute effects – repair kinetics, repopulation. There are no published data allowing calculation of the effects of repair kinetics and repopulation on lung treatments.

Late effects – repair capacity. In the RTOG trial [16] alluded to above, late pulmonary toxicity included pneumonitis, pulmonary fibrosis, atelectasis, pleural effusion, pneumothorax, and pulmonary edema occurring after 90 days from the start of treatment. Late effects were lower in the 69.6-Gy hyperfractionation arm than in the conventional arm, and by two-regimen comparison for late pulmonary toxicity $\alpha/\beta < 3.8$ Gy. Dische et al. [19] found increased radiation myelopathy after treatment once/week with 5.8-Gy fractions, and the two-regimen comparison indicates that for late injury to the spinal cord $\alpha/\beta < 3.3$ Gy. Van Dyk et al. [20] reported an analysis of radiation-induced changes in lung density measured from CT scans. From the results of this prospective study $\alpha/\beta$ was estimated by direct analysis at $0.9 \pm 2.6$ Gy for patients scanned to 6 months (although this period includes the 90-day postirradiation interval used by the RTOG to define acute effects, the results have been entered into Table I under “late reactions” in view of the low value of $\alpha/\beta$). The combination of retrospective (pneumonitis 1 to 7 months after hemi-body irradiation) and the prospective data yielded $\alpha/\beta = 3.3 \pm 1.5$ Gy, consistent with the upper limit 3.8 Gy derived from two-regimen comparison.

Late effects – repair kinetics. No published data.

Late effects – repopulation. Van Dyk et al. [20] analyzed the effect of repopulation in the combined retrospective and prospective data. If treatments were given in 2-Gy fractions this was 0.45 Gy/day. As noted above in connection with telangiectasia, the possibility that the additional 0.45 Gy/day results from a slow-repair process cannot be excluded.

Tumor – repair capacity. Cox et al. [14] described the treatment of localized carcinoma of the lung by 1, 2, 3, and 5 fractions/week. Although the doses were given in rets, the doses that were used may be inferred from information given in the paper; the resulting tumor-control results from different fractionation patterns may then be subjected to direct analysis. Although there were insufficient data to permit precise estimation of $\alpha/\beta$ with confidence limits, the trend was for a very high value (in the range 50 to 90 Gy) to be most consistent with the data. This is in agreement with the preliminary results from the RTOG trials of hyperfractionation [16], where it was apparent that all the hyperfractionation arms produced results at least as good as those obtained by 60 Gy with conventional fractionation.

Tumor – repair kinetics, repopulation. No published data.

Pelvis treatments

Acute effects. No data.

Late effects – repair capacity. For bowel stricture and perforation following pelvis treatments $\alpha/\beta$ can be bounded from above [3] and below [21] using two-regimen comparisons: $2.2 \text{ Gy} < \alpha/\beta < 8 \text{ Gy}$.

Late effects – repair kinetics, repopulation. No data.

Tumor – repair capacity. An interesting sidelight of the Medical Research Council trial of hyperbaric oxygen with radiotherapy for carcinoma of the cervix was reported by Watson et al. [73] (see ref. [15], Table 3). Although the trial was not designed as a study of fractionation, the results can be interpreted by two-regimen comparison. Thus 37 Gy/5.75 Gy/fraction per 20 days resulted in 18% 3- and 5-year local recurrence-free survival, whereas for 45 Gy/2.25 Gy/fraction per 28 days the results were 60% (3-year) and 57% (5-year). This indicates that for cervical carcinoma $\alpha/\beta > 13.9$ Gy, and this value would likely be somewhat higher if the differences in overall time could be accounted for.

Tumor – repair kinetics, repopulation. No data.
Discussion

In this review we have presented a summary of the available data concerning factors that effect human response to fractionated radiotherapy. Of the original "four R's" (repair, repopulation, redistribution, and reoxygenation) formulated by Withers, only two (repair and repopulation) have been included, with particular emphasis on repair (i.e. recovery) where capacity (how much) and kinetics (how fast) were treated separately. This is not meant to diminish the importance of the latter two phenomena, and is more a reflection of the better success we have had in recent years with quantifying the effects of repair and repopulation. The degree of redistribution may, in fact, have a role in determining the ratio $\alpha/\beta$.[60, p. 82].

In any review of this kind it is inevitable that a high degree of selection must be applied, since the great majority of clinical data contains no information on the effect of changing fraction size (in most studies dose per fraction is more or less constant), total dose (roughly constant in most series), overall time (more or less the same for most patients), etc. There is moreover the worrisome possibility that such variation as exists may be related to patient selection: higher total doses in longer overall times given to the larger tumors, etc. According to the report of Maciejewski et al.[42] on head and neck cancer, for example, treatment was often prolonged because of advanced stage of disease, poor condition of the patient, age, or because slowly regressing tumors had an extra boost. All these factors would tend to produce an association between prolonged treatment and low local control, regardless of the rate of tumor proliferation. There is no way of guarding against these confounding influences in retrospective analyses such as the present one. It must be understood, therefore, that many of the quoted $\alpha/\beta$ ratios and dose equivalents of proliferation for human tissues and tumors are of low reliability, so that the utmost caution would be required in their use for tolerance calculations (in general the values derived from direct analysis would be more reliable than the upper and lower limits derived from the two-regimen approach).

The results show that the differences observed between values of $\alpha/\beta$ for early and late effects in animals also hold in humans (Table I). For early reactions in humans $\alpha/\beta$ is in the range of 7 to 11 Gy and for late reactions $\alpha/\beta$ is in the range of 2 to 4 Gy. These differences suggest a therapeutic gain from hyperfractionation [55], if $\alpha/\beta$ values for tumors are high (see below). This has been tested for head and neck tumors in a randomized trial in Europe [37] with $70 \times 1.15 \text{ Gy} = 80.5 \text{ Gy}$ in 7 weeks, and in a non-randomized study [48] in the U.S.A.: $65 \times 1.2 \text{ Gy} = 78 \text{ Gy}$ in 6½ weeks (reviewed in ref. [61]). Both these schedules are reported to give 10–15% more local tumor control than the control arm ($35 \times 2 \text{ Gy} = 70 \text{ Gy}$ in 7 weeks) with no extra late complications, as predicted on radiobiological grounds [55].

The $\alpha/\beta$ values for human tumors of the head and neck region, lung, and cervix are high, in agreement with the rodent data [75]. There are exceptions. Bentzen et al. [6] analyzed a subset of the data compilation of Overgaard et al. [45] on melanoma treatments, in which there was wide variation in dose, fraction size, and treatment time. For the response of melanomas $\alpha/\beta = 0.6 \text{ Gy}$, with 95% confidence interval (-1.1, 2.5) Gy; no detectable influence of treatment time could be found, but the size of the tumor was an important determinant of success (in fact there was no dose response when tumor size was not included). The opposite conclusion (time was important) was drawn in another study [64] where there were unfortunately no data on tumor size. While this does not settle the question of the time factor for melanoma one way or the other, the demonstrated confounding effect when tumor size was omitted from the analysis [6] raises the question of whether the conclusion regarding the time factor [64] is reliable.

A direct analysis of cases of liposarcoma surveyed in the literature by Reitan and Kaalhus [51] suggested that $\alpha/\beta = 0.4 \ (-1.4, 5.4) \text{ Gy}$ [59]. The low value of $\alpha/\beta$ for melanomas is to be contrasted with the $\alpha/\beta$ value for skin tumors: 8.5 (4.5, 11.3) Gy (unpublished direct analysis of previously published raw data [65]).

Data on repair kinetics in human tissues are
limited, but suggest that repair may be slower in human than in rodent tissues, a warning flag for MFD treatments. Direct analysis of skin reactions after post-mastectomy breast treatments indicates repair half-times of a little over 1h for early reactions, and 3h or more for late telangiectasia [72]. Worse early and late sequelae of twice-a-day head and neck treatments resulted when the interfraction interval was shorter than 4.5 h [43], and this is consistent with repair half-times somewhat longer than the 0.5 to 1.5 h typical of rodent tissues ([60] Table 3.6). However, in contradiction of these conclusions there are data [38] that have been interpreted to suggest that intervals of 0.5h do not lead to increased complication rates.

The influence of time is important for early reactions and many tumors, but usually not for late reactions (Table II). Repopulation kinetics is faster in the mucosa of the soft palate and faucial pillars (1.8 Gy/day) than in the head and neck tumors (0.3–1.0 Gy/day) for which data are available. Time may have a less important influence in the treatment of breast tumors (excepting inflammatory breast); it was significant in one study of melanomas [64], but when tumor size was accounted for time was not significant in a recent analysis of different data [6].

It is surprising that time was not important for acute skin reactions during postmastectomy breast treatments, but was a significant influence for late telangiectasia [72]. There is at present no explanation for this surprising finding.

In conclusion, the dissociation between acute and late effects in human tissues is reflected by high and low α/β ratios, respectively, in agreement with the animal studies. For tumors α/β ratios are somewhat more variable than in animals: high for tumors of the head and neck, lung, skin and cervix, but low for melanomas and liposarcomas. Repair kinetics may be slower in humans than in animals, but there are few reliable data. Finally, repopulation accounts for up to 1 Gy/day in head and neck tumors, and perhaps 1.8 Gy/day in the oral mucosa. An influence of time has been measured for late reactions in lung in animals, and the same is true in humans; in addition, time is important for late telangiectasia, and for one study of the late effects of head and neck treatments. It should be noted, however, that what we have interpreted as “repopulation” for late effects may, in fact, be a reflection of slow repair in these tissues.

Acknowledgements

The authors wish to thank Dr. J. D. Cox, Dr. G. H. Fletcher, and Dr. J. Overgaard for helpful suggestions and Ms. C. Seifert for expert assistance in preparation of the manuscript. This work was supported in part by Grants CA-29026 and CA-11430 from the NCI and DHHS.

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