Repair halftimes estimated from observations of treatment-related morbidity after CHART or conventional radiotherapy in head and neck cancer

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Received 3 February 1999; received in revised form 13 October 1999; accepted 15 October 1999

Abstract

Background and purpose: The CHART (Continuous Hyperfractionated Accelerated Radiotherapy) head and neck cancer fractionation schedule delivered 54 Gy in 36 fractions on 12 consecutive days and this was compared in a randomised controlled trial with conventional fractionation delivering 66 Gy in 33 fractions over 6–7 weeks. Patients receiving CHART experienced statistically significantly less treatment-related morbidity after 6 months than patients receiving conventional fractionation. However, this improved tolerance was much less than anticipated from existing knowledge of dose-fractionation effects on late-responding normal tissues. Here, the experience from the CHART study is analysed and repair halftimes for three types of late treatment-related morbidity of human tissues are estimated.

Patients and methods: The CHART trial was open for patient accrual from March 1990 to April 1995 and a total of 918 patients in 11 participating centres were randomised. All patients were followed at regular intervals for a minimum of 5 years or until the time of death. At each follow-up, a number of treatment-related morbidity items were evaluated and scored prospectively. Data for three late endpoints are analysed here: laryngeal oedema, skin telangiectasia and subcutaneous fibrosis. Differences in the incidence of these endpoints in the two trial arms were quantified by means of the ratio of hazard rates in a Cox proportional hazards model. Monte Carlo sampling was performed from distributions of fractionation sensitivity (quantified by the $\alpha/\beta$-ratio) and steepness of the dose-response curve (quantified by the normalised dose-response gradient, $\gamma_{50}$) with means and standard deviations derived from the literature. Each pair of values were used to convert a Monte Carlo sampled estimate of the difference in biological effect into an estimate of the repair halftime. From the distribution of 1000 Monte Carlo samples, the mean repair halftime and its 95% confidence interval were estimated.

Results: The estimated repair halftimes, with 95% confidence intervals in parentheses, were 4.9 h (3.2, 6.4) for laryngeal oedema, 3.8 h (2.5, 4.6) for skin telangiectasia and 4.4 h (3.8, 4.9) for subcutaneous fibrosis. Calculations show that these repair halftimes are consistent with the observations from two published randomised controlled trials of altered fractionation in head and neck cancer, the EORTC 22791 and 22851 trials.

Conclusions: These long repair halftimes for late effects in human normal tissues have to be considered in order to gain the full benefit from fractionation schedules employing multiple fractions per day. © 1999 Elsevier Science Ireland Ltd. All rights reserved.

Keywords: CHART; Monte Carlo sampling; Repair halftimes

1. Introduction

Perhaps the most intriguing biological observation from the large randomised controlled trial of CHART (Continuous Hyperfractionated Accelerated Radiotherapy) vs. conventional fractionation (CF) in radiotherapy for head and neck cancer is the relatively modest sparing of late normal-tissue morbidity from CHART. CHART did improve the therapeutic ratio relative to CF: an unchanged level of loco-regional tumour control was obtained with a statistically significant reduction in late treatment-related morbidity [13]. However, this reduction was much less than expected from the simple Linear-Quadratic (LQ) model assuming complete repair between fractions and no influence of overall treatment time on the incidence of late normal-tissue injury. It was the clinical impression that the late morbidity observed in the CHART cases just corresponded to what would be expected after about 60 Gy in 2-Gy fractions.

CHART delivered a total dose of 54 Gy in 36 fractions in 12 consecutive days to the regions with macroscopic tumour involvement. In order to facilitate a comparison with the CF arm of the trial, we express biological equivalent doses as

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the isoeffective dose delivered in 2-Gy fractions, the ID\textsubscript{2}. Assuming an α/β ratio for late effects of 2 Gy, the ID\textsubscript{2} for CHART would be 47.25 Gy. With the rather conservative assumption of α/β = 3.5 Gy, the ID\textsubscript{2} would be 49.1 Gy. Even under the extreme assumption of no sparing of late effects from hyperfractionation (that is, α/β infinite) the ID\textsubscript{2} of CHART would be equal to the nominal total dose, i.e., 54 Gy. These doses should be compared with the 66 Gy in 33 fractions over 6–7 weeks delivered in the CF arm of the trial. The estimated difference in dose between the CHART and the CF arms may be converted into an expected difference in response, that is, in the incidence of a specific late reaction. To this end, it is convenient to use a parameterisation of the dose-response curve in terms of its position and the normalised dose-response gradient, γ\textsubscript{50} [10]. For late normal-tissue endpoints γ\textsubscript{50} typically ranges between 2 and 5 [4]. Even at the lower end of this range, γ\textsubscript{50} = 2.0, an incidence of, say, 40% after CF should be reduced to 7% for ID\textsubscript{2} = 47.25 Gy and to 14% for ID\textsubscript{2} = 54 Gy. These changes should be easily detectable in a trial of the size of CHART, and one can conclude that the toxicity after CHART is higher than expected from the LQ model assuming complete repair between fractions.

Two features of CHART might conceivably have affected the level of late treatment-related morbidity: the short overall treatment time and the short interfraction interval of 6 h on each treatment day. For the former of these effects, the overall treatment time, there are fairly good data, mostly from studies of split-course radiotherapy, showing that there is no major influence, if any at all, of overall treatment time in itself [6]. Admittedly, these data stem from schedules that are considerably longer than 12 days, and the possibility that the short overall time could influence tissue recovery processes cannot be ruled out. Yet, there are no available data, clinical or experimental, demonstrating such an effect. This focuses on the multiple fractions per day (MFD) as the most likely explanation for the observations from CHART. As the interval between fractions in CHART were 6-6-12 h this would imply that repair is not complete by 6 h and there are in fact indications that repair of sublethal damage in the time interval between fractions may be considerably slower in the clinic than what has been inferred from experimental animal studies. Perhaps the most convincing evidence so far, that the interfraction interval may become important for MFD radiotherapy, comes from several clinical studies showing an unexpectedly large decrease of the incidence of mucositis when changing interfraction intervals from 4 to 6 h [8]. An analysis of these observations suggested a repair halftime in the order of 2–4 h.

In the present paper, the CHART experience will be analysed using the ‘overnight-interaction’ version of the incomplete repair model [14]. Repair halftimes for late morbidity in human tissue are estimated and discussed in view of recent experience from other randomised trials of radiotherapy for head and neck cancer.

2. Patients and methods

2.1. The CHART head and neck trial

The CHART head and neck trial was open for patient accrual from March 1990 to April 1995. Central randomisation was performed with a 3:2 allocation in favour of CHART. All patients over the age of 18 years with squamous cell carcinoma in the main sites within the head and neck region except for early T1N0 tumours were eligible for the study. Patients were excluded if they had evidence of distant metastasis or a WHO performance status of 2 or worse. A total of 918 patients was randomised in the 11 participating centres. Details of the pre-treatment investigations, the radiotherapy planning, the randomisation procedures, and the radiotherapy quality assurance programme have been given recently by Dische et al. [13].

Data management and the initial statistical analysis of the results were carried out at the Cancer Trials Office of the Medical Research Council in Cambridge. A complete copy of the database has been transferred to Mount Vernon Hospital where the analyses reported here, were performed.

2.2. Treatment technique and dose-fractionation schedules

Radiotherapy was given with a shrinking field technique. The large volume included the primary tumour, any involved lymph nodes and the relevant area of lymphatic drainage. The small volume included the primary tumour and the known nodal involvement with a margin. Doses were prescribed at the intersection point of the central axes and the range between minimum and maximum tumour dose was required by the protocol to be no more than 10%.

Conventional fractionation was delivered as 44 Gy in 22 fractions to the large volume and 22 Gy in 11 fractions to the small volume. Thus, a total dose of 66 Gy was delivered with 2 Gy per fraction, one fraction per day, 5 days a week. CHART was delivered with 1.5 Gy per fraction, three fractions a day, on 12 consecutive days including the weekend. The prescribed interfraction interval of 6 h was strictly adhered to. The large volume received 37.5 Gy in 25 fractions, and the small volume received 16.5 Gy in 11 fractions which gave a total dose of 54 Gy in 36 fractions.

2.3. Follow-up and scoring of late morbidity

Follow-up was scheduled at 8 weeks and 3 months after the first day of treatment, subsequently 3 monthly to 2 years, 6 monthly to 5 years and annually thereafter. In addition to the cancer-related status, treatment-related morbidity was carefully evaluated and scored at each follow-up. Details of the scoring of late reactions have been published recently [13]. Three endpoints are the main focus of the present study: laryngeal oedema was scored as to whether it was present or not, skin telangiectasia was scored as moderate/severe if there were more than 1 per cm\textsuperscript{2}, and subcutaneous fibrosis was scored on an arbitrary 4-point scale with Grade
indicating no fibrosis and Grade 2 and 3 described as moderate and severe fibrosis, respectively.

2.4. Non-mathematical summary of the method of analysis

For late treatment-related morbidity, where there are data showing that the effect of overall treatment time is negligible, the isoeffective dose of a given fractionation schedule for a specific endpoint depends only on the total dose, the dose per fraction and the time interval between fractions. The relationship between these is often assumed to be described by some mathematical model and the most frequently used is the Incomplete Repair (IR) version of the LQ model [22]. This model has two tissue-specific parameters: the $\alpha/\beta$-ratio, which quantifies fractionation sensitivity, and the repair halftime, $T_{1/2}$, characterising the kinetics of repair in the interval between dose fractions. Fig. 1 illustrates the interplay between these parameters in case of the CHART schedule. For short repair halftimes, that is, in the limit of complete repair between dose fractions, the isoeffective dose in 2-Gy fractions, the ID$_2$, for CHART is always less than the nominal total dose of 54 Gy. As $\alpha/\beta$ decreases, the ID$_2$ will decrease because of the sparing of normal-tissues arising from the hyperfractionation applied in CHART. However, with increasing $T_{1/2}$ the ID$_2$ will increase. The amount of unrepaired damage from one fraction to the next will be larger for tissues with a low $\alpha/\beta$, simply because a larger proportion of the damage is repairable in tissues with a high fractionation sensitivity.

Now, for a given difference in the incidence of a reaction after CHART relative to CF, the corresponding difference in ID$_2$’s might be calculated, provided that the steepness of the dose-response curve is known. Assuming further, that the $\alpha/\beta$ for the tissue endpoint in question is known, this difference in ID$_2$’s might subsequently be converted into a repair halftime, in principle by reading off the appropriate graph in Fig. 1.

The above simple recipe may be repeated multiple times with values of $\alpha/\beta$ and the measure of steepness of the dose-response curve that are consistent with the precision by which we know these parameters, see next section. This may be done by drawing random numbers from the appropriate statistical distributions, so-called Monte Carlo simulation. Also, the uncertainty in the estimated outcome needs to be taken into account. For each endpoint studied here, the strategy is then:

1. quantify the difference in the incidence of this endpoint between the CHART and the conventional arm, and evaluate the statistical uncertainty in this estimated difference;
2. draw at random values of the treatment difference, the $\alpha/\beta$-ratio and the normalised dose-response gradient, $\gamma_{50}$;
3. estimate the resulting value of $T_{1/2}$.

This procedure was repeated 1000 times and the statistical properties of $T_{1/2}$ were derived from the resulting Monte Carlo probability distribution. The mathematical outline of this method is given in the appendix. All computations were performed using Mathematica 3.0.1 running under Windows NT 4.0.

2.5. Radiobiological tissue parameters used in the analysis

In addition to the clinical observations from the CHART study, two radiobiological parameters and their statistical uncertainties are required in the present analysis, namely the fractionation sensitivity, as quantified by the $\alpha/\beta$ ratio, and the steepness of the clinical dose-incidence curve, quantified here by the normalised dose-response gradient at the 50% response level, $\gamma_{50}$. For three of the late endpoints evaluated in the CHART trial, laryngeal oedema, skin telangiectasia and subcutaneous fibrosis, fairly good estimates of these parameters are available from published clinical radiobiology studies and these are shown in Table 1. The sources for these estimates are briefly described in the following. Also, there are published data to elucidate the lack of an independent effect of overall treatment time per se for these three endpoints.

Laryngeal oedema after conventional and split-course radiotherapy was reported by Overgaard et al. [20]. The data were re-analysed by Bentzen [4] who estimated the steepness of the dose-response curve and the standard error of this estimate. The fractionation sensitivity has not been estimated with any useful precision. Here, $\alpha/\beta = 2.5 \pm 1.5$ Gy was assumed, a range of values covering most late reactions in the head and neck region. Overgaard et al. found no significant influence of overall treatment time for this endpoint, see also the review by Bentzen and Overgaard [6]. Further evidence for the lack of an independent effect of overall treatment time comes from the DAHANCA 6/7 trials of accelerated radiotherapy in head and neck cancer where the incidence of oedema was unchanged.
after shortening the treatment time by about 1.5 weeks (J. Overgaard, pers. commun., December 1998).

Telangiectasia of the skin has been extensively studied after postoperative radiotherapy for breast cancer. The $\gamma_{50}$ and $\alpha/\beta$ values used here, were derived from the analysis by Bentzen et al. [11] of data from the Gothenburg fractionation studies [23]. Overall treatment time is probably of no significant importance for this endpoint, as the introduction of a 3-week split in the Gothenburg study gave no sparing of telangiectasia. There is, however, some confusion concerning the interpretation of the Gothenburg observations, and this is discussed later in this paper. Overall treatment time was not significantly associated with the incidence of telangiectasia in the Aarhus postmastectomy radiotherapy patients, but admittedly the variation in overall treatment time was limited in that study [7].

Subcutaneous fibrosis has also been studied in detail after postmastectomy radiotherapy. The radiobiological parameters used in the present analysis are from Bentzen et al. [4,9]. Data to elucidate the possible influence of overall treatment time on subcutaneous changes are sparse. In the Aarhus postmastectomy radiotherapy study there was no significant influence of overall treatment time for subcutaneous fibrosis, but as discussed above there was a limited variability in treatment duration in that study.

### 3. Results

The incidence of specific types of normal-tissue morbidity after CF and CHART was estimated by the inverse Kaplan–Meier estimate. Fig. 2 shows the data for three endpoints: laryngeal oedema, skin telangiectasia and subcutaneous fibrosis. The 5-year estimates were taken as representative for the ultimate incidence of these complications [11]. An estimate of the difference in biological effect between the two trial arms was obtained by the ratio of hazard rates estimated from a Cox Proportional Hazards model with treatment arm as the only covariate. In the case of laryngeal oedema, the analysis was restricted to patients with cancer of the larynx, oropharynx and hypopharynx, and the Cox modelling was stratified according to these three anatomical subsites. The ratios of hazard rates, or relative risks, were subsequently converted into a resulting estimate of the difference in response probability (see [5,13] and the standard error of this estimate (Table 1). Fig. 3 shows the estimated repair half-times from 1000 Monte Carlo runs for laryngeal oedema. From the distribution of these 1000 samples, the average value of $T_{1/2}$ and an approximate 95% confidence interval for this were calculated (Table 2).

### 4. Discussion

#### 4.1. The case for long repair half-times

Interestingly, the three late endpoints studied here all come out with very long estimated $T_{1/2}$ values, around 4–5 h. This is much longer than what was generally reported from experimental animal studies in the early 1980s when the CHART schedule was designed. The first warning that interfraction intervals of 6 h might not be sufficient to ensure complete repair between fractions came from the unexpected observation of four cases with radiation myelitis after CHART [12]. Animal experiments on repair kinetics in the spinal cord soon revealed quite long repair half-times for at least a component of the damage [1]. Yet, modelling studies suggested that even these longer repair half-times observed in animal models might still be too short to explain the human data [14]. Subsequent experimental studies have shown evidence of long repair halftimes, typically modelled as biphasic repair, in several normal tissues (e.g. [17,18]).

Another remarkable observation is that the three late CHART endpoints analysed here seem to have similar repair halftimes. One possible explanation would be that the radiation pathogenesis of these endpoints, at least in part, involved a common underlying mechanism. However,
in neural tissue these repair halftimes could possibly be even longer, thus explaining the radiation myelopathy cases after CHART.

Several other late endpoints were evaluated and recorded in the CHART database. Some of these, like mucosal ulceration, deep necrosis or trismus, were rare with a long-term incidence of less than 10%. This leads to wide confidence intervals for the difference in response between CHART and conventional radiotherapy and to low local values of $\gamma$ as we are operating on the foot of the dose-response curve. These factors in combination leads to a very wide distribution of estimated differences in ID$_2$ and therefore to estimates of $T_{1/2}$ that are too uncertain to contain useful information. Other endpoints were less suited for a quantitative analysis like the present one, either because the radiobiological characteristics of these endpoints are poorly known, like for dryness of the mouth, or because they are composite, functional endpoints, like late dysphagia.

Data in support of long repair halftimes have been published for telangiectasia of the skin. Nyman and Turesson [19] compared the incidence of moderate and severe telangiectasia after postoperative radiotherapy for breast cancer with $25 \times 2.0$ Gy delivered in either 33 days with single daily fractions, 5 days a week, or delivered BID in 17 days with 8-hour interval. The BID schedule produced a significant increase in the incidence of telangiectasia, thus suggesting that repair still takes place in the interval between 8 and 24 h. In an earlier study, Turesson and Thames [24] used a multivariate dose-response model to estimate the radiobiological dose-fractionation characteristics of the same endpoint. The study population was an independent series of patients treated in the Gothenburg fractionation study of postoperative radiotherapy for breast cancer. The analysis estimated a repair halftime for moderate and severe telangiectasia of 3.4 h with 95% CI (2.8, 4.2) h, in remarkable agreement with the present analysis. However, it should be noted that the model included a

Table 2

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>$T_{1/2}$, MC average (h)$^a$</th>
<th>2.5%-tile, MC (h)$^b$</th>
<th>97.5%-tile, MC (h)$^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laryngeal oedema</td>
<td>4.9</td>
<td>3.2</td>
<td>6.4</td>
</tr>
<tr>
<td>Skin telangiectasia</td>
<td>3.8</td>
<td>2.5</td>
<td>4.6</td>
</tr>
<tr>
<td>Subcutaneous fibrosis</td>
<td>4.4</td>
<td>3.8</td>
<td>4.9</td>
</tr>
</tbody>
</table>

$^a$ MC, Distribution parameters derived from a Monte Carlo sample of 1000 runs (see text).

$^b$ Approximate lower bound of the 95% confidence interval.

$^c$ Approximate upper bound of the 95% confidence interval.
term for overall treatment time, which was estimated at about 0.28 Gy/day in 2-Gy fractions. The inclusion of an overall-time factor in the model was in direct contrast to the observation from Gothenburg that a 3-week break in a split-course radiotherapy schedule caused no sparing of telangiectasia relative to a similar schedule without the break, and Turesson and Thames interpreted the overall-treatment time factor in the model in terms of very slow repair.

Data on repair kinetics are sparse for other human normal tissue endpoints but there are clinical data supporting repair halftimes of 2–4 hours for early mucosal reactions [8].

4.2. Application to the EORTC studies

Speculations were made in the original report that the marked increase in late severe connective tissue damage after accelerated fractionation (AF) in the EORTC 22851 accelerated split-course trial could be caused by a too short interfraction interval [15]. Radiotherapy was delivered with $3 \times 1.6$ Gy per day in a split course schedule delivering 28.8 Gy in 8 days in the first part, followed by a 12–14 days break, and then a second course of RT delivering 43.2 Gy in 11 days. The minimum interfraction interval was 4 hours but during the last third of the trial accrual period longer intervals were aimed for. Assuming a repair halftime of 4 h, the ID$_2$ for the AF arm becomes around 90 Gy with interfraction intervals around 5 h. The 5-year incidence of severe connective tissue damage was 15% after CF, and using the formula of Peto et al. [21], see also Bentzen et al. [8]. An approximate 95% confidence interval for the latter estimate from Table 1, 90 Gy corresponds to an expected incidence of severe connective tissue damage of about 85%. The observed incidence of this endpoint at 5 years was 50% after AF. The uncertainty in this estimate may be evaluated using the formula of Peto et al. [21], see also Bentzen et al. [8]. An approximate 95% confidence interval for the latter incidence is (18%, 82%), that is the upper bound is in the same range as the above expected incidence. At 7 years the incidence of severe connective tissue damage had risen to 60% but with few patients at risk and therefore with a wide confidence interval. Thus, the increased toxicity observed in the accelerated radiotherapy arm of the trial could be explained by incomplete repair between fractions if we accept the repair halftimes estimated from CHART.

Another randomised controlled trial of interest in this context is the EORTC 22791 trial comparing hyperfractionated radiotherapy (HFX) with 80.5 Gy delivered with two fractions per day of 1.15 Gy in 7 weeks versus CF with 70 Gy given as one 2-Gy fraction per day in the same overall time [16]. This study has had a major impact because of its demonstration of a significantly improved local tumour control with an equal level of late effects after HFX. It has been suggested that the toxicity after HFX was indeed increased in the trial [3]. However, there was no statistically significant difference between the normal-tissue morbidity in the two trial arms [2]. Still, even if the equivalence or near-equivalence of late toxicity in the HFX and CF arms is accepted, the incidence of fibrosis in the HFX arm is unexpectedly high. With $\alpha/\beta = 1.7$ Gy and assuming complete repair in the 4–6-h interval between fractions, the ID$_2$ for the HFX arm is only 62.0 Gy, that is about 11% less than in the CF arm, thus suggesting sparing of subcutaneous fibrosis in the HFX arm. According to Horiot et al. [16] around 80% of the patients had 4-6 h interfraction intervals, and the remainders had longer intervals. Assuming an ‘average’ interfraction interval of 5 h and that repair is complete during the weekend gap, the ID$_2$ for $T_{1/2}$ equal 4.0 and 4.4 h may be estimated at 74.0 and 75.5 Gy, respectively. The observed 5-year incidence of moderate/severe fibrosis was around 40% after CF and 34% after HF. A rough estimate of the uncertainty in these figures may be obtained using the method above, and this gives a 6% decrease in the 5-year incidence of moderate/severe fibrosis of 6% with 95% CI –23–35%. The lower bound of this interval corresponds to a 23% increase in the incidence of fibrosis in the HFX arm. A dose-response analysis with $T_{1/2}$ equal to 4.0 or 4.4 h predicts an incidence increase in the HFX arm of 20 or 27%, respectively. Thus, the repair halftimes derived from CHART are consistent with the observations from the EORTC study.

The above calculations suggest, that the optimal estimates of $T_{1/2}$ from the two EORTC studies might come out slightly lower than the estimates from CHART. Note, however, that the estimated confidence intervals for the outcome of the EORTC trials do not include uncertainties arising from uncertainty in the fractionation sensitivity or the steepness of the dose-response curve. A large clinical radiobiological study, the Fractionation IMPACT study (Intergroup Merger of Patient data from Altered or Conventional Treatment schedules), is currently in progress. This is a co-operative study co-ordinated at the Gray Laboratory/Mount Vernon Hospital. In this study, detailed individual patient data are merged from five large randomised trials of altered fractionation in the head and neck, namely the hyperfractionation trial from the Princess Margaret Hospital in Toronto, the EORTC 22791, 22811 and 22851 trials and the CHART trial. The total number of patients is 2470. Among many other questions, the Fractionation IMPACT study will also address the issue of repair halftimes.

4.3. Clinical implications

Before speculating on the possible implications of the present analysis, it should be stressed that the less-than-expected sparing of late effects in the CHART arm is a basic clinical observation that is independent of the underlying mechanistic interpretation. This in itself is a warning of the possible problems with schedules delivering three fractions per day, even when intervals are kept longer than 6 h.

Here, a quantitative analysis is performed using the overnight-interaction version of the incomplete repair model assuming mono-exponential repair kinetics. The repair half-
times estimated suggest that not only CHART but also two of the altered fractionation schedules studied by the EORTC deliver a higher isoeffective dose in 2-Gy fractions than what has been thought until now. Other repair kinetics models have been proposed including models with multiple repair components or the reciprocal repair model proposed by Fowler (pers. commun.). As only one time-interval was used in the CHART schedule it is not possible to discriminate between mono-exponential and other repair models. What is available from the CHART study is the dose-equivalent of incomplete repair in the CHART arm.

One missing piece of information is whether squamous cell carcinomas in the head and neck region have similarly long repair halftimes. If so, short time intervals between dose fractions could in theory still be beneficial depending on the specific values of $T_{1/2}$ and $\alpha/\beta$ for tumour and critical normal tissue. However, the tumour response after CHART was not better than what would be expected from standard assumptions concerning the effect of shortening of overall treatment time in itself, and this could indicate that the tumour is less affected by incomplete repair than the normal tissues.

5. Conclusion

CHART has produced a strong case that the sparing of late morbidity in the head and neck region for several late endpoints is less than expected if 54 Gy was delivered with 1.5 Gy per fraction with complete repair between fractions. Analysis of the CHART data using an Incomplete Repair model with mono-exponential repair kinetics yields repair halftimes in the range 4–5 h. Even the lower end of these confidence intervals are around 3 h or more. This suggests that even with 6 h between dose fractions, MFD schedules are associated with a loss of tolerance compared to a similar complete repair schedule. Again, this means that to gain the full benefit from an accelerated regime of radiotherapy, the long halftimes of repair in normal tissues have to be considered and total doses chosen accordingly.

Acknowledgements


Appendix A. Summary of the formulae used

Differences in the incidence of late-normal tissue complications over time were quantified by means of the ratio of hazard rates in a Cox Proportional Hazards Model with treatment arm, i.e. CHART vs. conventional, as the only co-variate. The relative risk of developing a specific complication after CHART relative to conventional fractionation and its standard error of the estimate (SEE) was calculated as

$$\Theta \pm \text{SEE}(\Theta) = \exp(\beta) \pm \exp(\beta) \cdot \text{SEE}(\beta)$$

where $\beta$ is the estimated regression coefficient from the Cox PHM analysis. This method assumes proportional hazards in the two groups, but it has the advantage of producing an estimate of difference in response based on the whole time-course of the incidence-time curves in contrast to a point estimate at one specific follow-up time. Also, the standard error of the estimated difference in biological effect includes the uncertainty in the estimation of the incidence curves in both trial arms.

Monte Carlo simulation was used to pick a specific $\Theta$ from the estimated distribution of $\Theta$ and the incidence of the endpoint in question in the CHART arm was calculated as

$$p_{\infty, \text{CHART}} = 1 - \left(1 - p_{\text{ref}}\right)^{\hat{\beta}}$$

where the reference probability of morbidity was chosen to coincide with the observed level at 5 years in the conventional arm.

The ultimate incidence of a specific complication, $p_{\infty}$ was assumed to follow a logistic dose-response model [10]

$$p_{\infty} = \frac{1}{1 + \exp\left(4 \cdot \gamma D_{50} \left(1 - \frac{D}{D_{50}}\right)\right)}$$

where again $\gamma$ is obtained by Monte Carlo sampling from a normal distribution with mean and standard deviation derived from literature data. For each value of $\gamma$ the $D_{50}$ was calculated from the reference incidence and the $D_{\text{conv}} = 66$ Gy.

The isoeffective dose in 2-Gy fractions for CHART was calculated on a two-dimensional grid of repair halftimes and $\alpha/\beta$ values by means of the ‘overnight interaction’ incomplete-repair model [8,14]. For fixed values of $\alpha/\beta$ cubic spline interpolation was used to find an approximate inverse function yielding repair halftime as a function of dose. This function was used to establish $T_{1/2}$ as a function of pairs of dose and $\alpha/\beta$-values on an evenly spaced two-dimensional grid. Bi-variate cubic spline interpolation was used to produce an approximate function giving $T_{1/2}$ as a function of $\alpha/\beta$ and the isoeffective dose in 2-Gy fractions.

Triplets of parameter values ($\Theta_{\gamma}, \alpha/\beta$) were drawn from three independent normal distributions with mean values...
and standard deviations derived from the CHART data ($\Theta$) or from the literature ($\gamma_0$ and $\alpha/\beta$).

References


