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FROM THE DEPARTMENT OF RADIATION PHYSICS, KAROLINSKA INSTITUTET, S-10401 STOCKHOLM, SWEDEN.

DOSIMETRIC PRECISION REQUIREMENTS IN RADIATION THERAPY

A. BRAHME

Abstract

Based on simple radiobiologic models the effect of the true distribution of absorbed dose in therapy beams on the response of uniform tumor volumes are investigated. Under assumption that the dose variation in the beam is small it is shown that the response of the tumor to radiation is determined by the mean dose to the tumor volume. Quantitative expressions are also given for the loss in tumor control probability as a function of the degree of dose variations around the mean dose level. When the dose variations are large the minimum tumor dose is best related to tumor control. It is finally shown that high tumor control rates can only be achieved with a very high accuracy in dose delivery. If the normalized dose response gradient is higher than 3, as is frequently the case, the relative standard deviation of mean dose in the target volume should be less than 3 per cent to achieve an absolute standard deviation in tumor control probability of less than 10 per cent.

It is often observed that the dose-response-relationship for tumor cell killing and for concomitant normal tissue reactions follow sigmoidal curves at high doses. The therapeutic ratio therefore depends on the relative positions and slope of these response curves. To establish the dose-response-relationship for malignant as well as normal tissues for a given radiation modality it is necessary to know the absorbed dose and its fractionation, the biologic properties of the tissue concerned, and the frequency of the observed end point.

In the present paper the dependence of the tumor response on the shape of the absorbed dose distribution in the target volume is analysed based on a simple biologic model. Under assumption of a given acceptable loss and uncertainty in tumor control the required precision in dose delivery is derived.

Radiobiologic model

Cell survival curve

The relationship between the surviving cell fraction, S, and the absorbed dose deposited in a single irradiation of a given cell population in vitro is described by the cell survival curve (cf.Fig. 1).

The shape of the cell survival curve is generally well described by an equation of the type (4, 20, 21):

$$S(D) = e^{-(\alpha D + \beta D^2)} \quad (1)$$

The coefficient α of the linear term in absorbed dose determines the slope of the survival curve at small doses. The coefficient β of the quadratic term is a measure of the shape of the shoulder of the survival curve. A collection of survival parameter data for human tissues was published by FERTIL & MALAISE (8).

An approximate but more simple cell survival curve model is given by an expression of the type

$$S(D) = f e^{-D/D_0} \quad (2)$$

where f is the extrapolated cell fraction at zero dose assuming the slope of the almost linear portion of the cell survival curve in a logarithmic diagram to be constant. D_0 is the absorbed dose that reduces the proportion of surviving clonogenic cells to e^{-1} around the central dose of interest D_c (see Fig. 1).

The parameters D_0 and f can be related to α and β through simple relations if for the dose range of interest the logarithm of the cell survival around the central dose, D_c, can be approximated by a straight line.

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The D_0 value can be obtained by equating the tangent of eq. (1) at D_c with eq. (2) giving

$$D_0 = 1/(\alpha+2\beta D_c) \tag{3}$$

The extrapolation number, f, is similarly given by

$$f = e^{\beta D_c^2} \tag{4}$$

Finally, the quasithreshold dose D_q may be obtained from

$$D_q = \beta D_c^2 D_0 \tag{5}$$

These relations hold only for the dose range around D_c where the true cell survival is sufficiently well approximated by the tangent at D_c.

As seen from Fig. 1 it is possible to fit the more accurate eq. (1) quite well by straight lines over limited intervals, for example over the range 2 to 3 Gy. The values of D_0 and f will naturally be quite different depending on the dose regime. However, it will be seen below (cf. eq. 8) that eq. (2) is very useful because it can be used with fair accuracy over the often limited dose range of interest in fractionated radiation therapy.

When the dose per fraction is constant an expression even simpler than eq. (2) is sometimes useful:

$$S(D) = e^{-D/D_{0,\mathrm{eff}}} \tag{6}$$

where $D_{0,\mathrm{eff}}$ is the effective D_0 for a given dose level (38). If this dose level is D_c, $D_{0,\mathrm{eff}}$ is given simply by $(\alpha+\beta D_c)^{-1}$ which is always larger than D_0 as given by eq. (3) and clearly seen in Fig. 1.

The value of D_q and D_0 for cells in vitro varies over a wide range, and is related to a number of factors, such as the cell type concerned, the distribution of cells into different phases of the cell cycle and the capacity to repair potential and sublethal injury.

The shape of the survival curve as determined by the factors mentioned will in the first approximation determine the response of a given cell system or organ to fractionated irradiation.

Dose response relation

Based on the shape of the cell survival curve after a single irradiation in vitro the response of a tumor or an organ to multiple irradiations in vivo can be estimated. A detailed analysis is quite complex as it has to consider the capacity of the resting cells to enter the cell cycle, the growth delay of the different

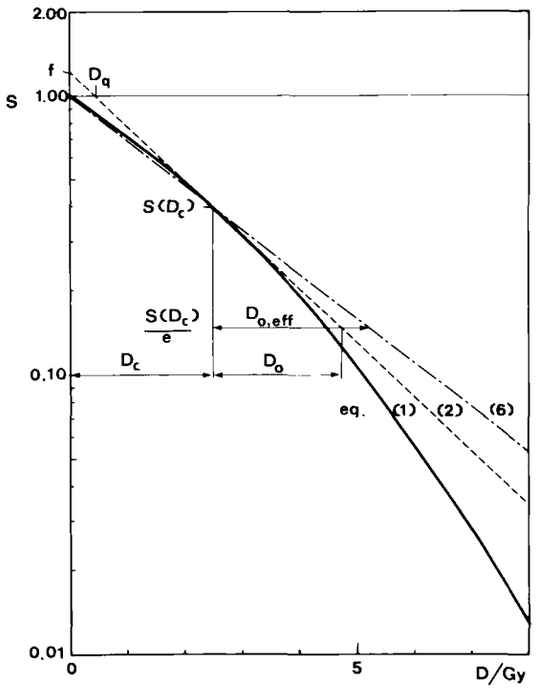

Fig. 1. Comparison of different cell survival curve models.

phases of the cell cycle, the efficiency of repair processes (e.g. oxygen and nutritional factors), the condition of the vascular system (2) and the radiation modality used (e.g. particle type, energy and dose rate). An interesting model was proposed by COHEN & SCOTT (6). For the present purposes only the gross radiation effects are included in order not to complicate the mathematics. The above effects are therefore neglected and it is assumed that all cells are of equal sensitivity, uniformly distributed over the tumor volume, and that in the reference situation they are irradiated to the same absorbed dose with no repair between doses.

Under these simplifying assumptions the mean number of clonogenic cells that will survive in an organ originally consisting of $N(0)$ cells after n irradiations each to an absorbed dose D_i and a survival $S(D_i)$ is given by the product of $N(0)$ and the individual surviving fractions:

$$N(n) = N(0)\prod_{i=1}^{n} S(D_i) \tag{7}$$

It is seen from this relation that the simple cell survival given by eq. (2) is very convenient as the product of the individual survivals is transformed to a summation over the corresponding doses:

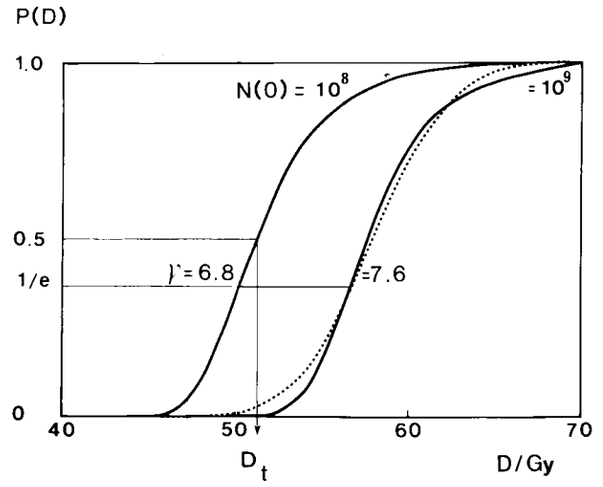

Fig. 2. The shape of the dose response relation given by eq. (9) for 10^8 and 10^9 tumor cells. The dotted line is a cumulative normal probability curve fitted by eye to the larger cell population.

$$\prod_{i=1}^{n} S(D_i) = \prod_{i=1}^{n} f e^{-D_i/D_0} = f^n e^{-\sum_{i=1}^{n} D_i/D_0} = f^n e^{-D/D_0} \quad (8)$$

The net survival under these assumptions is thus determined simply by the total dose $D(=\Sigma_{i=1}^{n} D_i)$ and the number of fractions (n). For the more accurate cell survival curve model eq. (1) the mathematics becomes more complicated. Equation (6) will be even simpler as the f factor disappears, but it is less accurate if the dose per fraction varies somewhat around D_c.

In order to control a tumor the number N(n) has to be quite small and the true number of clonogenic cells will be approximately Poisson distributed with the probability of no surviving tumor cells being given by (cf. 26, 28)

$$P(D) = e^{-N(n)} \quad (9)$$

The resultant tumor control probability is plotted in Fig. 2 as a function of the total dose under the assumption that the dose per fraction is constant and that the tumor cell survival is given by eq. (8). The specific values of the cell survival data used in Figs 1 and 2 are α=0.286 Gy^{-1}, β=0.032 Gy^{-2} (38) and D_c=2.5 Gy with corresponding values of D_0=2.24 Gy, f=1.22, D_q=0.45 Gy and $D_{0,\mathrm{eff}}$=2.73 Gy. With these values the difference in survival between eqs (1) and (2) is less than about half a per cent in the dose range 2 to 3 Gy. For comparison the corresponding difference between eqs (1) and (6) is about five per cent.

As should be expected the curves in Fig. 2 are of sigmoidal shape displaced to increasing doses with increasing tumor size (N(0)). Under the present assumptions the dose response curves are slightly asymmetric with the steepest point somewhat below 50 per cent control probability. The exact value is at the inflection point obtained by setting the second derivative of P equal to zero, giving $P_{infl}=1/e\approx 0.37$.

From Fig. 2 it is seen that the response is an almost linear function of the total absorbed dose about 30 per cent on either side of the inflection point or from about 10 to 70 per cent tumor control probability. From eq. (9) this slope may be calculated using the simple cell survival given by eq. (8). If it is assumed that the number of fractions is constant the response gradient at the inflection point becomes simply:

$$\left(\frac{dP}{dD}\right)_n = \frac{1}{eD_0} \quad (10a)$$

In Fig. 2 a constant dose per fraction was instead assumed. The corresponding response gradient is slightly lower as given by

$$\left(\frac{dP}{dD}\right)_D = \frac{1}{eD_0} - \frac{n \ln f}{eD} \quad (10b)$$

Thus at the steepest part of the dose response curve a dose increase of D_0 increases the tumor control by about 37 per cent. However, the dose increase should preferably be measured relative to the total dose when effects of dosimetric uncertainties are investigated. A more important quantity with regard to precision requirements in radiation therapy is therefore the normalized dose gradient γ defined by

$$\gamma = D \cdot \frac{dP}{dD} \quad (11)$$

This parameter is a dimensionless number which describes how large a change in tumor control probability is to be expected for a given relative increase in absorbed dose (see eq. 14). In fact a dose increase of one per cent on the linear part of the dose response curve will result in an increase in tumor control probability of precisely γ per cent. Under assumption of a constant number of fractions and that only the dose per fraction is changed the normalized response gradient at the inflection point, γ_n, becomes:

$$\gamma_n = \frac{\ln N(0) + n \ln f}{e} \quad (12a)$$

Table 1

Clinically observed normalized dose response gradients for malignant tissues

Site	γ_c	References
Nasopharynx		
T1/2	2.8	METZ et coll. (25)
T3	1.0	
Tongue		
T1	1.7	LEES (23)
T2	1.4	
Squamous cell carcinoma	3.5	PATTERSON (27)
Squamous cell carcinoma	5.9	HLINIAK et coll. (15)
Glottic carcinoma T2	4.6	HARWOOD (12)
Larynx		
T3	4.0	STEWART & JACKSON (33)
T3/4	8.0	MACIEJEWSKI et coll. (24)
T2/3	3.5	SHUKOVSKY (31)
Larynx	3.0	KIM et coll. (22)
Larynx	2.4	ARISTIZABAL & CALDWELL (1)
Glossopalatine sulcus	3.7	SHUKOVSKY et coll. (32)
Hodgkin's disease	0.4	KAPLAN (19)
Melanoma metastasis	4.0	TROTT et coll. (36)

If instead the dose per fraction is kept constant the normalized response gradient is reduced simply to:

$$\gamma_D = \frac{\ln N(0)}{e} \qquad (12b)$$

These expressions show that the normalized gradient under the present simplifying assumptions increase logarithmically with tumor size. The response gradients of the curves in Fig. 2 for example are $\gamma=6.8$ and 7.6 for $N(0)=10^8$ and 10^9 cells, respectively. This increase is caused by the fact that large tumors require higher doses for eradication whereas the tumor control probability becomes large only when very few tumor cells remain, i.e. after the last 2 to 3 D_0 independent of tumor size. One would thus expect larger tumors to have somewhat steeper normalized response gradients. A comparison with clinically observed gradients in Table 1 indicates rather the reverse but also that the observed gradients in general are significantly lower than those calculated using the present model.

These discrepancies are mainly due to the assumption of a perfectly uniform cell population. In clinical materials cells of different sensitivities are often present (10, 35), the tumor size could vary considerably and so could the absorbed dose delivery to the tumor volume. All these factors lead to a decreased slope of the clinically observed dose response relation relative to a uniform cell line of fixed size.

These effects are particularly severe for large tumors where in addition the risks for normal tissue complications are larger than for small tumors and in practice limit the possibilities to increase the dose as much as desirable. This explains the low control rates and low response gradients observed for large tumors.

From the high response gradients in Table 1 for small tumors in the head and neck region it can be concluded that the assumption of a uniform cell population is more realistic. The following theoretical treatment will therefore be more relevant for small well defined tumors. It is also probable that for such tumors the clinically observed response gradient is mainly affected by the uncertainty in dose delivery as will be discussed in further detail below.

A number of other models for the shape of the dose response relation are available such as the cumulative normal probability model (11, 25, 29, 34) and the logistic model (7, 9, 13).

The different models all result in sigmoidal survival curves of rather similar shapes (Fig. 2 and (37)) even though the inflection point of the last mentioned models is at 50 per cent control probability. The choice of a specific model therefore depends more on the ease with which a statistical treatment can be performed. To simplify the comparison of different uncertainties in radiation therapy procedures the normal probability or probit method has special advantages as the dose response gradient, γ, may be interpreted directly in terms of a variance, σ_t^2, in an apparent threshold absorbed dose, D_t, below which there is no tumor control and above which there is complete tumor regression. By equating the slope of the error function with the response gradient one obtains:

$$\frac{\sigma_t}{D_t} = \frac{1}{\sqrt{2\pi}\,\gamma} \qquad (13)$$

where D_t is most naturally related to the dose needed to achieve 50 per cent tumor control probability. Thus a high response gradient, γ, implies a small standard deviation and thus a small increase in dose from D_t to $D_t + 2\sigma_t$ will ensure practically complete tumor control (p=0.95). The importance of γ and σ_t for the required precision in dose delivery in radiation therapy will now be discussed in further detail.

Influence of the distribution of absorbed dose on the local tumor control

Fundamental considerations

In the preceding section it was assumed that the distribution of absorbed dose was perfectly uniform over the entire tumor volume. In practice the dose distribution is seldom uniform and different parts of the target volume may also have different sensitivities. Differences in local sensitivity and absorbed dose delivery will influence the tumor control in a similar way during fractionated therapy as the local variations in surviving fraction after each treatment are multiplied together to give the net effect of a complete series of treatments. For simplicity only the case of non-uniform dose distributions will therefore be treated.

The dependence of the control probability on a change in the absorbed dose level can in the uniform case easily be expressed under assumption that the dose variation falls on a sufficiently linear portion of the dose response curve. The increase in control probability due to a dose increase ΔD may be approximated by:

$$P(D+\Delta D) = P(D)+\frac{dP}{dD}\Delta D = P(D)+\gamma\frac{\Delta D}{D} \quad (14)$$

where γ is the dose response gradient defined in eq. (11).

Assume now that the initially N cells can be divided in two populations of N_a and N_b cells of equal sensitivity irradiated to somewhat different dose levels D_a and D_b, respectively. The control probability of each cell population is then given by an expression of the type:

$$P_a = e^{-N_a\prod_{i=1}^{n} S(D_{a,i})} \quad (15)$$

where $S(D_{a,i})$ is the survival after each dose fraction $D_{a,i}$ to the population a with $\Sigma_{i=1}^{n} D_{a,i} = D_a$, compare eqs (7) to (9).

The probability to control the total cell population P is given by the conditional probability that b is controlled when a is known to be controlled. If, as a first approximation, it is assumed that the actions on a and b are statistically independent, P is expressed by:

$$P = P_a \cdot P_b \quad (16)$$

which may be rewritten:

$$P_t = e^{-\left[N_a\prod_{i=1}^{n} S(D_{a,i})+N_b\prod_{i=1}^{n} S(D_{b,i})\right]} \quad (17)$$

This expression is in agreement with eq. (9) as the terms inside the square brackets give the expected mean number of surviving cells.

If, for a moment, it is assumed that the dose delivery is the same for both populations eq. (15) may be rewritten:

$$P_a = P^{\frac{N_a}{N}} = P^{\frac{m_a}{m}} \quad (18)$$

where the last step relies on the assumption of a constant cell mass throughout both cell populations of masses m_a and m_b, respectively ($m=m_a+m_b$). It is seen that this expression is consistent with eqs (16) and (17) because $m_a/m+m_b/m=1$. This is an explicit expression showing that the dose response curve is shifted to higher control rates and lower doses as the number of cells, the tumor mass, or the volume decreases in general agreement with Fig. 2. Under assumption of a constant tissue density a related expression was used by GOITEIN (11) and SCHULTHEISS et coll. (30).

The increase of the control probability of the whole tumor when a fraction Δm of the tumor mass m is receiving an excessive dose ΔD can now be expressed by combining eqs (14) and (18)

$$P(D+\Delta D, \Delta m) = \left(P(D)+\gamma\frac{\Delta D}{D}\right)^{\Delta m/m} P(D)^{(1-(\Delta m/m))} \quad (19)$$

which may be rewritten:

$$P(D+\Delta D, \Delta m) = \left(1+\gamma\frac{\Delta D}{P(D)}\right)^{\Delta m/m} P(D) \quad (20)$$

If it is now assumed that $\Delta D/D$ and $\Delta m/m$ are so small that a power expansion is valid the change in control probability may be approximated by the first order term given by:

$$\Delta P \approx \gamma\frac{\Delta D}{D}\cdot\frac{\Delta m}{m} = \gamma\frac{\Delta\bar{\varepsilon}}{\bar{\varepsilon}} \quad (21)$$

which clearly illustrates how dose and mass errors combine as an integral dose error in the first approximation. The second equality relies on the definition of the related quantity mean energy imparted, $\bar{\varepsilon}$ (18). In the first approximation it is thus relative changes from the desired mean energy imparted in the tumor volume that alter the control probability.

This result has important consequences for dose specification in radiation therapy. If the dose variations are small the mean absorbed dose to the tumor volume should be used as reference value according to the definition:

$$\bar{D} = \frac{\bar{\varepsilon}}{m} = \frac{\int D(\mathbf{r})\,\mathrm{d}m}{\int \mathrm{d}m} = \frac{\int D(\mathbf{r})\varrho(\mathbf{r})\,\mathrm{d}V}{\int \varrho(\mathbf{r})\,\mathrm{d}V} \tag{22}$$

where $D(\mathbf{r})$ and $\varrho(\mathbf{r})$ are the absorbed dose and density of the tumor at position $\mathbf{r}$ and $\mathrm{d}V$ is the differential volume element. The use of $\bar{D}$ will make the increased and decreased cell killing in hot and cold areas, respectively, compensate each other in the first approximation. This is so because in the hot part of the tumor volume the error in mean energy imparted $\Delta\bar{\varepsilon}_+$ is larger than zero whereas in the cold part $\Delta\bar{\varepsilon}_-$ is less than zero but according to the definition of mean dose $\Delta\bar{\varepsilon}=\Delta\bar{\varepsilon}_+ + \Delta\bar{\varepsilon}_- \equiv 0$. In the first approximation according to eq. (21) ΔP is therefore equal to zero and the tumor control should be quite close to that expected for a uniform dose distribution. When the density of the tumor $\varrho(\mathbf{r})$ is constant eq. (22) may also be expressed as a volume average:

$$\bar{D} = \frac{\int D(\mathbf{r})\,\mathrm{d}V}{\int \mathrm{d}V} \tag{23}$$

The simple two volume case treated in eqs (19) to (21) may serve as a clear illustration as $\bar{D}$ in this case is given by:

$$\bar{D} = \frac{(m-\Delta m)D + \Delta m(D+\Delta D)}{m} = D\left(1+\frac{\Delta m}{m}\frac{\Delta D}{D}\right) \tag{24}$$

By comparison of this expression with eq. (21) it is seen that the change in control probability is in the first approximation exactly proportional to the change in mean dose to the tumor volume.

It can thus be concluded that when the dose variations in the beam are small ($\Delta D << D$ or more exactly when $|\Delta\bar{\varepsilon}|_- = |\Delta\bar{\varepsilon}|_+ << \bar{\varepsilon}$) the best possible correlation between dose delivery and tumor response is obtained when the mean dose according to eq. (22) is used. This is particularly important if different dose distributions are being used for the same patient or group of patients. Owing to the requirement of small dose variations this conclusion is mainly valid for external beam therapy.

Under assumption that the mean absorbed dose according to eq. (22) is used as reference we will now try to find a more general expression for the control probability. This is possible by generalizing eq. (20) in such a way that it holds for arbitrary dose distributions by allowing Δm and the number of mass fractions to decrease and increase, respectively, without bound and taking the product of all the individual probabilities. After taking the logarithm and conversion of the sum to an integral the control probability for this general case takes the form:

$$\mathrm{P}(D(\mathbf{r})) = \mathrm{P}(\bar{D})\,\mathrm{e}^{1/m\int \ln[\mathrm{P}(D(\mathbf{r}))/\mathrm{P}(\bar{D})]\,\mathrm{d}m} \tag{25}$$

If it is assumed that $\bar{D}$ is on the linear part of the dose response curve and $D(\mathbf{r})$ does not deviate much from $\bar{D}$ eq. (14) may be used to expand eq. (25). The integral in eq. (25) may thus be approximated by:

$$\frac{1}{m}\int \ln\left(1+\gamma\frac{D(\mathbf{r})-\bar{D}}{\mathrm{P}(\bar{D})\bar{D}}\right)\mathrm{d}m \approx \frac{1}{m}\int\left[\gamma\frac{D(\mathbf{r})-\bar{D}}{\mathrm{P}(\bar{D})\bar{D}} - \frac{\gamma^2}{2}\left(\frac{D(\mathbf{r})-\bar{D}}{\mathrm{P}(\bar{D})\bar{D}}\right)^2 \ldots\right]\mathrm{d}m \tag{26}$$

where the first term inside the square bracket gives no contribution to the integral owing to the definition of $\bar{D}$. The complete eq. (25) may thus to the second order be approximated by:

$$\mathrm{P}(D(\mathbf{r})) = \mathrm{P}(\bar{D}) - \frac{\gamma^2}{2\mathrm{P}(\bar{D})}\left(\frac{\sigma_D}{\bar{D}}\right)^2 \tag{27}$$

where σ_D^2 is the variance of the dose distribution in the tumor volume as defined by:

$$\sigma_\mathrm{D}^2 = \frac{\int (D(\mathbf{r})-\bar{D})^2\,\mathrm{d}m}{\int \mathrm{d}m} \tag{28}$$

The negative sign of the quadratic term in eq. (27) shows that all variations in the dose distribution that introduce deviations from the mean dose level reduce the control probability for a given mean tumor dose or mean energy imparted. This should be expected as the increased survival in low dose areas can never be completely compensated by the decreased survival in high dose areas.

Application on semirealistic therapy beams

In order to illustrate the magnitude of the effects described the present model will be applied on common types of beam non-uniformities encountered in external beam therapy. In order to simplify the analysis and elucidate the principal mechanisms on one type of tissue it is assumed that adverse radiation

Table 2

The decrease or increase in tumor control as a function of increasing departure from uniformity with the central axis dose as reference

Shift; Fig. 3						Underflattened					Overflattened			
$-\Delta\bar{\varepsilon}/\bar{\varepsilon}$ %	$\Delta x/x$ %	$-\Delta D/D$ %	$-\Delta P$, %			$-\Delta\bar{\varepsilon}/\bar{\varepsilon}$ %	$-\Delta D/D$ %	$-\Delta P$, %			$+\Delta D/D$ %	$+\Delta P$, %		
			$\gamma=3$	$\gamma=5$	$\gamma=7$			$\gamma=3$	$\gamma=5$	$\gamma=7$		$\gamma=3$	$\gamma=5$	$\gamma=7$
0.05	1	10	0.2	0.4	0.7	0.5	1.5	1.5	2.6	3.8	1.5	1.5	2.4	3.3
0.2	2	20	1.0	2.8	6.8	1.0	3.0	3.2	5.6	8.3	3.0	2.8	4.6	6.2
0.45	3	30	3.3	12.0	32.9	1.5	4.5	5.0	9.0	14.1	4.5	4.1	6.6	8.8
0.8	4	40	8.5	34.0	50.0	2.0	6.0	6.9	13.1	22.9	6.0	5.4	8.5	11.3
1.25	5	50	18.4	49.5		2.5	7.5	9.0	18.5		7.5	6.6	10.3	
1.8	6	60	33.1			3.0	9.0	11.4	26.8		9.0	7.7	11.9	

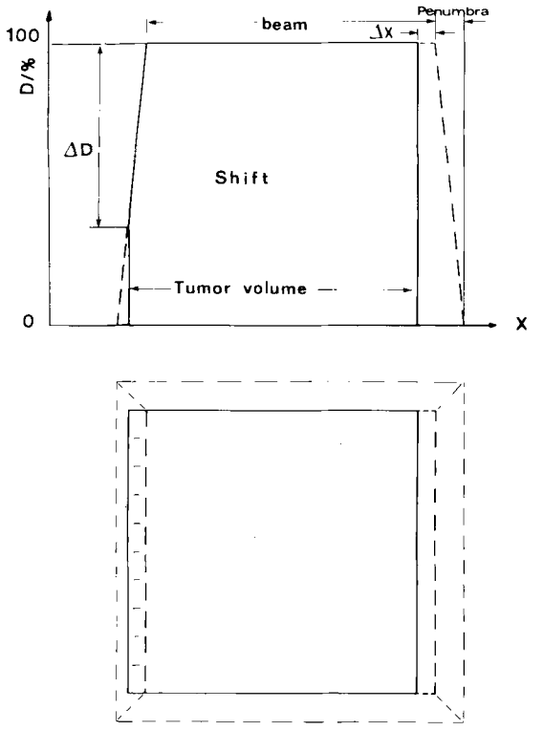

Fig. 3. Beam model used to determine the influence of misalignment on the tumor control probability. No margin for movements of the beam or changes in the shape of the tumor volume were included.

effects are small. As the primary goal of curative radiation therapy is to eradicate the tumor, attention will be focused mainly on tumor control. However, a similar analysis could be made for the probability of complications which often has to be taken into account for instance for large radiation resistant tumor volumes and for beam misalignments with nearby organs at risk. In the following practical applications (Figs 3, 4) it is also assumed for simplicity that the dose distribution along the beam axis is constant as is approximately the case in electron or parallel opposed photon beam techniques.

Beam misalignment. The most fatal case of beam non-uniformity over the tumor volume is probably when the beam is shifted relative to its desired position as illustrated in Fig. 3. This implies sometimes that part of the tumor volume will be in the penumbra region.

To illustrate the effects of a misalignment it is assumed for simplicity that the beam is perfectly uniform over the tumor volume with a rapid linear decrease to zero dose one tenth of the field width outside the uniform area (realistic figure for a 10 cm × 10 cm field). As the dose variations over the field are quite large the complete eq. (25) with the double exponential dose response relation (eqs 3, 7, 9) was used in the calculations. The beam shift data in Table 2 were derived under assumption of three different values of the dose response gradient. If it is assumed that the field size is 10 cm × 10 cm the $\Delta x/x$ values in per cent in the table correspond to the shift in mm of the radiation beam relative to the tumor volume.

From the decrease in control probability (ΔP) it is seen that a shift of more than 2 mm at a dose response gradient $\gamma=7$ and 4 mm at a response gradient $\gamma=3$ is highly undesirable. If these shifts are larger than the set-up accuracy normally achieved clinically a corresponding safety margin must be included in the target volume. Expected normal movements and shape variations for example due to breathing and food intake and uncertainties in patient set-up should be taken into account (17).

The very steep decrease in control probability

Table 3

The decrease in tumor control with increasing non-uniformity when the mean dose to the tumor volume is used as reference (see Fig. 4)

$\Delta\bar{\varepsilon}_{\pm}/\bar{\varepsilon}$ %	Step				Slope				Underflattened				Overflattened			
	ΔD/D %	−ΔP, %			ΔD/D %	−ΔP, %			ΔD/D %	−ΔP, %			ΔD/D %	−ΔP, %		
		γ=3	γ=5	γ=7		γ=3	γ=5	γ=7		γ=3	γ=5	γ=7		γ=3	γ=5	γ=7
0.5	1.0	0.1	0.3	0.5	2	0.1	0.3	0.7	1.5	0.1	0.3	0.6	0.8	0.1	0.3	0.5
1.0	2.0	0.4	1.0	2.0	4	0.5	1.4	2.8	3.0	0.4	1.3	2.7	1.5	0.4	1.0	2.0
1.5	3.0	0.8	2.3	4.6	6	1.1	3.3	7.3	4.5	1.0	3.1	6.9	2.3	0.8	2.3	4.3
2.0	4.0	1.5	4.2	8.6	8	2.0	6.4	16	6.0	1.9	6.1	15.7	3.0	1.5	3.9	7.4
2.5	5.0	2.3	6.7	14.3	10	3.3	11.9		7.5	3.1	11.1		3.8	2.3	6.0	11.3
3.0	6.0	3.4	10.0	22.9	12	5.0			9.0	4.7			4.5	3.2	8.4	

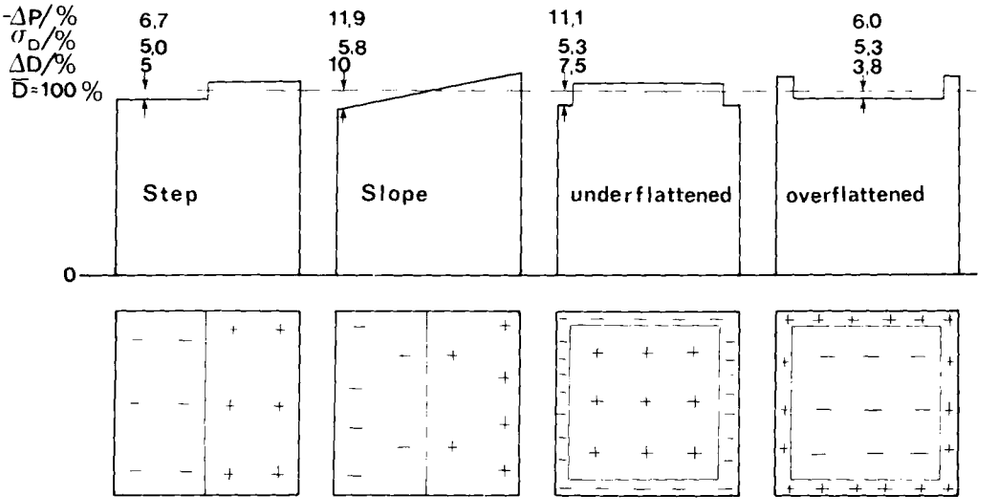

Fig. 4. Influence of different types of beam non-uniformity on the dose variance and the tumor control probability. For all beams the numerical values pertain to $\Delta\varepsilon_{\pm}$=2.5 per cent and γ=5.

with increased misalignment of the beam is of course due to the quite low dose in the penumbra region which increases the probability for local survival of tumor cells.

Suboptimum beam flattening. The most common dose non-uniformity encountered systematically in clinical practice is when the beam is not perfectly flattened. Two types of suboptimum beam flattening can be distinguished. Most often there is a decrease in dose towards the edges of the beam that makes it underflattened as shown in Fig. 4c. In modern treatment units a considerable overflattening is not unusual (Fig. 4d) in order to achieve perfect flatness at large depths (generally 10 cm). The flattening of the beam at a particular depth can be achieved by designing an appropriate flattening filter for that depth. However, due to variations in mean photon energy across high energy photon beams and the considerable influence of phantom scatter in low energy megavoltage beams the flattening will generally vary with depth. For high-energy photon beams these effects can be counteracted by simultaneous energy fluence and spectral flattening (5). This is more complicated in low energy beams and a depth dependent flattening has to be accepted.

The influence of suboptimum beam flattening will be discussed under two different assumptions on the reference dose level. First it will be taken as the central axis absorbed dose value and subsequently the mean dose in the tumor volume is used.

To simplify calculations the generally smooth dose distribution is approximated by a central uniform region over 80 per cent of the field width surrounded by a 10 per cent region of decreased or

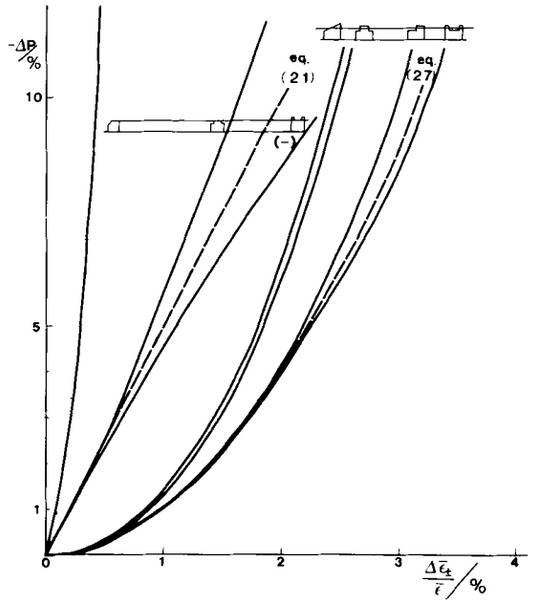

Fig. 5. The loss in tumor control probability with increasing deviation from perfect uniformity of the dose distribution. To simplify comparisons the dose deviation is specified by the relative change in mean energy imparted (cf. eqs 21–23).

increased dose as shown in Fig. 4c and d. The resultant absolute change in tumor control probability, compared with a 50 per cent control in a uniform field receiving the same dose as on the central axis of the under- or overflattened beam, is given in Table 2. From the values in Table 2 it is seen that for a 5 per cent dose decrease or increase in the peripheral parts of the field the control probability drops by about 10 per cent to 40 per cent or increases by about 7 per cent to 57 per cent, respectively, at a response gradient of 5. A decreased or increased control is achieved in these two cases as seen from eq. (21) because the mean dose to the tumor volume is decreased or increased. In general a tumor control probability of better than 50 per cent is aimed at. The percentages in the table are, however, approximately valid also at other mean control rates provided the decreased γ value (eq. 11) at these points has the value used in the table.

A more stringent comparison could be made if the mean dose level in the tumor (see eq. 22) is used for reference as illustrated in Fig. 4. When this is done the change in control probability given in the left half of Table 3 results. A comparison with the values of Table 2 shows that the changes particularly at small departures from perfect flatness is substantially reduced.

This is in general agreement with eq. (27) that predicts a quadratic dependence for small dose variances when the mean dose is used as reference, in contrast to the linear dependence in eq. (21) when the central axis dose is referred to. It is also seen that a change in flatness from the mean dose level always results in a decrease in control probability. However, a significant difference exists between the overflattened and underflattened cases. For a maximum dose decrease or increase of 5 per cent at the periphery relative to the mean dose level the loss in control probability is now about 4 or 3 per cent, respectively. This difference is due to higher order terms in the expansion not included in eq. (27).

It is thus somewhat better to have an overflattened beam than an underflattened one. This could be understood from the fact that the low dose central area of the overflattened beam is not as deep as the peripheral region of the underflattened beam and thus reduces the risk for recurrences.

It is also of considerable practical importance that even if the maximum dose variation in this latter case was increased to 7.5 per cent (see Fig. 4, Table 3) from 5 per cent in Table 2 the change in control probability decreased to less than half the former value due to the use of the mean tumor dose as reference. This indicates that when the dose variations across the beam are small it is highly desirable that dose specifications are really made in terms of the mean dose to the tumor or target volume (see eq. 22).

Beam asymmetry. A common form of impaired beam uniformity is obtained when the center of the beam misses the center of the flattening filter. This results in a too high dose on one half of the radiation field and too low in the other half. In photon beams the transition between the two uniform dose levels is generally step-like as shown in Fig. 4a. In electron beams a more gradual dose variation is often seen, Fig. 4b, of course depending on the design of the beam flattening system.

The resultant changes in control probability are given to the left in Table 3. It is seen that the loss in control is rather similar to the case of under- and overflattened beams when the deviations from uniformity are expressed in terms of the net positive or negative local departure, $\Delta\varepsilon_{\pm}$, from the mean energy imparted. Fig. 4 is based on a constant value of $\Delta\varepsilon_{\pm}$ of 2.5 per cent. This similarity is in general agreement with the second order term given in eq. (27) because $\sigma_D/\bar{D} \approx 2(\Delta\varepsilon_{\pm}/\bar{\varepsilon})$. In fact a comparison of ΔP values for a given value of the relative vari-

ance σ_D/D gives an even closer agreement between the effects than shown in Table 3 where $\Delta\varepsilon_{\pm}$ was chosen to allow a comparison with Table 2.

Conclusions. From the numerical examples given it can be concluded that the tumor control probability depends primarily on the first two moments of the dose distribution according to eq. (27). It is thus the mean dose and the relative dose variance that in the first approximation determines the tumor control probability. As the dose variance appears in quadrature with negative sign this term is a measure of the loss in tumor control due to a non-uniform dose distribution at a given mean dose. This also indicates that small dose variations are not very serious (e.g. is $\Delta P < 1$ per cent for a $\sigma_D < 2$ per cent of $\bar{D}$) as long as the mean dose in the target volume is used as reference. However, large dose variations could be very severe as the loss in control rises steeply when σ_D rises above 4 per cent of $\bar{D}$.

In order to compare the loss in tumor control with the common non-uniformity modes discussed the decrease in control probability with the departure from perfect uniformity is plotted in Fig. 5. For comparison eqs (21) and (27) have also been included in this figure as dashed lines.

It is seen that the case with misalignment is most severe. The other curves are rather well described by the two simple equations depending on whether the central axis dose or the mean dose is used as reference. As a general rule it can be concluded that for a given variance in mean energy imparted as specified by $\Delta\varepsilon_{\pm}$ the loss in control probability is most severe for the case where the lowest dose to the tumor volume is seen.

This result implies that the minimum dose in the tumor volume is the most important dosimetric concept when there are large dose variations over the tumor volume in good agreement with the practice in intracavitary or interstitital treatments. In external beam therapy where dose variations are generally smaller the need to avoid underdosage for example when two beams are placed side by side, is clearly indicated. In fact a small local overdosage is the least harmful case as shown by the curve for an overflattened beam and should therefore generally be preferred.

It is also of great practical importance to see that small inhomogeneities are unimportant as long as the mean dose to the target volume is used as dosimetric variable. For example, the loss in tumor control is only about one per cent when the local departure from the mean energy imparted is less than one per cent. This corresponds to a beam asymmetry of less than ±2 per cent or a dose decrease or increase of less than 3 per cent near the field edges. A conclusion of practical clinical value is that when there are such small dose variations there is no need for using compensators provided the mean tumor dose is known and used as reference.

Influence of the uncertainty in dose delivery on tumor control

The variability in the clinical situation with regard to organs at risk and their radiobiologic characteristics as well as the level of side effects that may be accepted for the treatment, makes it impossible to make a general, yet simple, statement on the required precision in dose delivery. Rather it will be necessary for each institution to define for the particular clinical situation the acceptable level and frequency of side effects for a reasonable probability of tumor control and then with a knowledge of the absorbed dose variation in the particular situation, prescribe the dose to be aimed at. It will probably then be found that the requirement with respect to side effects of therapy will generally demand a reproducibility in absorbed dose better than 5 per cent (16) and sometimes as low as 3 per cent. A more stringent analysis should instead start from an acceptable uncertainty in tumor control (for example chosen in such a way that it is marginally observable in the population at hand) or complication rate, and then from established or estimated dose response relations determine the required precision in dose delivery.

From the above analysis it is clear that in several cases very steep dose response relations can be expected clinically (see Table 1 and eqs 12a, b). Normalized response gradients as high as $\gamma=5$ are not unusual and $\gamma=3$ are very common resulting in an increase in local control rate of 50 and 30 per cent, respectively, for an increase in absorbed dose of 10 per cent at least on the steep quasilinear portion of the response curve. An absolutely necessary prerequisite for precise radiation therapy, and for the determination of such steep dose response relations, is therefore a high accuracy in the delivery of absorbed dose to the target volume. Uncertainty in delivery of absorbed dose would result in an increase in the number of patients suffering from

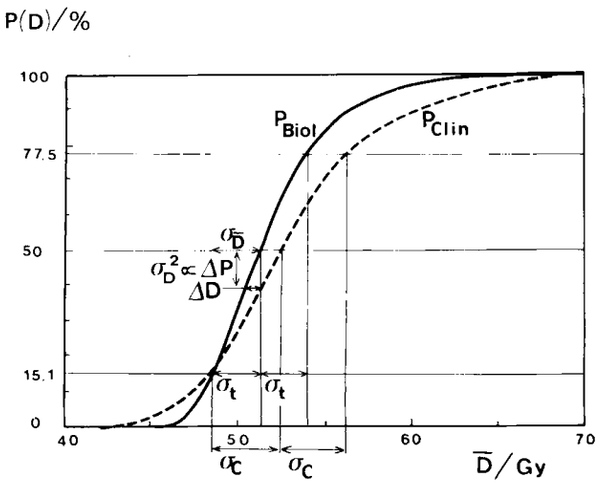

Fig. 6. The change of the biologic expected tumor control probability P_{Biol} observed on a clinical material (P_{Clin}) when the effects of uncertainties in dose delivery are taken into account. The relative standard deviations of the mean dose and the dose distribution are 5.5 and 5.1 per cent, respectively. The increased tumor control at low doses is due to the uncertainty in mean dose to the tumor which causes better control in some patients.

Table 4

Maximal relative standard deviations in dose delivery (per cent) corresponding to a σ_P of 10 per cent and ΔP of −5 per cent

	γ=1	γ=2	γ=3	γ=5	γ=7
$\sigma_{\bar{D}}/\bar{D}$	10	5	3.5	2	1.5
$\sigma_b/\bar{D}$	22	11	7.5	4.5	3
$\sigma_{tot}/\bar{D}$	24	12	8	5	3.5

complications and recurrences due to over- and underdosage, respectively, and in an erroneous observed dose response, which is not as steep as the true one. A qualitative discussion of these problems was given by HERRING (13).

The tumor control is influenced in two different ways by uncertainties in dose delivery as can be seen from eq. (27). The variance in the mean absorbed dose to the tumor volume, $\delta^2_{\bar{D}}$ has a direct influence on the slope of the observable dose response relation as also may be seen from eqs (14) and (21). However, the variance in the relative distribution of absorbed dose inside the tumor volume, σ^2_D, shifts the dose response curve to lower control probabilities and higher doses.

The former effect can be expressed in a more quantitative way by postulating that the variance in biologic sensitivity (cf. 29) or rather the variance in apparent absorbed dose threshold, σ_t^2, (see eq. 13) is increased when determined on a clinical material by the variance in mean absorbed dose to the target volume, $\sigma^2_{\bar{D}}$, as they both characterize approximately normal and statistically independent distributions. Thus:

$$\sigma_c^2 = \sigma_t^2 + \sigma^2_{\bar{D}} \tag{29}$$

where σ_c^2 is the clinically observed dose response variance (cf. 34). This implies that all the observed dose response gradients in Table 1 in reality are steeper than the clinically observed values. The true normalized response gradient can thus be obtained by combining eq. (29) with the relation between γ and σ in eq. (13).

$$\gamma = \gamma_c \sqrt{\frac{\sigma_c^2}{\sigma_c^2 - \sigma^2_{\bar{D}}}} \tag{30}$$

Eq. (29) pertains to the present model where all cells are identical and uniformly distributed in the tumor volume. In a more realistic clinical situation σ_t^2 should be substituted by the total biologic variance σ_b^2 as given by

$$\sigma_b^2 = \sigma_t^2 + \sigma_d^2 + \sigma_s^2 + \sigma_f^2 \tag{31}$$

where σ_d^2 is due to the non-uniform distribution of cells in the target volume, σ_s^2 is due to the difference in sensitivity in different parts of the tumor and σ_f^2 finally due to uncertainties in the time dose fractionation. The variance σ_s^2 naturally includes contributions from variations over the target volume of factors like cell differentiation, oxygenation, synchronisation and nutrition. The variance σ_t^2 includes only the contribution from a completely uniform cell line.

As a result of the variance in mean dose to the tumor volume the tumor control probability will have a corresponding variance given by:

$$\sigma_P^2 = \left(\frac{\gamma \sigma_{\bar{D}}}{\bar{D}}\right)^2 \tag{32}$$

as can be derived from eq. (14).

The quantification of the loss in tumor control due to variations in the relative distribution of absorbed dose inside the target volume was given already by eq. (27). Over the quasilinear portion of the response curve this corresponds to a positive shift of the curve along the dose axis given by:

$$\Delta D = \frac{\gamma \sigma_D^2}{2P(\bar{D})\bar{D}} \tag{33}$$

These effects on the clinically observable dose response relation are illustrated in Fig. 6 using the response relation for 10^8 cells as shown in Fig. 2 and fairly realistic figures on $\sigma_{\bar{D}}$ and σ_D (5.5 and 5.1 per cent, respectively of $\bar{D}$).

It is seen that the true biologic response is considerably modified by the variance in mean dose and dose distribution. It is seen that the shift ΔD ($\approx$1 Gy, eq. 33) and the control loss ΔP (12 per cent, eq. 27) are quite significant at this quite steep response gradient. The standard deviations are: σ_t=2.7 Gy, $\sigma_{\bar{D}}$=2.8 Gy and σ_c=3.9 Gy with the corresponding response gradients γ=6.8 and γ_c=5.2. These figures are in general agreement with the values in Table 1 for small well defined tumors of the head and neck.

The most important effect seen in Fig. 6 is perhaps that the largest effects of dosimetric inaccuracies are found at the highest tumor control probabilities. When normal tissue complications are a problem complete tumor control cannot be achieved without severe complications unless the dosimetric uncertainties are very small. Uniform and precise dose delivery is therefore one of the corner stones of accurate radiation therapy.

Dosimetric precision requirements

In order to have a reasonable probability to detect the outcome of different treatment techniques or dose distributions on patient groups of a few hundred persons, an uncertainty in tumor control probability of no more than $\pm$10 per cent and preferably less than $\pm$7 per cent is desirable (3). For ethical reasons the loss in tumor control probability due to dose variations over the tumor volume should be less than 5 per cent. Based on eqs (32) and (27) the maximum allowable standard deviations in mean dose and dose distribution (eq. 28) can then be calculated as given in Table 4. Also included is the total dosimetric standard deviation.

It is seen that for normalized dose gradients, γ, larger than about 5 the total standard deviation in dosimetry should be less than 5 per cent. The strictest demands relative to the present situation in radiation therapy are set by a standard deviation in control probability of less than 10 per cent. From the present results it can be concluded that the relative standard deviation of the mean dose in the target volume should be less than 5 per cent when the normalized response gradient γ is less than 3 and for cases where the expected response gradient is higher than 3 (cf. Table 1, eq. 30) preferably as small as 3 per cent to have a reasonable control of the treatment outcome.

In principle a large standard deviation of the dose distribution is less severe than in the mean absorbed dose as the former could be compensated by a slight overdosage at least when the accompanying additional risk for complications can be tolerated.

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