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The Reverse Protraction Factor in the Induction of Bone Sarcomas in Radium-224 Patients

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More than 50 bone sarcomas have occurred among a collective of about 800 patients who had been injected in Germany after World War II with large activities of radium-224 for the intended treatment of bone tuberculosis and ankylosing spondylitis. In an earlier analysis [H. Spiess and C. W. Mays, in *Radiation Carcinogenesis.* (C. L. Sanders *et al.,* Eds.) pp. 437–450. USAEC Symposium Series 29, CONF-720505, 1973] it was concluded that, at equal mean absorbed doses in the skeleton, patients with longer exposure time had a higher incidence of bone sarcomas. The previous analysis was based on approximations; in particular, it did not account for the varying times at risk of the individual patients. In view of the implications of a reverse protraction factor for basic considerations in radiation protection, the need was therefore felt to reevaluate the data from the continued follow-up by more rigorous statistical methods. A first step of the analysis demonstrates the existence of the reverse dose-rate effect in terms of a suitably constructed rank-order test. In a second step of the analysis it is concluded that the data are consistent with a linear no-threshold dose dependence under the condition of constant exposure time, while there is a steeper than linear dependence on dose when the exposure times increase proportionally to dose. A maximum likelihood fit of the data is then performed in terms of a proportional hazards model that includes the individual parameters, dose, treatment duration, and age at treatment. The fit indicates proportionality of the tumor rates to mean skeletal dose with an added factor $(1 + 0.18 \cdot \tau)$, where τ is the treatment time in months. This indicates that a protraction of the injections over 15 months instead of 5 months doubles the risk of bone sarcoma. © 1990 Academic Press, Inc.

INTRODUCTION

The follow-up of patients who were injected with high doses of the short-lived α emitter ^{224}Ra in Germany from

1944 to about 1964 continues to provide important information on various late effects, such as cataracts, tooth breakage, or severe kidney diseases (*1–3*). There are also recent indications of increased incidences of breast and liver tumors (*4*).

The bone sarcomas, which were the most dramatic and a most severe consequence, began to appear only a few years after the treatment; their increased risk appears to be eliminated by now. It must be assumed that all 56 reported bone sarcomas were due to the ^{224}Ra injections. On the basis of population statistics in the Federal Republic of Germany, less than one spontaneous bone sarcoma would have been expected during the follow-up period among the patients, and there is no evidence that the rate of bone sarcomas is increased due to ankylosing spondylitis or bone tuberculosis, the two illnesses that prompted the treatment with ^{224}Ra.

The cohort of patients comprises a broad range of ages at treatment and of injected doses. Furthermore, there is considerable variation in the temporal distribution of the series of injections, from short durations up to many months. The nearly complete follow-up allows, therefore, a detailed analysis of the time and dose dependence of the ^{224}Ra-induced bone sarcomas, but beyond this it permits conclusions on the possible influence of added factors such as the age at treatment or the duration of treatment. The focus of the present analysis is on this latter factor.

The short-lived ^{224}Ra accumulates on bone surfaces. The mean absorbed dose in the skeleton for juveniles under 16 years of age at injection was estimated (*5*) to be 0.16 Gy/MBq (= 0.6 rad/µCi) injected activity per kilogram body weight. For juveniles between 16 and 20 years of age at injection a conversion factor of 0.11 Gy/MBq was obtained, and for adults 0.054 Gy/MBq. The subsequent analysis employs mean skeletal doses according to these values. To avoid meaningless discontinuities at ages 16 and 20, a linear interpolation is used for this age group between the value 0.16 Gy/MBq for 16 years and 0.054 Gy/MBq for 20 years. This is a slight deviation from earlier analyses where

the simpler step function was employed, but it affects only 7% of all patients and only 3% of those with bone tumors. All subsequent computations were run with and without the modification; this did not indicate that the modification was critical for any of the conclusions. The mean skeletal absorbed dose according to the above assumptions is used as reference quantity in the subsequent considerations, and it is simply termed dose wherever the meaning is clear from the context.

A central finding of the epidemiological study was the occurrence of bone sarcomas in a temporal wave after treatment which reached a maximum 8 years after first injection and continued, at decreasing rates, to about 30 years after treatment. A linear dose dependence had first been estimated for the probability of the occurrence of a bone sarcoma with the coefficient 0.018 per Gy ($6, 7$). A later more detailed analysis in terms of the proportional hazards model has indicated a linear–quadratic dose dependence ($8, 9$). In this dependence the linear term was 0.085 per Gy, i.e., it was reduced by a factor of 2; the quadratic component corresponded to the increased bone-sarcoma frequencies per unit dose in the patients subjected to higher doses.

The inferred dose–response relationship may, of course, be codetermined by possible confounding factors such as sex, age at treatment, original illness, and temporal distribution of the injections, and these factors may therefore be considered in any quantitative analysis.

A previous analysis (8) led to the conclusion that neither sex nor original illness plays a noticeable role; both factors can consequently be disregarded in the analysis of time and dose dependences.

Age at treatment, too, was not found to influence the bone-tumor response; the analysis in terms of a proportional hazards model gave substantially the same temporal dependence and the same absolute frequencies at a given mean skeletal dose in the adult and juvenile cohorts. However, the age dependence of the dose conversion factors is somewhat uncertain, and this implies some uncertainty also in the dose–effect relationship, because the patients with higher dose were on average considerably younger.

A substantial correlation exists between mean skeletal dose and duration of treatment (see Fig. 2). The duration of treatment increases somewhat less than proportionally to injected activity, and the enhanced durations of exposure at higher doses could be fully or partially responsible for the deviation of the dose–effect relationship from linearity that was inferred in the earlier analysis ($8, 9$). This possibility will be examined here. Spiess and Mays studied the problem earlier (5), and they concluded that the incidence of bone sarcomas is increased at longer irradiation times. Such a 'reverse' protraction factor was suggested in earlier investigations in mice (10). While the findings in animals have been confirmed, at least at high doses, it is more difficult to quantify, or even to establish rigorously, a protraction fac-

tor in the patients injected with ^{224}Ra. The finding of a protraction factor, and especially a reverse protraction factor, for a stochastic effect of α rays on humans, on the other hand, has considerable implications for the basic principles of radiation protection, and this has led us to reexamine the earlier conclusions by methods which are not based on an assumed linearity of the dose–effect relationship and which take into account the different times at risk of the individual patients.

SYNOPSIS OF THE DATA

The data are summarized in Table I. Additional details are given in several earlier reports ($1–3$). The classification in the table follows the one adopted by Spiess and Mays. Among 900 patients, 89 with unknown dose or injection span (among them 10 with bone sarcoma) were excluded from the analysis. The patients who incurred a bone tumor had a median further survival less than 4 years, but of the 44 patients with known dose and injection span who incurred bone sarcomas, one developed a second bone sarcoma 16 years later. The inclusion of this additional tumor has no substantial influence on the results, and it is therefore ignored in the analysis.

The majority of the intravenous injections of ^{224}Ra were given at weekly intervals, with the total injection span ranging from a few weeks to a maximum of 2.5 years. In a few cases only a single injection was given. The injection span is taken to be the time in months between the first and the last injection. For the few patients (four juveniles and eight adults) who had received two or more series of injections, the total injection span was set equal to the sum of the individual spans. To simplify the data, the injection spans were rounded up to integer numbers of months. The short half-life of ^{224}Ra of a few days makes the effective exposure time of the skeleton approximately equal to the injection span.

The subsequent analysis is, when not otherwise specified, performed in terms of the variable injection span, τ. This quantity appears more suitable than related variables, such as the ratio of mean skeletal dose to injection span, D/τ, because it will remain unaffected by possible future dosimetric revisions.

Figures 1 and 2 give the distribution of the patients with and without bone sarcomas in mean skeletal dose vs age at treatment and vs injection span. Figure 1 serves merely to illustrate the basic data. Figure 2 is relevant to the analysis of the dependence of the bone-sarcoma incidence on dose and injection span. Considering narrow bands in treatment time, one recognizes readily the trend of the heavy dots to occur at relatively higher doses than the light dots. Conversely one would recognize a higher probability of bone sarcomas at longer treatment durations by an upward vertical shift of the heavy dots relative to the light dots; however,

TABLE I
Synopsis of Data through 1987

| | Number of patients | Number with bone sarcoma | Mean age[a] | | | Mean skeletal dose (Gy)[a] | Mean treatment span (months)[a] |
			At first injection	At last follow-up	At bone sarcoma		
All adults	587	11	38.7 (10.8)	62.0 (11.5)	47.5 (11.3)	2.12 (1.50)	5.5 (4.0)
Ankylosing spondylitis	341	5	41.2 (9.5)	63.8 (10.0)	58.2 (4.4)	1.44 (1.00)	3.6 (2.7)
Tuberculosis	205	6	33.5 (10.7)	59.0 (12.7)	38.7 (6.6)	3.31 (2.25)	8.8 (7.0)
Other	41	0	43.9 (12.2)	61.4 (13.8)	— (—)	1.83 (1.24)	4.3 (3.4)
Male adults	435	9	39.3 (10.2)	62.6 (10.9)	49.2 (11.5)	1.87 (1.53)	5.0 (4.7)
Ankylosing spondylitis	321	5	41.1 (9.5)	63.8 (10.1)	58.2 (4.4)	1.42 (1.00)	3.6 (2.7)
Tuberculosis	96	4	32.9 (9.9)	59.4 (11.9)	38.0 (6.8)	3.32 (2.05)	9.5 (6.9)
Other	18	0	41.1 (10.3)	58.8 (14.3)	— (—)	2.10 (1.37)	5.4 (3.6)
Female adults	152	2	36.9 (12.3)	60.2 (13.1)	40.0 (6.0)	2.83 (2.24)	6.8 (6.5)
Ankylosing spondylitis	20	0	41.3 (9.7)	64.5 (8.7)	— (—)	1.68 (0.97)	3.4 (1.9)
Tuberculosis	109	2	34.1 (11.3)	58.7 (13.4)	40.0 (6.0)	3.29 (2.41)	8.2 (7.1)
Other	23	0	46.2 (13.1)	63.5 (13.1)	— (—)	1.62 (1.09)	3.3 (2.9)
Children and juveniles	198	33	11.6 (5.3)	38.5 (13.1)	19.9 (5.8)	10.71 (8.78)	10.9 (8.7)
Boys	102	16	11.6 (5.3)	39.2 (12.9)	22.2 (6.4)	11.57 (9.68)	11.5 (9.1)
Girls	96	17	11.7 (5.3)	37.6 (13.1)	17.7 (4.1)	9.81 (7.62)	10.4 (8.2)

Note. Number of patients included in analysis, 785. Number of patients with bone sarcoma, 44 (double: 1). Number of patients excluded from analysis because of missing dose or injection duration, 89 (10 with bone sarcoma (double: 1); lost to follow-up, 26.

[a] Mean and (standard deviation).

such a shift, if present, is not evident, and its identification therefore requires a statistical analysis.

The numerical evaluation can be based on a maximum likelihood fit to appropriately chosen analytical expressions for the dependence of bone-sarcoma incidence on dose, treatment duration, and time after treatment. However, it is desirable to precede this evaluation by a nonparametric examination of the existence of a time factor. The nonparametric evaluation is free from bias that may result from the

choice of analytical expressions for the dependence on dose, duration of treatment, and time after treatment, and it will provide guidance for the subsequent choice of suitable analytical expressions.

THE PRESENCE OF A PROTRACTION FACTOR

Analysis in Terms of Dose Bands

Spiess and Mays have in their earlier analysis (5) examined the influence of the time span over which injections
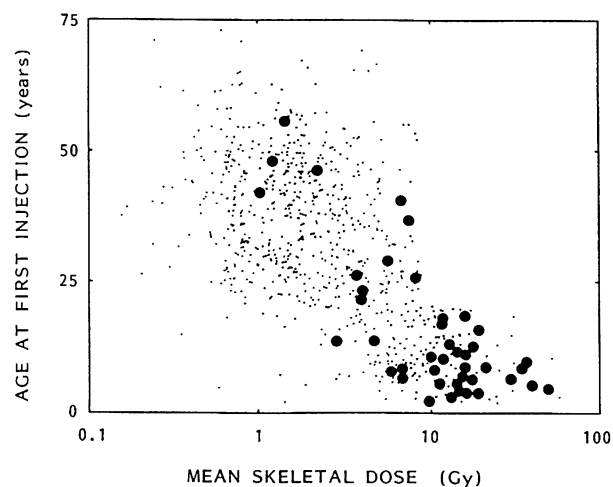
FIG. 1. Scatter diagram of age at treatment versus mean skeletal dose. Each patient is represented by a dot. A patient who, at later age, developed a bone sarcoma is represented by a heavy dot.
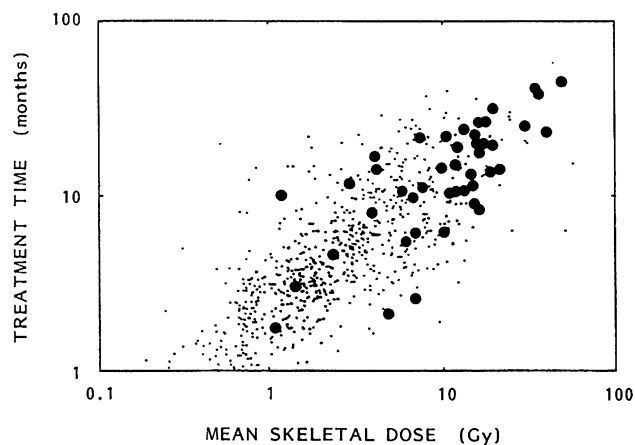
FIG. 2. Scatter diagram of treatment duration versus mean skeletal dose. Each patient is represented by a dot. A patient who, at later age, developed a bone sarcoma is represented by a heavy dot.

TABLE II
Results of the Rank-Order Test

	No. of patients (No. of bone sarcomas)	Mean rank[a] (SD)	Level of significance[b] (one-sided test)
Ranking in treatment duration in dose bands of width ±25%			
All patients	785 (44)	0.586 (0.043)	0.02
Juveniles	198 (33)	0.572 (0.050)	0.07
Adults	587 (11)	0.564 (0.087)	0.2
Ranking in age at injection in dose bands of width ±25%			
All patients		0.464 (0.043)	0.2
Juveniles		0.433 (0.050)	0.08
Adults		0.548 (0.087)	0.3

[a] The values in brackets are the standard deviations of the mean rank from 0.5 under the null hypothesis that the ranks are equidistributed.

[b] Against the null hypothesis that the ranks in treatment duration or in age are uniformly distributed.

were given on the incidence of bone sarcomas. They divided the entire cohort of patients into nine dose groups and divided each of the groups equally into the patients below and above the median treatment span. An excess of bone-sarcoma cases was then found among the patients with longer treatment spans although the average doses were about the same in the group of patients with longer and shorter treatment spans. This was a valid approach, but it contained features that can be improved. The particular importance of this singular data set and the possible implications of a reverse protraction effect for radiation protection therefore suggested an extension of the analysis.

The earlier treatment did not account for the different times at risk of the individual patients. That this omission could introduce a bias is readily understood. There is, for example, the possibility that the patients with extended treatment span survived on average longer than patients with the same mean skeletal dose but shorter treatment span. Their increased time at risk could then have been the reason for a higher number of bone sarcomas. This particular explanation is not suggested by the data; but there could be similar influences, and this necessitates an analysis that corrects for different times at risk.

In the present approach we use the same principle as in the earlier analysis, i.e. the durations of treatment for the patients with bone sarcomas are compared to the durations of treatment in other patients with equal or similar doses. However, the approach is modified insofar as each patient with bone sarcoma is compared only to patients who were at risk for, at least, a duration after treatment that equals the time to the diagnosis of the bone sarcoma. A second modification is introduced by comparing the duration of treatment of the patient with bone sarcoma not merely with the

median duration for the comparison patients, but by using the rank among all durations as a more precise measure. The third modification relates to the use of dose groups in the earlier analysis. The choice of separate dose classes was somewhat arbitrary, and a more general procedure is obtained by comparing each patient with bone sarcoma with those patients whose estimated doses differ by less than ±25%. This means that every patient is ranked in his own dose band with regard to treatment span, against all other patients who are in this dose band and who had been at risk for at least the same time. We call this the comparison group, and one must note that each patient with bone sarcoma has his own comparison group, depending not only on his dose but also on the time after treatment when his tumor occurred.

As a further improvement a correction is employed in this analysis in establishing the normalized ranks. Since each bone-sarcoma patient is ranked against patients with somewhat different doses, a linear regression is performed between the logarithms of the dose and the logarithms of the duration of treatment within the dose band. The regression coefficient is then utilized to scale the durations of treatment in the comparison group so that they correspond to the dose of the patient with bone sarcoma.

Under the null hypothesis that the treatment span has, at equal doses, no effect on the frequency of bone sarcomas, there would be no tendency that the tumor occurred preferentially among the patients with either longer or shorter treatment spans. The rank would therefore be expected to be equally distributed between 1 and the number, N, of patients in the comparison group. It is convenient to use, instead of the absolute rank, n, the relative rank,

$$r = (n - 0.5)/N. \tag{1}$$

The lowest and the highest possible ranks are then $0.5/N$ and $(N - 0.5)/N$. Under the null hypothesis the relative ranks are uniformly distributed among the possible values with mean 0.5 and, as can be readily shown (see Appendix), with variance $\sigma^2 = (1 - 1/N^2)/12$. The mean relative rank for a group of K patients with bone tumors is then, under the null hypothesis, distributed with mean 0.5 and variance

$$\sigma^2 = \frac{1}{12 \cdot K} \sum_{k=1}^{K} \left(1 - \frac{1}{N_k^2}\right), \tag{2}$$

where N_k is the number of patients in the comparison group of patient k with bone sarcoma. The values N_k vary between 7 and 120, and the term $1/N_k^2$ in Eq. (2) is thus always small. σ^2 is consequently close to $1/12 \cdot K$. Since K equals 44, the distribution is very nearly Gaussian.

A mean rank larger than 0.5 for the patients with bone sarcoma indicates enhanced risks for longer treatment dura-
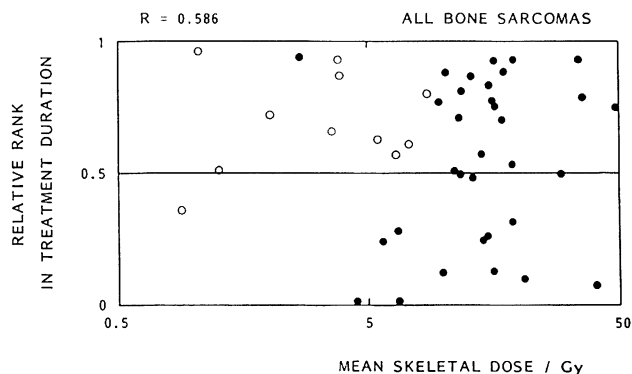
FIG. 3. The relative ranks in treatment duration for the 44 patients with bone sarcomas. The results are obtained if each patient with bone sarcoma is ranked among patients whose doses do not differ by more than ±25%. The mean relative rank is 0.586. The filled dots refer to juvenile patients who developed a bone sarcoma, the open dots to adult patients.

FIG. 4. Sum distributions of the relative ranks with regard to treatment duration. The results are obtained if each patient with bone sarcoma is ranked among patients with dose differences up to ±10%, ±20%, or ±30%.

tions at equal doses. In fact, one finds that the average relative rank is 0.586 for the 44 patients with bone sarcomas. With a standard deviation $\sigma = 0.043$ under the null hypothesis one obtains a one-sided level of significance of 0.023 (see Table II).

Figure 3 gives the results in explicit form by showing the relative ranks for the patients with bone sarcoma and their doses. Especially at low doses, one recognizes a tendency of the ranks to be high, this suggests a reverse dose-rate effect, i.e., a more frequent occurrence of the bone tumors in patients with longer treatment spans, even at low doses. This observation at low doses, however, is not significant by itself; when the test is performed for the adult patients only, one obtains an elevated mean rank that exceeds the expectation only on a one-sided level of 0.25. For the juvenile patients alone the significance level is 0.07.

It is found that the width of the dose bands is fairly uncritical. Between values of ±10% to ±30% the resulting mean ranks remain substantially unchanged. Figure 4 illustrates this point in terms of the sum distribution of the ranks; it gives a superposition of the distributions that result if the values ±10%, ±20%, or ±30% are chosen.

Age as a Possible Confounder

While duration of treatment is strongly correlated with dose, there is also a (negative) correlation of dose with age. It is therefore of interest to see whether the bone-sarcoma rates are, at a specified dose, dependent on age. The same type of analysis was consequently performed with regard not to the duration of treatment but to age at treatment. Figures 5 and 6 give the results obtained from the rank test. There is a slight indication of higher bone-sarcoma rates at equal doses for lower ages at treatment, but the difference is not significant.
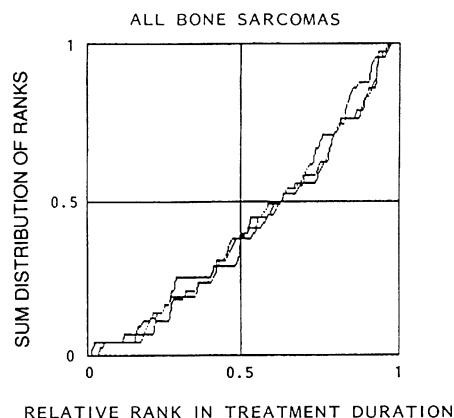
If, on the other hand, one considers juveniles only, i.e., if all those who were older than 20 at the time of the treatment are removed from the analysis, one obtains a somewhat stronger indication of enhanced bone-sarcoma rates at equal doses for the younger ages. However, this result, too, does not reach significance, even on the one-sided 5% level. The apparent trend can, of course, be a result of the rather crude dose factors which have been discussed in the introduction and which may underestimate somewhat the doses for the younger children.

In view of the indication that there may be some dependence—artificial or real—of the bone-sarcoma incidences on age at treatment, one must ask whether this could partly account for the apparent dependence on the duration of treatment. If there were a negative correlation at specified doses between duration of treatment and age, one could not readily distinguish whether the enhanced bone-sarcoma
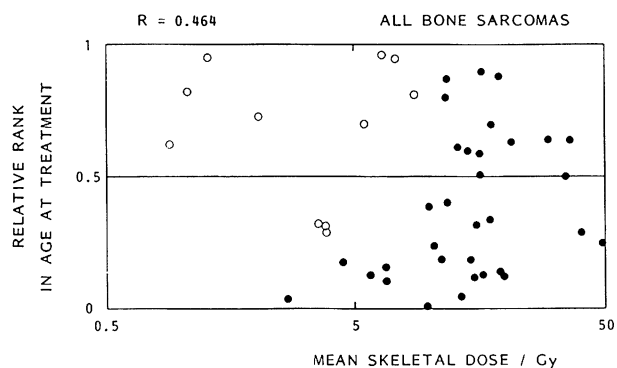
FIG. 5. The relative ranks in age at treatment that result if each patient with bone sarcoma is ranked among patients whose doses do not differ by more than ±25%. The mean relative rank is 0.464. The filled dots refer to juvenile patients who developed a bone sarcoma, the open dots to adult patients.
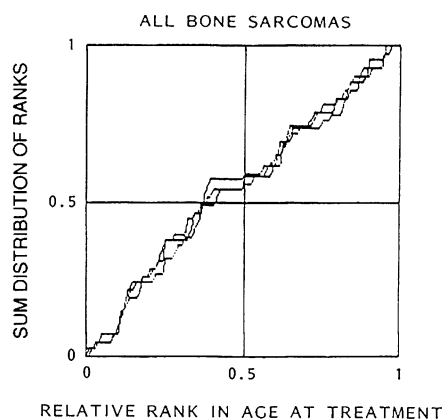
ALL BONE SARCOMAS

FIG. 6. Sum distribution of the relative ranks with regard to age at treatment. The results are obtained if each bone sarcoma patient is ranked among patients with dose differences up to ±10%, ±20%, or ±30%.

rates are due to the younger ages or the longer treatment times.

For this reason Fig. 7 gives for all patients and for the juveniles the correlation of the relative ranks, at equal doses, in treatment duration and in age at treatment. There is no evident correlation, and the Spearman correlation coefficient of the relative ranks in duration and in age has even slightly positive values. This strengthens the conclusions that the reverse protraction effect is real.

The results obtained with the rank-order test demonstrate that the longer treatment spans are, at equal mean skeletal doses, associated with higher incidences of bone sarcomas. The next step in the analysis is then to ask whether the earlier finding (8, 9) of a linear–quadratic dose relationship was a mere reflection of the higher average treatment spans at higher doses, and whether the dose relationship would be linear, if all exposures had the same duration.

EXPLORATION OF THE NATURE OF THE DEPENDENCE ON DOSE AND TREATMENT DURATION

The quantitative analysis of the dependence of the bone-sarcoma incidence on dose and duration of treatment can be facilitated by a preliminary step that provides guidance on the general nature of the dependence. For this purpose, too, one can use the nonparametric approach.

Two simple possibilities will be explored. One is dose proportionality at equal treatment durations, the second is dose proportionality at "constant dose rate," i.e., at injection spans that are proportional to mean skeletal dose.

The two assumptions are examined in terms of a rank-order test that is similar to the one applied in the preceding section, but that compares patients in classes of the same treatment duration, τ, or of the same "dose rates," D/τ.

Consider first the assumption that dose proportionality applies at constant values, τ, of the treatment duration. In a group of patients with equal τ but different doses, the bone sarcomas should then be distributed among the patients with probabilities proportional to their doses. To examine this possibility the patients of the group are ordered according to their doses, and the doses are summed in this order. Each patient is then assigned a rank equal to the percentile of the "collective dose" that corresponds to his position. If dose proportionality were to apply, the percentiles for the patients with bone sarcoma would have to be uniformly distributed between 0 and 1. If the dependence on dose were steeper than proportionality there would be a tendency for higher percentile values of the bone sarcoma patients.

Again the analysis is complicated by the fact that each patient who has incurred a bone sarcoma needs to be ranked in his own comparison group. The comparison

ALL BONE SARCOMAS   JUVENILES · BONE SARCOMAS
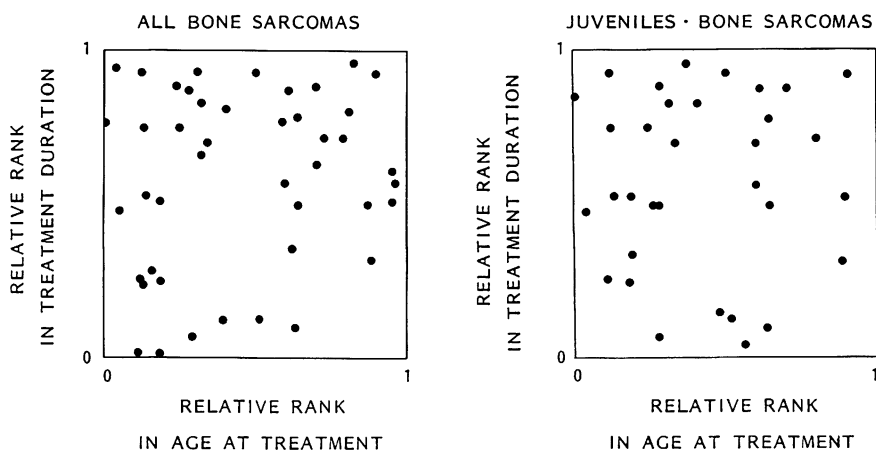
FIG. 7. Correlation diagrams for the relative ranks in treatment duration and age at treatment. Each patient with bone sarcoma is ranked with patients whose doses do not differ by more than ±25%.

group contains those patients who were still at risk at a time after treatment equal to the time to the bone sarcoma, and who had a treatment duration that differs by less than ±25%. Accordingly one establishes for each patient, k, with a bone sarcoma a comparison group, and the patient is assigned the percentile value, i.e., the relative rank, r_k, in collective dose, in his comparison group:

$$r_k = (\sum_{D_j < D_k} D_j + D_k/2)/D_{\Sigma}. \qquad (3)$$

D_k is the dose received by the patient with bone sarcoma, the D_{Σ} is the sum of all doses in the comparison group. If the null hypothesis holds, i.e., if the probability to incur a bone sarcoma is proportional to dose, the values of r_k should be uniformly distributed between 0 and 1, i.e., they should have expectation value 0.5 and variance $\sigma^2 = 1/12$. In actuality only discrete values of r_k within the interval from 0 to 1 are possible that depend on the dose values D_j in the group. This deviation from the uniform distribution does not change the expectation value 0.5 under the null hypothesis, but it causes a slight decrease of the variance (see Appendix).

The test statistic is, as in the previous section, the mean of the values r_k for all the patients with bone sarcoma, and this statistic, too, has the expectation value 0.5 under the null hypothesis that the bone-sarcoma incidence is proportional to dose.

The same test is also applied to examine the second hypothesis, i.e., that of dose proportionality at constant dose rates, D/τ. For each sarcoma a comparison group is established with those patients who were at risk for a sufficiently long duration and who do not differ by more than the same fraction ±25% in their dose rate, D/τ. The rank assigned to each patient with bone sarcoma is obtained with the same expression as in Eq. (3).

The results are given in Figs. 8 and 9 for the two tests, one with comparison groups of the same treatment duration, τ, and one with comparison groups of the same dose rates, D/τ. The tests show that linearity in dose for constant τ cannot be rejected. Linearity in dose for constant D/τ is rejected at the high level of significance of 0.002.

One concludes that the data are distinctly at variance with the assumption of dose proportionality under the condition that exposure time, i.e., treatment duration, is proportional to dose. Under this condition there is a steeper than linear increase of the bone-sarcoma incidence with mean skeletal dose. On the other hand, one finds that the data are consistent with the assumption of simple dose proportionality for constant exposure times. On the basis of these conclusions one can go a step further and ask for the quantitative dependence of the bone-sarcoma incidence on exposure time, τ, or on dose rate, D/τ.

FIG. 8. The relative ranks in "cohort dose" of the patients with bone sarcoma. The results are obtained by comparison to patients whose injection durations do not differ by more than ±25%. Top: Relative ranks in cohort dose versus treatment duration. The mean relative rank is $R = 0.536$, which is in agreement with dose proportionality. The standard deviation of R under the null hypothesis is 0.031. Bottom: Sum distribution of the relative ranks.

ANALYSIS IN TERMS OF AN EXTENDED PROPORTIONAL HAZARDS MODEL

Our earlier analysis of the ^{224}Ra data was based on a proportional hazards model (8). Such a model implies that the time dependence of the appearance of the bone sarcomas after injection does not depend on the other parameters such as dose. This premise appears to apply very well to the ^{224}Ra data. In our analysis we had considered only the parameter dose, and accordingly the cumulative rate of bone sarcoma was given by the expression

$$R(t, D) = R_0(t) \cdot f(D). \qquad (4)$$

This led to a linear–quadratic dependence of the bone sarcoma incidence on mean skeletal dose. The analysis was not aimed at a separation of the influences of dose and treatment duration, and on the basis of the present results one must conclude that the deviation from linearity is due

CONSTANT D/τ IN THE BANDS (± 25%)

FIG. 9. The relative ranks in "cohort dose" of the patients with bone sarcoma. The results are obtained by comparison to patients whose "mean dose rates," D/τ, do not differ by more than ±25%. Top: Relative ranks in cohort dose versus mean dose rate, D/τ. Th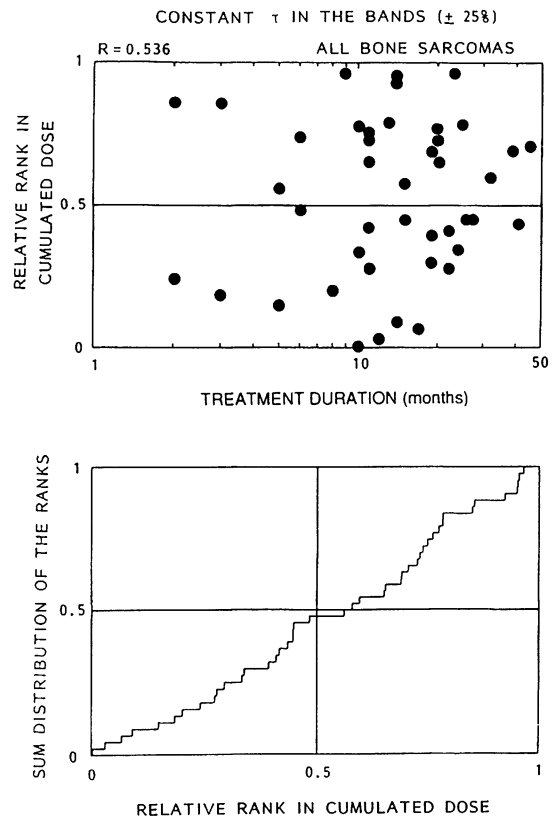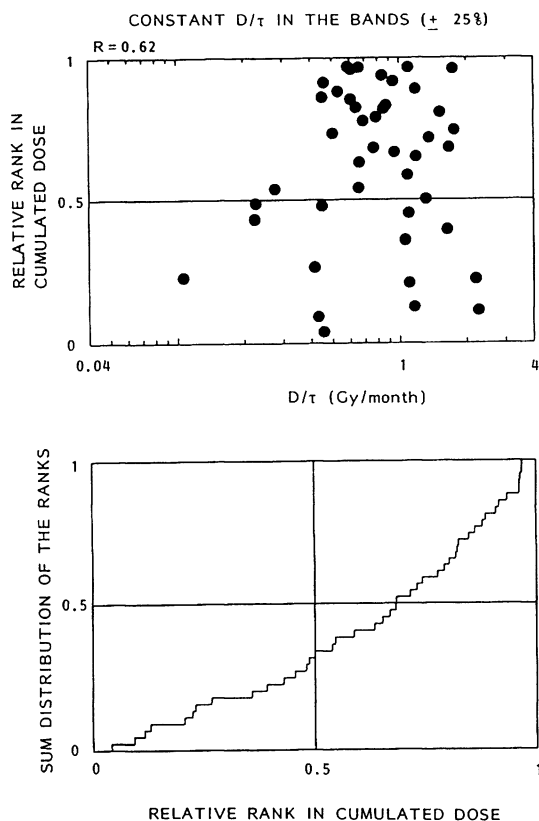e mean relative rank is $R = 0.62$, which is inconsistent with dose proportionality. The standard deviation of R under the null hypothesis is 0.043. Bottom: Sum distribution of the relative ranks.

to the increase, on average, of the treatment durations with increasing injected activities, i.e., with increasing doses.

To quantify the dependence of the bone-sarcoma rate on dose and exposure time, one must include the variable τ, i.e., the treatment span, in the proportional hazards analysis. For this purpose different analytical expressions were examined within a general proportional hazards model, i.e., the following dependence for the cumulative bone-sarcoma rate, at time t after exposure was considered:

$$R(t, D, \tau) = R_0(t) \cdot f(D) \cdot g(\tau). \qquad (5)$$

A simple expression that led to a satisfactory fit was

$$R(t, D, \tau) = R_0(t) \cdot (\alpha D + \beta D^2) \cdot (1 + \gamma \tau). \qquad (6)$$

$R_0(t)$ is the time dependence of the cumulative incidence, normalized to 1 at the end of the expression period. The duration of the expression period is set equal to 33 years,

which is the longest time elapsed between treatment and the occurrence of a bone tumor.

The influence of the different terms of Eq. (6) on the quality of the maximum likelihood fit can be judged from the results that are listed in Table III. The poorest value of the likelihood is obtained with a mere linear fit. The resulting coefficient α is close to the value obtained in the earlier, simple linear analysis (6, 7). The utilization of the additional parameter β, under exclusion of γ, improves the likelihood. However, a substantially better likelihood results if the quadratic term in dose is omitted and the dependence $(1 + \gamma \tau)$ is used instead. There is virtually no further increase of the likelihood if the quadratic term in dose is introduced in addition to the factor $(1 + \gamma \tau)$; the very small positive value of β can therefore be disregarded, and the resulting optimum fit is

$$R(t, D, \tau) = R_0(t) \cdot \alpha \cdot D \cdot (1 + \gamma \tau) \qquad (7)$$

with

$$\alpha = 0.0055/\text{Gy} \quad \text{and} \quad \gamma = 0.18/\text{month}.$$

The nonparametric dependence $R_0(t)$, i.e., the distribution of bone sarcomas in time after treatment, was found to be largely independent of the particularities of the model, and the form obtained in the fit of the data to Eq. (7) (Fig. 10) is virtually identical to the dependence obtained in the earlier analyses (8, 9), which did not account for the role of the exposure duration.

The integrated risk over the entire expression time is

TABLE III
Maximum Likelihood Analysis in Terms of Eq. (5)

$R(t, D) = R_0(t) \cdot \alpha D$:
$\alpha = 0.017/\text{Gy}$
Max.Log − Likelihood: $L = -246.9$

$R(t, D) = R_0(t) \cdot (\alpha D + \beta D^2)$:
$\alpha = 0.010$ Gy, $\beta = 0.00065/\text{Gy}^2$
Max.Log − Likelihood: $L = -244.8$

$R(t, D, \tau) = R_0(t) \cdot \alpha D \cdot (1 + \gamma \tau)$:
$\alpha = 0.0055/\text{Gy}$, $\gamma = 0.18/\text{month}$
Max.Log − Likelihood: $L = -242.2$

$R(t, D, \tau) = R_0(t) \cdot (\alpha D + \beta D^2) \cdot (1 + \gamma \tau)$:
$\alpha = 0.0056/\text{Gy}$, $\beta = 1.6 \cdot 10^{-4}/\text{Gy}^2$, $\gamma = 0.16/\text{month}$
Max.Log − Likelihood: $L = -242.2$

$R(t, D, \tau, a) = R_0(t) \cdot \alpha D \cdot (1 + \gamma t) \cdot \beta(a)$
$\alpha = 0.0051/\text{Gy}$, $\gamma = 0.13/\text{month}$, $\beta = 1.48$
$a_0 = 20$ years
Max.Log − Likelihood $L = -242.1$

$$R(D, \tau) = \alpha D(1 + \gamma\tau) \quad (8)$$

with the values α and γ that are listed above.

This relationship is equivalent to

$$R(D, \tau) = \alpha\left(D + \frac{\gamma}{\rho}D^2\right), \quad (9)$$

where $\rho = D/\tau$ is the dose rate.

One obtains, therefore, linear dose dependences (Eq. (8)) for constant values of τ, and linear-quadratic dependences (Eq. (9)) for constant dose rates, D/τ. This is exemplified in Fig. 11, which gives the dose dependences for two values each of τ and of D/τ, that are in the range of typical values for the patients injected with ^{224}Ra.

The general trend among the cohort of patients is closer to the situation of constant D/τ than of constant τ. This explains the effectively linear-quadratic dose dependence inferred in the earlier analyses (8, 9). In actuality, however, one deals with an intermediate situation.

The nonparametric analysis had indicated, but not on a level of statistical significance, a higher occurrence of bone sarcomas at equal doses for the younger patients. To quantify this observation the parametric analysis was extended to include the parameter age at injection. Since the present analysis uses an approximative and somewhat uncertain relationship between the injected activity and the mean skeletal dose, it would not be justified to use anything but a simple model. Equation (7) was therefore modified to

$$R(t, D, \tau, a) = R_0(t) \cdot \alpha \cdot D \cdot (1 + \gamma\tau) \cdot \beta(a) \quad (10)$$

with

$$\beta(a) = \begin{cases} \beta & \text{for } a \leqslant a_0 \\ 1 & \text{for } a > a_0. \end{cases}$$

One obtains the value $\beta = 1.5$ (Table III). This indicates, in agreement with the preceding analysis, an increased sensi-
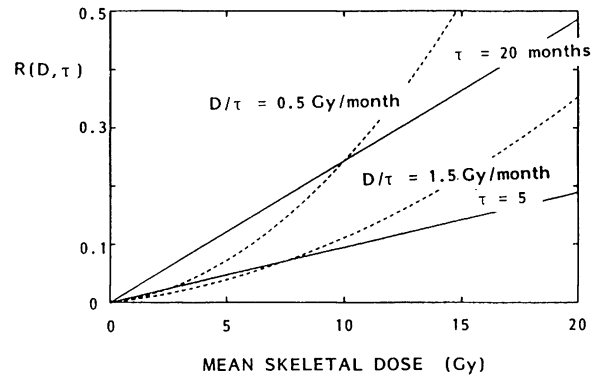
FIG. 11. Bone sarcoma expectation, $R(D, \tau)$, over the entire expression period, according to Eqs. (8) and (9). The full curves represent, according to Eq. (8), the risk for constant exposure durations $\tau = 5$ months and $\tau = 20$ months. The broken curves correspond to constant values $D/\tau = 0.5$ Gy/month and $D/\tau = 1.5$ Gy/month.

tivity at younger age; however, β does not differ from 1 with statistical significance.

CONCLUSIONS

A reverse protraction factor for bone sarcomas induced by ^{224}Ra had first been suggested in animal experiments (10) and it was subsequently inferred also for the patients injected with ^{224}Ra (5).

The latter conclusion, however, remained somewhat tentative, because the numerical evaluation was based on a number of approximations. The present analysis employs more rigorous mathematical techniques that confirm and quantify the earlier conclusions by Spiess and Mays.

Among the cohort of patients there is a broad variation of injected activities and of the resulting mean skeletal doses. This variation reflects partly the reduction of dosages during the years, when harmful effects due to the ^{224}Ra treatment began to be recognized. On average the larger doses were given in a larger number of fractions over longer periods of time, up to a maximum of 2.5 years. Even at the same mean skeletal doses there is, however, a broad range of treatment spans. This broad variation of doses and of treatment spans, the nearly complete follow-up, and the absence of an appreciable spontaneous bone-tumor rate have permitted the assessment of the separate influence of dose and treatment duration that has been the objective of this study.

On the basis of the present results it is concluded that the seemingly linear-quadratic dependence that had earlier been inferred is, in fact, the combined result of proportionality of the bone-sarcoma incidence on dose at constant exposure time and of an increase of the incidence with longer exposure times at specified dose. For instance, the inci-
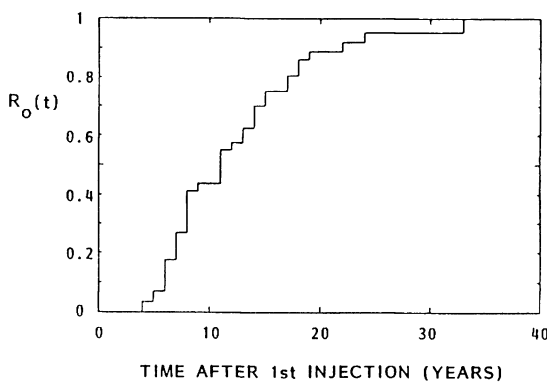

FIG. 10. The cumulative distribution, $R_0(t)$, of bone sarcomas in time that results from the maximum likelihood fit of Eq. (7) to all bone sarcoma data. The steps of the function occur at those times after treatment when bone sarcomas were diagnosed.

dence is roughly doubled when the exposure is protracted over 15 months instead of being given in 5 months.

The notable result of these interdependences is a linear dose relationship for constant exposure time, and a linear–quadratic relationship for exposures with constant dose rate or with treatment durations proportional to dose in a fractionated exposure. The result has evident implications for considerations of radiation protection with regard to internal α emitters.

The observation of a reverse protraction factor for densely ionizing radiation is in line with a number of earlier experimental findings that suggest the possibility of enhanced effects of densely ionizing radiations in protracted or fractionated exposures (10–14). In human studies analogous relationships have been seen in uranium miners exposed to high levels of radon (15, 17) and recently also in tin miners (18). The present finding appears, therefore, to support and to extend earlier observations. One should, however, note important differences between miners and ^{224}Ra patients. Uranium miners are exposed to radon and its daughter products over a period of several or many years; the durations of exposure in the ^{224}Ra patients vary from months to about 2.5 years. Furthermore the time distribution of the appearance of the bone tumors is well defined, while that of the lung cancers includes an uncertain extrapolation in time. Moreover for the miners of the Colorado plateau it was estimated that the risk increases by 10% if the same exposure is protracted over 20 years rather than 2 years; the increases inferred in the present study are substantially larger. One must further note that the conclusions drawn with regard to the miners may be linked to complexities of the relative risk models that are still insufficiently understood, such as the reduction of the relative risk with time after exposure, as it has been inferred for the British ankylosing spondylitis patients (19), and as it has been postulated for the uranium miners by the BEIR V committee (20).

The main result of the present study is the reverse dose-rate dependence. However, in agreement with the earlier suggestions by Spiess and Mays, there is also an indication of increased sensitivity at younger ages. But the observation does not reach statistical significance. We feel that the issue could be settled only on the basis of a better assessment of the dose to the skeleton, or specifically to the endosteal layer, per unit of activity injected at different ages.

In the present analysis there is no indication that the reverse time factor applies only to the larger doses. Nevertheless it must be noted—and this is a further difference from the epidemiological studies of lung cancer in miners—that the data relate generally to high doses to the critical tissue that resulted from a past practice of ^{224}Ra therapy. The actual dose to the endosteal cells is several times larger than the mean skeletal dose, and even the individual injections of up to about 3 MBq of ^{224}Ra were therefore sufficient to cause several traversals of α particles per endosteal cell. It is evident that under such conditions a 'saturation effect' can occur for short time exposures. It is also conceivable that the initial fractions of a treatment induce cell proliferation that makes the endosteal layer more sensitive to later fractions. An extrapolation of the present findings to the much smaller doses that are relevant under the normal conditions of radiation protection must therefore remain tentative and cannot be supported by the present data.

A comparison of the results to the present low-dose therapy for ankylosing spondylitis with ^{224}Ra is somewhat less tenuous. The treatment consists in general of 10 weekly injections of about 1 MBq (28 μCi) of ^{224}Ra, and the mean skeletal dose for an adult of 70-kg body weight is then estimated to be 0.56 Gy. Entering this dose and $\tau = 3$ months into Eq. (8), one infers a bone tumor risk of slightly less than 0.005 for the current treatment with low doses of ^{224}Ra. This agrees with our previous estimate in terms of the linear–quadratic dependence (8, 9) that was reduced by a factor of 2 at low doses in comparison to the estimate from a simple linear model (6, 7). The follow-up of the patients for the low-dose treatment with ^{224}Ra is still incomplete (21), but it does not, up to now, suggest bone-sarcoma risks in excess of our present estimate.

APPENDIX

Formulae for the Variance of the Ranks

In the tests one uses only certain discrete values of the relative ranks, r_i, rather than the continuous variable that is uniformly distributed between 0 and 1 under the null hypothesis. In the simple, unweighted form of the test (see The Presence of a Protraction Factor) the discrete values $r_i = (i - 0.5)/N$ correspond to the 'slices' $r_i \pm \Delta r/2$ of the uniform distribution, with $\Delta r = 1/N$. In the weighted test (see Exploration of the Nature of the Dependence on Dose and Treatment Duration) $\Delta r_i = D_i/D_\Sigma$.

A 'randomization' of the tests, which transforms the discrete statistic to the uniformly distributed statistic, replaces each value r_i by the associated slice of the uniform distribution. Each slice is symmetrical around its central value, r_i; accordingly the transformation does not change the mean value. The discrete statistics therefore has, under the null hypothesis, the same mean value, 0.5, as the continuous uniform distribution between 0 and 1.

The variance of the discrete statistic has the value

$$\sigma^2 = \left(1 - \sum_{i=1}^{N} \Delta r_i^3\right)/12 \qquad (A.1)$$

under the null hypothesis, as can most readily be shown by a comparison between the contribution, δm_i, to the second moment of the discrete value r_i and the contribution, Δm_i,

of its associated slice in the uniform distribution. The probability of the value r_i in the discrete distribution and the probability in the continuous uniform distribution of a value within the slice are both equal to Δr_i.

Accordingly one has the contributions to the second moment,

$$\delta m_i = r_i^2 \cdot \Delta r_i$$

$$\Delta m_i = \int_{r_i - \Delta r_r/2}^{r_i + \Delta r_i/2} x^2 dx = r_i^2 \cdot \Delta r_i + \Delta r_i^3/12. \quad (A.2)$$

Summing all terms, one concludes that the second moment of the continuous uniform distribution between 0 and 1 exceeds the second moment of the discrete distribution by $\sum_{i=1}^{N} \Delta r_i^3/12$. The mean values of the two distributions are equal. The difference of their variances equals, therefore, the difference of the second moments. Since the variance of the uniform distribution is $1/12$, one obtains Eq. (A.1). For $\Delta r_i = 1/N$ Eq. (A.1) reduces to the more familiar formula $\sigma^2 = (1 - 1/N^2)/12$.

The variance of the sum of K ranks equals the sum of the variances of the individual ranks. This determines the variances of the average ranks.

ACKNOWLEDGMENTS

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