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Observations on Pulmonary Metastases in Patients After Single Doses and Multiple Fractions of Fast Neutrons and Cobalt-60 Gamma Rays

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Abstract—*Pulmonary metastases have been irradiated with single and fractionated doses of fast neutrons and cobalt-60 gamma rays. The response to radiation was measured on volume changes of the lesions and thus RBE values could be derived. A correlation was found between grading of the tumour and volume doubling time and also between RBE and volume doubling time. This suggests an advantage for high LET radiation of slowly growing, well differentiated tumours. Furthermore the RBE for multiple fractions tends to be higher than for single doses. Calculation of the N exponent of the Ellis formula indicated that hardly any shoulder exists when neutrons are applied.*

INTRODUCTION

ALREADY in 1971 Breur and van Peperzeel [1] had pointed out possible clinical models for quantitative comparison of effects of different types of radiation on tumours. Up till now the lung metastases model as described by Breur [2] and used by van Peperzeel *et al.* [3] is one of the few human *in vivo* models that provided some clinically estimated RBE values for tumour response after neutron and photon irradiation. Metastatic skin lesions from a variety of tumours can also be used for quantitative analysis after irradiation; however, the measurements are less accurate than measurements of the volume of pulmonary metastases and hence only incidentally used to derive RBE values.

In this paper pulmonary metastases of human tumours have been used to estimate the response to irradiation with fast neutrons and cobalt-60 gamma rays. The data determined by van Peperzeel were re-evaluated and new data from single dose measurements and from some multiple fraction experiments were added.

MATERIALS AND METHODS

In many patients with blood-borne metastases, lesions commonly appear in the lungs. These tumours on chest X-rays are often described as "coin lesions" because of their circular shape. Observations of these lesions at different time intervals in general show an exponential volume increase [4]. By measuring the diameter on subsequent chest X-rays it is possible to describe the volume increase as a function of time by the volume doubling time (T_d). Since the first publication on this subject by Breur in 1966 data has accumulated from 190 patients with a variety of primary tumours. As was suggested by Malaise [5], a correlation can be made with tumour type and also with grading of the primary tumour. In Table 1 this correlation between tumour type, grading, site and doubling time is given for our patient material. As the differentiation of tumours depends on tumour type, a classification into groups of differentiation is difficult and arbitrary. In the table the grading is given according to the pathologist's description of the primary tumour. In sarcomas, low grade malignancies with few mitoses are classified as "well differentiated", whereas high grade malignant tumours with many mitoses are classified as "poorly differentiated". If these indications were not present in the pathological report, the tumour was classified as "moderately differentiated". Until now it is not clear what intrinsic factors in the tumour cause this difference in growth pattern.

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Table 1. *Volume doubling time of pulmonary metastases of different primary tumours, according to grade and tumour type*

	Undifferentiated tumours	Differentiated tumours	Well differentiated tumours
Embryonal tumours	Testis MTU: 9, 10, 12, 13, 13, 13, 14, 14, 16, 17, 17, 19, 32, 32 Embr. rhabdomyosa: 15 Wilms tumour: 13	Testis MTI: 11, 29, 33, 45, 58 Spermatocytic seminoma: 21	Testis TD: 205, 270
Lymphomas	Non Hodgkin lymphomas: 19, 25, 27	M. Hodgkin, lymphocytic depletion: 35	Malignant thymoma: 100
Epithelial tumours	Squamous cell ca bronchus: 19, 24 Squamous cell ca head & neck: 20, 22 Transitional cell ca bladder: 12, 18, 23, 27	Squamous cell ca head & neck: 36, 65 Squamous cell ca vagina: 76 Squamous cell ca cervix: 34, 85	Squamous cell ca bronchus: 86, 107, 153 Transitional cell ca bladder: 135, 193 Squamous cell ca bladder: 125
Sarcomas	Stroma sa uterus: 17 Anaplastic sa: 16, 19, 30, 31, 31, 35, 38, 45	Giant cell sa: 32, 61 Synovio sa: 30, 32, 33, 49 Osteosa: 16, 17, 17, 21, 23, 25, 26, 27, 31, 36, 39, 43, 52, 55, 56, 69, 91 Fibrosa: 20, 27, 32, 33, 42, 48, 52, 54, 67, 70, 77, 85, 87, 97, 122, 212, 225, 238, 257 Rhabdomyosa: 15, 23, 35, 41 Leiomyosa: 29, 38, 44, 52, 72, 135 Liposa: 13, 47 Ewing sarcoma: 75	Haemangio-pericytosa: 115, 162, 420 Chondrosa: 1100 Melanomas: 31, 40, 61, 64, 70, 71, 86, 102, 107, 112 Osteosa: 253
Adenocarcinomas	Thyroid: 13, 18, 19, 37 Breast (solidum): 23, 39	Thyroid: 44, 51 Uterus: 41, 44, 45, 48, 83 Large bowel: 31, 39, 56, 63, 63, 63, 70, 76 Breast: 52, 59, 69, 73 Parotid gland: 27, 33, 68 Ovaries: 51	Thyroid: 112, 175 Parotid gland: 84, 110, 145, 188, 280, 330, 700 Bronchus: 78 Breast scirrhus: 108, 159, 177, 745 Hypernephroma: 123, 153, 157 Large bowel: 70, 78, 91, 106, 107, 117, 117, 129, 130, 135, 140, 560 Cylindroma: 37, 200, 307 Uterus: 102, 547

Furthermore, the detectable part of the tumour growth is only a small proportion of the total life span from one tumour cell till death of tumour. Whether exponential growth exists before the tumour is detectable (viz. less than about 10^8 tumour cells, approximately 1 cm^3) is still uncertain.

Nonetheless, during the period when lung metastases are visible, the exponential volume accrual can be used to estimate the response of the tumour to radiation. After irradiation of a metastasis the tumour volume decreases, followed by a resumption of growth initially rapid and subsequently slowing to the pre-irradiated volume doubling time. By extrapolation of this part of the growth curve to the time of first irradiation the "extrapolated residual volume" (V_{res}) relative to the volume at the time of irradiation can be derived. The growth delay (G_d), defined as the time in days required to attain the pre-irradiation volume, can be measured directly from the growth curve (Fig. 1). Assuming an exponential growth rate, the extrapolated tumour volume and the growth delay are related by the formula:

$$\ln V_{res} = -\ln 2.G_d/T_d.$$

Groups of tumours can be distinguished according to their volume doubling time: 10–20 days, 20–40 days, 40–80 days, 80–160 days and more than 160 days [2]. For a group of tumours with approximately similar growth rates response to the same dose of radiation is generally of the same order [6].

If two or more metastases in the same patient could be treated separately, the effectiveness of different kinds of radiation was compared by irradiation of one metastasis with fast neutrons and another with X or gamma rays. If more than two metastases were present, both single and multiple fractions of neutrons and gamma rays have been used. If only one metastasis was present, the derivation of an RBE was possible by first irradiating with one type of radiation, followed by irradiation with the other type after resumption of the growth to its pre-irradiation volume. If only one metastasis was present and the condition of the patient did not allow a second irradiation, an approximate RBE value was derived by assuming that the response to photons would have been similar to that of the group with corresponding volume doubling times. For this purpose the data from former studies [3, 6] have been used to derive mean values of extrapolated residual volumes as a function of the dose (Fig. 2).

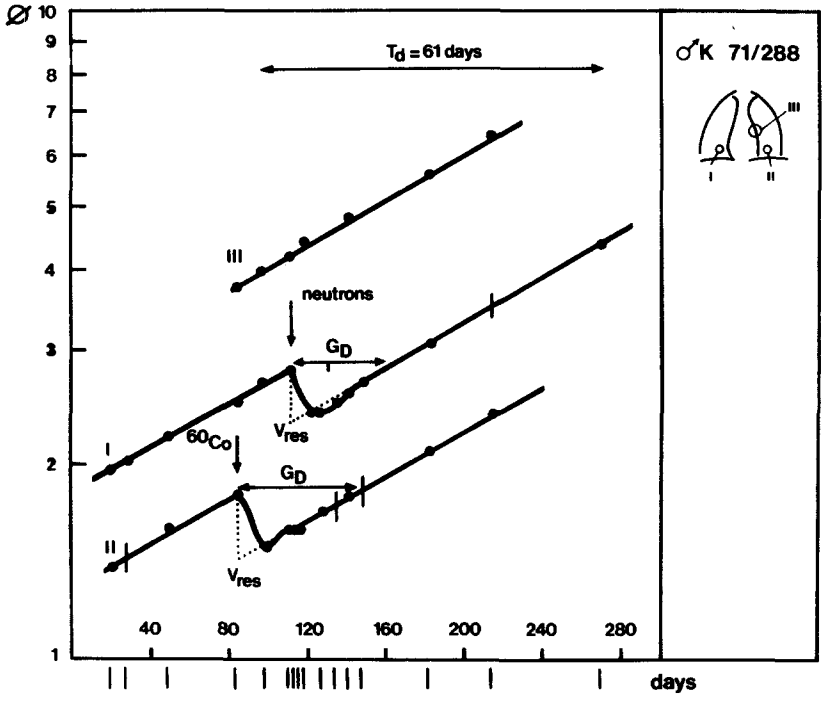

Fig. 1. Growth curve of metastases of a patient with a melanoma, indicating the volume doubling time (T_d), *the growth delay* (G_d) *and the extrapolated residual volume* (V_{res}) *after irradiation with neutrons* (174 cGy) *and gamma rays* (726 cGy). *From the derived data an RBE of* 3.3 *was calculated.*

Patients were irradiated with fast neutrons and/or cobalt-60 gamma rays. In the former studies 15 MeV d+T fast neutrons were produced by the electrostatic accelerator at TNO, Rijswijk. Later data were derived with the 14 MeV d+T Philips fast neutron generator, installed at the Antoni van Leeuwenhoek Hospital, Amsterdam. At Rijswijk a fixed horizontal beam with a target to skin distance of 45 cm was employed. At Amsterdam patients could be treated in prone and supine positions with a target to skin distance of 80 cm. All patients were irradiated

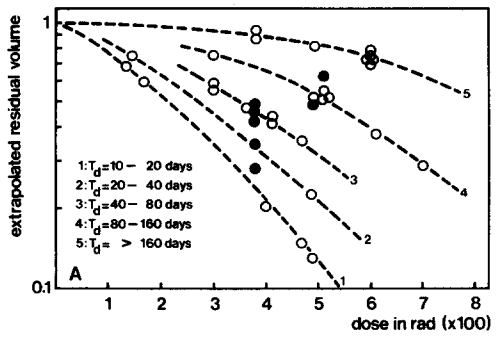

Fig. 2. Extrapolated residual volumes of pulmonary metastases of different tumours as a function of cobalt-60 gamma rays. The curves represent average values for doubling times of 10–20, 20–40, 40–80, 80–160 *and more than* 160 days (*adapted from H. A. van Peperzeel* et al., 1974).

with an anterior and posterior field. A correction for lung density was made using data from phantom measurements [7, 8]. The dose is expressed as total absorbed dose. The neutron doses used by van Peperzeel were corrected with 10% because of a reconsideration of some physical data [9]. The low LET radiation was given with cobalt-60 gamma rays, also applying two fields. Again a correction for lung tissue was made. Phantom measurements with the cobalt-60 gamma beam indicated that the lower lung density results in an approximately 20% higher dose relative to that in muscle tissue.

To derive RBE values, it was assumed that in contrast to photons, neutron irradiations have no appreciable shoulder in a dose–effect curve in which the extrapolated residual volume is plotted as a function of the dose (Fig. 3). Besides the basic radiobiological data for this assumption, this effect was also observed on some experiments using different neutron doses on pulmonary metastases in one patient [3]. Comparison of the effect of a cobalt-60 gamma dose with the corresponding point on the curve makes it possible to calculate the

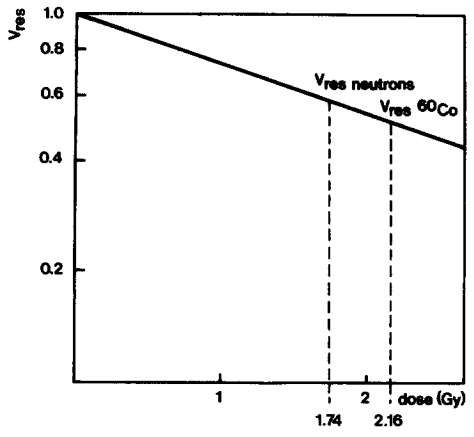

Fig. 3. Extrapolated residual volume as a function of fast neutrons, comparing the results of neutrons and cobalt-60 gamma rays in the same patients.

RBE of fast neutrons relative to cobalt-60 gamma rays. In patients with only one metastasis, irradiated with fast neutrons, the data from Fig. 2 were used to estimate an RBE value, according to the method described by van Peperzeel. The data from that paper were reconsidered, using the described "no shoulder" method. As we believe the latter method to be more accurate, these data are mainly used in further conclusions.

RESULTS

The data from Table 1 giving the correlation between tumour type, grading and volume doubling time were further analysed using the Welch–James approximation to the distribution of the residual sum of squares in a weighted linear regression [10]. From this analysis it can be concluded that:

(*a*) no correlation exists between tumour type and volume doubling time ($P=0.31$);

(*b*) a significant relation exists between grading and volume doubling time ($P<10^{-8}$);

(*c*) the relation between grading and doubling time is independent of tumour type ($P=0.37$).

In Fig. 4 the volume doubling times according to grade are plotted on a probit log scale. A log normal distribution of volume doubling times for human tumours was also found by Malaise [5].

For 34 patients the results of a single dose of neutrons and cobalt-60 gamma rays on lung metastases expressed as V_{res} and G_d are listed in Table 2. The methods to derive these data were discussed above and are demonstrated in Fig. 1. The patient from this figure

had bilateral pulmonary metastases from a melanoma. From measurements of the diameter of these metastases on subsequent chest X-rays a volume doubling time of 61 days could be calculated. After irradiation of one lesion with fast neutrons and another with gamma rays, growth delay and extrapolated residual volume were found for each treatment modality. As can be learned from this figure, the volume decrease is followed by a short period of accelerated regrowth and subsequent resumption of the pre-irradiation growth rate.

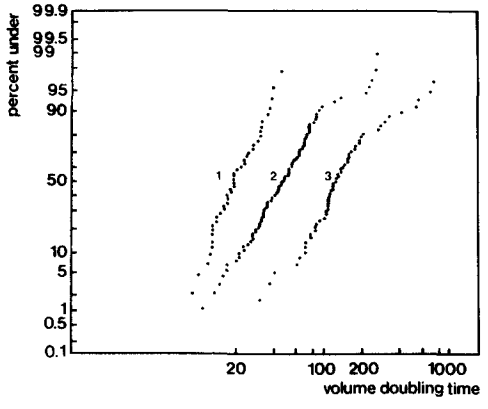

Fig. 4. Log normal distribution of volume doubling times for human tumours according to their differentiation: poorly differentiated (curve 1), moderately differentiated (curve 2) and well differentiated (curve 3).

In Table 2 the RBE values are also given, both after calculation with the "no shoulder" method and with the former method of van Peperzeel (estimated values). In patients who received exclusively neutron irradiation only the latter method could be used.

In eight patients both neutrons and gamma rays were given in multiple fractions. The subsequent data are given in Table 3. RBE values were estimated in the same way as described for single doses.

Data of single and multiple fractions of fast neutrons in 11 patients were used to compute the $\mathcal{N}$ exponent in the Ellis formula. We assumed that the time factor was negligible if only few fractions (5 or less) were applied to tumours with doubling times of several weeks to several months. The "effective single dose" of multiple fractions was found by the same "no shoulder" method as described above. The data from these experiments are listed in Table 4.

DISCUSSION AND CONCLUSIONS

This paper describes a method to derive RBE values of single and fractionated doses of neutron and gamma rays. For a variety of primary tumours RBE values were computed after single dose irradiation (Table 2). A comparison of these data with those presented in Table 3 shows that the RBE values tend to be higher for fractionated treatments than for single doses. This is in agreement with the suggestion that the shoulder in the cell survival curve for neutrons is much smaller than for photon irradiation. Also the results of the calculations of the $\mathcal{N}$ exponent in the Ellis formula as given in Table 4 show that the effect of fractionation is less important in neutron therapy (mean $\mathcal{N}$ exponent 0.10). This is in accordance with observations of Field [11]. From these data it can be concluded that the initial hypothesis of the lack of a shoulder in the dose response curve is justified. However, it also means that the RBE value is dose dependent.

In Fig. 5 the RBE values derived from the volume reduction of pulmonary metastases after single dose irradiations are plotted as a function of the volume doubling time. A wide range of RBE values exists, with a significant increase in RBE with a longer doubling time. Radiobiological data and some clinical observations of skin and intestinal damage [12] suggest normal tissue RBE values of about three for 14 MeV d+T neutrons relative to gamma rays. This implies that for only a proportion of patients can a therapeutic gain be expected when fast neutrons are used in the treatment of cancer. Thus, tumours with volume doubling times of 100 days and more seem suitable for high LET radiation. In our observations of volume doubling times, as summarized in Fig. 6 on a probit log scale for 192 tumours, this means that around 70% of the analysed tumours will not benefit significantly from neutron irradiation. As was stated above, a good correlation was found between the grading of tumours and their volume doubling time. Thus, in general it can be said that the RBE for well differentiated tumours will be higher than for poorly differentiated lesions.

Empirical experience gathered in the past ten years has taught us that some tumour types, like salivary gland tumours, are particularly favourable for neutron treatment [13, 14]. This is in agreement with the observations described in this paper, because salivary gland tumours are in general slowly growing, well differentiated cancers. In pilot

Table 2. Data concerning radiation-induced volume changes of pulmonary metastases after single doses of neutrons and/or cobalt-60 gamma rays

No.	Histology primary tumour	T_d	14 MeV neutrons			Cobalt-60			RBE values (rel. cobalt-60)	
			Dose (cGy)	Growth delay	Extrapolated res. volume	Dose (cGy)	Growth delay	Extrapolated res. volume	Measured	Estimated
74/1440	Anaplastic thyroid ca	13	238	8	0.64	726	16	0.41	1.5	
vP 1	Malign. teratoma undiff. testis	13	184	27	0.24	545	24	0.28	3.3	2.9
76/1912	Osteosarcoma	16	184	102	0.03	726	120	0.01	2.5	
76/148	Uterus sarcoma	17	243	71	0.02	726	67	0.02	3.0	
vP 2	Anaplastic thyroid ca	18	211	17	0.52	—	—	—	—	1.4
vP 3	Anaplastic thyroid ca	19	151	19	0.50	545	24	0.42	2.9	2.6
vP 4	Sq. cell ca floor of mouth	22	167	36	0.32	—	—	—	—	3.0
76/1708	Fibrosarcoma	23	194	16	0.60	847	24	0.48	3.0	
vP 5	Reticulum sarcoma	25	265	39	0.34	545	38	0.35	2.1	2.2
76/2516	Adenoca rectum	39	180	52	0.55	726	92	0.39	2.3	
vP 6	Adenoca large bowel	39	157	33	0.56	545	40	0.49	2.8	2.8
76/772	Adenoca corpus uteri	48	177	100	0.22	968	158	0.10	3.0	
76/1499	Uterus sarcoma	52	237	62	0.46	726	44	0.56	4.0	
71/288	Melanoma	61	174	46	0.58	726	58	0.51	3.3	
76/106	Adenoca urachus	64	216	138	0.45	—	—	—		2.6
vP 7	Osteosarcoma	69	205	90	0.41	—	—	—		2.7
77/703	Melanoma	69	243	50	0.46	484	30	0.70	4.3	
vP8	Adenoca large bowel	76	157	83	0.47	545	86	0.46	3.8	3.1
75/1773	Sq. cell ca vagina	76	179	64	0.57	—	—	—		2.7
vP 9	Sq. cell ca bronchus	86	277	122	0.41	696	88	0.49	3.8	3.6
vP 10	Adenoca large bowel	91	232	110	0.43	726	60	0.63	5.7	4.8
75/730	Soft tissue sarcoma	91	162		0.49	—	—	—		3.3
WG	Adenoca rectum	107	178	44	0.75	726	60	0.67	3.0	
vP 11	Sq. cell ca bronchus	107	221	112	0.48	—	—	—		3.5
75/937	Melanoma	112	246	98	0.55	726	52	0.72	5.3	
75/1442	Hypernephroma (Grawitz)	123	251	198	0.30	726	123	0.43	4.2	
76/1138	Adenoca rectum	130	108	38	0.79	—	—	—		2.9
76/2583	Uterus sarcoma	135	176	110	0.51	968	190	0.34	3.7	
73/505	Adenocystic ca	145	244	184	0.40	726	104	0.62	5.7	
77/142	Adenoca rectum	153	260	140	0.53	—	—	—		3.1
75/616	Trans cell ca bladder	193	216	310	0.27	968	350	0.24	4.1	
vP 12	Teratoma diff. testis	270	238	172	0.64	—	—	—		4.7
77/2681	Adenoca rectum	560	259	240	0.71	726	160	0.82	4.8	
vP 13	Chondrosarcoma	1100	211	608	0.68	—	—	—		4.6

studies on other tumour types often impressive and rapid regression of massive tumour was noticed. However, the results of controlled clinical trials up till now are less encouraging; in most of the trials no advantage has been found for neutron therapy. These disappointing results in part are due to the poor beam characteristics of most neutron machines that are in clinical use at the moment. To obtain similar dose distributions in the treatment of a deep seated tumour (e.g., bladder) with multiple fields, 14 MeV d+T neutrons should be compared with 300 kV X-rays. Also the selection of patients in a clinical trial can easily

Table 3. Data concerning radiation-induced volume changes of pulmonary metastases after single and multiple fractions of neutrons and/or cobalt-60 gamma rays

No.	Histology primary tumour	T_d	14 MeV neutrons Dose (cGy)	Fract.	Growth delay	Extrapolated res. volume	Cobalt-60 gamma rays Dose (cGy)	Fract.	Growth delay	Extrapolated res. volume	RBE (rel. cobalt-60) Fract.	Single
76/1708	Fibrosarcoma	23	351	5x	28	0.42	1331	5x	37	0.49	4.5	3.0
79/1885	Anaplastic thyroid ca	44	540	5x	154	0.09	2540	7x	170	0.08	4.5	—
78/968	Adenoca large bowel	63	480	5x	172	0.13	2420	5x	220	0.10	4.5	—
76/524	Adenoca rectum	63	1728	19x	154	0.15	6050	20x	90	0.37	6.5	—
75/1442	Hypernephroma (Grawitz)	123	502	5x	244	0.25	1452	5x	210 (?)	0.26 (?)	3.0 (?)	4.2
73/505	Adenocystic ca	145	480	5x	350	0.17	1452	5x	122	0.53	8.0	5.7
72/665	Thyroid ca	175	1404	20x	240 (?)*	0.39 (?)	4800	20x	250 (?)	0.41 (?)	3.6 (?)	—
77/2681	Adenoca rectum	560	260	4x	208	0.75	1815	5x	184	0.79	8.2	4.8

* (?): Only few data were available from the moment of irradiation; regrowth estimated from lowest point of volume reduction measured.

Table 4. Data concerning radiation-induced volume changes of pulmonary metastases after single and multiple fractions of neutrons; the relation with the N factor of the Ellis formula

			14 MeV single			Fractionated					
No.	Histology primary tumour	T_d	Dose (cGy)	Growth delay	Extrapolated res. volume	Dose (cGy)	Fract.	Growth delay	Extrapolated res. volume	Effective single dose	N exponent
76/1708	Fibrosarcoma	23	194	16	0.60	351	5x	28	0.42	335	0.03
74/2516	Adenoca rectum	39	180	52	0.55	192	2x	50	0.53	190	0.02
76/772	Adenoca corpus uteri	48	177	100	0.22	594	5x	230	0.03	415	0.22
76/1499	Uterus sarcoma	52	237	62	0.46	480	5x	96	0.29	380	0.14
77/703	Melanoma	69	243	50	0.46	484	4x	128	0.30	385	0.16
75/1773	Sq. cell ca vagina	76	179	64	0.57	502	5x	158	0.22	465	0.05
75/1442	Hypernephroma (Grawitz)	123	251	198	0.30	502	5x	244(?)*	0.25 (?)	575 (?)	−0.08 (?)
76/2583	Uterus sarcoma	135	176	110	0.51	480	5x	252	0.20	425	0.08
73/505	Adenocystic ca	145	244	184	0.40	480	5x	350	0.17	465	0.08
77/142	Adenoca rectum	153	260	140	0.53	260	3x	140	0.54	250	0.01
77/2681	Adenoca rectum	560	259	240	0.71	260	4x	208	0.75	210	0.15

*(?): Only few data were available from the moment of irradiation; regrowth estimated from lowest point of volume reduction measured.

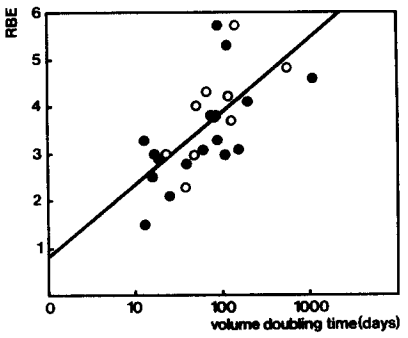

Fig. 5. RBE values relative to cobalt-60 gamma rays for volume changes of pulmonary metastases as a function of the volume doubling time. The dots indicate the measured RBE values, the open circles are estimated values when only neutron irradiation was given.

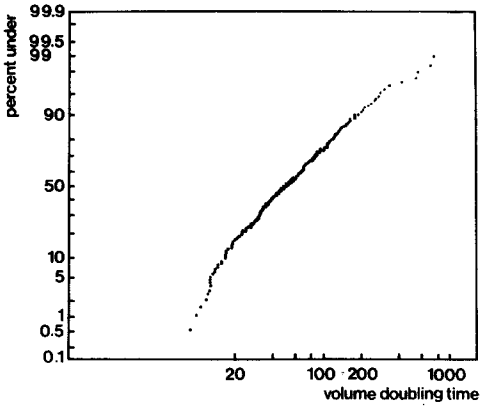

Fig. 6. Log normal distribution of volume doubling times for 192 *human tumours. It can be learned from this figure that* 70% *of these tumours have doubling times of less than* 100 days.

result in a mixed bag of tumours with various tumour characteristics like grading and proliferation rate. As was demonstrated above, only a proportion of these tumours will benefit from high LET radiation. So, the good results for some tumours will be outweighed by the worse results of a larger group of tumours that will not benefit from neutron irradiation. More radiobiological and clinical investigations are required to distinguish those patients which will obtain a significant gain from high LET radiation. The lung metastases model in humans can be helpful in this selection.

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