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CELL KINETIC APPROACH TO OPTIMISING DOSE DISTRIBUTION IN RADIATION THERAPY

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The results of tumour treatment by irradiation is, among other things, determined by the distribution of tumour cells, the sensitivity of tumour and healthy tissue and the distribution of radiation dose in space and time.

Before an optimum treatment can be selected it is necessary to be able to predict the effect of different dose distributions on a tumour of given type and extent. There is little hope that controlled clinical trials will provide an understanding of the conditions in detail (GRAFFMAN & JUNG 1970), but the problem may be approached by using models.

The tumour response models in current use might be classified in three categories. To the first category belong the mental models used in ordinary clinical work. These are based on principles regarding e.g. the importance of an even dose distribution over the tumour region, the value of dose to stations with possible lymphatic spread, and tolerable doses to critical organs or tissue. These models have gradually developed from clinical experience and have been under clinical test for tens of years. However, they often call for an intuitive evaluation and are often spiced with local believes. They are not well documented and not amenable for an analytical approach with algorithms giving a quantitative measure of goodness of treatment.

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Another approach has been to give a mathematical description of parameters considered by a set of clinicians in their mental evaluation of dose distributions and to derive heuristic score functions yielding verdicts as close as possible to the physician's judgements (HOPE et coll. 1967). Whenever the treatment strategy changes, the parameter values have to be changed so that the model again agrees with the therapists.

The models in the third category are based on cell kinetics. They consider the tumour (and sometimes also healthy tissue) as a population of cells which is influenced by the radiation dose and by the temporal distribution of dose delivery during radiation therapy. Such models often use, or easily include, biologic concepts such as shoulder curves, oxygen effect, tumour cell density, rate of cell division, re-oxygenation etc. (ELLIS 1966, FISCHER 1969, COHEN 1971, KIRK et coll. 1971, NIEDERER & CUNNINGHAM 1972, PREWITT 1972).

Cell kinetic models have often been strongly, and probably also correctly, criticized as being too crude and not in accord with clinical experience (cf. e.g. SUIT et coll. 1967). It might be expected, however, that the models will gradually approach reality and that, in the meantime, they may be used as a tool in selecting the best set of field parameters (beam widths, weights, and angles etc.) from the multitude of alternatives which may be taken into account with computer techniques.

The present investigation aims at an evaluation of a simple, tumour-cell radiation-response model which gives a simple figure of merit for selecting the best dose distribution in external radiation therapy. The behaviour of this figure, when the weights, widths and angles of the radiation beams and the total dose are varied under different assumptions regarding density, oxygenation, sensitivity and distribution of tumour cells, has been analysed as well as the limits on the treatment parameters imposed by a tolerable, dose–volume relationship in healthy tissue.

Methods

Local tumour response. It appears to be a reasonable inference from radiation biology that tumour cells are sterilized mainly by the dose received by the cells and that the risk of recurrence is depending on the number of vital tumour cells remaining after treatment.

The surviving fraction of tumour cells, S, after a dose, D, was calculated from the formula

$$S = 1 - (1 - \exp(-D/D_0))^n \tag{1}$$

where D_0 is the mean lethal dose, and n is the extrapolation number (FISCHER 1969).

Measure of goodness of treatment. The measure of goodness was taken as a probability, C, that no tumour cells survive the irradiation. This quantity was calculated according to the formula

$$C = \exp\left(-\int S^m \zeta dv\right) \tag{2}$$

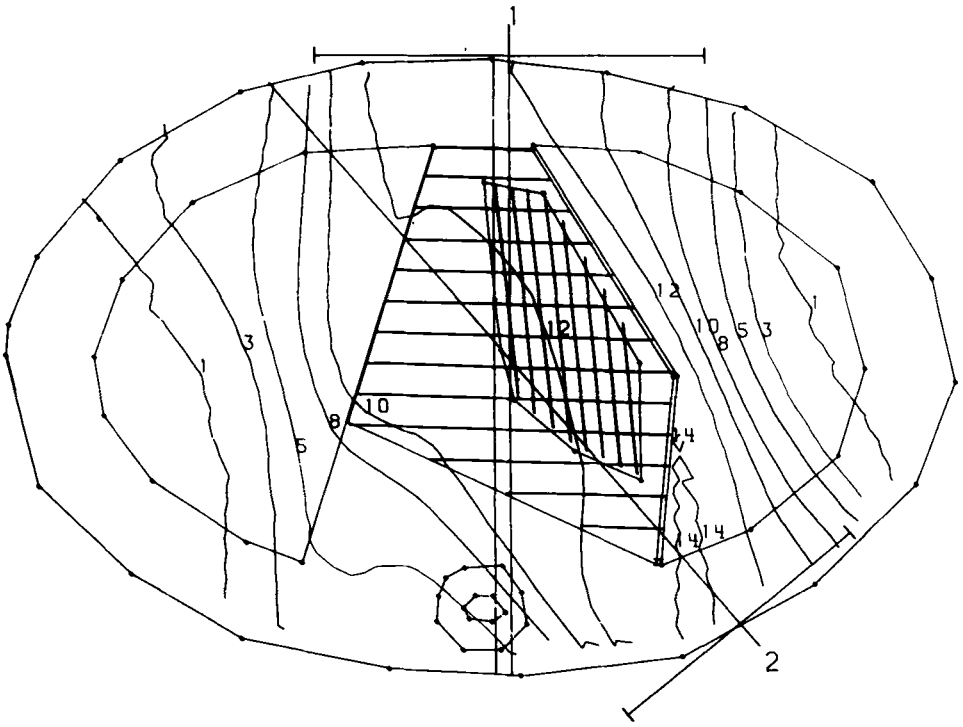

Fig. 1. The simulated therapeutic situation. The inner and outer regions of the tumour are indicated by shaded areas.

where ζ is the local tumour cell density, m the number of fractions and the integration is carried out over all tumour tissue.

Measure of tolerance. The radiation effect on healthy tissue limits the dose that may be given to tumour tissue. The consequence of irradiation may be related to the fraction of an organ that is irradiated above a certain critical dose (cf. e.g. RUBIN & CASARETT 1973).

The measure of tolerance was therefore defined by a factor, T, which approaches unity when less than X′ per cent of the organ receives more than the critical dose and is almost zero when more than X″ per cent receives more than the critical dose. Between the limits X′ and X″ the tolerance factor decreases in a sigmoidal way. For each organ, or part of an organ, which should be given special consideration, the limits X′ and X″, as well as the corresponding critical accumulated doses, have to be defined. Several critical dose levels with corresponding limits X′ and X″ may be defined for each organ.

The simulated therapeutic situation. A simplified case, simulating bronchial carcinoma (Fig. 1) was considered. The body outline and the outline of the lungs were

described by ellipses. The tumour was divided in an inner region of constant cell density and an outer region, in which the density of tumour cells decreased radially from the tumour centre in a sigmoidal fashion. Two different subpopulations, one euoxic and one hypoxic were assumed in the two tumour regions. The mean lethal doses for euoxic and hypoxic tumour cells and the associated extrapolation numbers were chosen so (Table) that C approached a clinically reasonable local cure level (≈ 0.5) under conventional treatment conditions, i.e. 30 fractions with a total mean dose of about 6 000 rad (Bloedorn 1966) and a reasonable estimate of initial tumour-cell density.

Dose calculations were performed in two dimensions using a subroutine in UASDOS, a program used for automatic dose planning at the University Hospital. This subroutine utilizes curved decremental lines and corrects for build-up effects, oblique incidence and heterogeneities (cf. GRAFFMAN et coll. 1975).

The dose distributions were normalized so that the maximum accumulated dose in any point in the body cross section was 6 960 rad for the reference case.

Computation methods. The numerical computation of formulas (1) and (2) was performed as follows: The cross-section of the body at the tumour site was covered with a rectangular grid with gridpoints (i, j) $i = 1, 2 \ldots, K$, $j = 1, 2 \ldots, L$. The dose calculation program gave the relative dose D(i, j) in these points. A relationship between this distribution and the actual dose was given by the maximum dose, M rad, to any of the gridpoints. A constant α was determined such that

$$\alpha \cdot \max_{\substack{1 \leq i \leq K \\ 1 \leq j \leq L}} D(i, j) = M$$

The absolute dose values were then recalculated from $D(i, j) = \alpha \cdot D(i, j)$. Eq. (1) determined the fraction S(i, j) of cells surviving the dose D(i, j). After m fractions $(S(i, j))^m \cdot N_0(i, j)$ cells remain in the point (i, j). $N_0(i, j)$ stands for the initial number of tumour cells associated with the point (i, j).

Summation over all points gave the total number of surviving cells $= N_s$. With the assumption that the probable number of surviving cells obeys a Poisson distribution with the expected value N_s, the probability for zero survivors equals $C = \exp(-N_s)$.

The number of cells per gridpoint in the outer region of the tumour was given by

$$N_0(i, j) = a(i, j) \cdot N_0 \tag{4}$$

with

$$a(i, j) = \int_{-\infty}^{x(i, j)} \frac{6}{b(i, j)\sqrt{2\pi}} \exp\left(-\frac{36 \cdot (t - b(i, j)/2)^2}{2 \cdot b(i, j)^2}\right) dt \tag{5}$$

Table

Parameter values in the reference case

Tumour data

Initial cell surface density 10^9 cells/cm^2
Initial fraction of hypoxic cells;
  inner region 10 %
  outer region 5 %
Mean lethal doses and extrapolation numbers
  euoxic cells $D_0 = 88$ rad, $n = 3$
  hypoxic cells $D_0 = 264$ rad, $n = 1$

Treatment data

	anterior	posterior field
Beam direction	0°	226°
Weight	1.00	1.00
Width	11.5 cm	9.5 cm

Number of fractions 30
  total maximum dose $30 \times 232 = 6\,960$ rad

where N_0 is the constant initial number of tumour cells per gridpoint in the inner tumour region; b(i, j) is the distance between the inner and outer tumour boundaries as measured along a straight line through the point of computation (i, j); and x(i, j) is the distance from the outer boundary to the same point.

The calculations were performed for each subpopulation of euoxic and hypoxic tumour cells with appropriate values of D_0, n and $N_0(i, j)$. The total curability was calculated as the product of the curabilities for the subpopulations. It should be noted that the euoxic and the hypoxic populations were kept apart in the computations, which means that no reoxygenation was taken into account.

The measure of tolerance was calculated as

$$T = \int_x^{100} \frac{6}{(X'' - X')\sqrt{2\pi}} \cdot \exp\left(-\frac{1}{2} \cdot \frac{(t - (X' + X'')/2)^2 \cdot 36}{(X'' - X')^2}\right) dt \qquad (6)$$

where X′ and X″ have been defined above and X is the percentage of the organ which has received a dose greater than the critical dose.

The choice of a proper grid size is dependent on how large the dose changes are that occur over a small area. Particularly for the computation of the measure of tolerance the grid size is of importance since two or three points receiving a dose just above or just below the critical dose may mean great changes in function value. The choice of the limits X′ and X″ should take this into account. The curability function will also depend on the grid size; with a finer grid the local effects are better taken into account and do not give undue merit to overkill. This should not, however —for a reasonable choice of grid—mean any significant changes in the optimum setting of the field parameters.

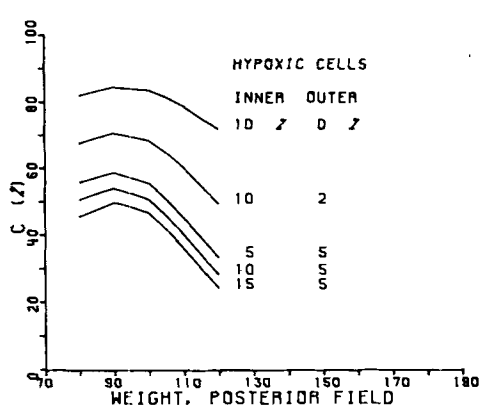

Fig. 2

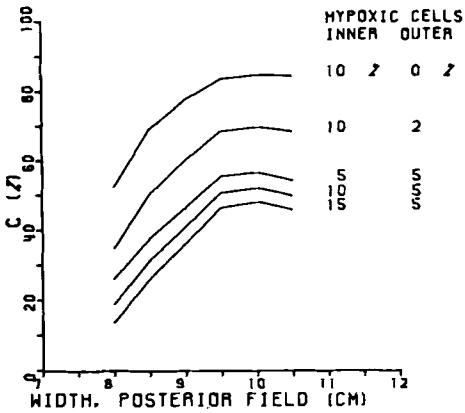

Fig. 3

Fig. 2. The curability function for variations of the weight of the posterior field. The various curves correspond to various percentages of hypoxic cells in the inner and outer tumour region. The other parameters are kept at their reference values.

Fig. 3. The curability function for variations of the width of the posterior field. The various curves correspond to various percentages of hypoxic cells in the inner and outer tumour region. The other parameters are kept at their reference values.

Results

The variations in the analysed parameters were centred around a reference case, for which the parameter values are given in the Table. This reference case, selected after trial-and-error calculations with the model, was chosen as an optimum from conventional clinical considerations taking into account injury to healthy critical organs.

The effect of variation in the weight of the anterior and posterior fields on the curability appears in Fig. 2, under five assumptions regarding the fractions of hypoxic cells in the inner and outer tumour regions.

The effect of variation in the width of the posterior field on the curability under five assumptions regarding the oxygenation of the inner and outer tumour region is given in Fig. 3.

The effect on the curability of a variation in posterior field direction from 219° to 229° appears in Fig. 4, for various assumptions regarding the maximum dose delivered per fraction, the number of fractions being kept constant equal to 30.

The changes of the tolerance factor of the healthy lung with regard to various directions of the posterior field are illustrated in Fig. 5. The three curves refer to three critical dose levels and three corresponding percentages of lung tissue describing the marginal zone between no and maximum risk.

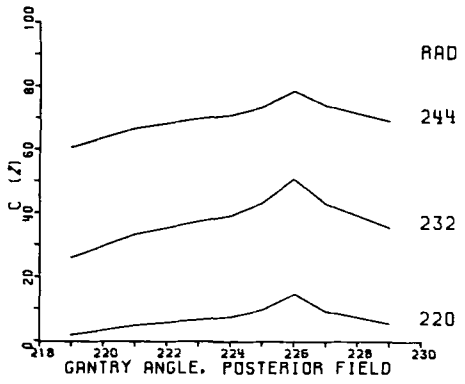

Fig. 4

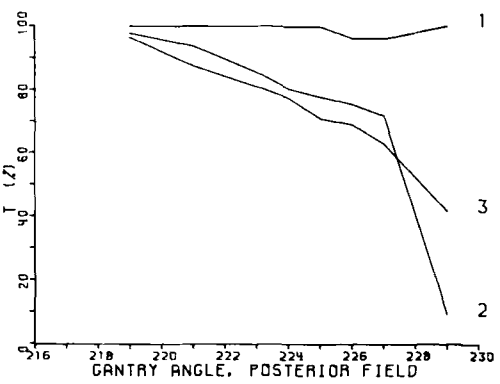

Fig. 5

Fig. 4. The curability function for variations of the direction of the posterior field. The various curves correspond to various values for the maximum dose delivered per fraction. The other parameters are kept at their reference values.

Fig. 5. The tolerance factor for variations of the direction of the posterior field. (1) critical dose 3 000 rad; percentages $X' = 25\,\%$ and $X'' = 60\,\%$; (2) critical dose 4 000 rad; $X' = 20\,\%$ and $X'' = 40\,\%$; (3) critical dose 5 000 rad; $X' = 10\,\%$ and $X'' = 26\,\%$.

Discussion and Conclusions

The optimum setting of the posterior beam angle, the weight of the anterior and posterior fields and the width of the posterior field are much independent on various assumptions regarding the maximum dose to the tumour area, and the fraction of hypoxic cells in the inner and outer tumour region (Figs 2–4). The general behaviour of the curability function is rather smooth and suboptima are not frequent or accentuated. From these viewpoints the type of model applied here may suitably be used in an automatic optimisation procedure.

The behaviour of the tolerance factor is critically depending on the assumptions regarding radiation effect on healthy tissue (Fig. 5). The sharp decrease in one of the curves (No. 2) may indicate a forbidden sector. The tolerance factor may, alternatively, be included directly in the objective function for the optimisation procedure.

Obviously the curability is critically depending on the assumption regarding the distribution of tumour tissue in the patient. At present, the model does not allow the clinical judgement of the patient with respect to tumour cell spread to be included in a probabilistic way. This possibility might be of value and should be tested when the necessary techniques and basic information are available.

In the calculations the larger part of the computer time was spent on dose calculation and only a small fraction (about 10 %) on calculation of curability. Also rather complicated models for estimating the goodness of a treatment therefore seem to be practical.

The technique applied here is similar to that introduced by COHEN (1971) with regard to tumour tissue effect. It is extended, however, from single points to an area, approximating a three-dimensional volume. COHEN applied cell kinetic techniques also for estimating probable radiation effects in normal tissue. The approach taken here allows a similar treatment of the local effects on healthy tissue.

The validity of the tumour model and especially the measure of curability is, however, highly questionable. Curability is here only used as a technical term and should not be related to cure in the clinical sense. It is believed, however, that a treatment giving a higher curability is more probable to cure the patient than a treatment giving a low curability. It might also be hoped that the selection of optimum field parameters is not critically depending on the detailed characteristics of the applied cell model and that all reasonable models (and hence also the correct one) yield effectively the same set of optimum field parameters. This question has not been analysed in the present report, but will be thoroughly investigated. It also remains to apply cell models of the present type to a number of clinical situations and compare the model predicts with the judgements by clinicians.

SUMMARY

A simple tumour-cell radiation-response model was coupled to a dose-calculation routine and applied to a clinical situation in radiation therapy. The dose distributions resulting from various settings of two radiation fields, as well as the tumour response under various assumptions regarding sensitivity and distribution of tumour cells, were calculated automatically. The probability of zero surviving tumour cells after 30 fractions was taken as a measure of goodness of the dose distributions and was found to vary rather smoothly over the parameter intervals considered. For some parameters a distinct optimum was found, rather insensitive to different assumptions regarding cell response. A tolerance factor for healthy tissue, based on a dose-volume relationship, was also considered. It is concluded that a cell kinetic approach to automatic optimisation of field parameters in external radiation therapy might be realistic both from computational and economic points of view.

ZUSAMMENFASSUNG

Es wurde ein einfaches Tumor-Zell Strahlen-Respons-Modell einer Dosis Berechnungsroutine zugeordnet und bei der klinischen Situation der Strahlentherapie verwendet. Die Dosisverteilung von verschiedenen Plazierungen von zwei Strahlenfeldern sowie die Tumor-Respons unter verschiedenen Annahmen für die Empfindlichkeit und Verteilung der Tumorzellen wurde automatisch kalkuliert, Die Wahrscheinlichkeit, dass keine Tumorzellen nach 30 Fraktionen überleben, wurde als Gütemass der Dosisverteilung gewählt und erwies sich als ziemlich gleichmässig über die gewählten Parameter-Intervalle verändernd. Es wurde ebenfalls ein Toleranzfaktor für das gesunde Gewebe, der sich auf die Dosis-Volumen Beziehung stützte, gewählt. Es wird geschlossen, dass ein zellkinetischer Ansatz zu einer automatischen Optimierung der Feldparameter bei der externen Strahlentherapie sowohl vom kalkulatorischen als vom ökonomischen Gesichtspunkt realistisch sein kann.

RÉSUMÉ

Un modèle simple de réponse des cellules tumorales aux radiations a été associé à un calcul de dose de routine et appliqué aux conditions cliniques en traitement par les radiations. Les auteurs ont calculé automatiquement les distributions de dose résultant de différentes dispositions de deux champs d'irradiation ainsi que la réponse de la tumeur dans diverses hypothèses concernant la sensibilité et la distribution des cellules tumorales. La probabilité d'une survie nulle de cellules tumorales après 30 fractions a été prise comme une mesure de la qualité de la distribution de dose. Les auteurs ont constaté qu'elle varie de façon assez faible et régulière dans les intervalles de paramètres étudiés. Pour certains paramètres on a trouvé un optimum net, assez peu sensible aux différentes hypothèses concernant la réponse des cellules. Les auteurs ont aussi étudié un facteur de tolérance du tissu sain, basé sur une relation entre la dose et la volume. Les auteurs concluent qu'une approche par la cinétique cellulaire de l'optimisation automatique des paramètres de champs dans le traitement par l'irradiation externe pourrait être réaliste aussi bien du point de vue économique que du point de vue calcul par ordinateur.

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