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RADIOBIOLOGIC DETERMINATION OF THE TOTAL DOSE IN RADIOTHERAPY

by

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The end-result of radiotherapy depends on factors among which total dosage is most important. The direct cell action model derived from cell survival investigations in vitro and applied to tumour cell populations in vivo suggests that the dosages administered in radiotherapy are not sufficient to result in local neoplastic control. This is based on the assumption that if even a single tumour cell survives recurrence may develop. In clinical practice, however, 6 000 to 7 000 rad over 6 to 8 weeks of fractionated irradiation causes local cure of a significant number of neoplasms. There is, thus, some contradiction between the cell survival models and the results of clinical radiotherapy.

Physical treatment planning and dose determination are routine procedures in clinical radiotherapy. It has recently been reported (SPRING & MALMIO 1969) that iso cell survival curves based on a single-hit, multi-target model correspond with adequate accuracy to the isodose curves of the physical dose distribution. Given this, it is possible to examine the cell survival fractions instead of the radiation doses. The authors have applied this method in the present work to an autopsy material consisting of irradiated patients with carcinoma of the lung (RISSANEN et coll. 1968) in order to analyse the relations between the radiobiologic dose distribution and local cure against failure.

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Material and Methods

The material consisted of 57 histologically verified cases of inoperable carcinoma of the lung treated during the period 1963—1967 by megavoltage therapy and examined by autopsy 2 months to 4 years and 1 month (average 9 months) later (RISSANEN et coll.). The histologic type was verified prior to treatment by biopsy in connection with bronchoscopy, tumour puncture, mediastinoscopy, scalenus biopsy or thoracotomy. Together with roentgenography these methods were used also to determine the size and localization of the growth.

Forty cases were treated with 33 MeV photons and 17 cases with a 3 000 curie ^{60}Co unit. The weekly tumour dose was 1 000 to 1 100 rad and the tumour dosage ranged from 4 000 to 7 000 rad over 5 to 8 weeks. Some of the cases were treated with the split-course technique (HOLSTI 1969).

The findings have been divided into four groups according to the type of primary growth at autopsy: (1) no carcinomatous tissue evident, (2) no definite malignancy macroscopically, but microscopically fibrosis with obvious islets of carcinoma cells, (3) necrotic areas with malignant infiltration, and (4) viable malignant tissue in the treatment area.

1. *No carcinomatous tissue.* Eighteen cases of the total series (18/57 = 32 per cent) had no carcinomatous tissue in the treatment area either macro- or microscopically. Partial resection of the growth was performed in six and exploratory thoracotomy in two of these eighteen cases. The tumour dose was 4 800 to 6 250 rad. Fourteen (78 per cent) cases of this group were treated by the split-course method and four received the entire course of irradiation as continuous therapy. The pre-planned treatment scheme was fulfilled in all the cases and there were no complications.

2. *Fibrosis with islets of carcinoma cells.* The group comprised nine cases (9/57 = 16 per cent). Partial resection of the tumour was performed in one and exploratory thoracotomy in another of these cases. The dosage was 4 700 to 7 000 rad. Four of these cases were treated by the split-course method and five received continuous irradiation.

3. *Necrotic areas containing carcinomatous tissue.* The group comprised nine cases. Treatment had to be discountinued in three, leaving only six (6/57 = 10 per cent) cases that received the planned dosage. Three cases were subjected to exploratory thoracotomy. The radiation dosage was 4 000 to 5 900 rad. In only three cases was it possible to complete the therapeutic course according to schedule. Six cases had complications (e.g. anemia, fever) necessitating interruption of the therapy. Five cases were managed by the split-course method and four cases received continuous treatment.

4. *Viable carcinoma tissue in the treatment area.* The fourth group comprised twenty-one cases. Treatment had to be discontinued in four of them, and thus viable carcinomatous tissue was demonstrable both macro- and microscopically in the treatment area in seventeen (17/57 = 30 per cent) cases that received roughly the planned dosage. Exploratory thoracotomy was performed in three cases and partial resection of the tumour in one case. The dosage was 4 000 to 6 000 rad. The split-course method was employed in eleven and continuous radiotherapy in ten cases. The therapy was completed according to schedule in only eleven cases. In the other ten complications (e.g. anemia, fever) interfered with, and in three of these prolonged, the treatment time to 114 to 133 days.

Metastases were demonstrated in fifty-two cases of the total autopsy material.

The single-hit, multi-target model

The main model used in radiotherapeutic calculations is the single-hit, multi-target model, which means that the cells irradiated consist of m targets, each of which must receive one hit to make the cell react, i.e. lose its reproductive integrity. The following formula is then valid:

$$S = 1 - (1 - e^{-D/D_0})^m \quad (1)$$

where S is the proportion of the cell population that survives the dose D (rad) and D_0 the 37 per cent dose, the dose required to reduce the survival proportion to 37 per cent of its initial value (on the straight region of the logarithmic survival curve). The extrapolation number m may be considered as the average number of targets (sensitive sites) in the cell but should rather be regarded as a mathematical parameter with no morphologic or biochemical significance.

It has been found that this formula provides a good description of the survival of a cell population given a single dose. Usually, m lies between 2 and 10, and D_0 between 100 and 180 rad for oxygenated cells. For anoxic cells, D_0 increases to about 400 rad.

If it is assumed that the parameters D_0 and m do not change during fractionated treatment (irradiation), the following formula may be applied for calculation of the cell survival fraction S at a particular point of the irradiated region:

$$S = \pi_{i=1}^{i=N} [1 - (1 - e^{-D_i/D_0})^m] \quad (2)$$

where D_i (rad) is the dose delivered to the point at each irradiation.

Most of the calculations in this work were performed with the parameters $D_0 = 160$ rad and $m = 2$, but these values are realistic only if the oxygen tension of the tumour tissue is assumed to be high during the whole treatment time.

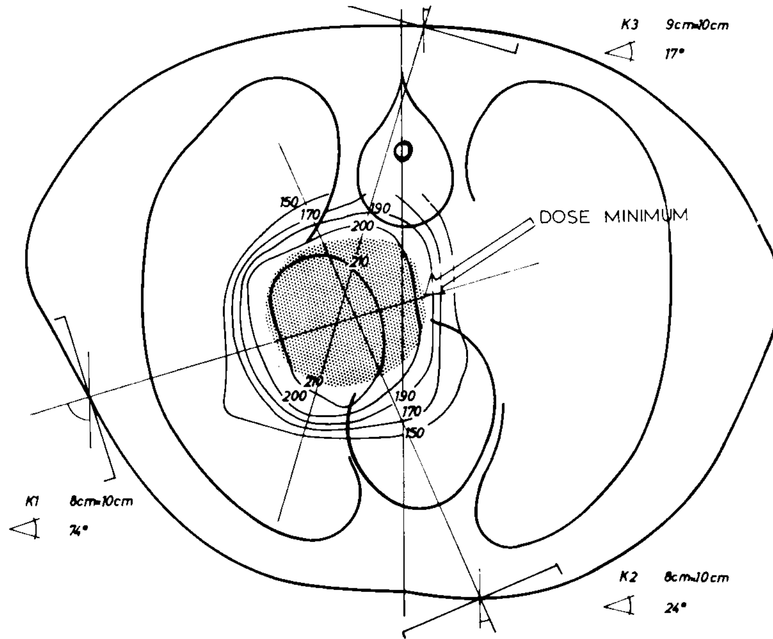

Fig. 1. Treatment plan with the point of dose minimum used in the calculations of cell survival fraction values; 33 MeV betatron photon treatment.

Experimental results of fractionated irradiation of tissues (FOWLER 1965, COHEN 1968) cannot properly be described with the assumption of constant values of D_0 and m (SPRING & HOLMBERG 1968, SPRING & PAASIKALLIO 1970). More realistic values are $D_0 = 300$ rad and $m = 1.5$. The lower D_0 value and the higher m value at the beginning of the treatment do not affect the final S values to such a degree that the S values obtained should be considered unrealistic.

Autopsy finding and survival fractions

The exact site of the treated region from which the autopsy findings were made was not known. The survival fraction values were therefore calculated for the point of the tumour where the dose had a minimum value (Fig. 1). Fig. 2 reveals that the calculated S value corresponds to the maximum survival fraction value (SPRING & MALMIO 1969).

The S values of the dose minimum point were calculated from formula (2) according to the treatment plan used.

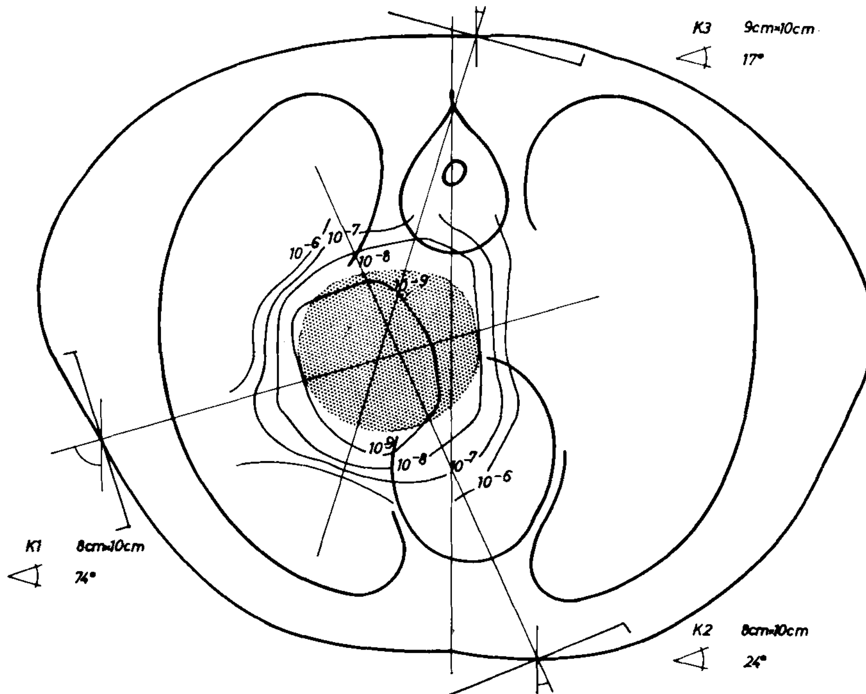

Fig. 2. 'Radiologic' treatment plan of the case of fig. 1. The iso survival curves indicated in the figure are calculated with formula (2) and the parameter values D_0 = 160 rad and m = 2 (SPRING & MALMIO 1969); 33 MeV betatron photon treatment.

The results obtained are presented graphically in Fig. 3, grouped together into width classes of 10^{-1}. The figure includes the mean values of the logarithms of the survival fraction values. They indicate that the mean value for the material where no carcinoma tissue was present at the primary tumour site was about 10^{-1} lower than for the other material.

The figure includes two boundary lines drawn from a closer analysis of the S values. With the parameter values $D_0 = 160$ and $m = 2$, these boundaries are about 10^{-5} and 0.3×10^{-8}. The first value signifies that if the S value is higher than this boundary value malignant tissue always persists after the therapy in the region treated. The S values calculated according to the treatment plan at the dose minimum point should therefore be lower than 10^{-5} to reach the region where complete destruction of the malignant tissue can be achieved. The other boundary is about 0.3×10^{-8}, below which no malignant tissue was present at autopsy of the material examined. This means that, to destroy completely this tissue in the treated region, the treatment plan must be drawn up in such a way

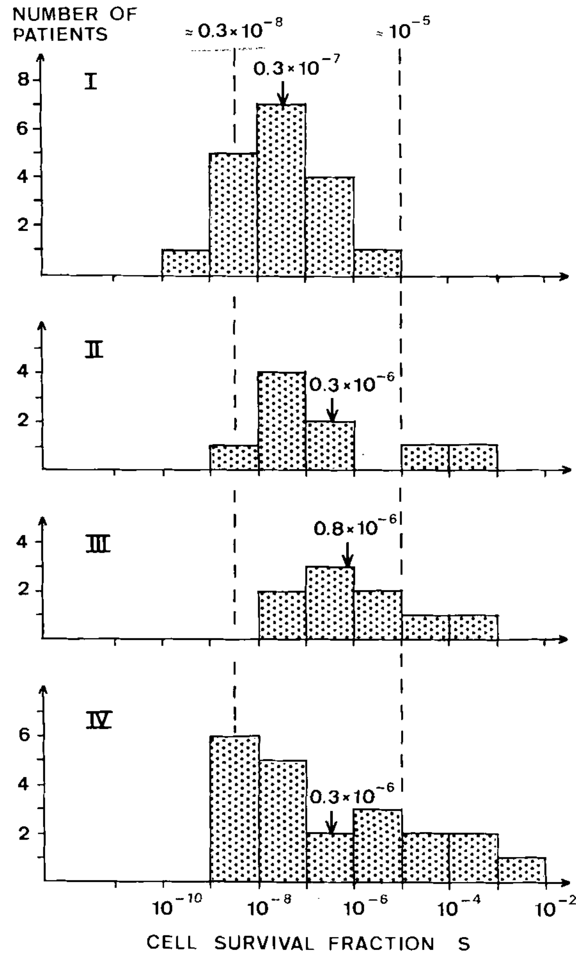

Fig. 3. Distributions of the autopsy findings in various groups (I = no carcinomatous tissue, II = fibrosis with islets of carcinoma cells, III = necrotic areas containing carcinomatous tissue, IV = viable carcinoma tissue in the treatment area) according to their corresponding cell survival fraction values, calculated with formula (2), D_0 = 160 rad and m = 2.

that the survival fraction value at the dose minimum point reaches a value lower than 0.3×10^{-8}.

The above-mentioned boundary values are valid only if the calculations are made with formula (2) and $D_0 = 160$ rad and $m = 2$. As mentioned earlier, these values are assumed to be too optimistic in calculations of fractionated radiotherapy. Fig. 4, which indicates schematically the probability of finding malignant tissue after the treatment in the cases of carcinoma of the lung in this investiga-

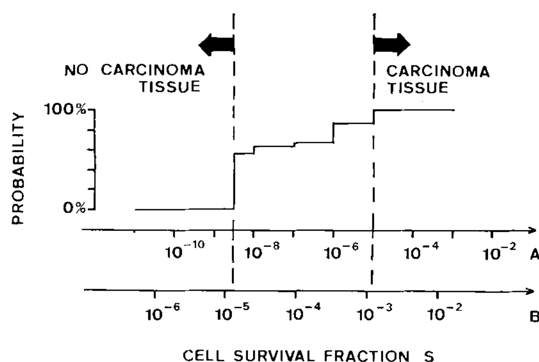

Fig. 4. Graphic presentation of the findings indicating the propability of finding carcinoma tissue in the region treated after the therapy according to the corresponding calculated cell survival values. The survival fraction values are arrived at with formula (2) with D_0 = 160 rad and m = 2 (scale A) and D_0 = 300 rad and m = 1.5 (scale B).

tion, has two scales A and B. Scale A corresponds to calculation with the parameter values $D_0 = 160$ rad and $m = 2$, and scale B to those with $D_0 = 300$ rad and $m = 1.5$. It is assumed that the later scale gives a more realistic representation of the situation. It indicates that even in cases in which 0.1 per cent of the malignant cells survive the irradiation no malignant tissue remains in the treated region after the termination of the therapy. This explains perhaps the recovery of patients treated with 190 kV roentgen rays, where the treatment plan takes account of a survival fraction of this magnitude (SPRING & MALMIO 1969).

Discussion and Conclusions

Most solid tumours in vivo are partially or wholly hypoxic (CLIFTON et coll. 1966, THOMLINSON 1968) when of clinically detectable size, and few will be cured by radiotherapy based on predictions from cell survival curves. Because it is possible after all to irradiate such growths with good results, other than direct effects of radiation on malignant cells may well have an influence on the response observed. A variety of indirect effects may in fact contribute to the tumour response in vivo (MARUYAMA 1968). From the indirect effects (CLIFTON et coll., MARUYAMA), solid tumour behaviour and response to radiation in human subjects are more complex than has been presumed from observations in cell cultures.

The assumption that if one malignant cell remains alive after treatment the neoplasm may start to re-grow and the treatment fails is less probable from the results obtained in this investigation. It may be assumed that there is a boundary

value below which the cell survival fraction must go before the primary purpose of radiotherapy, the destruction of the malignant tissue, is achieved.

The results in this investigation more or less confirm that such boundary lines exist. Depending upon the parameter values for the 37 per cent dose and the extrapolation number in the calculation with formula (2), the boundary values are about 10^{-5} and 0.3×10^{-8} or 10^{-3} and 10^{-5}. The former values are obtained with $D_0 = 160$ rad and $m = 2$, and the latter with $D_0 = 300$ rad and $m = 1.5$. This investigation of cases of carcinoma of the lung indicates that the former value is the one below which the cell survival fraction must fall to make destruction of the tumour tissue at least possible. The latter value indicates the region where the tumour tissue is destroyed with high probability if the cell survival fraction value during the treatment sinks below the boundary value. This value, if known, may be used to calculate the total treatment dosage needed to reach a survival fraction value at which the tumour tissue in the region treated is probably destroyed.

It must be stressed that this is only one factor of the whole treatment for so many others influence the success or failure of radiation therapy.

SUMMARY

Autopsy findings in carcinoma of the lung treated with megavoltage radiotherapy were analysed according to their calculated cell survival fraction values. The results indicate two boundary lines for cell survival values; the calculated value should be below the first line to give any probability at all, and below the second line to produce a high probability of no malignant tissue remaining in the region treated.

ZUSAMMENFASSUNG

Die Autopsiebefunde bei Carcinomen der Lunge, behandelt mit der Megavolt-Therapie, wurden im Hinblick auf die berechneten Fraktionen über lebender Zellen hin analysiert. Die Ergebnisse deuten auf zwei Grenzlinien für Zellüberlebenswerte hin; der berechnete Wert sollte unter der ersten Linie liegen, um überhaupt eine Wahrscheinlichkeit zu erhalten, und unter der zweiten Linie liegen, um eine hohe Wahrscheinlichkeit zu erhalten, dass nicht-malignes Gewebe im Behandlungsgebiet übrig bleibt.

RÉSUMÉ

Les auteurs ont examiné les résultats d'autopsie dans le cancer du poumon traité par radiothérapie à mégavoltage en fonction des taux calculés de survie cellulaire. Les résultats mettent en évidence deux lignes limites des taux de survie cellulaire; le taux calculé devrait être au-dessous de la première ligne pour donner une probabilité de disparition du tissu malin dans la région traitée et au-dessus de la deuxième ligne pour donner une haute probabilité de disparition du tissu malin.

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