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EFFECT OF DIFFERENT RADIATION FRACTIONATION SCHEDULES ON METASTASES FROM AN OESOPHAGEAL CARCINOMA

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The results of radiation therapy of a malignant tumour depend on several factors, the most important in clinical routine being the type and size of the tumour, the proper delineation of the target volume, the size of the total target absorbed dose and its fractionation, and the application of chemical or physical agents that may modify the radiation response.

Most biologic information is derived from in vitro cell systems and experimental animal tumours. These systems cannot be said to reflect the complex in vivo conditions of spontaneously appearing tumours in man. The present investigation is an attempt to characterize some inherent biologic properties of a human tumour in vivo from the results of irradiation of metastases from an oesophageal carcinoma, using different fractionation schedules.

Material and Methods

A 70-year-old woman with a previous history only of psoriasis developed swallowing disturbances. At radiography a bulging tumour was demonstrated in the oesophagus, measuring 8 cm × 4 cm × 4 cm on the films. Biopsy (Fig. 1 a, b) showed an anaplastic, probably epithelial, malignant tumour without definite glandular or squamous differentiation. No features of malignant lymphoma or melanoma were found. Assuming the tumour to have the form of a cigar-shaped rotation ellipsoid, its volume was calculated to be 65 cm^3. The patient was considered inoperable, and external irradiation was given using a 6 MV linear accelerator. One anterior and one posterior field (16 cm × 8 cm) were irradiated with beam directions 0° and 180°, respectively. One fraction was administered daily for 5 days a week and a total absorbed dose of 40 Gy was given in 20 fractions over 29 days, the dose specification being in agreement with the recommendations in the ICRU Report 29 (1978). The tumour regressed rapidly and was no longer demonstrable 6 and 12 weeks after conclusion of treatment. Four months after the last irradiation day a local recurrence was demonstrated at radiography.

When the oesophageal tumour was still in complete remission the patient developed multiple subcutaneous tumours, all being of the same microscopic type as the oesophageal tumour, as confirmed by means of fine needle aspiration biopsy (Fig. 1 c, d).

It was decided to irradiate the metastases. Since the oesophageal tumour had responded well initially, the fractionation schedule used, i.e., 40 Gy in 20 fractions with treatment 5 days a week, was taken as a reference. Then other schedules were chosen, giving the same radiation effect on normal connective tissue in terms of Cumulative Radiation Effect (CRE=13.4; KIRK et coll. 1971). An attempt was made to analyse the corresponding responses with

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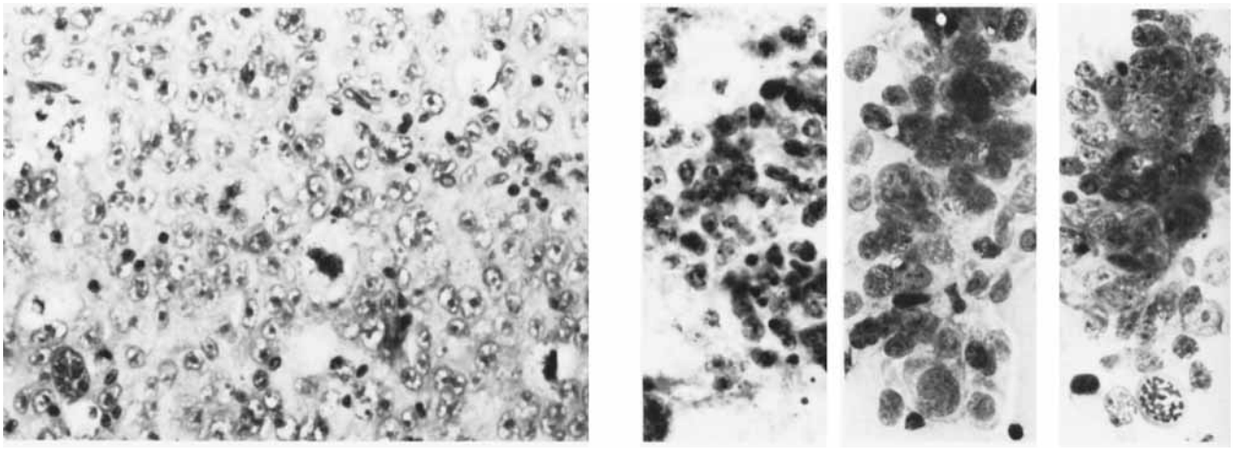


a b c d

Fig. 1. a) Biopsy from oesophagus: undifferentiated malignant tumour with cellular pleomorphism and many mitoses. H & E. ×360. b) Imprint preparation from the same specimen. H & E. ×360. c) and d) Fine needle biopsies from two metastases on left upper arm. Cell clusters with some vague epithelial formations. MGG. ×360.

respect to biologic effect, even if the parameters of the schedules selected were restricted by the clinical situation. Five different fractionation schedules were used and altogether 7 metastatic tumours were irradiated (Fig. 3). These were also given with low LET radiation with the same RBE value: 11 MeV electrons from a Betatron or ^{60}Co gamma rays. The field sizes were chosen to encompass the palpable tumours with a margin of at least 2 cm. Chemotherapy was not administered. Each field irradiated with electrons was evaluated for any skin reaction at each fraction and during the subsequent follow-up. The reactions were divided into two groups: erythema (=1) and dry desquamation (=2).

As the metastases were subcutaneous, their sizes and shapes were easily evaluable by means of palpation, and all tumours were well demarcated. The skin was freely movable and the distance from the tumours to the skin surface was measured to be 3 mm. All the tumours had the form of rotation ellipsoids, one being disc-shaped and the others cigar-shaped. The volume of a rotation ellipsoid is given by

$$V=\frac{\pi}{6} d_1 d_2 d_2$$

where d_1 and d_2 are the two independent axes of the ellipsoid (the longest and shortest diameters), and d_2 is the smaller axis for a cigar-shape while it is the larger axis for a disc-schape. At each irradiation and on several occasions after treatment, the two axes d_1 and d_2 were measured with callipers independently by three examiners and the tumour volume calculated according to the formula mentioned.

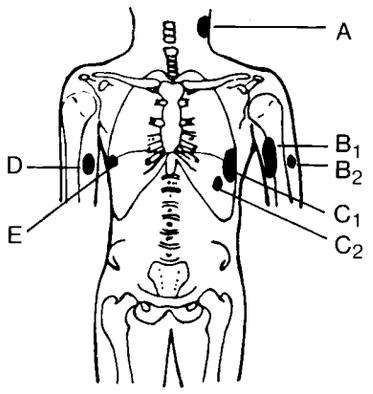
The location and initial size of the different tumours as well as data on the absorbed dose and fractionation are given in Fig. 2.

One additional tumour was not irradiated but followed for 57 days and then extirpated. This tumour had the same morphology as the other tumours.

Results and Discussion

In Fig. 3, the increase in accumulated absorbed dose with time is given for the 5 fractionation schedules together with different kinds of skin reactions, both when first noticed and when most marked. After conclusion of treatment, all observed skin reactions subsided. Skin reactions occurred only with the two schedules having the largest number of fractions, whereas no reaction at all occurred with those having few fractions, even though the CRE value was the same for all the schedules. However, as TURESSON & NOTTER (1975) stated: "equal CRE values during the radiation treatment are not simultaneously related to identical skin reactions as these are delayed. It is therefore difficult to compare the reactions during the period of treatment itself and to assess the results at the last occasion of treatment."

The tumour followed for 57 days progressed steadily before surgical excision and increased in size by approximately a factor of 11 (from 0.38



Tumour and symbol	Volume (cm^3)	Absorbed dose (Gy)		No. of fractions	No. of days
		Accumulated	At each fraction		
A ▲	3.68	40	2.00	20	30
B_1 ○	8.66	30	3.34	9	11
B_2 ●	0.64				
C_1 □	4.63	29	5.80	5	30
C_2 ■	1.03				
D ◆	1.64	17.80	8.90	2	3
E +	0.65	35.40	2.95	12	30

Fig. 2. Site and volume at start of treatment of the different subcutaneous tumours and data on target absorbed dose and fractionation. Tumours B_1 and B_2 were treated with ^{60}Co, the other tumours with electrons (11 MeV) from a Betatron.

cm^3 to 4.18 cm^3). From the two observations made, the tumour volume doubling time T_d may be calculated, assuming exponential tumour growth, to (16±5) days.

The size of the different tumours as measured during and after the treatment period appears in Fig. 4. The uncertainties in all the measurements of the linear dimensions of the metastatic tumours were estimated to ±1.5 mm. This gives the following approximate uncertainties in the volume calculations, taken at three representative levels: (5.0±1.0) cm^3, (0.50±0.25) cm^3 and (0.050±0.045) cm^3.

All metastases regressed completely and did not recur during a follow-up time of 8 months. Therefore, it is not possible to state if the absorbed dose was in excess of the necessary one to achieve cure. On the other hand, the primary oesophageal tumour recurred after 4 months.

It appears from Fig. 4 that no decrease of the tumours occurred during the first week of irradiation, rather an increase, in particular when large doses were given at each fraction. It is reasonable to attribute this increase to an initial oedema, even if 'killed' tumour cells, i.e., cells incapable of dividing, may still add to the tumour volume. Moreover, it cannot be ruled out that the increased tumour volume might reflect an accelerated growth rate of the surviving cells (HILL & BASERGA 1975).

In fractionated radiation several factors determine if all tumour cells will be destroyed or not.

Repair of sublethal injury is usually considered to take place within hours, and at least before the next fraction in daily irradiation schedules. The size of the absorbed dose necessary to overcome the level of only sublethal injury was demonstrated by ELKIND & SUTTON (1960) as the initial shoulder of the cell survival curve in in vitro setups. The cell survival curve, which is usually obtained by plotting the proportion of cells in a population that survive to divide against the absorbed dose, was often assumed to have a zero initial slope (Fig. 5, curve A), as originally described by ELKIND & SUTTON. However, many data indicate that the initial slope may be non-zero (Fig. 5, curve B; WAMBERSIE & DUTREIX 1974). The problem was extensively discussed by ELKIND (1976). Considerable evidence indicates a wide variation among different tumours with respect to the ability to repair sublethal injury. Some tumours, e.g. malignant lymphomas, are usually on clinical grounds considered to have relatively narrow shoulders, and then even small daily absorbed doses are useful (LANDBERG et coll. 1973, FRIEDMAN 1975). Some tumours probably have broad shoulders. An example of this is malignant melanoma, where conventional fractionation with a daily absorbed dose of 2.0 Gy may be ineffective (BARRANCO et coll. 1971, THOMSON et coll. 1975), and larger absorbed doses of the order of 4.8 Gy at each fraction are being explored (ROFSTAD et coll. 1977).

Repopulation by tumour cells between successive fractions could be expected to present a clinical problem in tumours with a very high growth rate. This has been shown to be the case for some undifferentiated squamous cell carcinomas (FRIEDMAN) and is also observed in Burkitt's lymphoma, where conventional daily fractionation has proven insufficient, whereas a schedule with several fractions each day, superfractionation, has proven to be effective (NORIN et coll. 1971). In most other malignant lymphomas, however, repopulation between fractions seems to be of little importance; the total treatment period may well be extended over a long period of time for one and the same total absorbed dose (KAPLAN 1966, LANDBERG et coll.).

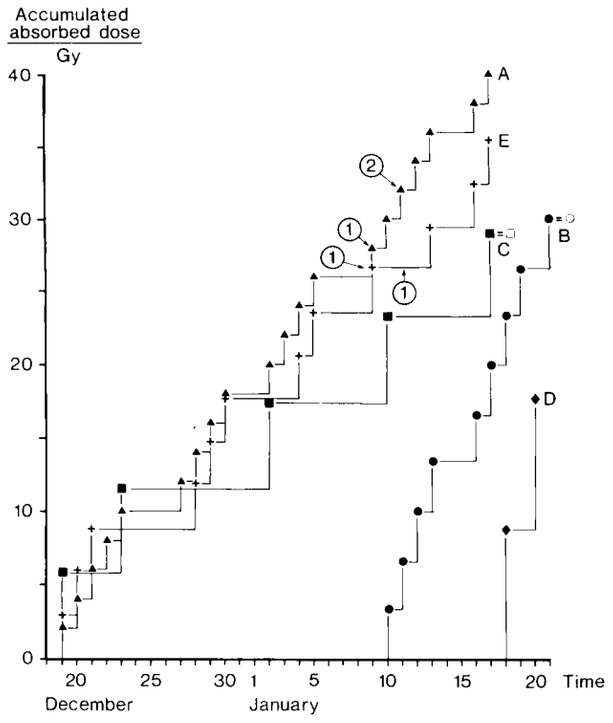


Fig. 3

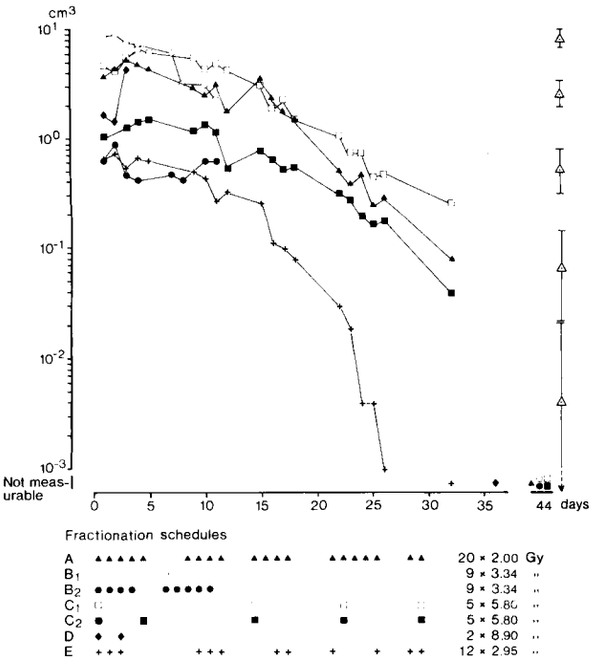


Fig. 4

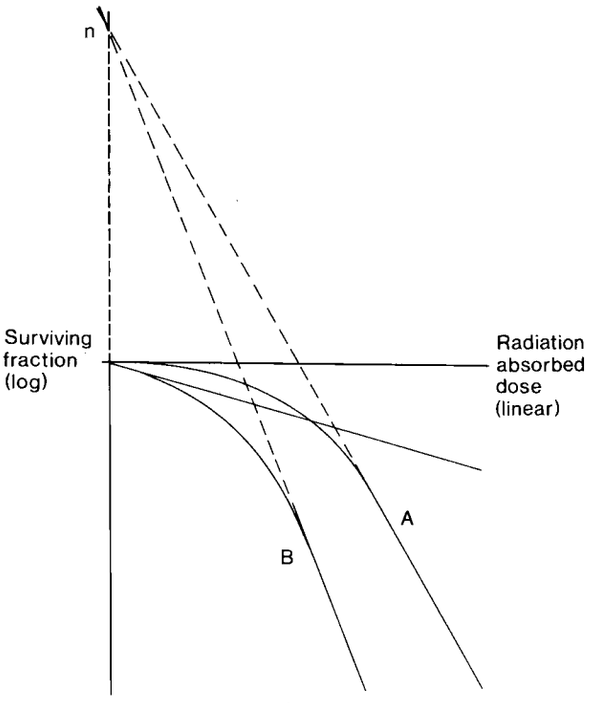


Fig. 5

Fig. 3. Increase in accumulated absorbed dose with different fractionation schedules and different kinds of skin reactions, when first observed and most marked (only for sites irradiated with electrons): erythema (=1) and dry desquamation (=2). For explanation of symbols see Fig. 2.

Fig. 4. Size of the different tumours when measured at the beginning of, during and after radiation treatment. The uncertainties in the volume measurements are indicated in the right-hand margin of the figure. For explanation of symbols see Fig. 2.

Fig. 5. Cell survival curves: A with initial slope zero, and B with initial slope non-zero (see review by ELKIND 1976).

Reassortment of cells into different phases of the cell cycle, making surviving cells enter a period of increased proliferative activity, has been described for human tumours. Thus, TERZ et coll. (1977) showed that during radiation therapy of solid tumours a significant increase in the thymidine incorporating cells occurs, which was considered as increased proliferating activity of the tumour cell

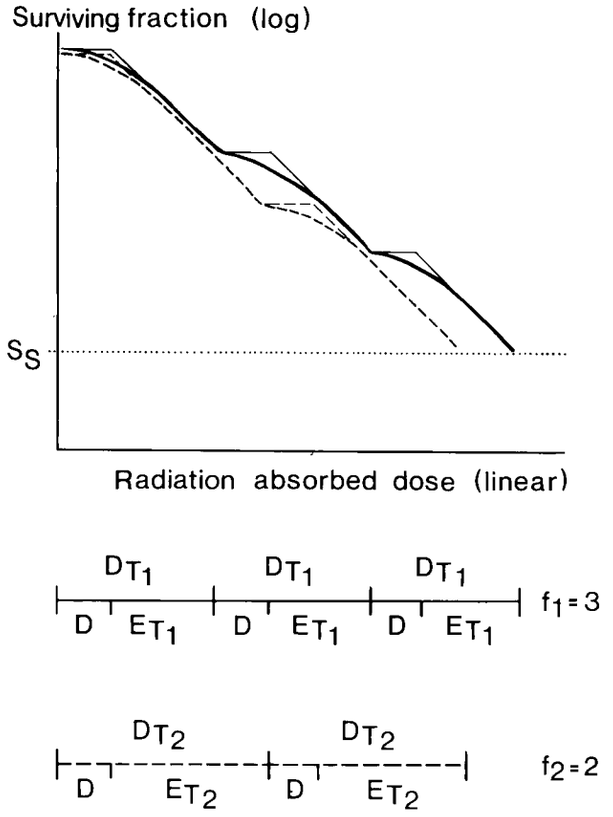


Fig. 6. Schematic presentation of two different radiation fractionation schedules giving the same final cell population survival (fractions S_S). D_{T_1}: absorbed dose at each fraction for schedule 1. D: absorbed dose necessary to overcome the shoulder of the cell survival curve. E_{T_1}: 'effective' absorbed dose at each fraction ($=D_{T_1}-D$) for schedule 1. f_1: number of fractions for schedule 1.

population. However, this phenomenon seems to be of only limited importance during a fractionated treatment over a long time (FOWLER 1972).

Reoxygenation of hypoxic cells may be of importance, causing a tumour to respond better (other factors unchanged) if the total treatment period is prolonged.

The size of the tumour is of importance because a larger tumour, in comparison with a smaller one, contains more tumour cells, relatively more resting cells (G_0 phase; STRAUS & MORAN 1977) and also may be assumed to contain larger hypoxic regions (THOMLINSON & GRAY 1955). That a clear correlation exists in the clinical situation between tumour size and dose necessary for local control has been shown by FLETCHER (1973) for different squamous cell carcinomas and adenocarcinomas.

The absolute preirradiation tumour size does not predict the dose needed, but how this size has been reached seems to be of importance. Thus, carcinomas of the oropharynx and maxillary antrum, being shrunk before irradiation with an intra-arterial infusion of methotrexate, had not a better local control rate than far more advanced lesions with the same total absorbed dose (NERVI et coll. 1978).

The response to irradiation may vary considerably between the metastases from the same primary tumour and probably even within the same metastasis. Such a variation in sensitivity by a factor of 2 or even more has been demonstrated by FRIEDMAN and TERZ et coll. On the other hand, STRAUS & MORAN demonstrated but little interlesional heterogeneity in cell cycle distribution in patients with solid tumours (long-standing tumours). FOWLER remarked in his analysis of the results of SHUKOVSKY (1970) that they supported the simple cell survival-curve theory, the variation in sensitivity being small.

An attempt was made to use the present observations to estimate the size of the shoulder of the cell survival curve, some reasonable assumptions having been made. It must be assumed that the different tumours did not differ with respect to biologic characteristics and that, as a first approximation, the effects of repopulation, reassortment and reoxygenation were the same in the different metastases. These assumptions are implicit in the calculation of the tumour volume doubling time T_d. Furthermore, if the tumour volume is supposed to be proportional to the number of tumour cells, then the time needed for doubling the number of tumour cells is T_d as well. Apparently, none of these assumptions can be substantiated by data, which demonstrates a common difficulty in clinical radiation biology. Most biologic work on the effect of radiation has been performed with in vitro cell systems and animal tumours. This can never tell what happens in vivo in man, and has even led to some misconceptions in the past (RUBIN & SCARANTINO 1978). Thus, data from human beings are needed, although due consideration must be given the several assumptions made in the evaluation of the results as well as the clinical situation. As FRIEDMAN rightly stated: "Most published isoeffect curves of human cancer are based on impressment of data, somewhat against their consent, into a formula by the expedients of accepting data uncritically, overlooking the enormity of the standard error, and plotting data directly into logarithmic paper as to appear scientific".

The present observations indicate that the target absorbed doses given seem to have been at least

sufficient to eradicate the metastases but insufficient to cure the much larger primary lesion. The overall treatment times for the primary tumour and the four tumours A, C_1, C_2 and E are the same, hence these metastases were chosen in the estimation of the shoulder in order to minimize the number of varying parameters. During the period, the relative changes in volume of these four tumours are approximately the same (Fig. 4). The curves do not only illustrate tumour cell killing, but also that other factors may be of importance, e.g. variation in tumour cell loss and stromal tissue reactions. For the present purpose it is assumed that such factors are of the same relative importance for the different sites, allowing for a comparison with respect to tumour cell killing if certain precautions are taken. Since the difference in initial size of the tumours A and C_1 is insignificant and it is reasonable to assume that the fractionation schedules used in the treatment of these two tumours finally result in the same surviving fractions, consequently also equal absolute numbers of tumour cells survive. The same situation applies for the two tumours C_2 and E. The fractionation schedules for the tumours C_1 and C_2 are identical, and according to the assumptions made this means equal surviving fractions for these tumours. Thus, the surviving fractions may be assumed to be equal for all four metastases, the variation in initial sizes being within a factor of 5.

The assumption that equal surviving fractions are reached using the three fractionation schedules A, C and E, makes it possible to estimate the quasithreshold dose D, i.e., the width of the shoulder of the single cell survival curve. The quasithreshold dose D is the dose at which the extrapolated high dose straight part of the dose–response curve cuts the dose-axis, when a presentation as in Fig. 5 is used. Thus, the dose D is determined solely by the behaviour for large doses of the cell survival curve.

Two fractionation schedules resulting in the same surviving fraction S_S are compared in Fig. 6. The doses absorbed at each fraction are denoted D_{T1} and D_{T2} and the number of fractions f_1 and f_2, respectivity. The doses D_{T1} and D_{T2} are presumed to be large enough to result in surviving fractions characterized by the straight part of the dose–response curve. This is the case in all the fractionation schedules analysed. The dose absorbed at each fraction D_T can be considered as divided into two parts, where D is the dose needed to overcome the shoulder and E_T is the 'effective' dose.

Table

Total 'effective' absorbed dose and volume of the tumours

Tumour	Effective absorbed dose (Gy)	Initial volume of the tumour (cm^3)
A	25.20	3.68
B_1	23.40	8.66
B_2	23.40	0.64
C_1	25.30	4.63
C_2	25.30	1.03
D	16.32	1.64
E	26.50	0.65
Primary tumour	25.20	65.0 (recurred)

$$D_T = D + E_T$$

When the same surviving fraction S_S is reached, the effective doses delivered by the two different treatment schedules are equal, that is

$$f_1 \times E_{T1} = f_2 \times E_{T2}$$

which means

$$(D_{T1} - D) \times f_1 = (D_{T2} - D) \times f_2$$

The width D of the shoulder is then given by

$$D = \frac{D_{T1} \times f_1 - D_{T2} \times f_2}{f_1 - f_2}$$

No conclusions about the specific shape of the shoulder can be made in such an analysis. In fact, if the condition on the size of the doses is satisfied, then the initial shape of the cell survival curve is arbitrary.

Comparison between the schedules for tumours A and C_1 results in the value D_{AC}=0.73 Gy for the shoulder dose, tumours C_2 and E give the value D_{CE}=0.93 Gy and the schedules A and E give D_{AE}= 0.58 Gy. Thus, the mean value D_{ACE}=0.74 Gy is an estimation of the shoulder of the cell survival curve, based on equal surviving fractions in tumours A, C_1, C_2 and E. Using the calculated value of the shoulder, total effective target doses can be determined. These effective doses are given in the Table.

The primary tumour had a volume 20 to 100 times larger than the four tumours and was treated identically to tumour A. Even if the same surviving frac-

tion of tumour cells was reached in the primary as in the smaller tumours, the absolute number of surviving cells was higher, leading to the recurrence of the primary tumour. It is generally considered necessary to administer a higher dose to eradicate a larger tumour. For instance, calculations according to COHEN's model (1971) give for a squamous cell carcinoma, when a total dose of 60 Gy is given in 30 fractions over 41 days, a 93 per cent chance of a lethal effect on a tumour with a diameter of 1 cm, while this chance is reduced to 75 per cent for a tumour with a diameter of 7 cm (350 times larger volume). A total dose of 67 Gy should be needed in order to reach the level of 93 per cent for this larger tumour, the number of fractions and the overall time being the same. FOWLER stated that "a subclinical metastatic deposit 1 mm in diameter containing 10^6 cells can be eradicated by a dose which is two-thirds as high as that required to eradicate a primary tumour of 10^9 cells".

FRIEDMAN stated that accelerated recovery from sublethal injury occurs in some squamous cell carcinomas when the destructive effect on the tumour is mild, either because of a low daily dose (1.0 Gy), or because the tumour is very resistant.

The shoulder width arrived at seems reasonable from general clinical impressions.

The results of different well defined in vitro experiments may only be clinically useful if they are properly applied to the complex in vivo situation. What properly is, can only be evaluated from observations in clinical work, where on the other hand an investigation can be performed only if the end result is ethically acceptable. Therefore, deductions from a clinical investigation should be viewed with the greatest caution.

SUMMARY

Subcutaneous metastases from an oesophageal carcinoma were irradiated using different schedules. The results have to be evaluated with greatest caution but indicate that with the same CRE value, few fractions caused less skin reactions than several, and the size of the shoulder of the cell survival curve was of the order of 0.7 Gy.

REFERENCES

BARRANCO S. C., ROMSDAHL M. M. and HUMPHREY R. M.: The radiation response of human malignant melanoma cells grown in vitro. Cancer Res. 31 (1971), 830.

COHEN L.: A cell population kinetic model for fractionated radiation therapy. Radiology 101 (1971), 419.

ELKIND M. M.: Fractionated dose radiotherapy and its relationship to cancer survival curve shapes. Cancer Treat. Rev. 3 (1976), 1.

— and SUTTON H.: Radiation response of mammalian cells grown in culture. I. Repair of x-ray damage in surviving chinese hamster cells. Radiat. Res. 13 (1960), 556.

FLETCHER G. H.: Clinical dose–response curves of human malignant epithelial tumours. Brit. J. Radiol. 46 (1973), 1.

FOWLER J. W.: Current aspects of radiobiology as applied to radiotherapy. Clin. Radiol. 23 (1972), 257.

FRIEDMAN M.: Aspects of radiation biology and radiation pathology observed during the treatment of cancer in man. Brit. J. Radiol. 48 (1975), 81.

HILL B. T. and BASERGA R.: The cell cycle and its significance for cancer treatment. Cancer Treat. Rev. 2 (1975), 159.

ICRU. International Commission on Radiation Units and Measurements. Report 29. Dose specification for reporting external beam therapy with photons and electrons. Washington 1978.

KAPLAN H. S.: Evidence for a tumoricidal dose level in the radiotherapy of Hodgkin's disease. Cancer Res. 26 (1966), 1221.

KIRK J., GRAY W. M. and WATSON E. R.: Cumulative radiation effect. Part I. Fractionated treatment regimes. Clin. Radiol. 22 (1971), 145.

LANDBERG T., LIDÉN K. and FORSLO H.: Split-course radiation therapy of mediastinal Hodgkin's disease. TSD and CRE concepts. Acta radiol. Ther. Phys. Biol. 12 (1973), 33.

NERVI C., ARCANGELI G., BADARACCO G., CORTESE M., MORELLI M. and STARACE G.: The relevance of tumour size and cell kinetics as predictors of radiation response in head and neck cancer. Cancer 41 (1978), 900.

NORIN T., CLIFFORD P., EINHORN J., EINHORN N., JOHANSSON B., KLEIN G., ONYANGO J., DESCHRYVER A. and WALSTAM R.: Conventional and superfractionated radiation therapy in Burkitt's lymphoma. Acta radiol. Ther. Phys. Biol. 10 (1971), 545.

ROFSTAD E. K., BRUSTAD T. and JOHANNESSEN J. V.: Effect of clinically relevant irradiation regimes on human malignant melanomas grown in athymic nude mice. Acta radiol. Ther. Phys. Biol. 16 (1977), 273.

RUBIN P. and SCARANTINO C. W.: The bone marrow organs. The critical structure in radiation–drug interaction. Int. J radiat. Oncol. Biol. Phys. 4 (1978), 3.

SHUKOVSKY L. J.: Dose, time, volume relationships in squamous cell carcinoma of the supraglottic larynx. Amer. J. Roentgenol. 108 (1970), 27.

STRAUS J. M. and MORAN R. E.: Cell cycle parameters in human solid tumors. Cancer 40 (1977), 1453.

TERZ J. J., LAWRENCE JR W. and COX B.: Analysis of the cycling and noncycling population of human solid tumors. Cancer 40 (1977), 1462.

THOMLINSON R. H. and GRAY L. H.: The histological structure of some human lung cancers and the possible

implications for radiotherapy. Brit. J. Cancer 9 (1955), 539.

THOMSON L. F., SMITH A. R. and HUMPHREY R. M.: The response of a human malignant melanoma cell line to high LET radiation. Radiology 117 (1975), 155.

TURESSON I. and NOTTER G.: Skin reactions after different fractionation schedules giving the same cumulative radiation effect. Acta radiol. Ther. Phys. Biol. 14 (1975), 475.

WAMBERSIE A. and DUTREIX J.: Cellular repair after X or gamma irradiation determined for several 'gross' criteria on animals and patients. Europ. J. Cancer 10 (1974), 235.