The Radiobiology of Radium and Thorotrast

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81 Figures and 99 Tables

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A Proportional Hazards Analysis of Bone Sarcoma Rates in German ^{244}Radium Patients*

D. Chmelevsky, A. M. Kellerer, H. Spiess, C. W. Mays

Introduction

An important result of the continuing follow-up and analysis of the German ^{224}Ra patients is the nearly equal sensitivity of the juvenile and the adult patients to bone-sarcoma induction. This conclusion has been obtained from a competing risk corrected determination of the cumulative tumor rates [5, 7]. The present study extends the analysis in terms of the proportional hazards model.

Analysis in Terms of the Proportional Hazards Model

The analysis is based on the continuing follow-up of the patients up to June 1984 [6], with only minor changes compared to the earlier published listing [11]. Of the total of 899 patients, the 38 with unknown doses (6 with bone sarcomas) were excluded from the analysis. Of the 53 patients that incurred bone sarcomas two patients developed an additional bone sarcoma, believed to be a new primary tumor and therefore included in the analysis. The diagram of Figure 1 represents all patients in terms of their estimated average skeletal dose [12] and their age at the beginning of the treatment. The diagram demonstrates the inverse correlation between age at treatment and average skeletal dose. It also shows the high bone-sarcoma frequencies at high doses.

Figure 1 does not contain some essential additional information, such as the time at risk for the individual patients. It also does not give the durations of treatment which vary substantially and tend to increase with increasing dose. The time at risk is taken into account in the subsequent analysis, but possible dose-rate effects are not assessed.

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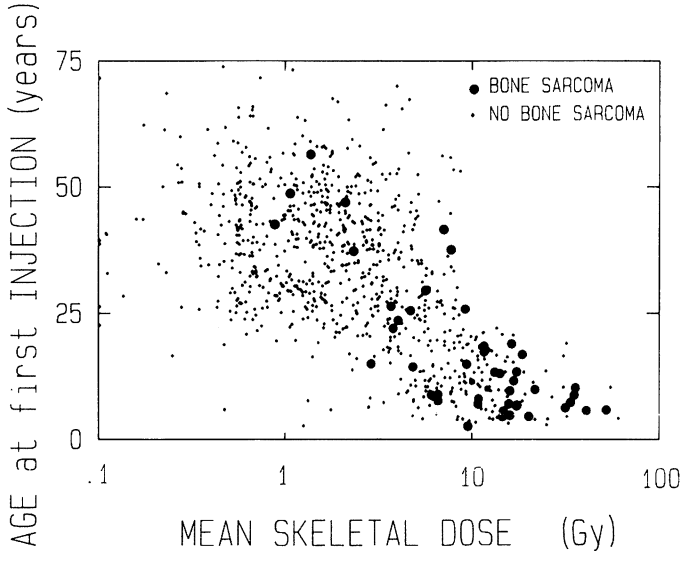

Fig. 1: Distribution of ages of the ^{224}Ra patients at the beginning of treatment and of mean skeletal doses. Each symbol represents a patient.

Table 1. Dose Classes for the Non-Parametric Analysis

Group Number	Dose Classes (gray)	Mean Skeletal Dose ± St. Dev. in Group (gray)	Number of Patients	Number of Bone Sarcomas	Cum. Tumor Rate** at t = 25 years
Adults (Males and Females)					
1	$D < 1$	.58 ± .21	214	1	.0061 ± .0060
2	$1 \leq D < 2$	1.43 ± .26	189	2	.013 ± .010
3	$2 \leq D < 4$	2.82 ± .58	163	5 (+ 1)*	.046 ± .020
4	$4 \leq D$	5.79 ± 1.33	83	5	.072 ± .033
Juveniles (Boys and Girls)					
5	$D < 4$	2.40 ± 1.1	34	1	.036 ± .036
6	$4 \leq D < 8$	5.95 ± 1.1	63	4 (+ 1)*	.086 ± .035
7	$8 \leq D < 12$	9.95 ± 1.1	52	8	.19 ± .06
8	$12 \leq D < 16$	13.9 ± 1.2	30	7	.29 ± .12
9	$16 \leq D < 20$	17.8 ± 1.0	13	7	.78 ± .30
10	$20 \leq D$	32.5 ± 10	19	7	.67 ± .24
Σ			860	49	

* double bone sarcoma
** from the proportional hazards analysis

Non-Parametric Analysis

In an extension of the earlier analysis that corrected for competing risks [5] juvenile and adult patients were subdivided into several dose groups (Tab. 1). For the individual groups of patients separate estimates of the cumulative tumor rate, R(t), were then derived in their dependence on time, t, after treatment. The sum-limit estimate [4, 5] is used for this purpose.

The resulting curves are represented in Figure 2. They show a consistent trend with mean skeletal dose. For easier readability of the graphs the standard deviations are not indicated; as to be expected with the relatively small number of tumors per group, they are substantial. The difference between groups 9 and 10 is not significant. The data indicate the general trend of the bone-sarcoma rates. But the separate estimates are not very suitable to derive the dose dependence quantitatively. A more sophisticated approach is, therefore, required, and the apparent absence of any variations of the latency period suggests that the familiar proportional hazards model [3] is most suitable for the analysis.

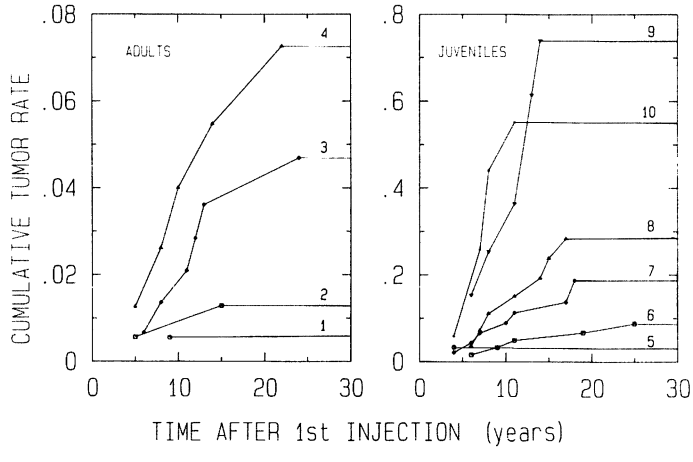

Fig. 2: Cumulative tumor rates calculated from the sum-limit estimate for the dose groups specified in Table 1.

The essential assumption of this model is that the tumor rates (hazard functions) after treatment – and therefore also the cumulative tumor rates – are the same for all dose groups, except for a factor that depends on dose. This is expressed by the equation:

$$R(t,D) = \beta(D)\, R_o(t) \qquad (1)$$

$R_o(t)$, the so-called base-line function, is a dependence on time that is not a priori specified; $\beta(D)$ is a function of absorbed dose or mean absorbed dose. An analysis in terms of this model is called non-parametric, if no analytical expressions are postulated for the form of the two functions $R_o(t)$ and $\beta(D)$. The algorithm [3] developed from earlier results of Cox [1] determines those two relations that fit the data best in the sense of maximum likelihood. In the analysis with separate dose groups one obtains values of the function $\beta(D)$ only for the average skeletal doses assigned to the groups.

The proportional hazards analysis has, in a first step, been performed separately for the juvenile patients and the adult patients. The results are given as plain lines in the two panels of Fig. 3. Comparing the curves in the two panels one notes that the dependences are similar for those two pairs of dose groups of juveniles and adults that have roughly the same average skeletal dose (groups 3 vs. 5 and 4 vs. 6). As a next step the analysis has therefore been performed jointly for all 10 groups; i.e. identity of the base-line function, $R_o(t)$ has been postulated for juveniles and adults, and the optimal shape of this function and optimal values of the proportional hazards coefficients, β_i (i = 1 to 10), have been obtained. The results, which are given by the lines with dots in the panels of Fig. 3, are in striking agreement with the data from the separate analysis. There is, from the separate analysis, no indication of a difference in the time course of the bone-sarcoma rates between the groups of juvenile and adult patients. The influence of the differing skeletal dose is expressed merely in the factors β_i for the various groups (i = 1 to 10). These values are proportional to the numbers in the last column of Table 1.

The points in Fig. 4 give the total bone-sarcoma risk divided by the mean skeletal dose for the different dose groups of juvenile and adult patients. The risk equals the cumulative tumor rate reached at the end of the expression period at t = 25 years. The standard errors are obtained by a bootstrap method, i.e. by random simulations of the distribution of bone sarcomas into the different dose groups under the assumption of the estimated values β_i. With this method the standard errors are derived from a large number of simulations with subsequent proportional hazards analysis. The magnitude of the standard errors shows that the difference between the last two groups is not statistically significant.

A linear regression for the groups below 8 Gy in yields the dose coefficient 0.013/Gy for the inci-

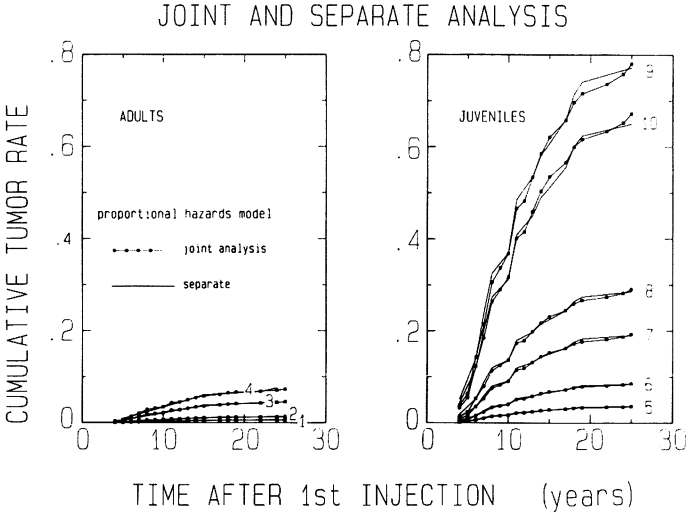

Fig. 3: Cumulative tumor rates calculated according to the proportional hazards model. The numbers refer to the groups specified in Table 1.

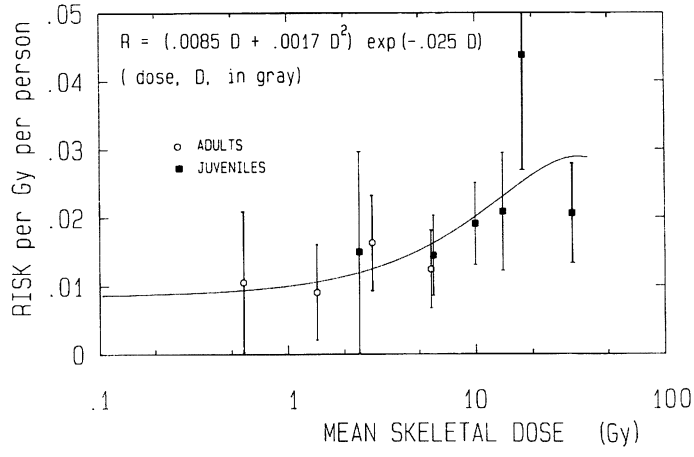

Fig. 4: Risk per person per gray vs. mean skeletal dose. The points with their standard errors result from the proportional hazards analysis (see Eq[1]) with separate dose classes. The solid line results from an analysis according to Eq(3) without formation of dose classes.

dence of bone sarcomas. However, the data points in Figure 4 are indicative of a dose-effect relation that is not linear. A further step in the analysis must therefore aim at the determination of the most likely shape of the dose-effect relation. This will also bear on the problem of saturation at high doses.

Parametric Analysis

To assess a possible non-linearity in the dose-effect relation one must replace the non-parametric dose dependence of the proportional hazards coefficients, β, by a suitable analytical expression. The analysis aims then at the estimation of the parameters in this expression. The familiar linear-quadratic dose dependence with added exponential term at high doses is utilized:

$$R(t,D) = (\alpha D + \beta D^2) \exp(-\gamma D) \cdot R_o(t) \qquad (2)$$

No a priori assumption is made on the base-line function, $R_o(t)$, for the time dependence of the cumulative tumor rate, i.e. this part of the analysis remains non-parametric. One determines the function and the parameters that are in best agreement with the entire set of data, without the need to establish dose groups. With this model, the numerical solution can not be based on the Cox algorithm. Instead another procedure is required that utilizes a non-linear optimization algorithm for the likelihood. This is merely a technical matter that does not alter the essence of the approach.

The resulting dose dependence (with D in gray):

$$R(t,D) = (0.0085\ D + 0.0017\ D^2) \exp(-0.025\ D) \cdot R_o(t) \qquad (3)$$

is represented in Fig. 4 (solid line) in terms of the total bone-sarcoma risk 25 years after treatment, R(25 yrs), divided by D. The base-line function, $R_o(t)$, i.e. the temporal dependence of the cumulative tumor rate is nearly the same as that obtained in the preceding non-parametric analysis; it is therefore not represented. The linear coefficient in the estimated dose relation is 0.0085/Gy, i.e. somewhat less than the value, 0.013/Gy, obtained from fitting a constant to the first 6 points in Figure 4. A linear regression to all data without formation of dose classes is rejected with error level $p = 0.02$; but if overall linearity were postulated, the risk factor 0.018/Gy would be obtained.

Control incidences have not be accounted for in the preceding computations. To estimate a control incidence we have used age dependent bone-sarcoma rates for West-Germany averaged over the calendar years 1970–1978*. Integrating these bone-sarcoma rates over the distribution in age of

* Data kindly provided by Dr. Frentzel-Beyme, Deutsches Krebsforschungszentrum, Heidelberg. German bone-sarcoma rates from a published compilation [14] lead to the same conclusions. The rates for bone sarcomas during the years 1970–1978 were utilized. They conform to the revision of the ICD (International Classification of Diseases) which excludes certain tumors, such as plasmocytomas, that were earlier counted among the bone sarcomas.

the total number of years at risk one obtains the value 0.0004 as the control risk for bone sarcoma per patient. This value is sufficiently small not to influence the results of the computations. There is no evidence that either ankylosing spondylitis [10] or tuberculosis [2] increase the incidence of bone cancer in non-irradiated patients.

Discussion

The competing-risk corrected analysis of the bone-sarcoma rates in the ^{224}Ra patients has been carried further in the present investigation. The data are in agreement with the postulate of the proportional hazards model. No indication is found that supports the assumption of a shortening of the latency period with increasing doses. The results support also the conclusion of equal sensitivity of the juvenile and the adult patients. The expression period of bone sarcomas appears to be nearly terminated 25 years after the treatment; the integrated incidence per individual at risk during the whole expression period can, therefore, be given. The best estimate of the dose-effect relation is a linear-quadratic dependence according to Eq(3), as given in Figure 4. The risk coefficient, 0.0085/Gy, obtained in this way for small doses is substantially smaller than the value 0.018/Gy which would be obtained from a linear regression. This linear regression without dose classes is rejected with error level p = 0.02.

The mean skeletal dose is inversely correlated with age at treatment (see Fig. 1) and is correlated with treatment time (see Fig. 5). The nonlinearity of the dose-effect relation could therefore, in principle, be due to one of the two confounding factors. Age at treatment appears to play no major role (see Fig. 3). The increased protraction times at higher doses, however, may influence the observed dose dependence. An enhancement of the α-ray effectiveness due to protraction, as earlier suggested by Spiess and Mays for these patients [12], has been demonstrated in animal experiments with ^{224}Ra [9].

Regardless of the remaining uncertainties in the interpretation, the estimate on the basis of the linear-quadratic model seems appropriate for the estimation of the risk factor for small doses given over several weeks. In the current treatment of ankylosing spondylitis patients with ^{224}Ra the mean skeletal doses are about 0.56 Gy over 10 weeks [13]. The estimates from our analysis are applicable to this group. The risk factor of 0.0085/Gy for the induction of skeletal sarcomas will, in the years to come, be measured against the continuing follow-up of the current group of ^{224}Ra patients [15].

Summary

Forty-nine bone sarcomas have occurred among 861 patients injected with known amounts of ^{224}Ra corresponding to average skeletal doses from 0.06 to 57.5 Gy. A competing risk corrected analysis of

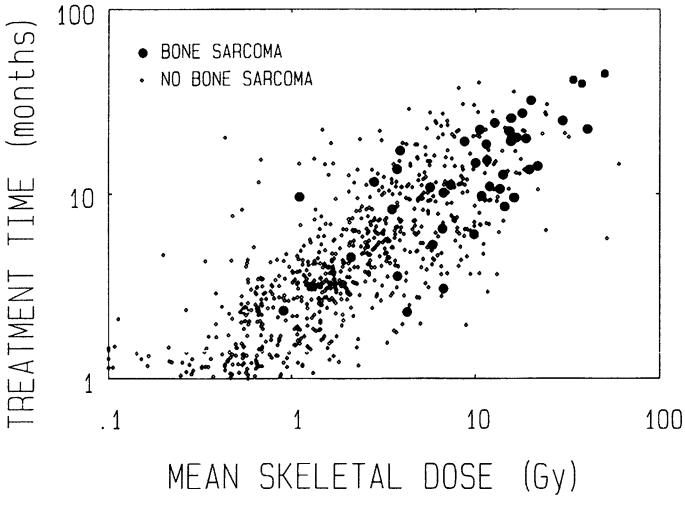

Fig. 5: Distribution of mean skeletal doses and treatment times. Each symbol represents a patient.

the data in terms of the Cox proportional hazards model indicates equal sensitivity and equal time course of the bone tumor rates in juvenile and in adult patients at comparable mean skeletal doses. The proportional hazard coefficients follow a linear-quadratic dependence on absorbed dose, and the cumulative bone sarcoma risk (R) over the expression period of about 25 years is: $R = (0.0085\ D + 0.0017\ D^2)\exp(-\ 0.025\ D)$, where D is the mean skeletal dose in gray. A simple linear fit up to mean skeletal doses of 8 Gy yields the relation $R = 0.013\ D$.

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