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THE HAZARD OF ACCELERATED TUMOR CLONOGEN REPOPULATION DURING RADIOTHERAPY

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Abstract

When analysis of results of radiotherapy for nearly 500 patients with oropharyngeal cancer showed evidence for rapid tumor regrowth during extensions of treatment from about 5 weeks to about 8 weeks, we searched the literature on radiotherapy for head and neck cancer to determine whether it revealed similar evidence of accelerated tumor regrowth. Estimates of doses to achieve local control in 50% of cases (TCD_{50}) were made from published local control rates, and the dependence of these doses on overall treatment duration was evaluated. In parallel, published scattergrams were analyzed to estimate the rate of tumor regrowth over the period of 4–10 weeks from initiation of therapy. Both analyses suggested that, on average, clonogen repopulation in squamous cell carcinomas of the head and neck accelerates only after a lag period of the order of 4±1 weeks after initiation of radiotherapy and that a dose increment of about 0.6 Gy per day is required to compensate for this repopulation. Such a dose increment is consistent with a 4-day clonogen doubling rate, compared with a median of about 60 days in published reports of unperturbed tumor growth rates. The values presented here are average values for a large number of patients: it is necessary, not only to verify the results of these retrospective analyses in prospective studies, but also to develop methods to predict the time of onset and rate of accelerated tumor clonogen repopulation in the individual patient.

Key words: Therapeutic radiology; tumor growth kinetics, adjuvant chemotherapy, head and neck cancer, dose fractionation, isoeffect curves, tumor biology, hypoxic cell sensitizers, logistic regression, repopulation, radiation dose responses for tumors.

A clonogen is a cell capable of indefinite reproduction and capable, therefore, of causing a recurrence: it is to be distinguished from the majority of cells in a tumor which have a limited lifetime.

The purpose of this paper is to analyze the effect of *accelerated* repopulation of tumor clonogens during a course of radiotherapy on the probability of treatment success: it is not addressed to the effect of unperturbed tumor growth on the probability of cure. It is not concerned with that small proportion of rapidly-growing carcinomas, sarcomas and lymphomas which manifest detectable growth during 'workup', or in the early stages of treatment, and which 'escape' when therapy is given at a standard rate. It is concerned with the insidious threat to treatment success from the accelerated growth of tumor clonogens during treatment in that great proportion of tumors which show no evidence of rapid growth at the time treatment is initiated.

By the time human tumors reach a clinically-detectable size, most of them are growing fairly slowly, doubling in volume at rates which vary from patient to patient, but with a median time of about 2 months (9, 62). The kinetic parameters of tumors (cell loss factor, growth fraction, cell cycle time) do not change significantly over one or two doublings of tumor volume. Therefore, the median of 2 months required for a doubling in tumor volume is also the median doubling time for malignant clonogen number. Of course, the malignant clonogens cycle more quickly, e.g. every 2–4 days (62), but their rate of increase is slowed by the loss from the clonogenic pool of a large proportion of the daughter cells through one or more mechanisms (e.g. differentiation, apoptosis, necrosis, exfoliation, invasion into the lymphatic or blood vascular system). If malignant clonogens were to continue growing with an unchanged 2 month median doubling time throughout a 6–8 weeks course of radiotherapy, their growth would not materially affect the chance of cure: for example, if treatment lasted 2 months, the median increment in dose to balance tumor growth would be that

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required to reduce tumor cell survival to one half. From clinical and laboratory (76, 78) data, the halving dose can be estimated to be between 2 and 3 Gy. (See Footnote.) If treatment lasted only 6 weeks, the counterbalancing dose would be about 1.4 to 2.1 Gy. Such a small influence of growth on the dose required for tumor control would be undetectable in a clinical study. Conversely, if there were an easily detected increment in the total dose necessary for a certain rate of tumor control as a function of increasing overall treatment time, or any decrement from shortening it, *accelerated* clonogen growth is the most likely cause, and its rate can be estimated from the magnitude of the change in dose.

A change in the dose for a fixed rate of tumor control with change in treatment duration is, in fact, the only way accelerated repopulation can be detected. Measurements of cell cycle parameters are of no value because, with a logarithmic decrease in cell survival with increase in dose, the majority of cells are dead after only a few treatments. Furthermore, even if clonogenic cells were identifiable from their more numerous nonclonogenic brethren, their rate of increase would be modified by the unpredictable clonogenicity of their offspring. Clinically detectable growth of a tumor during treatment can signal a rapidly growing tumor but lack of detectable growth does not denote a lack of clonogen repopulation. Accelerated repopulation late in treatment involves only a small absolute number of surviving cells and hence their growth does not contribute to a detectable change in tumor volume. (If the effective D_0 for the survival curve for tumor clonogens exposed to a series of 2 Gy fractions was 3.5 Gy (76, 78), and accelerated repopulation by tumor clonogens began after delivery of 20 fractions of 2 Gy, the fraction of clonogens retaining the potential for indefinite growth after a 4-week treatment would be $e^{-40/3.5}$, that is, about 1 in 100000. Thus, if the tumor originally contained 10^8 malignant clonogenic cells, the absolute surviving number would be about 1000 and rapid repopulation by so few cells would not be detectable as a change in volume of the total tumor mass.) Furthermore, the gross tumor mass, being composed mainly of sterilized cells, is most likely to be seen regressing at a time when surviving clonogens are regrowing rapidly, as has been demonstrated in experimental animals (27, 35). Thus, the lack of visible growth of a tumor, or even more misleadingly its continuing regression, may conceal a rapid repopulation response in a previously slowly-growing tumor.

This paper will survey the literature for evidence of changes in dose required for a constant rate of tumor control as a function of differences in overall treatment duration, making adjustments in the total biologically-effective dose, when necessary, to account for variations in size of dose fractions. The analysis is confined to squamous cell carcinomas of the head and neck (5, 7, 8, 12, 15–17, 19–26, 28, 30–32, 34, 37–46, 48, 49, 51, 52, 54–56, 58–61, 64, 65, 67, 71–73, 80).

Footnote. If there were 10^8 tumor clonogens in a 1 cm diameter tumor deposit, and if 64 Gy in 2 Gy fractions resulted in about 50% (specifically 63%) chance of sterilizing the mass, and if it were assumed there were no growth during treatment, the dose (D_{10}) to reduce cell survival by 1 logarithm to 10%, would be 64/8=8 Gy. Since $D_{10}=2.3\times D_0$, the 'effective' D_0 for 2 Gy fractions, i.e. the dose in 2 Gy fractions necessary to reduce survival by e^{-1}, to 37%, would be 8/2.3 Gy=3.5 Gy. The dose required to reduce survival to 50% would be ln (0.5)×3.5 Gy=2.4 Gy. Thus, 2.4 Gy of a 2 Gy per fraction regimen would counteract the effect of 1 doubling in clonogenic cell number. This value is consistent with cell survival curves determined from multifraction experiments in mice (76) and man (4) using 2 Gy per fraction. However, the estimated effective D_0 value would be less than 3.5 Gy if a 1 cm diameter mass were assumed to contain more than 10^8 malignant clonogens, or if a lower dose than 64 Gy in 2 Gy fractions was necessary for 63% chance of cure, or if there were tumor growth during treatment.

Material and Methods

TCD_{50} Analysis. Results which permitted a reasonably accurate assessment of local control rate, dose per fraction, total dose and overall treatment duration were taken from the literature. Approximate median values for total dose, dose per fraction and overall treatment time were used to determine the effect of treatment time on local tumor control for 59 sets of data. A follow-up time of at least 2 years was usually required but in some instances (e.g. 22) results from shorter follow-up were included. Some tumor control rates were determined actuarially and some were absolute rates. Some data were read from figures with the attendant possibility of errors. Groupings of data (e.g. for stage of disease) were those of the various authors, although, in some instances, we sub-grouped data sets from within one publication. When possible, carcinoma of vocal cord was considered separately from supraglottic tumors. To minimize errors in extrapolating doses from the median dose actually used to the dose estimated to control 50% of the tumors (TCD_{50}), a few reports of very high or very low control rates were excluded. However, high (max. 0.86) or low (min. 0.18) rates were accepted from treatment schemes for which alternative data were not plentiful (22, 51, 72). Many papers were excluded because it was impossible to reconstruct treatment parameters from doses expressed after conversion to a single number using the NSD concept (14), or one of its derivatives, TDF (47) or CRE (33). Since it is rare, even in protocol studies, for all patients, even with the same stage of disease, to receive exactly the same dose regimen, some liberty was taken in assigning median doses and treatment times (Table 1, Fig. 1) where treatments were not uniform but where the author implied that deviations from the usual routine were minor and/or relatively infrequent. No attempt was made to allow for variations in dosimetry methods (e.g. calibration, dose specification). When kilovoltage x-rays had been used (37–39), doses were increased by an RBE factor of 1.15.

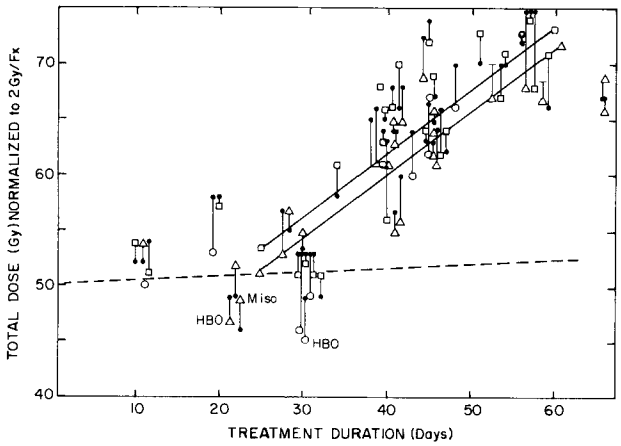

Fig. 1. TCD_{50} as a function of overall treatment time for squamous cell carcinomas of head and neck (Table 1). Data relate to T2 (○), T3 (□) or a combination of more than 2 stages (△). Total doses are normalized to the dose equivalent to that from a regimen of 2 Gy fractions using an α/β value of 25 Gy. Doses and times are best estimates of median values. The dose and control rate reported in the literature from which the TCD_{50} value was calculated is presented (●) to show the extent of the extrapolation. Rate of increase in TCD_{50} predicted from a 2 month clonogen doubling rate. (---). Estimated increase in TCD_{50} (——) with time for 'T3' (□) and mixed T stages (△) from independent scattergram analyses (Tables 2, 3) involving different data sets from those presented in this figure.

Normalizing total doses for influence of fraction size. MACIEJEWSKI et al. (38, 39) have previously analyzed data from nearly 500 patients with oro-pharyngeal cancers treated in Gliwice, Poland, and correlated the influence of total dose, dose per fraction and overall treatment time with the probability of control of the primary lesion. By parametric and nonparametric analyses, it was determined that the effectiveness of a total dose in obtaining tumor control was not very sensitive to change in dose per fraction between about 1.8 Gy and 3.5 Gy. The best estimate for the α/β ratio in the linear-quadratic isoeffect formula (79) was 25 Gy. Therefore, in the present analysis, total doses were normalized to that which would have been isoeffective if given in 2 Gy fractions using the formula (79)

$$D_x = D_{2\,Gy} \cdot \frac{\alpha/\beta + 2}{\alpha/\beta + x}$$

where $D_{2\,Gy}$ and D_x are total doses in fractions of 2 Gy or x Gy, and α/β was taken as 25 Gy. To check the importance of the assumed α/β ratio to the conclusions drawn, an alternative series of calculations was made using an α/β value of 10 Gy, a value within a range commonly found for acutely-responding normal tissues in experimental animals (18, 74, 76). Relative to a value of 25 Gy, an α/β ratio of 10 Gy slightly increases the adjustment made to the total dose.

Calculating TCD_{50} values. To intercompare data in which control rates were usually different from 50%, TCD_{50} values were calculated based on Poisson assumptions regarding cell killing (57) in which the slope of the dose response curve reflected an effective D_0 value of 5 Gy.

Change in dose to achieve P_{cure} of $0.5 = n \times_{eff} D_0 = n \times 5$ Gy where $n = \ln\left(\frac{\ln 0.5}{\ln P_{observed}}\right)$.

The value of 5 Gy, rather than a lower value, e.g. 3.5 Gy, which would be more relevant to clonogenic cell survival, was chosen on the presumption that there would be heterogeneity of tumor and treatment characteristics affecting the slope of tumor control probability curves (78). However, choosing values different from 5 Gy would have little influence on the analysis because extrapolations were limited by selecting reports where control rates were not greatly different from 50%: 40/59 data sets had local control rates between 30 and 70%, and 51/59 were between 25 and 75%.

Analysis of scattergrams. Published scattergrams showing the total dose, treatment time and result of treatment (control or failure) for a specific tumor site and stage (Tables 2, 3) were analyzed. Data points on the scattergrams at extremes of treatment time and dose were excluded because the assumptions of our model may not be appropriate to such extremes and, furthermore, they are of little relevance to the clinical problem of treatment of squamous cell carcinoma of the head and neck. Thus, total doses less than 45 Gy, and overall times shorter than 10 days, or longer than 70 days, were not considered. Other reasons for excluding results at the extremes of overall time were that no information on variations in fraction size was given on the scattergrams, and low total doses in short overall times may have involved the use of a few large dose fractions; also treatment times larger than 70 days were infrequent and it is reasonable to suppose that they were associated with individual disruptions of treatment not described in the text. Since the point of interest was not the overall control rate for each data set, but rather the control rate for specific treatment regimens, no information was lost through excluding uninteresting data at the extremes. In a summary of the scattergram data used in the analysis (Table 2) the limits of each data set were indicated by the 10–90 percentile ranges for dose and time.

The aim of the scattergrams analysis was to quantify the effect of overall treatment time on the dose necessary to achieve a certain tumor control rate, expressing the effect in terms of dose necessary to balance one day's extension of treatment.

The analysis is based on the statistical model $\log\frac{P}{1-P} = A_0 + A_1 \times \text{total dose} + A_2 \times \text{time}(25) + A_3 \times \log(\text{tu-}$

Table 1

Data used to determine TCD_{50} values as a function of overall treatment duration. Median values for doses and times were estimated. NTD = normalized total dose = dose equivalent to that actually given if it had been given in 2 Gy fractions, assuming an α/β ratio of 25 Gy

Tumor	No. of pats.	Dose/fx Gy	Total dose Gy	NTD Median	Overall time Median	Local control %	TCD_{50} α/β = 25 Gy	TCD_{50} α/β = 10 Gy	Reference and No.
Oropharynx T3	13	2	48–56	52	11	31	54	54	Peracchia et al. (54)
Larynx T2–4 (excl. cord)	6	1.6–2.3	47–55	52	11	33	54	52	Svoboda (65)
Vocal cord T2	6	2.0	47–53	50	11	50	50	50	Svoboda (65)
Head & neck T4	9	1.8	54	54	12	66*	51	50	Gonzales et al. (22) (6 mo)
Larynx T2	144	3.7	55	58	20	77	53	58	Stewart et al. (64)
Larynx T3	133	3.7	55	58	20	58	57	62	Stewart et al. (64)
Laryngo-pharynx T2–4	98	4.5	45	49	22	28	52	57	Henk et al. (26)
Oro, hypo, laryngo-pharynx T2–4 HBO	48	4.5	45	49	22	66	47	52	Henk (25)
Head & neck—'not early' misonidazole	162	4–4.5	40–45	46	22	32	49	53	MRC–Miso. working party (42)
	89	2.5–2.9	50–57	55	28	34	57	59	MRC–Miso. working party (42)
Head & neck (excl. N–P) T2–3	60	2.75	55	57	27	70	53	55	MRC–Neut. w. party Edinb. photon (43)
Glottis T4 (cartilage)	23	2.2–2.5	50–55	53	29	61	51	52	Harwood et al. (24) – Fig. 3
Glottis T2 mobile	121	2.2–2.5	50–55	53	29	86	46	47	Harwood et al. (23) – Table 3
Glottis T2 impaired mobility	55					59	52	53	
Hypopharynx T1–3 N0	33	2.2–2.5	50–55	53	29	33	55	56	Keane et al. (32) – Table 2
Tonsil T1–2	81	2.2–2.5	50–55	53	29	73	49	50	Garrett et al. (20) – Tables 3, 4
Tonsil T3	60					61	51	52	
Head & neck st 2 HBO	25	4.5	45	49	31	72	45	51	Denham et al. (12) Table 5
st 3	65					34	51	56	Denham et al. (12) Table 5
Head & neck T3–4	94	1.2	60	58	34	30	61	59	Marcial et al. (41) – Fig. 2
Oropharynx T3–4	27	1.6	64	63	40	83	56	55	Wang (72)
Larynx—all stages	208	1.9	57	57	41	63	55	55	Hjelm-Hansen (28) – Table 3
	97	2.0	60	60	41	74	56	56	
Oro, hypopharynx T3–4	26	1.2	70	68	39	46	68	65	Horiot et al. (30)
	77	1.1	76	74	45	65	72	69	
Pharyngeal wall T3–4	98	2.0	65	65*	40	46	66		Thames et al. (67)
Tonsillar fossa T3–4	38	2.0	68	68*	40	63	66		* Dose from isoeffect
Base of tongue T1–2	62	2.0	66	66*	40	76	61		curves for a 40 day
Base of tongue T3–4	69	2.0	64	64*	40	59	63		treatment to yield
Supraglottic larynx T2–3	124	2.0	65	65*	40	73	61		local control rate actually achieved.
Oral cav. oropharynx T2–4	16	2.15	64	64	41	56	63	64	Henk (25)
Laryngo, hypopharynx T2–4	33	2.15	64	64	41	41	65	66	Henk (25)
Base of tongue T3–4	68	2.2	66	66	41	25	70	71	Marcial et al. (40) – Fig. 1
	78	3.0	60	62	48	35	64	67	
Head & neck T2–4	23	1.0–2.0	69	68	42	69	65	64	Knee et al. (34)
Supraglottic larynx T2	15	2	64	64	43	74	60	60	Fayos (15) Table 2B
Tonsil & base of tongue T2 N0	41	2–2.5	66	67	45	78	62	62	Weller et al. (73) – Tables 6 & 9
T2 N1–3	47	2–2.5	66	67	45	47	67	67	
T3 N0–3	120	2–2.5	66	67	45	34	69	69	
Hypopharynx & larynx T2–3	40	1.2	75	73	45	72	69	67	Parsons et al. (52) – Table 4

(Table 1 Continued)

Tumor	No. of pats.	Dose/fx Gy	Total dose Gy	NTD Median	Overall time Median	Local control %	TCD_{50} α/β = 25 Gy	TCD_{50} α/β = 10 Gy	Reference and No.
Hypopharynx T3	7	1.8–2.0	66	66	47	71	62	62	Parsons et al. (51) –
	11				59	18	71	71	Table 3
Oral cavity T3	32	2.1	63	63	45	44	64	64	Sealy et al. (58) – Table 5
Glottis—all stages	364	2.0	64	64	45	70	61	61	Overgaard et al. (50) –
Supraglottis—all stages	214					47	64	64	Fig. 2
Pharynx—all stages	317					38	66	66	
Tonsil T2–3	26	1.8	62	63	46	58	62	62	Perez et al. (55) – Fig. 3
Head & neck T3–4	93	1.9	70	70	51	29	73	73	Marcial et al. (41) Fig. 2
Tonsil T2–4	95	1.8–2.0	70	70	54	70	67	67	Wong et al. (80) – Table 5
Ant 2/3 tongue T3	17	1.8–2.0	70	70	54	41	71	71	Fletcher (16) Table 3–16
Floor of mouth T3	25	1.8–2.0	70	70	54	64	67	67	Fletcher (16) Table 3–17
RMT & ant fauc pill T2–3	164	1.8–2.0	75	75	57	82	68	68	Fletcher (16) Table 3–20
Pharyngeal wall T3–4	108	1.8	75	74	57	51	74	74	Fletcher (16) Table 3–21
Supragl larynx T3	23	1.8–2.0	75	75	57	83	68	68	Fletcher (16) Table 3–27
Vocal cord T2	175	2.0	70	70	48	74	66	66	Fletcher (16) Table 3–22
Base of tongue T2	35	1.8	72	72	56	46	73	74	Housset et al. (31) – Table 3
Tonsil—stage 3–4	53	1.8–2.0	68	68	59	55	67	67	Nussbaum et al. (46) – Table 3
Glottis—all stages	120	2.0±4.13		67	66	56	66		Overgaard et al. (50)
Pharynx—all stages	157					36	69		Fig. 4 DAHANCA II

mor volume) where P is probability of cure, time (25) = maximum of time (time −25) and zero, and the tumor volume is calculated based on an average diameter of 1.5, 3, 4.5 and 5.5 cm for T1, T2, T3 and T4 tumors respectively. A justification for this model is given elsewhere (38). The term for tumor volume was incorporated into the model to permit an analysis of data combined from various authors, the results of which are not presented here. The number of clonogenic cells in these (primary) tumors was assumed to be proportional to $(\text{diameter})^2$, rather than $(\text{diameter})^3$, but this assumption had no effect on the final estimates unless there were at least 3 T-stages represented separately by the same author. The square of the diameter, rather than the cube, was used on the premise that primary tumors in head and neck are generally more flat than spherical. When data were presented for a multiplicity of stages by one author, the use of the term A_3 introduced the requirement that the rate of increase in isoeffect dose with time (the slope of the isoeffect curve) be assumed to be the same for all T-stages, but allowed the TCD_{50} values to be different for different T-stages. Thus, although an author's data for each stage were analyzed separately, the curves fitted to them by logistic regression were forced to a common slope. In other words, it was assumed that when a small number of surviving clonogens accelerated their repopulation rate, that rate was unaffected by the pretreatment volume (T-stage) of the tumor. This justified the form of the model in which T-stage affected only the A_3 term. If 2 stages were grouped in a scattergram, a diameter equal to the weighted average of the T-stage specific diameters was used in calculating the tumor volume. The weights for these averages were chosen to be equal to the fraction of patients with the particular T-stage. When the TCD_{50} value was estimated for a 4.5 cm diameter tumor based on interpolation from 2 or more T-stages, the result was described as that for a 'T3' tumor (Tables 2, 3).

The maximum likelihood method (11) was used to estimate the parameters A_0, A_1, A_2 and A_3. Time(25) defines the time during which regeneration can occur. Since nearly all patients were treated in overall times longer than 25 days, and since a separate analysis showed TCD_{50} values

Table 2

Data derived from published scattergrams for head and neck cancer was used to calculate the increment in dose per day necessary to compensate for accelerated tumor clonogen repopulation beyond 25 days from the start of radiotherapy. The range of doses and overall treatment times to which the data relate are indicated by the 10–90 percentile limits

Reference	Site of primary	T stage	No. of patients	% cured	Average dose Gy	Dose range 10th–90th percentile	Average time	Range of times 10th–90th percentile
Maciejewski et al. (38)	Oral cavity	1	10	90	61	48–65	37	22–48
Maciejewski et al. (38)	Oral cavity	2	63	48	62	56–65	45	35–55
Maciejewski et al. (38)	Oral cavity	3	120	34	62	57–65	44	35–55
Maciejewski et al. (38)	Tongue	1	4	100	64	62–65	49	45–54
Maciejewski et al. (38)	Tongue	2	33	58	62	60–65	44	33–58
Maciejewski et al. (38)	Tongue	3	128	33	61	54–65	45	35–56
Maciejewski et al. (38)	Tonsil	2	26	81	61	57–65	41	36–50
Maciejewski et al. (38)	Tonsil	3	46	44	61	57–65	45	33–56
Maciejewski et al. (37)	Larynx	3, 4	310	50	63*	61–68*	43	33–57
Shukovsky et al. (59)	Glossopalatine sulcus	2, 3	44	73	67	60–73	43	35–52
Shukovsky et al. (60)	Tonsil	1	11	100	61	54–66	36	24–47
Shukovsky et al. (60)	Tonsil	2	28	82	64	60–70	41	31–48
Shukovsky et al. (60)	Tonsil	3, 4	42	67	65	60–73	40	30–48
Spanos et al. (61)	Tongue	1	26	88	64	60–70	39	28–47
Spanos et al. (61)	Tongue	2	37	62	67	60–71	42	34–49
Spanos et al. (61)	Tongue	3	47	70	68	61–74	45	35–56
Spanos et al. (61)	Tongue	4	19	32	64	53–80	42	32–55
Ghossein et al. (21)	Supraglottic larynx	1, 2	80	73	74	63–81	44	40–51
Ghossein et al. (21)	Supraglottic larynx	3, 4	104	56	75	63–86	45	39–51
Million et al. (45)	Larynx	2, 3	21	67	68	61–74	57	49–65
Million et al. (45)	Soft palate	2, 3	19	63	64	56–73	50	33–65
Million et al. (45)	Pharyngeal wall	2, 3	18	44	69	63–75	54	43–66
Million et al. (45)	Pyriform sinus	2, 3	15	60	66	54–75	54	44–64
Million et al. (45)	Base of tongue	2, 3	22	73	67	64–71	54	44–67
Million et al. (45)	Tonsil	2	15	67	63	57–70	44	34–50
Million et al. (45)	Vocal cord	1	85	95	61	57–64	37	33–38
Million et al. (45)	Vocal cord	2, 3	61	66	65	61–70	44	37–51
Million et al. (45)	Floor of mouth	3	18	50	71	64–79	50	28–68
Million et al. (45)	Oral tongue	2	22	68	70	58–81	41	18–67
Million et al. (45)	Oral tongue	3	15	47	72	69–87	44	28–56
Vikram et al. (71)	Nasopharynx	1, 2	35	69	66	60–71	57	48–66
Vikram et al. (71)	Nasopharynx	4	28	54	66	60–75	55	42–69
Barker et al. (5)	Retromolar Ant tonsil pillar	1, 2, 3	132	83	66	59–73	39	30–47
Meoz-Mendez et al. (44)	Pharyngeal wall	2, 3	90	64	68	60–74	45	37–53
Budihna et al. (7)	Larynx	1	29	83	66	60–76	51	35–68
Budihna et al. (7)	Larynx	2	15	47	64	55–78	47	31–67
Cardinale et al. (8)	Tonsil	2	21	57	62	57–68	50	43–62
Gardner et al. (19)	Base of tongue	1	6	67	66	62–70	57	49–64
Gardner et al. (19)	Base of tongue	2, 3	35	80	70	65–76	56	45–66
Gardner et al. (19)	Base of tongue	4	18	22	72	66–78	57	50–66

* Adjusted for $RBE_{x/\gamma}$ of 1.15 for ^{60}Co and 200 kVp x-rays.

that were relatively constant over a period of approximately 20–30 days (see later), we assumed repopulation began at 25 days after the initiation of treatment: that is, the back-extrapolation of the curves (Fig. 1) was stopped at 25 days. Thus, selecting a starting time less than 25 days would not affect the slope of the curves tracing the increase in dose per day, but only the estimate of the TCD_{50} value in the absence of repopulation. With this model, A_2/A_1 is an estimate of the dose necessary to balance an extra day's extension in treatment duration. Approximate standard errors were calculated from the asymptotic information matrix (11).

Results

TCD_{50} estimates. The data analyzed, and the best estimates obtained for TCD_{50}, are shown in Table 1, together with the intermediate steps in the calculations.

Table 3

Analysis of scattergrams. Doses to balance 1 day's extension of treatment time (beyond 25 days) and the TCD_{50} for a 'T3' tumor treated in 45 days calculated from the total data set (for all stages) at that site. When multiple stages were presented in separate scattergrams, they were analyzed separately, but the dose to balance 1 day's extension of treatment time was forced to a common value. When multiple stages were presented in one scattergram, the TCD_{50} is for the combination of stages

Reference	Site	Dose to balance 1 day extra beyond 25 days		TCD_{50} (±S.E.) (Gy) for time =45 days stage = 'T3' or other (*)
		Gy	(S.E.)	
Maciejewski et al. (38)	Oral cavity	0.64	(0.07)	65.9 (0.8)
Maciejewski et al. (38)	Tongue	0.72	(0.09)	65.1 (0.6)
Maciejewski et al. (38)	Tonsil	0.67	(0.13)	61.5 (1.0)
Maciejewski et al. (37)	Larynx	0.56**	(0.06)	65.0* (0.3)**
Shukovsky et al. (59)	Glossopalatine sulcus	1.33	(0.42)	63.5* (2.4)
Shukovsky et al. (60)	Tonsil	0.54	(0.30)	62.6 (3.3)
Spanos et al. (61)	Tongue	0.65	(0.29)	64.2 (3.0)
Ghossein et al. (21)	Supraglottic larynx	1.43	(0.86)	87.2 (12.7)
Million et al. (45)	Vocal cord	2.39	(2.15)	80.8 (21.4)
Million et al. (45)	Soft palate	−0.28	(0.54)	70.1* (6.2)
Million et al. (45)	Base of tongue	−0.90	(0.97)	81.4* (8.9)
Million et al. (45)	Pharyngeal wall	−2.09	(6.45)	77.6* (30.6)
Million et al. (45)	Tonsil	−1.05	(4.64)	70.6* (16.9)
Million et al. (45)	Pyriform sinus	2.90	(4.48)	33.5* (53.4)
Million et al. (45)	Larynx	0.58	(0.15)	59.3* (2.3)
Million et al. (45)	Oral tongue	1.15	(1.50)	82.3 (15.8)
Million et al. (45)	Floor of mouth	−0.04	(0.32)	71.2 (4.6)
Vikram et al. (71)	Nasopharynx	0.09	(0.27)	68.0 (5.6)
Barker et al. (5)	Retromolar trigone	1.03	(0.25)	63.4* (2.4)
Meoz-Mendez et al. (44)	Pharyngeal wall	1.36	(1.32)	55.1* (15.4)
Budihna et al. (7)	Larynx	0.74	(0.38)	63.2* (5.0)
Cardinale et al. (8)	Tonsil	0.88	(1.24)	54.2* (12.2)
Gardner et al. (19)	Base of tongue	0.34	(1.13)	77.3 (10.0)

* Denotes stages other than T3, i.e. 4.5 cm tumors; see Table 2.
** Adjusted for RBE 1.15.

The values for TCD_{50}, obtained using an α/β ratio of 25 Gy, are plotted against overall treatment duration in Fig. 1. Comparable estimates using an α/β ratio of 10 Gy are shown in Table 1, but not in Fig. 1.

Several features of Fig. 1 should be noted:

1) The data show a non-linear, two-component relationship between TCD_{50} and overall treatment time, there being no consistent change in TCD_{50} between overall times of about 11 to 30 days but a steep rate of increase thereafter.

2) The dashed line, originating arbitrarily at 50 Gy, traces the increase in TCD_{50} which would result from unperturbed tumor growth at a rate that would double the number of clonogens every 2 months, i.e. assuming no accelerated growth of tumor clonogens. (Its slope is based on an effective D_0 of 3.5 Gy for a 2-Gy per fraction regimen.)

3) TCD_{50} values do not increase consistently between 10 and 30 days, suggesting no change in tumor clonogen growth rate during approximately the first 4 weeks of treatment. By contrast, TCD_{50} values for a 6-week treatment are consistently greater than those for a 4-week treatment, implying a rapid repopulation by surviving tumor clonogens between 4 and 6 weeks. By 7 weeks the TCD_{50} values are all greater than 60 Gy. The solid lines in Fig. 1 are not fitted to the data but are calculated from the separate analysis of scattergram data (see below).

4) The full lines are based on *independent* data from scattergrams (Tables 2, 3, Figs 2, 3). The weighted average TCD_{50} at 45 days was calculated from the data presented in Table 3 for 'T3' (4.5 cm) tumors (11 sets of data) and a mixture of T-stages, mainly T2 and T3 (12 sets of data). The values were 64.9 Gy for 'T3' and 62.7 Gy for mixed stages. The lines shown are drawn through these 45-day TCD_{50} values with a slope reflecting a change in TCD_{50} of 0.61 Gy per day (see scattergram analysis later). It is apparent that 2 independent analyses show that the rate of change in estimated TCD_{50} values from percent tumor control analyses (Table 1, Fig. 1), and of increase in isoeffect dose per day from scattergrams (Tables 2, 3, Figs 2, 3) are consistent with one another.

5) The magnitude of the extrapolations to the TCD_{50} from the doses actually delivered in achieving the range of observed control rates (Table 1) is represented by the lengths of the lines from the closed circles (doses actually used) to the open symbols (estimated TCD_{50} values).

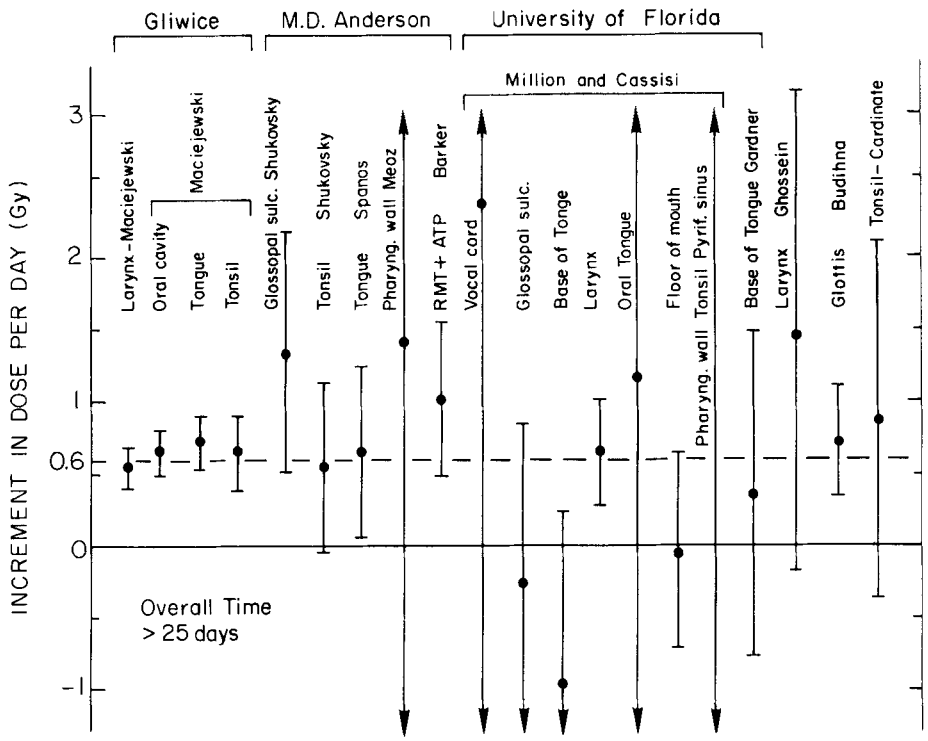

Fig. 2. Increment in dose per day for a constant (50%) probability of control of head and neck cancer with protraction of treatment, determined from logistic analysis of published scattergrams (Tables 2, 3) and 3 data sets of Maciejewski (38). Three small data sets (for pharyngeal wall, tonsil, pyriform sinus) have 95% confidence limits extending beyond the graph but are included for completeness. (---) at 0.6 Gy is encompassed by 22/23 of the 95% confidence intervals, implying that 0.6 Gy per day is a good estimate of the dose to compensate for tumor clonogen repopulation in head and neck cancer at times beyond 25 days.

6) In general, and in particular for an individual investigator, TCD_{50} values are lower for T2 tumors (circles), than for T3 and T4 tumors (squares), with the groups containing a range of T-stages (triangles), also showing values generally lower than those for T3 and T4 tumors.

7) To avoid overcrowding of data in Fig. 1, values were not plotted for TCD_{50} calculated using an α/β ratio of 10 Gy (instead of 25 Gy). However, they are presented in Table 1 and it can be seen that they do not affect in any significant way the conclusions drawn above. The main effect of using the lower α/β ratio was to raise the TCD_{50} estimates in regimens lasting 18–26 days. The cluster of data at 30–32 days would not be greatly affected, lying between 47–56 Gy with a median value of about 52 Gy, not different from the median value of 51 Gy for TCD_{50} values in treatments lasting 10–12 days.

8) The *predominant* factor determining the variation in TCD_{50} values for the various series of patients is not the stage of disease, nor the site of the tumor, nor the size of dose per fraction, but rather, the overall duration of therapy.

Scattergram analysis. Table 2 shows the characteristics of the scattergram data sets analyzed. Table 3 shows that, for most data sets, extending overall treatment time had a strong effect on the dose for a constant rate of tumor control. The dose required to counterbalance one day's extension late in a treatment regimen, averaged (with weights inversely proportional to the variance) from 23 data sets, was 0.61 (S.E.=0.22) Gy. Also shown in Table 3 are TCD_{50} values predicted from the scattergrams for treatments lasting 45 days, using the maximum likelihood logit analysis, for 11 sets of 'T3' tumors, 10 data sets containing multiple, but unidentified, stages, and two small sets of patients with T2 primary cancer of tonsillar fossa.

Fig. 2 plots the scattergram data from Table 3 for the increment in dose required for a constant tumor control rate for each day's protraction of treatment. The 95%-confidence intervals include the average value (of 0.61 Gy/day) in 22 of the 23 data sets for head and neck cancer, confirming that this value is not inconsistent with the data from nearly all the scattergrams.

Fig. 3 plots curves relating the TCD_{50} to overall treatment duration. Only those curves for which the standard error for the daily increment in TCD_{50} was less than 0.4 Gy per day (Table 3) were plotted. The location of the curves relative to the TCD_{50} ordinate depends upon the stage of tumor. The curves shown are those derived from an analysis which included all the data from each author. When the scattergram included results for multiple T-stages, identified separately, one curve for a tumor of average diameter 4.5 cm ('T3') was plotted, but its posi-

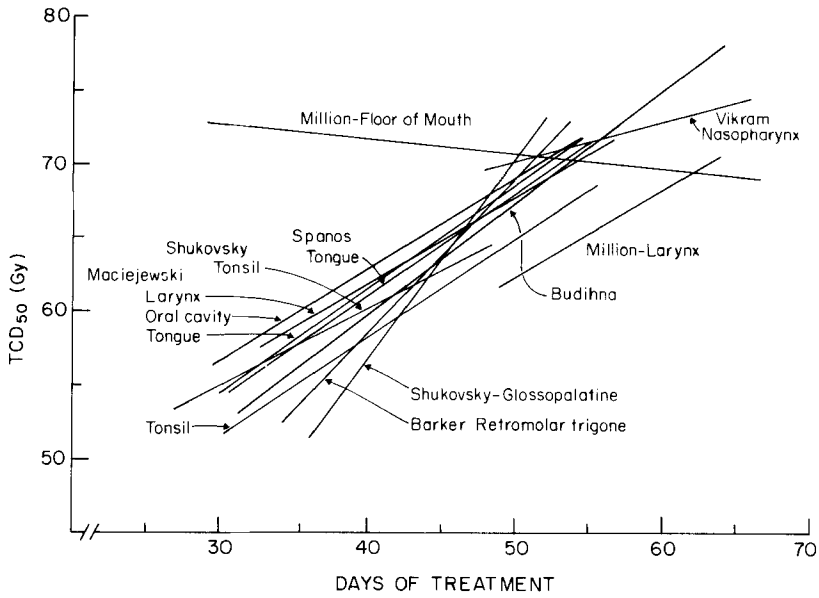

Fig. 3. Curves plotting the increase in dose for tumor control with increasing overall treatment duration. The data were derived from published scattergrams and from Maciejewski et al. (38). Only data with a S.E. less than 0.4 Gy/day were plotted (Table 3, Fig. 2). The positions of the curves relative to the ordinate were fixed at the TCD_{50} for treatment of a 'T3' tumor, or when T-stages were not identified, merely as the combination of multiple stages (Table 3).

tion and slope were influenced by data for all stages because the curves for all stages were forced to a common slope. When data for multiple stages were presented in one scattergram, but not identified separately, the curve is for the combination of stages (see asterisks in Table 3).

It should be noted that, in the analysis of scattergrams, no account was taken of possible variations in fraction size, except, perhaps, by the exclusion of extremes. With an α/β ratio of 25 Gy, variations in fraction size within the range 1.8–2.5 Gy have little effect on the total 'biologically-effective' tumor dose. Even if 3 Gy fractions were used, the biologically equivalent dose given in 2-Gy fractions would be less than 4% higher. For the data of most interest, that is, those including treatments longer than 28 days, the fraction size is presumed to vary relatively little, requiring no significant corrections, and leaving time and total dose as the dominant factors determining changes in tumor control probability. If there were a trend to the use of higher dose fractions in shorter treatment regimens, its effect would be to render our results a slight overestimate of the influence of repopulation.

From Table 3 and Figs 2 and 3 it is obvious that, in most instances, protraction of overall treatment time created the need for an increase in dose for a constant rate of tumor control. In general, those few examples in which this was not shown were also those having the largest error bars (Fig. 2).

Discussion

Pre-radiation tumor growth rate versus accelerated tumor clonogen repopulation. Data collected from the literature from predominantly retrospective analyses of results of treatment of head and neck cancer from a variety of institutions and over the span of about 2 decades is not the stuff for drawing firm conclusions regarding the precise time after initiation of treatment at which tumors begin an accelerated rate of clonogen repopulation.

However, Fig. 1 suggests that there is a period of about 4±1 weeks after the start of treatment during which there is, on average, little change in the TCD_{50}, but that, thereafter, this relationship changes quite dramatically. The dashed line in Fig. 1 illustrates that there would be a slight but undetectable increase in TCD_{50} as a result of the tumor continuing at its preradiation growth rate (T_d=60 days). In contrast to this constant slow increase in TCD_{50} predicted from a 2-month doubling time there is a sharp increase in TCD_{50} at overall times greater than about 30 days. This is convincing evidence that tumor clonogens accelerate their rate of increase after a lag period. This conclusion from non-scattergram estimates of TCD_{50} is independently corroborated by the analysis of scattergrams. The location and slopes of the solid lines in Fig. 1, which trace TCD_{50} estimates from scattergram data provide, by coincidence, a reasonable fit to the completely unrelated non-scattergram data points. Until the question is addressed prospectively, a very difficult undertaking, a reasonable working hypothesis is that there is a lag period of about 4 weeks after the start of radiotherapy before the average squamous cell carcinoma of the head and neck begins a burst of rapid repopulation.

It should be emphasized that such data (Tables 1–3, Figs 1–3), although very useful in designing general treat-

ment strategies, refer only to the average behavior: since human tumors are known to differ widely in their pretreatment growth rates (9, 62, 69), the average time of onset and rate of accelerated growth during treatment may also conceal wide variations, and may be of limited value in individualizing radiotherapy prescriptions.

Rate of accelerated repopulation. Rapid repopulation, at least at times beyond 25 days, leads to a daily increase in TCD_{50} of about 0.6 Gy, estimated from scattergram analysis (Table 3, Figs 2, 3). Little change in this value is found by varying the possible day of onset of regeneration between day 10 and 28 because most scattergram data related to treatments lasting longer than 28 days. It is reiterated that the scattergram data shed little light on the time of onset of the accelerated tumor repopulation. The effect of tumor clonogen repopulation on the dose to achieve tumor control estimated here from scattergrams is similar to that estimated by BUDIHNA et al. (7) and OVERGAARD et al. (50) from comparisons of continuous and split-course regimens. (Out method of analyzing the scattergram published by BUDIHNA et al. (7) yielded a greater increment per day in the isoeffect dose than determined by those authors (Table 3, Figs 2, 3).)

If it is assumed that it requires about 2.4 Gy in a 2-Gy/fraction regimen to compensate for each doubling in clonogen number, then a daily increment of 0.6 Gy in TCD_{50} is consistent with a clonogen doubling rate of 2.4/0.6=4 days. Cell cycle times of 2–4 days are commonly measured in unperturbed tumors (62), and, while this may shorten, the mechanism likely to contribute most to the reduction in clonogen doubling rate from 60 days to 4 days is a change in cell loss factor such that most daughters of a clonogenic cell division retain their clonogenicity instead of leaving the clonogen pool (e.g. by differentiation, apoptosis, etc.).

This result is not inconsistent with the slopes of 'exclusion' lines drawn on scattergrams by previous authors (for references, see Table 2). The difference is that, in the present analysis, the influence of fraction size, or number (except as the determinant of total dose), was ignored and the increase in isoeffect dose with time was attributed exclusively to repopulation. Also, we did not assume that the 'exclusion' line needed to be straight in its extrapolation to very short overall treatment times. While the data in the various scattergrams may have been derived from a variety of treatment regimens, the variation in fraction size within each set was probably relatively small. Since the tumor responses are not very sensitive to change in fraction size anyway (e.g. α/β ratio 25 Gy), this variable would have little influence on the slopes of 'exclusion' lines of past authors, or on the isoeffective dose (TCD_{50}) curves in our scattergram analyses.

Accelerated tumor repopulation in the individual. The present analysis of a spectrum of predominantly retrospective studies provides an estimate of the average lag time before accelerated clonogen growth reduces tumor control probability. However, this average may reflect a range of repopulation rates (Fig. 4a) or a range of times of onset of accelerated growth (Fig. 4b), or both. Although the implications of these different possibilities are the same for the 'average' patient they are clearly different when the oncologist aims at individualizing treatment prescriptions. Predicting the lag time before the onset of tumor repopulation in each individual patient should be an important aim of research. Meanwhile, even determining 'average' lag times and repopulation rates for tumors of various histologies and sites would improve our ability to design rational 'average' treatment schemes.

Optimum overall treatment duration. Historically, extending the overall treatment duration was aimed at minimizing acute toxicity in normal tissues. In most acutely-responding normal tissues, a repopulation response probably begins within about 2 weeks from the start of radiotherapy (3, 16, 70, 76). In oropharyngeal mucosa and skin, repopulation is rapid enough that during the latter part of a 6- to 7-week treatment regimen, the severity of responses to a 5-day per week regimen of 2 Gy per fraction remains stable, or even decreases (16), with clonally derived foci of regenerated epithelium sometimes appearing within the irradiated area (4). Thus, repopulation by normal epithelium can balance or outstrip the cytotoxicity of 10 Gy in 5 fractions per week at a time when only 4–5 Gy per week would be necessary to balance tumor clonogen repopulation in the average squamous cell carcinoma of the head and neck. Because of this, extension of treatment time provides a favorable differential between acutely-responding tissues and these tumors. This is particularly true in the interval between the onset of mucosal repopulation at about 2 weeks and the onset of tumor clonogen repopulation at about 3 to 5 weeks. Thus, shortening the overall treatment time to less than 3 weeks, and perhaps even to less than 4 or 5 weeks, would be predicted to reduce the therapeutic differential between normal epithelial tissues and the tumor. These ideas are illustrated by theoretical curves in Fig. 5, which plot the repopulation kinetics and therapeutic ratios for acutely- and slowly-responding tissues relative to an average squamous cell carcinoma of the head and neck.

The therapeutic advantage accruing to acutely-responding normal tissues from rapid repopulation during an extended treatment regimen would probably not be shared by slowly-proliferating, late-responding normal tissues (because their repopulation response is slow to begin). Therefore, the onset of tumor clonogen repopulation signals a progressive decrease in therapeutic differential between late responding tissues and the tumor (Fig. 5). For these tissues, a favorable therapeutic differential is derived only from differentials between their target cells and tumor clonogens in their respective capacities for repair of molecular injury. Such differentials are enhanced by using small doses per fraction, that is, by hyperfractionation (75, 77). Hence, the most favorable therapeutic

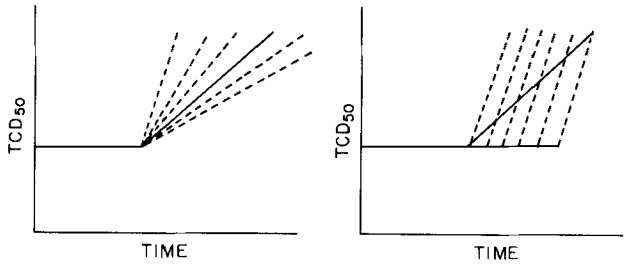

Fig. 4. Two generic repopulation responses that could yield the same 'average' rate of repopulation: a) a constant lag period with variable regrowth rates (---) to yield an average rate defined by the solid line: b) a variable lag period with constant regrowth rates (---) for the same average rate as in a). The two types of response are not mutually exclusive.

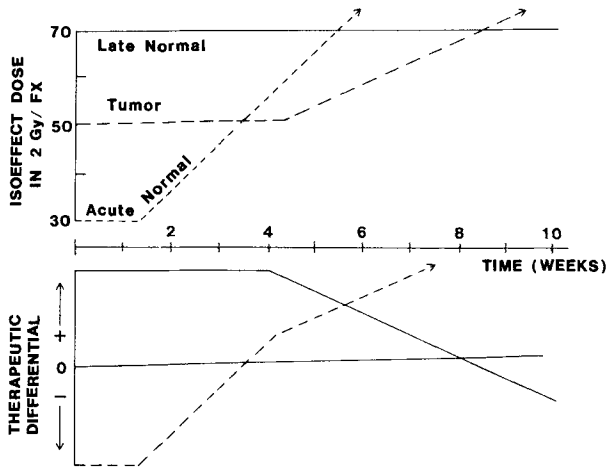

Fig. 5. Hypothetical curves to illustrate time-related changes in therapeutic differential. Upper panel, changes in isoeffect doses with time: lower panel, therapeutic differentials. Assumptions were: all treatments given in 2 Gy fractions, 'tolerance' =70 Gy for late responding tissues, 30 Gy for acutely-responding tissues in the absence of repopulation, tumor control dose in absence of clonogen repopulation during treatment =50 Gy, repopulation begins at day 10 in acutely-responding normal tissues, day 28 for tumors and is faster in normal tissues. The therapeutic differential between acutely-responding tissues and the tumor increases steeply between 10 and 28 days and then continues more slowly after the beginning of accelerated tumor growth. The therapeutic differential between late responding normal tissues and the tumor changes only very little until tumor growth accelerates, after which it declines. In summary, the maximum therapeutic differential would be achieved at 4 weeks, but only if the acutely-responding normal tissue would tolerate such a quick treatment. At shorter times, acute responses would be more severe than necessary and, at longer times, the differential between the late responding normal tissues and the tumor decreases. This model is only an example of general principles: quantitative values will vary for different tumor sites and for different patients. It should not be interpreted as advocating treatment in 4 weeks.

differential between late responding normal tissues and the tumor would be derived by using the smallest feasible doses per fraction, fractionation intervals long enough for complete repair of cellular injury, and an overall time equal to, or less than the time of onset of accelerated tumor repopulation. In the average squamous cell carcinoma of head and neck, the overall time for this particular therapeutic differential (late effects vs. tumor) should be less than about 3 to 5 weeks; but for individual patients, or in treating tumors of other sites and histologies, it may be shorter or longer. However, even for squamous cell carcinomas such rapid treatments may be suboptimal because the toxicity to acutely-responding normal tissues, which can be greatly modified by repopulation during more protracted regimens, may limit the total dose that could be given.

From consideration of both early and late responding normal tissues, and at least those tumors that show an early response to radiotherapy, the greatest overall therapeutic differential would be derived from using the smallest feasible dose per fraction and an overall treatment duration as short as consistent with achieving acceptable acute normal tissue toxicity, *without reduction in the total dose,* determined by the 'tolerance' of critical late responding tissue(s). The constraints on total dose, overall treatment time and dose per fraction will vary with the clinical situation, being affected by such considerations as tumor type, location and growth rate, critical normal tissue tolerances, risk factors, etc. Although 5 fractions of 2 Gy per week is an effective average treatment, there is no reason to consider it the optimum for all, or even the majority of clinical situations (75).

Strategies for accelerated treatment. As clearly illustrated in Fig. 1 and 3, it would be an advantage in the treatment of head and neck cancer, and probably also in cancers of other sites (1, 6, 10, 29, 53, 68, 69) if overall treatment times were shorter than the 6 weeks or longer commonly employed. There are several methods of shortening treatment duration (22, 54, 56, 64, 65, 68, 72, 75), and, if this can be achieved without reducing the prescribed tumor dose, and without increasing serious toxicity, especially acute toxicity, a therapeutic advantage should follow.

Initiation of radiotherapy. The influence of tumor growth during a delay in initiation of treatment on the probability of achieving tumor control is, on average, slight (see dashed line, Fig. 1). However, once treatment has begun it is incumbent on the oncologist to complete it as quickly as possible since the clonogen doubling time may shorten at some time during treatment, from an average of 60 days to an estimated average of about 4 days in head and neck cancer. If treatment delays can be predicted (e.g. public holidays, machine maintenance), it is advisable to delay the start of treatment rather than to introduce interruptions in the treatment after it has begun. Alternatively, lost days can be 'made up' by treating more than 5 times per week. Similarly, if a patient is scheduled to complete treatment on a Monday or a Tuesday, it may be possible, depending upon the severity of the acute responses, to treat 6 or 7 times per week in the preceding

week or weeks. (When more than 5 treatments are to be given in a Monday or Friday treatment week, 2 doses must be given on one or more days. To ensure complete repair of sublethal injury in slowly-responding tissues the fractionation interval should be as long as possible, preferably 6–8 h (2)).

Tumor regresssion and accelerated tumor growth. Clinically, most head and neck tumors are still regressing 4 weeks after the initiation of treatment and continue to do so over the following weeks. Therefore, the present analysis indicates that during the later stages of regression of the visible tumor mass there is a concomitant rapid, but subclinical, increase in tumor clonogens. This has been quantified previously in animal tumor systems (27, 35, 69). Thus, clinical observation of regression of a tumor is likely to be a snare and a delusion concealing an insidious and rapid subclinical repopulation by tumor clonogens equivalent, on average, to a loss of an average of at least 4 Gy per week in the biologically effective tumor dose in the case of head and neck cancer.

Chemotherapy before radiotherapy. Rapid repopulation by surviving tumor clonogens results from killing of tumor cells: it is not a specific response to x-irradiation. It is reasonable to expect that if chemotherapy were effective in killing cells and producing partial or complete tumor regression it would also lead to an accelerated regrowth of surviving clonogens similar to that occurring after irradiation (63). Since cell death after exposure to chemotherapy agents may be more rapid than after irradiation, the time of onset of such a regenerative response is unlikely to be later than that which follows radiotherapy, especially repeated daily radiation exposures which slow the rate of repopulation (3). Clinical experience, especially in randomized trials, has found that chemotherapy that has resulted in complete or partial regression of squamous cell carcinomas of head and neck has not improved control rates over those achieved with radiotherapy alone (36, 66). A likely cause for this unexpected lack of improvement is accelerated clonogen regrowth as a result of the chemotherapy (63), a reflection once again of the deceptiveness of tumor regression as an indicator of subclinical tumor behavior.

The use of 2 or 3 courses of chemotherapy prior to the initiation of radiotherapy was developed empirically and should be reconsidered. If the 2 modalities are combined, radiotherapy should begin as soon as possible after a single dose of chemotherapy or the cytotoxic drug should be delivered as soon after completion of radiotherapy as compatible with acceptable mucosal reactions. (An additional potential advantage of this latter scheduling is that a greater proportion of the viable tumor clonogens would be likely to be in active cycle).

Hypoxic cell sensitizers. Hypoxic cell sensitizers have been too toxic to administer in adequate doses with each radiation dose fraction. In the past, conflicting arguments regarding the scheduling of a less-frequent drug schedule have been that the sensitizer should be given early in the treatment regimen while the tumor was large and hypoxic cells numerous, or late when those tumors that reoxygenated poorly would have an enhanced ratio of hypoxic to euoxic cells. Our present analysis suggests that, in the average squamous cell carcinoma of head and neck, clonogens surviving after 4 weeks of radiotherapy are sufficiently well nourished to repopulate rapidly and that they are probably euoxic. Therefore, hypoxic cell sensitizers may be more likely to be beneficial if used early in a course of radiotherapy. It is interesting that the only clinical trial to have shown an advantage from the adjuvant use of misonidazole used the drug during only the first part of a split-course regimen (48).

Isoeffect formulae. Present knowledge regarding tumor biology and radiobiology indicates that isoeffect formulae, such as the NSD (14, 33, 47), have no biological validity (78). The effect on tumor control of change in fraction size, assuming the overall treatment time is fixed, appears to be less than previously considered, and may be modeled, at least over a modest dose range (e.g. 2–8 Gy per fraction) using a high value for the α/β ratio in the linear quadratic isoeffect formula (13, 18, 38, 74, 76, 79). There may be a spectrum of α/β ratios for different tumors or within similar tumors of different kinetic characteristics (13, 74). In general, however, α/β ratios for tumors are likely to be high (38, 74) making the size of dose fractions relatively unimportant in isoeffect relationships for tumor control using doses per fraction of 3 Gy and less.

Likewise, the effect of overall treatment time on the probability of tumor control is likely to vary among tumor types and among individual tumors of a given type. However, the pattern of accelerated repopulation beginning after a lag period, as illustrated in this paper, is likely to be as generic for tumors as it is for normal tissues (76). There are likely to be wide individual variations in tumor regrowth characteristics, not only among tumors of different sites but also within tumors of the same site in different patients. The development of 'average' models for calculating isoeffect dose relationships is useful as a general guide to treatment strategy, but should not obscure the need to develop methods for predicting the regrowth characteristics of individual tumors as a means of individualizing therapy.

Shortcomings of the analysis. The results of analysis of a variety of data sets from the literature, and MACIEJEWSKI et al. (38) were combined. The comparability of such diverse data can be questioned. There could be many between-author differences, in particular; in definitions of end-points, dosimetry, staging criteria, schemes for including patients who were lost to follow-up, criteria for treating with radiotherapy and for selecting fractionation parameters and total dose, ways of grouping tumor sites, etc. Also, our analyses grouped tumors from many different sites in head and neck.

Another caveat is that most of the data sets were retro-

spective. This could bias the results if, for each patient, the choice of treatment regimen was influenced by prognostic factors (such as node stage) which were not published and hence could not be controlled for in the analysis. For example, if within one T-stage, the more advanced disease was routinely treated in a longer overall time, then, for a given dose the probability of tumor control from more prolonged treatments would be lower, giving an effect similar to that from accelerated repopulation. This is a consideration only for the scattergram analyses: it would not affect the 'dog-leg' data in Fig. 1, in which a median time was plotted against total dose for each independent data set.

Heterogeneity of tumor stage within a data set is a source of bias: it was common for 2 or more tumor stages to be drawn on the same scattergram (Table 2) or grouped when presenting local tumor control rates (Table 1).

Another source of concern is publication bias, that is, the tendency to publish only results which show an effect. It is possible, although probably unlikely, that time-dose scattergrams were only published if there was clear evidence of an effect of protraction of overall time. This bias would cause the effect of repopulation to be overestimated.

There are various assumptions and approximations in the statistical analysis which are worth reiterating. The placement of the TCD_{50} values in Fig. 1 was based on the assumption that an effective D_0 of 5 Gy appropriately defined a tumor control probability curve, and that an α/β ratio of 25 Gy was valid. However, other reasonable choices for the effective D_0, or an α/β ratio greater than, say 8 Gy, would not qualitatively change the conclusion that the time component is an important determinant of the radiation response beyond about 3 to 5 weeks.

In the scattergram analysis, the logistic model is assumed to hold for all data sets; but this model is certainly only an approximation to the reality. The main purpose of the model is as a means of assessing the relative importance of time and dose: hence the form of the left hand side of the equation is of little importance. Calculations of the standard errors in Table 3 were based on the asymptotic information matrix (11) and as such are only approximate for small samples.

Although it is necessary to be aware of the limitations of the analysis, they do not introduce large and/or systematic errors. For example, assume that in one study used for constructing Table 1 and Fig. 1 an actuarial local control rate of 30% was reported, but that the absolute control rate, if reported, would have been 60%. Even in this extreme example, the TCD_{50} would be changed by only 4.28 Gy by a change in the method of reporting local control. Also, it should be remembered that some potential errors counterbalance one another, and that the TCD_{50} values were obtained by extrapolations from doses that gave both higher and lower control rates than 50%. More importantly, the magnitude of the increase in dose for tumor control with protraction of treatment time almost certainly overwhelms minor uncertainties in the data and the methods of their analysis. Also, given all these potential or real differences, it is encouraging that the TCD_{50} values (Fig. 1) and the dose to balance an extra day of treatment (Figs 2 and 3) showed relative consistency among the broadly-derived data.

Thus, although there may be some uncertainties regarding the precise averages for its time of onset and subsequent rate, the phenomenon of accelerated repopulation by tumor clonogens is clearly established: Its occurrence is usually undetectable in its early stages and, since it may occur during treatment, is an important cause for failure.

Some Conclusions

Some implications of our findings are:

1) Radiotherapy, at least for head and neck cancers, should be completed as soon as practical after it has begun: it is better to delay initiation of treatment than to introduce delays during treatment.

2) Accelerated growth involves small absolute numbers of tumor clonogens and, rather than being detectable clinically as tumor growth, occurs while the mass is still regressing.

3) Administration of 2 or more courses of chemotherapy before beginning radiotherapy may precipitate a regenerative response in the tumor and prejudice local control by radiotherapy.

4) In view of the above, complete or partial regressions should not be a primary aim of curative treatment, and regression should not blind the radiation oncologist or medical oncologist to the subclinical existence of accelerated repopulation, a potent cause of treatment failure.

5) Hypoxic cell sensitizers may be more useful if employed early in a course of treatment since rapid repopulation late in treatment suggests that surviving clonogens are well-oxygenated.

6) A simple isoeffect formula for changes in fractionation pattern cannot ever be valid because normal tissues and tumors vary, not only in their sensitivity to changes in fraction size, but also in their repopulation kinetics. Furthermore, repopulation kinetics change during treatment.

7) The doses necessary to achieve acceptable rates of local control in head and neck cancer vary widely among institutions worldwide: the major cause for this variation is probably the variation in overall treatment duration with resulting differences in extent of tumor clonogen repopulation during therapy.

These analyses and conclusions relate to the 'average' cancer of the head and neck: prospective quantification of the likely time of onset and rate of accelerated tumor clonogen repopulation is required for optimizing treatment for individual patients with head and neck cancer and should be an important goal of research. The findings for head and neck may be inappropriate to other sites: the effects of overall treatment time on the local control of

cancers of other histologies and sites in the body also needs investigation.

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