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The Effect of Differing Radiotherapeutic Schedules on the Response of Glottic Carcinoma of the Larynx

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Laryngeal tumours, especially T1N0M0 and T2N0M0 lesions, are readily controlled by radiotherapy. Studies have shown that control varies with the dose of radiotherapy delivered to the tumour. Other factors, including the dose per fraction and the time over which the treatment schedule is delivered are also important. The varying biological effectiveness of a number of different dose fraction time schedules used in the management of laryngeal tumours of different stages are considered, the end points being tumour control and associated morbidity. Special attention has been given to the length of time over which the schedule is delivered. Of the schedules examined the results would suggest that a dose of 60 Gy given in 25 fractions over a period of 35 days is the best of the six schedules studied for T1, T2, T3 and T4 lesions with minimal associated morbidity. It is possible, however, that the poor results shown on the Kaplan–Meier curves for patients treated with the schedule of 60 Gy in 30 fractions over a period of 42 days could be due to geographical misses of the tumours as 56% were treated without a beam directed shell. The poor result obtained when patients were treated with the schedule of 60 Gy given in 30 fractions over 49+ days may be due to tumour repopulation occurring during the rest period though the possibility of geographical misses may contribute to the poor tumour control results. Mathematical modelling using linear quadratic analysis suggests that the shorter the period of time over which the treatment is given the better chance of achieving tumour control irrespective of the stage of the disease. These models were developed for patients treated with a beam directed shell thus excluding those patients who are most likely to be at risk from a geographic miss of the tumour. Linear quadratic analysis of the treatment data suggests that the ratio α/β for tumour cells is estimated in the region of 13 Gy. For T1 lesions the tumour doubling time is in the order of 6 days, with longer doubling times for the more advanced stages. The analysis provides some support for investigative use of accelerated treatment schedules. This analysis also shows the importance of using beam directed shells when treating small fields especially in the head and neck region.
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INTRODUCTION

RADIOTHERAPISTS HAVE long regarded the management of laryngeal tumours as a testing area [1]. Glottic tumours metastasise infrequently, hence primary tumour control which is important in the management of many malignancies [2] is vital in these cases. Over the years, a number of mathematical models have evolved which correlate the treatment schedule factors (dose, fraction size, length of treatment time) to the biological effectiveness of the treatment [3–5]. Fletcher *et al.* [6] have shown that tumour control increases with total dose. Stewart and Jackson [7] have reported the relative importance of treatment time and dose fraction size. The efficacy of six treatment schedules is considered here to determine which gives the best tumour control with the minimum associated morbidity. In keeping with current concepts, the data have been subjected to a linear quadratic analysis to determine the relative importance of the three factors, dose, fraction number and overall treatment time in achieving tumour control.

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PATIENTS AND METHODS

Of the 651 patients with laryngeal tumours treated between 1968 and 1977, 377 had tumours arising in the glottis with no evidence of nodal involvement. 303 of these patients were treated by one of the six regimes listed in Table 1. The schedule chosen depended upon consultant preference, whether or not the patients were entered into the British Institute of Radiology fractionation trial and whether or not the consultant in charge wanted to give a break in the middle of treatment to minimise the acute reactions (the 60–30–49+ schedule).

The male to female ratio was 6.3 to 1. The average age of the patients was 62.3 years with a range of 36–91 years. All patients were treated on a linear accelerator (4–6 Mv photons). The field arrangement was a parallel pair—two lateral wedged fields—minimal field size 5 × 5 cm. 66% of patients had a beam directed shell constructed prior to treatment, the remainder were treated by a free hand set-up. The dose distribution throughout the volume was reasonably uniform and varied by no more than ±5%. These patients are used in the first part of the analysis to compare a number of treatment schedules.

As only 234 of the 377 patients treated between 1968 and 1977 were followed-up for at least 5 years or experienced a local recurrence, a further 305 patients treated between 1958 and

Table 1. Numbers of patients by treatment regime and stage T. Patients treated between 1968 and 1977 only

Regime (D–N–T)	T1	T2	T3/4	Total number treated in each regime
60–30–42	50 (22)	22 (15)	17 (8)	89
60–25–35	58 (47)	36 (34)	17 (16)	111
54–18–42	26 (2)	9 (2)	2 (0)	37
60–30–49+	9 (5)	8 (3)	11 (9)	29
56.5–25–35	11 (10)	3 (3)	1 (0)	15
51–15–35	14 (12)	7 (7)	1 (1)	22
Total number in the six regimes	168 (98)	85 (64)	49 (34)	303
Total number with each disease stage	202	110	65	377
% in six regimes	84	77	75	80

Regime: D = dose in Gy; N = number of fractions; T = treatment time in days. Regime 60–30–49+ includes all patients receiving 60 Gy in 30 fractions over a time period of 49 days or more. Numbers in brackets denote the numbers treated with a beam directed shell.

1967 were reviewed. 102 were eligible for analysis in the correct schedules. These patients were treated on a cobalt machine or a linear accelerator (4–6 Mv photons). The treatment set-up was a parallel pair of two lateral wedged fields and 12% had a beam directed shell. The dose distribution was ±8%. The male to female ratio was 9 to 1 and the average age was 61.4 years with a range of 17–87 years. The combined sample of 336 patients followed up for at least 5 years is used in the linear quadratic analysis.

Those dying of intercurrent disease have been censored. Censorship is the process whereby patients who have not died of carcinoma of larynx are removed from the study at the time of death from intercurrent disease or when lost from follow-up. In the case of tumour control (Figs 1–3, Table 2) an event arises

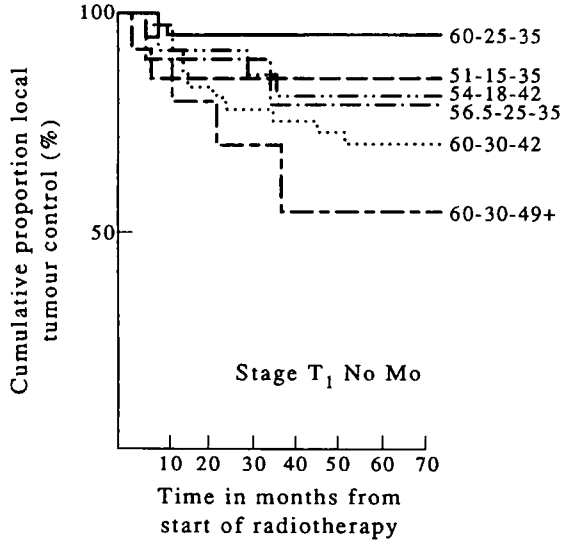

Fig. 1. Kaplan–Meier curve relating local tumour control to time from beginning of radiotherapy for different treatment schedules. The poor results obtained using the schedule 60–30–49+ could be partly due to geographical miss of the tumour as a number of the patients were treated without a beam directed shell.

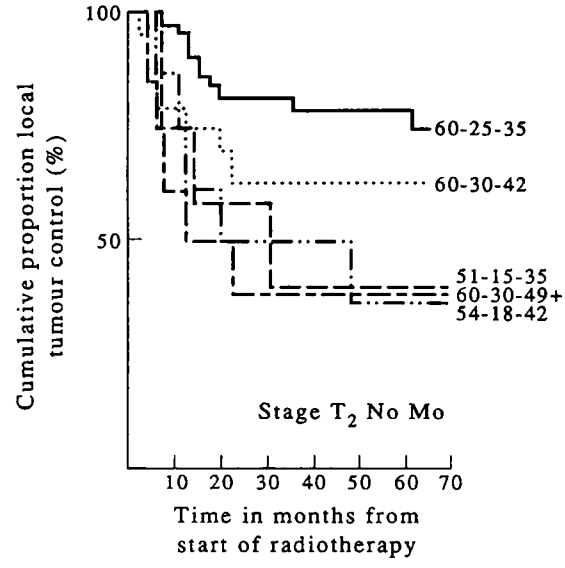

Fig. 2. Kaplan–Meier curve relating local tumour control to time from beginning of radiotherapy for different treatment schedules.

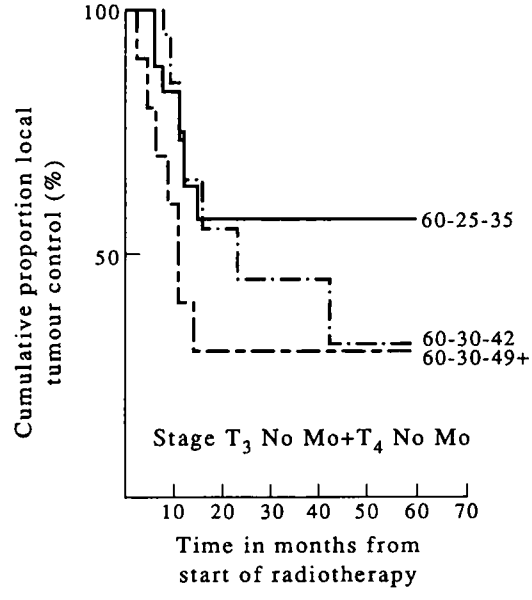

Fig. 3. Kaplan–Meier curve relating local tumour control to time from beginning of radiotherapy for different treatment schedules.

Table 2. 5-year local control for patients by radiotherapy alone. The percentages of all patients who were disease free for at least 5 years. Taken from Figs 1–3

Regime	T1	T2	T3/4	*Deff*(Gy)	Time (days)
60–30–42	70	62	32	60	42
60–25–35	95	75	56	62	35
54–18–42	81	37	—	58.5	42
60–30–49+	55	39	30	60	49+
56.5–25–35	80	—	—	57.7	35
51–15–35	85	40	—	56.9	35

Deff was calculated assuming α/β = 10 Gy, see text and Appendix 1.

either when the patient is found to have recurrent disease requiring laryngectomy or dies of recurrent disease. The tumour control curves were estimated using the product limit method of Kaplan and Meier [8]. The equality of these curves was investigated using the log rank test [9] and the generalised Wilcoxon test [10]. Both test statistics compare two or more curves but the generalised Wilcoxon statistic attaches more weight to the early observations and is less sensitive to late events which occur when few patients remain in the study. In cases of heavy censoring the test produced by Breslow [10] may be misleading. This heavy censorship, particularly for stage T1, means that the Mantel–Cox or log rank test is preferred. All calculations were carried out using the BMDP suite of programmes [11].

Over the years a number of mathematical models have been put forward in an attempt to correlate treatment schedules with biological effectiveness. The current model is the linear quadratic [5] which attempts to correlate treatment schedule parameters with tumour control and acute and late reactions in normal tissues. In this presentation we have carried out linear quadratic analysis on the results obtained. The linear quadratic analysis is only carried out on patients with a disease-free interval of 5 years or more or on those with evidence of local recurrence. If a patient is followed up for a period of 5 years with no local recurrence then we assumed that local control has been effected. Only patients followed up for at least 5 years are examined in this part of the study. Statistical details are discussed in Appendices 1 and 2.

All patients in this study have been staged retrospectively using UICC (1987) criteria [12].

RESULTS

Only the data for patients treated between 1968 and 1977 are used in Figs 1–3 and Tables 1 and 2. The local control rates achieved for patients with stage T1N0M0 disease treated by the six schedules listed in Table 1 are shown in Fig. 1. From Table 2 and Fig. 1 local control is reduced by 10–15% for T1 as treatment time is increased from 35 days and the treatment fraction size is also reduced. There was a similar reduction for T2 tumours as seen in Table 2 and Fig. 2 and T3/T4 tumours in Table 2 and Fig. 3. The decrease in local control of 25–40% corresponding to at least a 7-day extension in the treatment time is observed for all T categories. Although there are marked differences in the control rates achieved in different stages by different regimes there is only a statistically significant difference in the curves shown in Fig. 1 (Breslow test statistic = 9.1, $P = 0.11$; Mantel–Cox test statistic = 11.1, $P = 0.05$; 5 degrees of freedom).

Where the patient develops a recurrence he or she was referred for laryngectomy if considered fit for surgery—the results showed that 45–59% of those in each stage who were followed up for at least 5 years and who experienced local recurrence subsequently had surgery. Unfortunately 31–38% of all those referred for surgery subsequently died of carcinoma of the larynx. If non-cancer deaths are excluded radiotherapy and salvage surgery gives rise to a 93% overall 5-year survival for T1 N0 M0 lesions, a 71% overall 5-year survival for T2 N0 M0 tumours and a 63% overall 5-year survival for those with T3 and T4 N0 M0 tumours. Most deaths were from non-cancer causes, the most common being myocardial infarction, and the vast majority were tumour free at the time of death.

The morbidity associated with radiotherapy was poorly recorded. There were 3 cases of necrosis among the 956 cases reviewed but 204 patients had no morbidity recorded. The total necrosis rate therefore is 0.4%. The quality of voice was also poorly documented and there was no attempt to quantify it; hence it is impossible to make any comment. Recordings regarding the presence or absence of oedema following irradiation were also poor and were only present in 60% of cases analysed. Post-radiation oedema—protracted acute was noted in 30% of cases, there wasn't any in 30% of cases and there was no record in 40%. The percentage varies from schedule to schedule. However, when we allow for the numbers in each group and the completeness of data in each group there would appear to be no real difference in the incidence of post-radiation oedema produced by the various treatment schedules. Persistence of oedema does not predispose to an increased incidence of recurrent tumour.

Over the past 30 years a number of mathematical models have been evolved in an attempt to compare different radiation treatment schedules and to quantify their effect both in achieving tumour control and in producing morbidity—acute and chronic [1, 3, 4]. In an attempt to determine which of the three factors—total dose, time or number of fractions—were important in achieving tumour control a linear quadratic analysis of the data was carried out. Details are presented in the Appendices.

Linear quadratic analysis

The analysis assumes a linear quadratic dependence of log cell survival of dose (for each fractional dose) and exponential proliferation of surviving cells. The final surviving fraction of cells after N treatments, each of dose d, extending over total time T is then given by

$$\ln(S) = -N(\alpha d + \beta d^2) + \lambda T ,$$

where α and β are the parameters of the linear-quadratic survival curve and λ is the specific growth rate of repopulating tumour cells. This can also be written

$$\ln(S) = -D(\alpha + \beta d) + \lambda T ,$$

where $D = N d$ is the total given dose. Therefore the biological expectation is that treatment outcome [closely related to $\ln(S)$] should be governed by an equation with a term in D, a term in Dd and a term in T. Conceptually, the problem of fitting the clinical data consists of estimating the numerical parameters of these three terms, and in asking how well the relevant model then performs as a predictor of clinical outcome. In the first instance we will attempt to see how well the model performs as a predictor of clinical outcome before moving on to consider the estimation of the parameters α and β.

In practice, it is convenient to rearrange the algebra for the ease of statistical analysis. Following Maciejewski *et al.* [21] we introduce the 'biologically effective dose', *Deff*, for a given treatment schedule as that total dose which, if given as 2 Gy fractions and in the same overall time as the actual schedule would have the same biological effect as the actual schedule. By equating the $\ln(S)$ values for an actual schedule, and an equivalent schedule comprised of 2 Gy fractions, we obtain

$$Deff = D(\alpha/\beta + d)(\alpha/\beta + 2)^{-1} ,$$

or

$$D(\alpha + \beta d) = \beta\, Deff(\alpha/\beta + 2)$$
$$= Deff(\alpha + 2\beta)\ .$$

Substituting for $\ln(S)$ we have that

$$\ln(S) = -(\alpha + 2\beta)Deff + \lambda T$$
$$= -\gamma_1 Deff + \gamma_2 T$$

where $\gamma_1 = \alpha + 2\beta$ and $\gamma_2 = \lambda$. Therefore

$$S = \exp\{-\gamma_1 Deff + \gamma_2 T\}\ .$$

Now, on the statistical theory of cell survival, S gives the *average* surviving fraction following treatment, the actual surviving fraction in any one treatment being distributed in accordance with a Poisson distribution. Therefore the average number of cells remaining after treatment is SM_0, where there were M_0 cells initially. Local control is said to occur if the patient is disease free for at least 5 years. This is taken to imply that there are no cells remaining after treatment. Using a standard Poisson assumption for the distribution of the number of cells remaining the probability of local control, Pc, is given by

$$Pc = \exp\{-SM_0\}.$$

After rearrangement (details in Appendix 1) this reduces to

$$\ln[-\ln(Pc)] = \gamma_0 - \gamma_1 Deff + \gamma_2 T\ .$$

The parameters γ_1 and γ_2 measure the effects of the two treatment factors. In the formulation used here, γ_0 is a function of the probability of local control for a patient who receives 60 Gy at 2 Gy per fraction over 35 days (see Appendix 1).

In stage T1, the standard error of the coefficient of *Deff*, γ_1, is large compared to the estimate and the 95% confidence interval is wide (−0.182, 0.062) and spans zero (Table 3). Consequently the results suggest that *Deff* in the range examined (52–70 Gy) has virtually no effect on tumour control, Fig. 4(a). This is most unexpected in view of the results presented in Table 2 and Fig. 1 and is contrary to radiobiological theory.

Further investigation revealed that this unexpected result for T1 tumours could be explained in terms of the use of a beam directed shell. The parameter estimates are presented separately for patients who were treated wearing a beam directed shell and for those who were treated without a shell (Table 3 and Fig. 4b, c). These show that the use of a shell is beneficial in the case of T1 tumours as there is clear evidence that higher values of *Deff* are associated with increased values of *Pc* among patients with a beam directed shell, Fig. 4(b). These are the anticipated results. The predicted probabilities of a cure, *Pc*, based on the model with α/β = 10 Gy, are presented graphically in Figs 4 and 5 for stage T1. The results were substantially the same for the other values of the ratio α/β used and graphs are not presented here.

While the beam directed shell has a big effect on the relationship of *Deff* to *Pc* there was no significant difference between the values of γ_2 with and without the use of a beam directed shell and so the combined estimates are used in the calculation of the doubling time below. The treatment time is the more important variable and the 95% confidence interval for γ_2 for all T1 tumours and α/β = 10 Gy is (0.052, 0.166). As time increases the probability of a cure decreases (Fig. 5). The tumour doubling time is given by $\ln(2)/\gamma_2$ and for stage T1 is estimated as 6.3 days with an approximate standard error of 1.7 days. A 95% confidence range for this value is (2.9, 9.7) days.

For stages T2 and T3/T4 there were some areas of difference which are worthy of comment. The estimated coefficients were slightly more sensitive to changes in the values of α/β used. There was no evidence of a relationship between treatment time and the probability of a cure in stage T2 (Fig. 6) and with α/β = 10 Gy the doubling time is estimated as 40 days with a standard error of 55 days, yielding a 95% confidence interval of (0, 148) days, which clearly shows the imprecision in this

Table 3. (a) Parameter estimates for model 1. The standard errors of the estimates are in parenthesis

α/β(Gy)	γ_0	γ_1	γ_2
Stage T1			
5	−1.79(0.254)	−0.075(0.047)	0.117(0.030)
10	−1.66(0.230)	−0.060(0.062)	0.109(0.029)
15	−1.62(0.226)	−0.038(0.065)	0.108(0.029)
Stage T2			
5	−0.377(0.177)	+0.031(0.039)	0.009(0.022)
10	−0.446(0.178)	+0.075(0.046)	0.017(0.023)
15	−0.513(0.188)	+0.090(0.047)	0.022(0.023)
Stage T3/T4			
5	−0.078(0.276)	+0.132(0.080)	0.043(0.025)
10	−0.243(0.270)	+0.165(0.087)	0.052(0.025)
15	−0.327(0.278)	+0.164(0.085)	0.056(0.026)

(b) Parameter estimates for model 1 separately for those treated with a beam directed shell and those treated without. The standard errors of the estimates are in parenthesis.

α/β(Gy)	γ_0	γ_1	γ_2
Stage T1			
Beam directed shell			
5	−1.39(0.368)	0.119(0.110)	0.070(0.052)
10	−1.59(0.320)	0.206(0.135)	0.088(0.050)
15	−1.74(0.343)	0.212(0.132)	0.102(0.051)
No beam directed shell			
5	−1.88(0.369)	−0.112(0.054)	0.129(0.044)
10	−1.72(0.343)	−0.115(0.066)	0.116(0.042)
15	−1.65(0.335)	−0.102(0.072)	0.113(0.041)
Stage T2			
Beam directed shell			
5	−0.210(0.220)	0.122(0.060)	0.011(0.029)
10	−0.408(0.219)	0.172(0.074)	0.027(0.030)
15	−0.526(0.234)	0.181(0.072)	0.034(0.030)
No beam directed shell			
5	−0.601(0.345)	−0.054(0.046)	0.015(0.041)
10	−0.524(0.332)	−0.017(0.060)	0.015(0.041)
15	−0.546(0.342)	0.011(0.065)	0.018(0.041)
Stage T3/T4			
Beam directed shell			
5	0.172(0.326)	0.064(0.081)	0.033(0.028)
10	0.070(0.313)	0.062(0.092)	0.037(0.028)
15	0.038(0.322)	0.052(0.092)	0.039(0.028)
No beam directed shell			
5	−0.575(0.821)	0.425(0.239)	0.114(0.118)
10	−1.233(0.997)	0.589(0.337)	0.192(0.151)
15	−1.538(1.057)	0.588(0.323)	0.225(0.156)

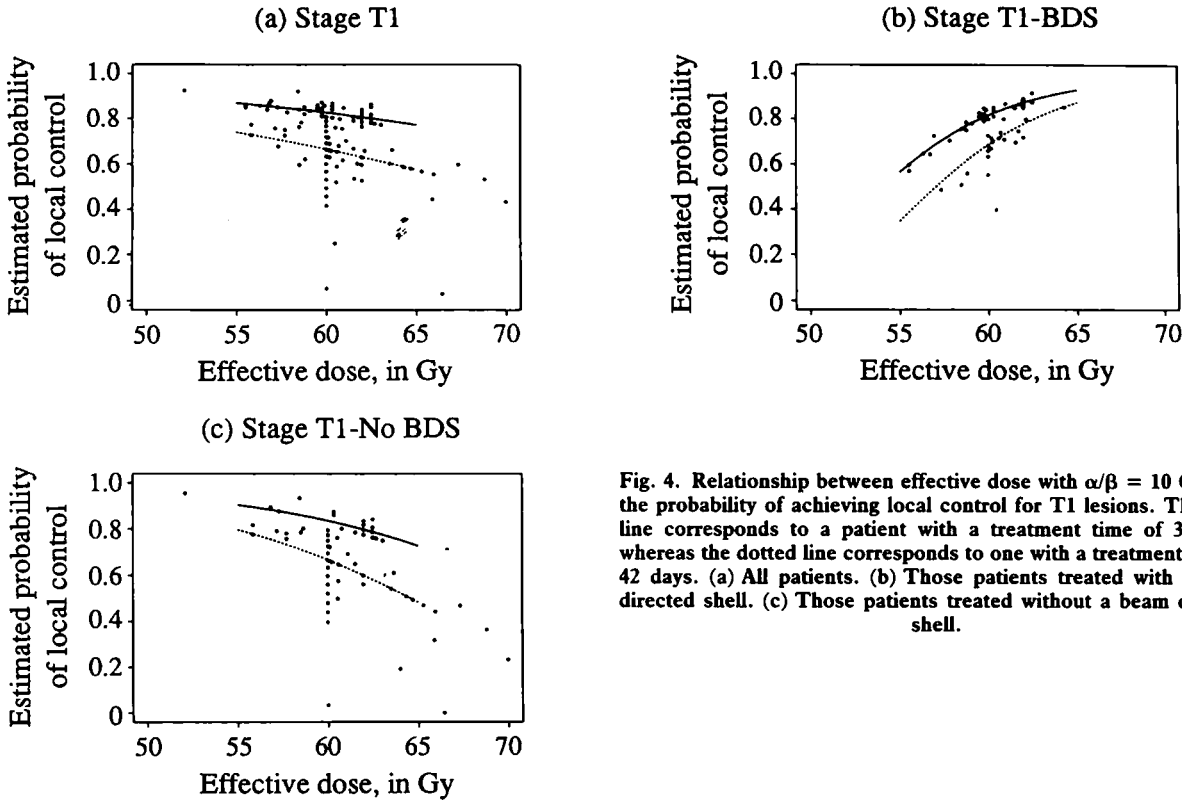

Fig. 4. Relationship between effective dose with α/β = 10 Gy, and the probability of achieving local control for T1 lesions. The solid line corresponds to a patient with a treatment time of 35 days, whereas the dotted line corresponds to one with a treatment time of 42 days. (a) All patients. (b) Those patients treated with a beam directed shell. (c) Those patients treated without a beam directed shell.

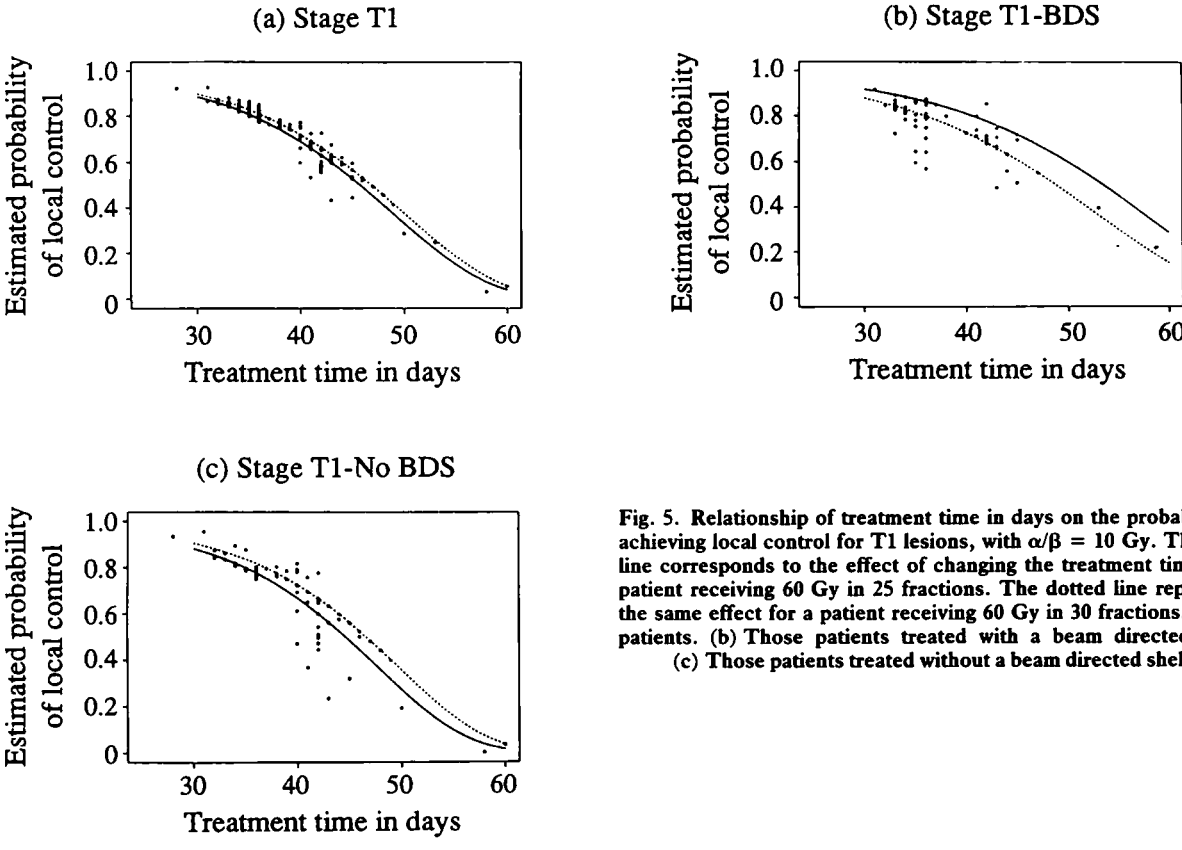

Fig. 5. Relationship of treatment time in days on the probability of achieving local control for T1 lesions, with α/β = 10 Gy. The solid line corresponds to the effect of changing the treatment time for a patient receiving 60 Gy in 25 fractions. The dotted line represents the same effect for a patient receiving 60 Gy in 30 fractions. (a) All patients. (b) Those patients treated with a beam directed shell. (c) Those patients treated without a beam directed shell.

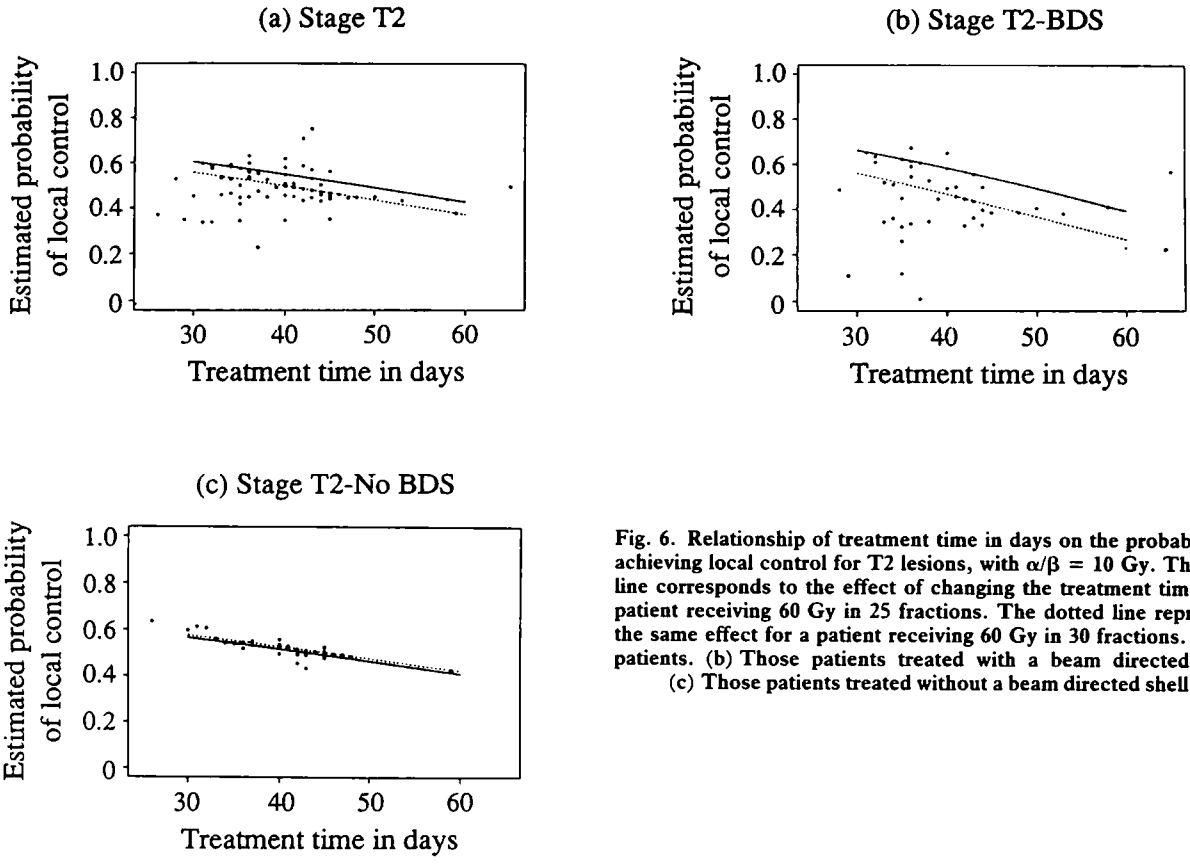

Fig. 6. Relationship of treatment time in days on the probability of achieving local control for T2 lesions, with α/β = 10 Gy. The solid line corresponds to the effect of changing the treatment time for a patient receiving 60 Gy in 25 fractions. The dotted line represents the same effect for a patient receiving 60 Gy in 30 fractions. (a) All patients. (b) Those patients treated with a beam directed shell. (c) Those patients treated without a beam directed shell.

estimate. There was an indication that the probability of a cure increased as *Deff* increased, (Fig. 7) especially among those with a beam directed shell, Fig. 7(b). For stage T3/T4 both *Deff* and treatment time are important (Figs 8 and 9), and the doubling time is estimated as 13 days with an approximate standard error of 6.4 days (95% confidence interval 0.5, 25.5 days) when α/β = 10 Gy. As treatment time increased the probability of local control decreased and as *Deff* increased so too did the local control probability. In this stage though, there was a steeper relationship between *Deff* and *Pc* for those not receiving a beam directed shell in contrast to the results for the other two stages.

There is a wide scatter of points in Figs 4–9. Each dot represents the estimated probability of local control for a single patient treated together with his or her biologically effective dose or treatment time. The scatter is a result of patients having slightly different doses and slightly different times and although the scatter appears to be diffuse it is similar to that shown by Maciejewski *et al.* [20–22].

One of the drawbacks of the above approach is that the ratio α/β has to be known. If the equation

$$S = \exp\{-N(\alpha d + \beta d^2) + \lambda T\}$$

is used for the surviving fraction then after some algebra (details in Appendix 2):

$$\ln[-\ln(Pc)] = \mu - \alpha D - \beta D d + \lambda T .$$

In view of the above discussion on the effects of the beam directed shell this model was only fitted to the data on patients who had a beam directed shell fitted. The results of fitting this model to patients on all three stages are presented in Table 4.

The main findings are consistent with the effective dose analysis in that estimated effects of the treatment time (λ) are similar to the estimates for γ_2 for patients using a beam directed shell in Table 3. The interpretation of the parameters are the same in all three stages: the signs of the estimates of α and β are both positive, as required by the model, indicating that the probability of local control (*Pc*) increases with increasing dose; λ has a positive sign indicating that longer treatment times are associated with poorer local control.

This analysis allows the α/β ratio to be estimated for each stage. These estimates are also presented in Table 4 along with the standard errors and 95% confidence intervals. In view of the relatively poor precision in the estimation of α and β, Table 4, the estimation of the ratio is not precise. For stage T1 the ratio is 13.8 Gy, for T2 it is 14.6 Gy and for T3/T4 it is 1.9 Gy. The estimate for stage T3/T4 is lower than for stages T1 and T2 but there is considerable overlap in the confidence intervals. As the use of a beam directed shell had little effect upon stage T3/T4 patients it is reasonable to combine all patients in this stage and if this is done then the estimate of the α/β ratio is 9.7 Gy which is more in line with the other stages. The reason that the ratio is not estimated precisely is that the standard errors of α and β are both large.

DISCUSSION

Radiotherapy is the treatment of choice for early-T1N0M0 and T2N0M0 laryngeal lesions. Finzi and Harmer first demonstrated in 1928 [13] that radium applied by a fenestration operation to the larynx could cure early tumours with minimal morbidity. Over the past two decades there has been extensive study into the relative values of different dose-fraction-time schedules [14–18, 20] and more recently hyperfractionated

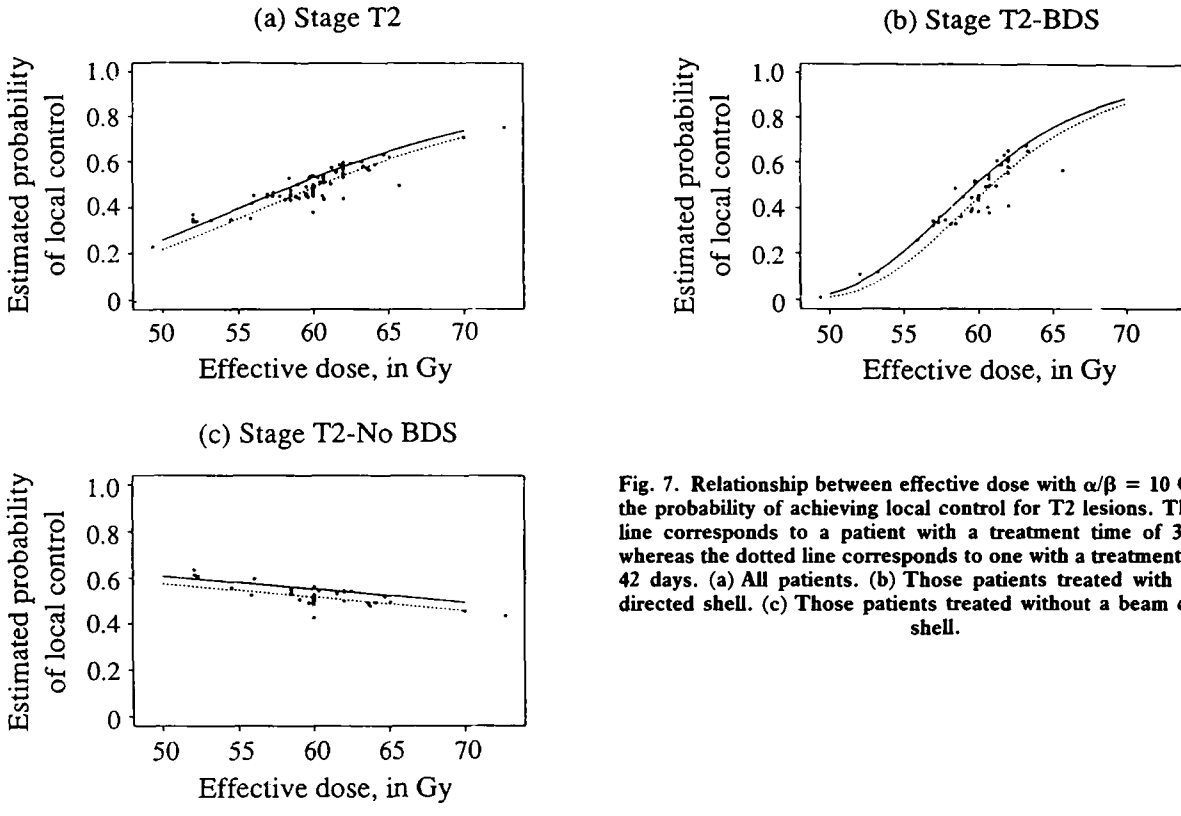

Fig. 7. Relationship between effective dose with α/β = 10 Gy, and the probability of achieving local control for T2 lesions. The solid line corresponds to a patient with a treatment time of 35 days, whereas the dotted line corresponds to one with a treatment time of 42 days. (a) All patients. (b) Those patients treated with a beam directed shell. (c) Those patients treated without a beam directed shell.

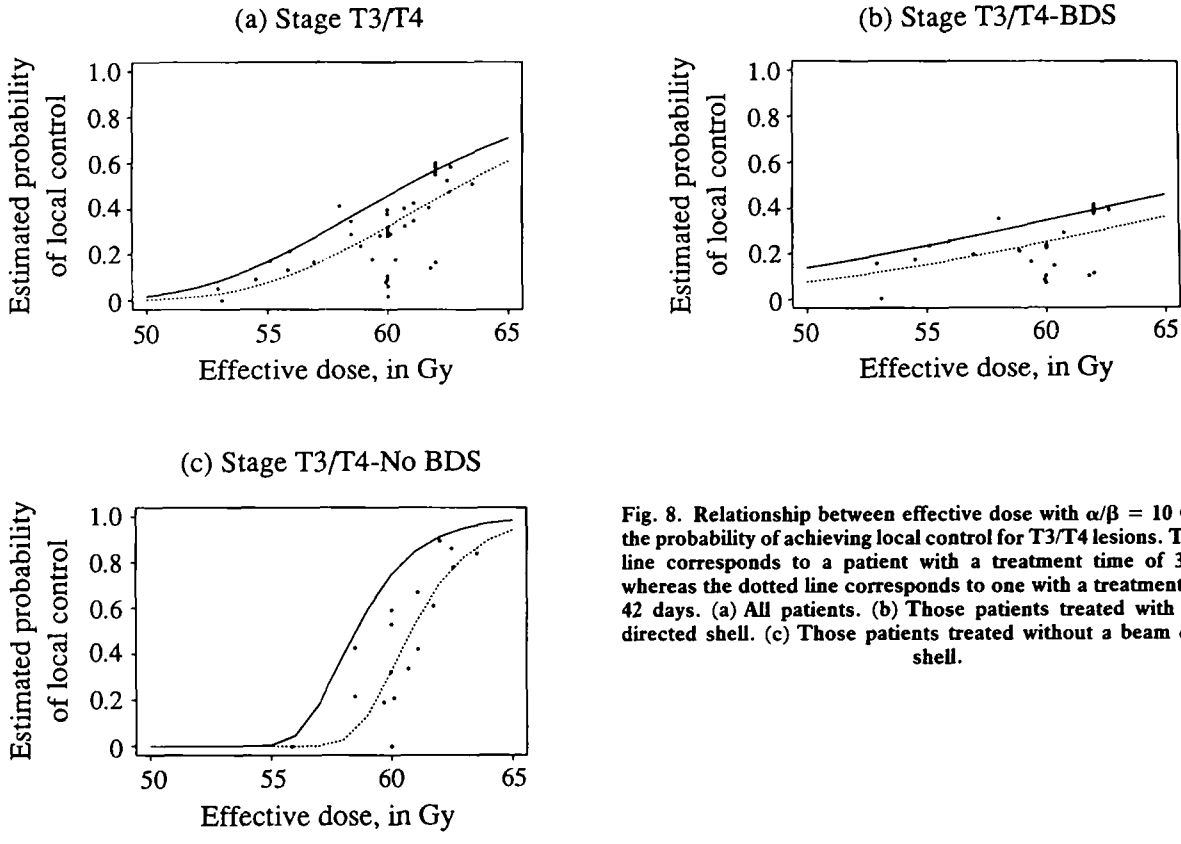

Fig. 8. Relationship between effective dose with α/β = 10 Gy, and the probability of achieving local control for T3/T4 lesions. The solid line corresponds to a patient with a treatment time of 35 days, whereas the dotted line corresponds to one with a treatment time of 42 days. (a) All patients. (b) Those patients treated with a beam directed shell. (c) Those patients treated without a beam directed shell.

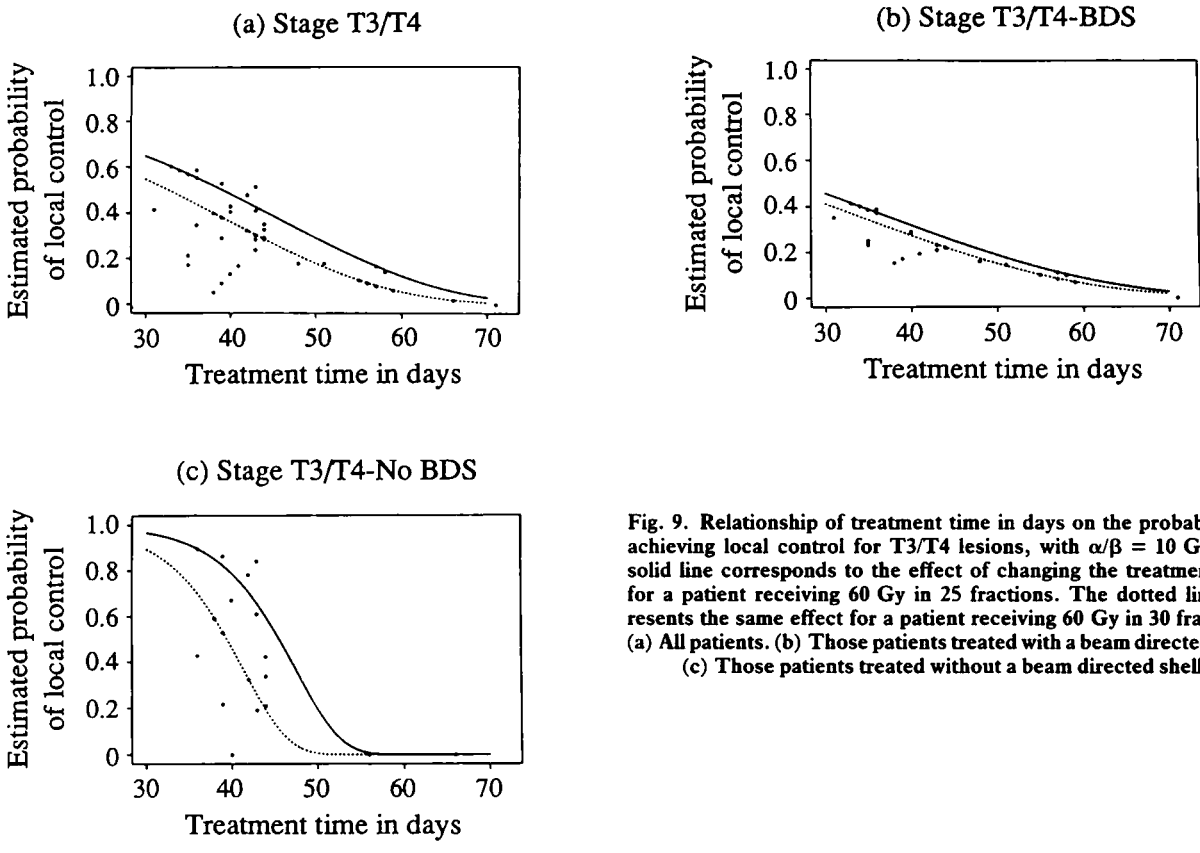

Fig. 9. Relationship of treatment time in days on the probability of achieving local control for T3/T4 lesions, with α/β = 10 Gy. The solid line corresponds to the effect of changing the treatment time for a patient receiving 60 Gy in 25 fractions. The dotted line represents the same effect for a patient receiving 60 Gy in 30 fractions. (a) All patients. (b) Those patients treated with a beam directed shell. (c) Those patients treated without a beam directed shell.

Table 4. Parameter estimates from model 2. The standard errors of the estimates are in parentheses. Only patients with a beam directed shell are included in this analysis

Stage	μ	$\alpha(Gy^{-1})$	$\beta(Gy^{-2})$	$\lambda(day^{-1})$
T1	−2.044(0.451)	0.187(0.117)	0.014(0.015)	0.099(0.057)
T2	−0.781(0.290)	0.159(0.064)	0.011(0.010)	0.034(0.032)
T3/T4	−0.004(0.377)	0.023(0.085)	0.012(0.015)	0.029(0.031)

	α/β(Gy)	Standard error	95% CI 2-tailed	95% CI 1-tailed
T1	13.8	12.9	−12.0,39.6	0,35.0
T2	14.6	12.9	−11.3,40.5	0,35.8
T3/T4	1.9	7.4	−12.9,16.7	0,14.1

CI = confidence interval.

schedules [23, 26, 28] with regard to resulting cure rates, local tumour control, and morbidity.

The results shown in Fig. 1 and Table 2 show a significant difference in local control rates achieved when T1 tumours were treated by the six schedules studied. The control rate achieved with the 60–30–42 schedule—70%—is lower than is expected from other literature reports [7, 14, 17]. Allowing for the small numbers treated—50 patients—the 95% confidence interval is from 57 to 83% which is within the lower limits of the range of published control rates (80–95%). Further analysis of the patients in this group revealed that only 44% had a beam directed shell prepared prior to their treatment. This compares unfavourably with the 81% of the 58 patients on the 60–25–35 schedule who had a shell prepared. The poor tumour control achieved by the 60–30–42 schedule may, in part, be due to geographic misses [6] resulting from the failure to prepare a beam directed shell to immobilise the patient and accurately localise the small treatment fields used to treat these lesions. A consideration of the results in Figs 1–3 and Table 2 suggests that the schedule 60–25–35 gives the best tumour control.

When linear quadratic analysis was carried out on the data for all T1N0M0 tumours the results, which suggested that there was no change in tumour control over the effective dose range of 52–64 Gy (Fig. 4a), were most surprising in view of the results in Fig. 1. This is contrary to the findings for T2N0M0 (Fig. 7a) and T3/T4N0M0 (Fig. 8a) where tumour control improves as effective dose increases. If the patients with T1N0M0 tumours are subdivided into those treated with a beam directed shell, Fig. 4(b), and those without, Fig. 4(c), then this inconsistency can be explained as those treated with a beam directed shell show an association between increasing effective dose and tumour control. Similarly for those with T2N0M0 tumours (Fig. 7b). These results emphasise the importance of a beam directed shell in the treatment of tumours using small fields. In this situation geographic miss is an important cause of failure to achieve tumour control. T3 and T4 lesions are treated with larger fields than T1 and T2 tumours and this may explain why a beam directed shell (Fig. 8b,c) is not so important in achieving tumour control in T3/T4 tumours.

Examination of the association between local control rate and overall treatment time in days (Figs 5, 6, 9) shows a definite relationship which is most obvious for T1 lesions. The shorter the treatment time the better the tumour control. This is in keeping with findings by other groups [20, 21, 26]. Certainly the introduction of gaps into the treatment schedule 60–30–49+ reduces the chances of achieving tumour control (Table 2). This has also been noted by other workers [20, 27] and is not simply

due to the fact that patients were treated without the preparation of a beam directed shell.

The hyperfractionated schedules adopted by Wang and coworkers [28, 29] and by the EORTC Head and Neck Group [30] have a gap in treatment to allow the acute reactions to subside to tolerable levels. The patients could not complete the treatment otherwise. While the overall treatment time for these schedules—40 days—is still less than that of the corresponding conventional schedules—50 days—the gap allows tumour repopulation to occur and some of the advantage gained by adopting a hyperfractionated schedule will be lost. The continuous hyperfractionated accelerated schedule (CHART) adopted by Dische *et al.* [23] which is completed over 13 days without a break, in keeping with the observations above, may well prove to be more efficacious than the other schedules.

Accelerated schedules have been introduced to improve tumour control in lesions where the tumour cells have short potential doubling times. Recent *in vivo* experiments involving BUDR [31] estimate that the potental doubling time, T_{pot}, of squamous carcinoma of the larynx is approximately 4.1 days. The T_{pot} value estimated from cell kinetic data has been taken as a measure of the actual doubling time of the tumour cells repopulating during therapy. From the linear quadratic analysis of the data presented the apparent doubling time for T1 lesions is 6.3 days (95% confidence interval of 2.9–9.7 days); for T2 lesions is 40 days (0–148 days) and for T3/T4 is 13 days (0.5–25.5 days). There is a marked variation, especially for T2 lesions, but the results support the findings that the actual doubling time is short and hence that repopulation is an important factor to consider when designing new treatment schedules.

α/β ratios are useful in quantifying the effects on acute and late responding tissues. The morbidity data associated with the study is relatively incomplete and for that reason we have been unable to estimate α/β ratios for the late phase [32]. Working on the premise that a beam directed shell is important for the treatment of T1 and T2 lesions but not T3/T4, where field size is larger, the α/β ratio for T1 lesions is 13.8 Gy, that for T2 is 14.6 Gy and for T3/T4 is 9.7 Gy. These values are in close association allowing for the poor precision of the estimation. The graphs show that there is a wide scatter about the lines drawn, however, this is in keeping with results of other workers who have had to cope with this difficulty when dealing with clinical data [20–22, 32]. The estimates of α/β support the calculations of Thames *et al.* [26] which estimate an α/β ratio of greater than 9.9 Gy for T *in situ* and T1 glottic tumours, for T1. They are in keeping with estimates for squamous carcinomas arising at other sites [26].

The patient's quality of life during and after treatment is important. Efforts have been made for a number of years to minimise morbidity. It was for this reason that a gap was introduced into the middle of the treatment to give rise to the 60–30–49+ schedule. Any advantage achieved through reducing mucositis, laryngeal oedema, etc. is completely negated by the loss in tumour control. An objective assessment of the incomplete morbidity data would suggest that there is no difference in the severity of the morbidity—acute and chronic—associated with the six schedules evaluated. It would appear that the persistence of oedema following a course of XRT while a suspicious occurrence is not indicative of persistent or recurrent tumour.

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APPENDIX 1

In this appendix statistical details for the linear quadratic analysis where the α/β ratio is specified are presented. In common with standard practice we consider each patient with a continuous period of 5 or more years free of the disease as having local control. If the surviving fraction of cell is denoted S, and there are M_0 clonogenic cells initially then at the end of the treatment there will be SM_0 clonogenic cells remaining, on average. The number of cells remaining is assumed to follow a Poisson distribution with a mean of SM_0. This gives the probability of local control, denoted Pc, as the probability that there are no surviving cells which is given by:

$$Pc = \exp\{-SM_0\} .$$

The surviving fraction is assumed to be based on a linear quadratic dose model with exponential repopulation [21]. If the effective dose is denoted *Deff*, called the normalised total dose by Maciejewski *et al.* [21], and the total treatment time by T then the surviving fraction is (see main text):

$$S = \exp\{-\gamma_1 Deff + \gamma_2 T\} .$$

Substituting in for S in the equation for Pc above yields

$$\begin{aligned} Pc &= \exp\{-M_0\exp\{-\gamma_1 Deff + \gamma_2 T\}\} \\ &= \exp\{-\exp\{\ln(M_0) - \gamma_1 Deff + \gamma_2 T\}\} \\ &= \exp\{-\exp\{\gamma_0 - \gamma_1 Deff + \gamma_2 T\}\} , \end{aligned}$$

where $\gamma_0 = \exp\{\ln(M_0)\}$. Rearranging this final equation yields

$$\ln(-\ln(Pc)) = \gamma_0 - \gamma_1 Deff + \gamma_2 T .$$

The parameter, γ_2, measures the rate of accelerated repopulation of clonogens and is expected to have a positive sign as longer treatment times give the tumour more time to regenerate during treatment. In fact, $\ln(2)/\gamma_2$ is a valid estimate of the doubling time of the tumour [24]. γ_1 measures the effect of *Deff* on the probability of local control. It should be positive as an increase in the effective dose is associated with an increased local control rate.

For each patient the total treatment time is known and his or her 5-year disease-free status. Once values for *Deff* are known then the parameters of this equation can be estimated. Now

$$Deff = D(\alpha/\beta + d)(\alpha/\beta + 2)^{-1} ,$$

and with appropriate values for the ratio α/β *Deff* can be calculated readily. Typical values for α/β are thought to be in the range 5–15 Gy. We have gone through this range by setting α/β equal to four distinct values 5, 10, and 15 and estimating the unknown parameters γ_0, γ_1, γ_2. The advantage of this approach is that we will be able to investigate any association between α/β and the effect of the variables *Deff* and T.

For a schedule which has 60 Gy over 30 fractions *Deff* = 60 and this value is close to the middle of the distribution of *Deff* over all 336 patients. Similarly 35 days is close to the middle of the distribution of the treatment time. To aid the estimation of the parameters [25], the model used is:

$$\ln(-\ln(Pc)) = \gamma_0 - \gamma_1(Deff - 60) + \gamma_2(T - 35) . \quad (1)$$

This has no effect on the interpretation of either γ_1 or γ_2. The interpretation of γ_0 is now clearer as $\exp\{-\exp\{\gamma_0\}\}$ is the estimated probability of local control for a patient who receives 60 Gy over 35 days.

APPENDIX 2

From the linear quadratic model the surviving fraction can be written

$$S = \exp\{-N(\alpha d + \beta d^2) + \lambda T\} ,$$

where N is the number of fractions, d the dose per fraction and T the treatment time it is possible to estimate α and β directly using the same methods as in Appendix 1.

Now, Pc denotes the probability of local control, i.e. the probability of zero surviving cells. If M_0 denotes the initial number of malignant cells and the Poisson distribution is used then

$$Pc = \exp\{-SM_0\} .$$

On substitution for S this reduces to

$$\begin{aligned} Pc &= \exp\{-M_0\exp\{-N(\alpha d + \beta d^2) + \lambda T\}\} \\ -\ln(Pc) &= M_0\exp\{-N(\alpha d + \beta d^2) + \lambda T\} \\ \ln(-\ln(Pc)) &= \ln(M_0) - N(\alpha d - \beta d^2) + \lambda T \\ &= \mu - \alpha D - \beta D d + \lambda T . \end{aligned} \quad (2)$$

If long treatment times are associated with a low probability of local control then it is expected that the coefficient of T should have a positive sign. Both α and β should have the same sign if valid estimates of the α/β ratio are to be obtained. If large doses are associated with a high local control rate then positive signs are required by the model.

Again $D = Nd$ is measured in Gy and the variables are centred around their midpoints as in Appendix 1. Thus D is centred on 60 Gy, Dd on 144 Gy^2 and T on 35 days. With this centring $\exp\{-\exp\{\mu\}\}$ represents the probability of local control for a patient on the 60–25–35 schedule.