coagulopathy and a non-steroid-related malaise syndrome [2]. Accordingly, much of the recent work pertaining to suramin has focused on developing an optimal, clinician-friendly dosing schedule that would minimise interpatient variability in plasma suramin concentrations and permit its more widespread clinical use [11, 12]. The response seen in this case of resistant thymoma treated with suramin reiterates the role of this compound as a potential therapeutic alternative in a variety of neoplasms otherwise refractory to conventional treatment modalities.

1. Lewis JE, Wick MR, Scheithauer BW, *et al.* Thymoma. *Cancer* 1987, **60**, 2727–2743.
2. La Rocca RV, Stein CA, Myers CE. Suramin: prototype of a new generation of antitumor compounds. *Cancer Cells* 1990, **2**, 106–115.
3. van Oosterom, De Smedt EA, Denis LJ, *et al.* Suramin for prostatic cancer, a phase I/II study in advanced extensively pretreated disease. *Eur J Cancer* 1990, **26**, 422–427.
4. Coffrey RJ, Leof EB, Shipley GD, Moses HL. Suramin inhibition of growth factor receptor binding and mitogenicity in AKR-2B cells. *J Cell Physiol* 1987, **132**, 143–148.
5. Spigelman Z, Dowers S, Kennedy D, *et al.* Antiproliferative effects of suramin on lymphoid cells. *Cancer Res* 1987, **47**, 4694–4698.
6. Gagliardi A, Haad H, Collins C. Inhibition of angiogenesis by suramin. *Cancer Res* 1992, **52**, 5073–5075.
7. Ruco LP, Pisacane A, Pomponi D, *et al.* Macrophages and interdigitating reticulum cells in normal human thymus and thymomas: immunoreactivity for interleukin-1 alpha, interleukin-1 beta and tumor necrosis factor alpha. *Histopathology* 1990, **17**, 291–299.
8. Lowenthal JW, Cerottini JC, McDonald HR. Interleukin 1-dependent induction of both interleukin 2 secretion and interleukin 2 receptor expression by thymoma cells. *J Immunol*, 1986, **137**, 1226–1231.
9. Mills GB, Zhang N, May C, *et al.* Suramin prevents binding of interleukin 2 to its cell surface receptor: a possible mechanism for immunosuppression. *Cancer Res* 1990, **50**, 3936–3942.
10. La Rocca RV, Cooper MR, Stein CA, *et al.* A phase 2 study of suramin in the treatment of progressive refractory follicular lymphomas. *Ann Oncol* 1992, **3**, 571–573.
11. Scher HI, Jodrell DI, Iverson JM, *et al.* Use of adaptive control with feedback to individualize suramin dosing. *Cancer Res* 1992, **52**, 64–70.
12. Cooper MR, Liebermann R, La Rocca RV, *et al.* Adaptive control with feedback strategies for suramin dosing. *Clin Pharmacol Ther* 1992, **52**, 11–23.

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Effect of Overall Time and Dose on the Response of Glottic Carcinoma of the Larynx to Radiotherapy

J. F. Fowler and R. Chappell

A MAJOR ANALYSIS of 303 patients with glottic carcinoma treated in Glasgow by radiotherapy was published recently in the *European Journal of Cancer* [1], and presented statistical coefficients for the effects of total dose and overall time. The purpose of the present communication is to translate these into changes in local control in terms of per cent per gray (increase with dose) or per cent per day (decrease with overall time).

The statistical model used for the analysis was the standard Poisson distribution of surviving cells and the linear quadratic dependence of cell survival on dose:

$$\log[-\log(P)] = C + A \times D + B \times d \times D - G \times T \quad (1)$$

Here P is the probability of local control at 5 years, C is a constant (different for different T-stages), A and B are the linear quadratic coefficients of dose and dose-squared, respectively, D is total dose, d is dose per fraction, T is overall time and G is the rate of decrease of local control (LC) with increasing overall time, after taking account of dose variations [2–9].

The factor $A + Bd$ is proportional to the increase of LC with total dose (for constant T and d) and G/A is the "time–dose trade-off", which is the rate at which total dose should be increased, on the average, to compensate for the deleterious effect of prolongation. However, these coefficients, as listed in the tables of [1], are in the statistical units of "log [−log(P)] per gray" (for A and Bd) or "log [−log(P)] per day" (for G). The coefficients can each be converted to percentages (change in local control per Gy or per day) through the usual procedure which we have used before [1, 10, 11]. Table 1 lists the approximate multiplying factors for use with either the logit [4–7] or the double-log formula [1, 8]; the latter is used here. The multiplying factors are here applied to the coefficient estimates only, although they may also be used to convert the standard errors and confidence intervals.

Although there are some discrepancies between the numbers of patients in their Table 1 and the text of [1], and details of the "heavy censorship" are not given, their conclusions do not differ grossly from those of other publications [4–9]. We have, therefore, taken the coefficients as presented by the authors in Tables 3 and 4 of [1] as our starting point.

Our Table 2 shows the application of the multipliers in our Table 1 to the coefficients estimated in the analysis under discussion. From A and B the apparent slope of the dose–response curve for tumour control can be calculated, after allowing for differences in overall time. The linearised factors $A + Bd$ give the percentage increase of local control per Gy. Here the median value of d is 2.5 Gy, which gives the per cent per Gy increases for the three T-stages as 5.54, 6.54 and 1.83, respectively. To convert these to the commonly used slope parameter "gamma-50" (per cent increase in LC for 1% increase

Table 1. Multipliers of coefficients to convert from parameter estimate to percentage change [2, 10, 11]

Probability of event	Logit multiplier*	Double log multiplier†
0.1	0.09	0.23
0.3	0.21	0.36
0.5	0.25	0.35
0.7	0.21	0.25
0.9	0.09	0.095

*Logit (p) = ln [p/(1−p)]. †See equation (1).

Correspondence to J.F. Fowler at the Dept. of Human Oncology.
J.F. Fowler is at the Department of Human Oncology and Medical Physics, K4/336, and R. Chappell is at the Department of Biostatistics, K6/430, University of Wisconsin-Madison, 600 Highland Avenue, Madison, Wisconsin 53792, U.S.A.
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in total dose at the steepest part, near 37% LC here), we have to multiply by $D/100$ where $D = 60$ Gy here.

The resulting gamma-50 values are 3.3, 3.9 and 1.1 for T1, T2 and T3T4 tumours, respectively, as shown in our Table 3. It is not unusual for the larger tumours, with their obvious heterogeneity, to show a shallower slope than the early or intermediate stages, which are here steeper than the median of the slopes reviewed by Thames and colleagues [12], but within the same range. The average slope for all stages, taking account of the stage distribution in Table 1 of [1] is 3.1, which is notably steep when the possible sources of heterogeneity are considered.

The second row of our Table 3 shows the calculated loss of local control per week of prolongation, after taking account of total dose; that is, if total dose remained constant. The values fall within the range of 3 to 25% as reviewed by Fowler and Lindstrom for head and neck cancers [5]. Although they differ for the three T-stages, the differences are not statistically significant. No differences were seen for the different stages in a previous anlaysis of tonsillar tumours [4]. The average loss is about 12% per week, close to the median value found in [5].

It should be noted that if the total dose is increased in step with prolongation, which is often but not always the case, the loss of local control would, of course, be minimised by the larger total dose. This leads us to the concept of the "dose–time trade-off".

The "dose–time trade-off" is shown at the bottom of our Table 3. This has become a popular way of expressing time factors, because it involves the ratio of two coefficients so that the linearisation factors deployed in our Tables 1 and 2 cancel out. It is not true, however, that the inhomogeneities leading to shallow slopes for LC versus dose are the same factors that could lead to shallowness for LC versus overall time, so the cancelling out of the linearisation factors is rather an illusory convenience. For this reason, the practical version of the time–dose trade-off is to be preferred to the simple ratio of coefficients. This simple ratio G/A would, in the absence (or identity) of heterogeneity, give us γ/α from the linear-quadratic equation [3], denoted λ/α in Table 4 of [1].

The practical dose–time trade-off is simply γ/α or G/A multiplied by the relative effectiveness (RE) $= 1 + d/(\alpha/\beta)$. Less dose will be required with finite doses per fraction than with the infinitely small fractions implied if the ratio γ/α is quoted. The average value found here for all stages is 0.56 Gy/day, close to those found for other tumours [4–9] which range from 0.4 to 1 Gy/day [8].

The confidence limits on all the above values are large, as shown in detail in the original analysis [1]. As the authors point out, this is a common problem of clinical data analysis. However, when a large number of different data sets yield estimated values which cluster around certain values—as here for α/β and γ/α [4–9]—our confidence in these values becomes somewhat better than the wide intervals which apply to any one set.

Table 2. Approximate percentage changes in 5-year local control per Gy, per Gy² or per day, converted from parameter estimates (Table 4, [1])

Parameter	Approx. p 5-year LC	Multiplier	Parameter estimate	Per cent change in 5-year LC
A (Gy^{-1})				% per Gy
T1	0.7	0.25	0.187	4.7
T2	0.5	0.35	0.159	5.6
T3T4	0.3	0.36	0.023	0.8
B (Gy^{-2})				% per Gy^2
T1	0.7	0.25	0.014	0.35
T2	0.5	0.35	0.011	0.39
T3T4	0.3	0.36	0.012	0.43
G (day^{-1})				% per day
T1	0.7	0.25	0.099	2.5
T2	0.5	0.35	0.034	1.2
T3T4	0.3	0.36	0.029	1.0

LC, local control.

Table 3. Factors derived from the linearised coefficients: variation of local control (LC) with total dose, for a fixed overall time; and variation with overall time, for a fixed total dose

Factor	Formula	Response	
Slope of dose–response curve for LC	Linearised $(A+Bd)$ 60/100	% increase LC per 1% dose	
	T1	3.3	
	T2	3.9	
	T3T4	1.1	
	All stages*	3.1	
Rate of loss of LC with prolongation	exp- (7 × linearised G)	% loss LC per week	
	T1	16.1	
	T2	8.1	
	T3T4	6.8	
	All stages*	12.3	
Dose–time trade-off	(G/A)/RE; G/A	Practical Gy/day	Initial slope γ/α (Gy/day)
	T1	0.45	0.53
	T2	0.18	0.21
	T3T4	1.00	1.25
	All stages*	0.46	0.56
	(RE $= 1+d/(A/B)$)		

*Taking account of the proportion of patients in each T-stage from Table 1 of reference [1].

1. Robertson AG, Robertson C, Boyle P, Symonds RP, Wheldon TE. The effect of differing radiotherapeutic schedules on the response of glottic carcinoma of the larynx. *Eur J Cancer* 1993, **29A**, 501–510.
2. Chappell R. Presenting the coefficients of the linear quadratic formula for clinical use. *Int J Radiat Oncol Biol Phys*, in press.
3. Fowler JF. The linear-quadratic formula and progress in fractionated radiotherapy. *Br J Radiol* 1962, **62**, 679–694.
4. Fowler JF, Tanner MA, Bataini JP, Asselain B, Bernier J, Lave C. Further analysis of the time factor in squamous cell carcinoma of the tonsillar region. *Radiother Oncol* 1990, **19**, 237–244.
5. Fowler JF, Lindstrom MJ. Loss of local control with prolongation in radiotherapy. *Int J Radiat Oncol Biol Phys* 1992, **23**, 457–467.
6. Lindstrom MJ, Fowler JF. Re-analysis of the time factor in local control by radiotherapy of T3T4 squamous cell carcinoma of the larynx. *Int J Radiat Oncol Biol Phys* 1991, **21**, 813–817.
7. Rezvani M, Fowler JF, Hopewell JW, Alcock CJ. Sensitivity of human squamous cell carcinoma of the larynx to fractionated radiotherapy. *Br J Radiol* 1993, **66**, 245–255.
8. Slevin NJ, Hendry JH, Roberts SA, Agren-Conqvist A. The effect of increasing the treatment time beyond 3 weeks on the control of T2 and T3 laryngeal cancer using radiotherapy. *Radiother Oncol* 1992, **25**, 251–260.
9. Withers HR, Taylor JMG, Maciejewski B. The hazard of accelerated tumor clonogen repopulation during radiotherapy. *Acta Oncol* 1988, **27**, 131–146.
10. Chappell R, Fowler JF. Steepness of dose-response curve for larynx cancer. *Radiother Oncol*, in press.
11. Chappel R. *Creating a Clinical Staging System Using Logistic Regression*. University of Wisconsin-Madison Department of Biostatistics Technical, Report No. 66.
12. Thames HD, Schultheiss TE, Hendry JH, Tucker SL, Dubray BM, Brock WA. Can modest escalations of dose be detected as increased tumor control? *Int J Radiat Oncol Biol Phys* 1991, **22**, 241–246.

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Magnetic Resonance Signal Alterations of the Brain in Asymptomatic Patients Treated With High-dose Cisplatin for Ovarian Carcinoma

J. M. Pumar, L. Arrojo, C. Seoane, R. Garcia, J. A. Castiñeira and J. Vidal

THE FEATURES of high-dose cisplatin-induced neurotoxicity have been described as transient acute cerebral dysfunction and chronic leucoencephalopathies [1,2].

We incidentally observed the presence of high-signal intensity lesions on T2 weighted images located in periventricular white matter in a patient under cisplatin chemotherapy treatment for ovarian carcinoma. The patient was neurologically asymptomatic.

This finding induced us to perform brain magnetic resonance (MR) on another 19 patients who were also under cisplatin treatment for ovarian carcinoma. All the patients were symptom-free and cisplatin dose was 120 mg/m^2 as a 4-h infusion in each cycle, administered over 3–5 days.

MR examinations were performed on the fifth day of treatment with a 0.2 T unit (Hitachi). Axial and saggital TI (500/30), PD and axial T2 weighted (1900/30–90) sequences were obtained. Intravenous GdTPA was administered in the axial TI sequence.

Of the 20 patients, 10 showed abnormalities of white cerebral matter, presenting as high signal intensity focal lesions on T2 weighted images. The lesions were well defined, with irregular margins, and were located preferentially in periventricular white matter. Intravenous GdTPA showed no signal changes. There was no ventricular dilatation or other cerebral abnormality in any case.

These lesions may be related to multiple foci of non-inflammatory leucoencephalopathy secondary to cisplatin adminstration, microclots or necrotising embolisms of tumoral tissues [3,4], although we were not able to obtain histological correlation.

1. Macdonald DR. Neurologic complications of chemotherapy. *Neurol Clinics* 1991, **9**, 955–967.
2. Van der Hoop RG, Van der Burg MEL, Van Houwelingen JC. Incidence of neuropathy in 395 patients with ovarian cancer with or without cisplatin. *Cancer* 1990, **66**, 1697–1702.
3. Lindeman G, Kefford R, Stuart-Harris R. Cisplatin neurotoxicity. *New Eng J Med* 1990, **323**, 64.
4. Rippe DJ, Edwards MK, Schrodt JF, *et al.* Reversible cerebral lesions associated with tiazofurin usage: MR demonstration. *J Comput Assisted Tomography* 1988, **12**, 1078–1081.

Correspondence to J. M. Pumar.
The authors are at the Radiology Department, Hospital General de Galicia, C/ Galeras s/n 15705, Santiago de Compostela, Spain.
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The Use of Carboplatin in Malignant Germ Cell Tumours

C. Bokemeyer, A. Harstrick and H. -J. Schmoll

CARBOPLATIN HAS been used in trials for patients with good risk germ cell tumours in order to avoid cisplatin-associated treatment toxicity [1]. In a phase II trial recently published in

Correspondence to C. Bokemeyer.
The authors are at the Division of Hematology and Oncology, Hannover University Medical School, Konstanty-Gutschow-Strasse 8, D-30623 Hannover, Germany.
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