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Radiation-Induced Systemic and Local Bone Tumors: Two Types of Late Effects with Possible Different Origins?[1]

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Bone sarcomas may be induced throughout the skeleton (systemic) in mice by relatively low internal α-particle doses that are distributed over the whole skeleton. The induction of local (periosteal) bone sarcomas after paratibial deposition of insoluble radiocolloids required much higher doses, and in addition high energies of emitted particles. Paratibial deposition of α-particle-emitting radiocolloids of ^{227}Th and ^{228}Th resulted in formation of both local and systemic bone sarcomas. The latter were most probably induced by the released radium daughters of the thorium isotopes and were distributed about the skeleton. Paratibial injections with β-particle emitters ^{144}Ce+^{144}Pr (29 kBq per mouse) showed an incidence of local bone sarcomas of more than 80%. An estimation of the local effective doses led to values of more than 1000 Gy for the β-particle emitter ^{144}Ce and around 150 Gy for the thorium isotopes. Thus induction of local bone sarcomas required doses considerably greater than those needed for systemic bone sarcomas. The local induction of bone sarcomas has been reported for high-energy β particles using similar high doses of ^{144}Ce+^{144}Pr in rats and for external ^{90}Sr+^{90}Y irradiation in mice. We conclude that the processes involved in the induction of local and systemic bone sarcomas by radiation may be quite different.

INTRODUCTION

The incorporation of bone-seeking radionuclides increases the risk of osteosarcoma at a number of sites in the skeleton related to the systemic distribution of the radionuclide. We will refer to these tumors as systemic. In these studies of these tumors, the spatial and temporal distribution of the radionuclides as well as the probability of induction of osteosarcoma have been determined over a broad range of doses including very low skeletal doses in several experimental animal species and also in humans (*1–6*). The results of these investigations have been incorporated into the radiation protection recommendations of the ICRP (*7, 8*).

In contrast to the systemic tumors, local bone sarcomas are induced only by relatively higher doses, administered to a limited area, for instance by insoluble radiocolloids in a concentrated form. Application of colloidal ^{144}Ce+^{144}Pr in rats was used as an experimental model for a therapeutic treatment of the bone tumors (*9–12*).

A further study of local bone tumor induction has been published by Ootsuyama and Tanooka (*13–15*), who fixed a powerful ^{90}Sr+^{90}Y source onto the back of mice, resulting in the induction of skin and bone tumors. Dose and dose-rate conditions were reported.

Our own studies have employed radiocolloids of the β-particle-emitting ^{144}Ce+^{144}Pr in mice and also those of two α-particle-emitting thorium isotopes (^{227}Th and ^{228}Th). The latter were able to release their soluble decay products throughout the skeleton. As a consequence, two bone tumor entities were observed: local bone tumors induced by the radiation from the insoluble radiocolloids at the injection site, and bone tumors induced systemically as a consequence of decay products released from the two thorium isotopes.

MATERIALS AND METHODS

Colloidal Radionuclides

Thorium-227 with a half-life of 18.7 days was produced carrier-free in our own laboratory from an ^{227}Ac (22-year half-life) source (*16*). Carrier-free ^{228}Th (half-life 1.9 years) as thorium nitrate and ^{144}Ce (half-life 285 days) as cerium chloride were purchased from Amersham, Braunschweig, FRG.

All three nuclides were converted into colloidal form by adding the same element as carrier: for the two thorium isotopes 20 μg/ml of the long-lived ^{232}Th, and for ^{144}Ce 20 μg/ml of stable cerium. The pH was standardized between 7.5 and 9 by addition of sodium hydroxide. These alkaline pH values were important preconditions for the stability of the radiocolloids, in particular after injection. (See also Dosimetry.)

Animals and Injection Method

Female NMRI/Nbg mice from our barrier-sustained breeding colony were used in all experiments. Animals were 10–12 weeks old at the start of the experiments with a mean weight of 30 g. They were maintained in

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a 12 h light/12 h dark cycle, five animals per cage, and given free access to food (Altromin) and water (*17*).

The radiocolloids were injected in a volume of 50 µl by a needle placed in the muscle layer posterior to the right tibia which we refer to as paratibial. The injection was made from a position close to the bone surface. Because of the injection procedure animals had to be anesthetized. All animals were weighed before the injection and the radioactivity was measured by whole-body counting after injection. The animal experiments were carried out under license number AZ 211-2531-135/87 of the Bavarian Government.

Pathology

The animals were observed over their life span and checked 5 days per week. Mice which obviously had a tumor or were severely sick were killed. All these animals and all animals found dead were autopsied. Bone tumors included in the evaluation were those which could be detected macroscopically at autopsy or by a functional effect (paralysis of hind legs, distended bladder or congestion of the tail in the case of tumors of the vertebral column). The majority of the tumors were also confirmed by X-ray examination. In the ^{227}Th group, tumors were also studied histologically and the diagnosis of osteosarcoma was confirmed. We arbitrarily defined all tumors found directly at the injection site at the right tibia as local radiation-induced bone tumors ("local tumors"); all bone tumors occurring at other parts of the skeleton and spontaneous tumors (e.g. in controls) were defined as "systemic tumors."

DOSIMETRY

Doses were determined both locally and for the whole skeleton (systemically) after the radioactivity concentrations of bone samples were measured at various times after injection. For the systemic doses the calculations of average doses (*18*, *19*) were used.

For the local dose a special assumption was made insofar that a tissue mass of 0.1 g was taken to be the target; this means that the injection of 1 kBq of a nuclide resulted in an activity concentration (C_a) of 1 kBq/0.1 g. The minimum of affected mass is 0.05 g, corresponding to the injection volume of 50 µl, which dispersed in a relatively small area around the injection site. More than 95% of the activity remains in a volume which rarely exceeds 0.1 ml, corresponding to a mass of 0.1 g. This was demonstrated by autoradiographs (Fig. 1) and also by measuring the main part of the injected activity in tissue samples down to masses as small as 0.1 g. The nature of the tissue was not determined in detail but, as Fig. 1 shows, the radioactivity appears to be retained as a highly concentrated colloid after injection and is only partly spread (much less concentrated) to cells in the proximity of injection site. The measured α-particle radioactivity concentration refers mainly to the tissue and fluid adjacent to the periosteum of the tibia. Because of the very short range of α particles, the α-particle doses as calculated below must be considered as maximum values for the periosteal surface; the calculated doses must be considered as maximum doses, due mainly to the following reasons: a sharp upper limit is given by the injected volume amount of 50 µl and its initial concentration. The doubled value of 50 µl, i.e. 0.1 g, is somewhat arbitrary and corresponds to the minimum mass in which more than 90% of the activity could be found. Similar effects were also found by Klein *et al.* (*12*) after injection of 50 µl colloidal cerium: more than 99% of the initial dose was within a distance of 0.29 cm, which would correspond to a spherical mass of about 0.1 g, in agreement with our own assumption for the thorium colloid.

In the case of systemic tumors we deal with a physiological process, whereby the daughter products, radium isotopes—as alkaline earths—are distributed in a manner similar to calcium to the respective parts of the organism.

For the two thorium nuclides special conditions must be taken into account with respect to decay products (radium and radon and further daughter products). Those have completely different chemical and physiological properties from the mother nuclides. Radioactivity concentrations in different skeletal parts were measured at a range of time in parallel distribution studies after paratibial colloid injection. The determination of ^{228}Th and of its daughter ^{224}Ra (plus its decay products) was performed as follows: The first measurement (for the estimation of ^{224}Ra in the sample) of the 238 keV γ-line of ^{212}Pb (by an NaI Crystal sampler) was carried out 3–7 days after sacrificing of the animals, when ^{212}Pb was in equilibrium with ^{224}Ra. A second measurement of the same γ-line was performed at least 36 days after the first measurement, when ^{224}Ra had decayed to 10^{-3} of its initial value. Any isotope detected is due to the parent product ^{228}Th. The latter, however, was found to be below the detection limit (about 10 Bq) in skeletal parts outside the injection site, which is far less than 1% of the amount injected at any of the doses used. Since the solubility of the thorium colloid is of the same order of magnitude as that of cerium, a similar percentage of systemic skeletal dose can be expected, which was measured to be 0.8×10^{-4} of injected amount in the case of cerium (see also ^{144}Ce dosimetry). Therefore, ^{228}Th itself was not considered for the systemic skeletal dose. For the calculation of average skeletal dose by ^{224}Ra and decay products released from ^{228}Th we developed the following formula. The values of α-particle energies were taken from ref. (*20*).

Thorium-228

The basic definition of systemic skeletal dose rate D_sR_o at the start of incorporation is

$$D_sR_o = 0.01385 \times E \times C_{a_{Ra}} \text{ (Gy/day)}.$$

E = 26.48 MeV (sum of α-particle energies of ^{224}Ra). $C_{a_{Ra}}$ is the initial activity concentration in the skeleton which is defined by the percentage p of built-up ^{224}Ra + decay products per marrow-free skeletal mass (*18*) (9% of 30 g body weight = 2.7 g). For p we found a value of 0.136. Thus we obtained for 1 kBq ^{228}Th injected per mouse

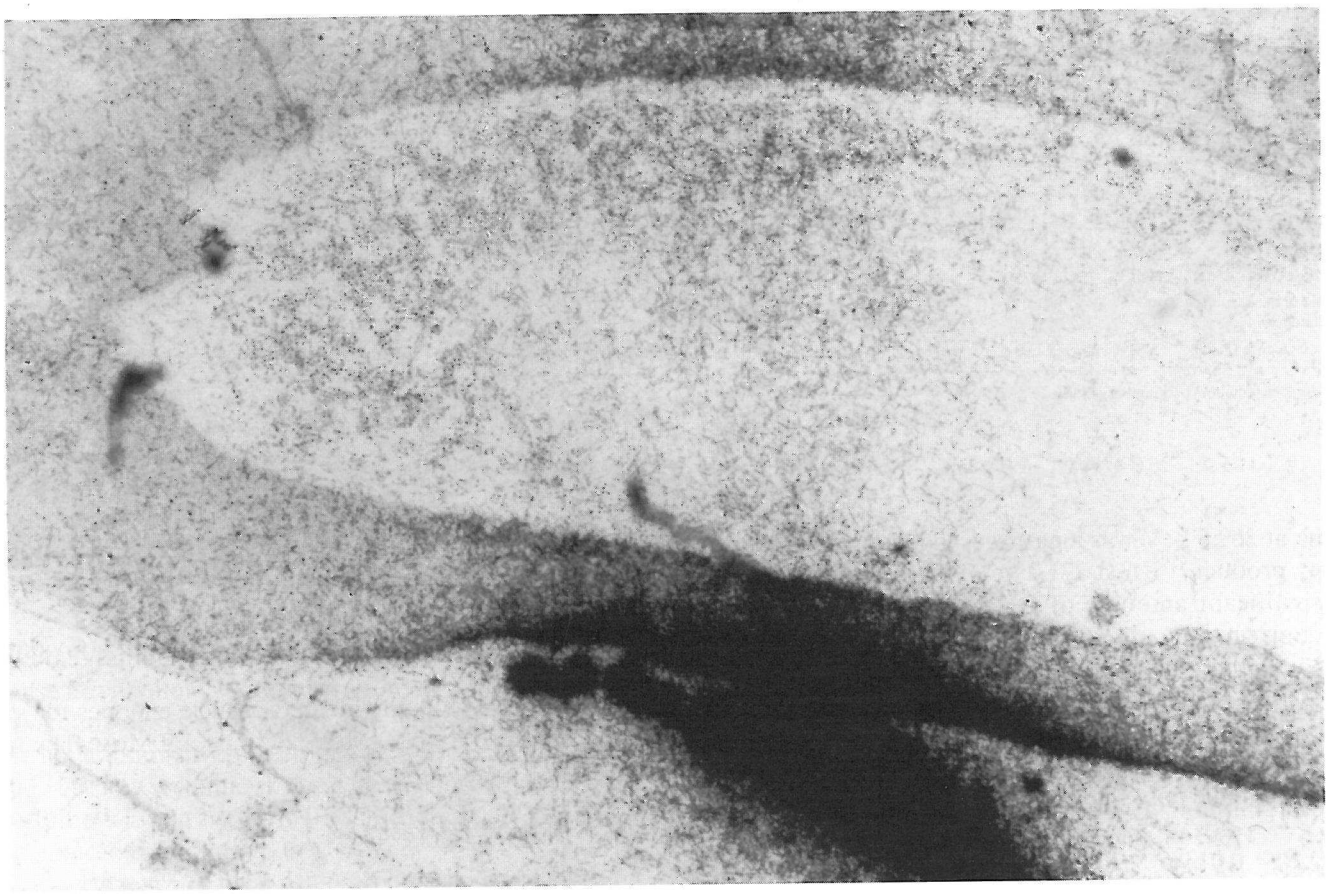

FIG. 1. Autoradiography 48 h after paratibial administration of thorium (^{227}Th, 18.5 kBq).

$$D_sR_o = 0.01385 \times 26.48 \text{ MeV} \times 0.136 \times \frac{1 \text{ kBq}}{2.7 \text{ g}}$$

$$= 0.0185 \text{ (Gy/day)}.$$

The total systemic skeletal dose is defined as

$$D_{s\,tot} = D_sR_o \int_o^{Tms} e^{-\lambda_{eff}t}\,dt \text{ (Gy)}.$$

Tms = integration interval = mean survival time in days (Table II). $\lambda_{eff} = \lambda_b + \lambda_p$ is the effective decay constant and was determined by measurements of activity in representative skeletal samples at a range of time points as described above. We found for $\lambda_{eff} = 0.001869$ day^{-1}; $\lambda_b = 0.000877$ day^{-1}, biological exponential constant; $\lambda_p = 0.000992$ day^{-1}, physical exponential constant (^{228}Th half-life = 698.7 days).

For the calculation of the local (periosteal) dose the radioactivity of the injection site was measured over longer periods showing that, while the majority of ^{228}Th remained, only 10% of decay products were localized at the injection site.

We obtained for the initial local dose rate and total dose:

$$D_LR_o = 0.01385\ (E_{228_{Th}} + 0.1E_{\text{Decay products}} \times C_a)$$

$$= A_o = 1.12 \text{ (Gy/day)};$$

$$D_{L\,tot} = A_o \int_o^{Tms} e^{-(\lambda_p + \lambda_b)t}\,dt \text{ (Gy)};$$

E = α-particle energy in MeV.

Effective exponential constant, $\lambda_{eff} = 0.00179$ day^{-1}; physical exponential constant, $\lambda_p = 0.000992$ day^{-1}; biological exponential constant, $\lambda_b = 0.000797$ day^{-1}; $E_{228_{Th}} = 5.4$ MeV; $E_{\text{Decay products}} = 26.48$ MeV.

The analogous measurements and calculations were performed for ^{227}Th, but because of the similar physical decay constants of ^{227}Th and ^{223}Ra, a larger part of the decay products (27%) was seen to remain at the injection site. The ^{227}Th and ^{223}Ra concentrations were measured simultaneously in special distribution studies using a high-resolution germanium detector. For detection of ^{227}Th its γ-lines at 234.9 keV and 236 keV (combined) were used; for ^{223}Ra its

TABLE I
Local and Systemic Dose Rates and Total Doses after Paratibial Administration of ^{228}Th, ^{227}Th and ^{144}Ce and Incidences of Bone Sarcomas

Injected activity (kBq/mouse)	^{227}Th						^{228}Th						^{144}Ce		Controls	
	2.9		8.9		25.0		1.03		3.02		9.66		29		0	
Number of mice	20		20		20		25		25		25		49		98	
	Local	Systemic	Local	Systemic	Local	Systemic	Local	Systemic	Local	Systemic	Local	Systemic	Local	Systemic	Local	Systemic
Initial dose rate (Gy/day)	5.3	0.1	16.1	0.3	5.3	0.9	1.15	0.02	3.4	0.06	10.8	0.18	5.19	0.004	0	0
Total dose (Gy)	138.5	2.8	425	8.5	1194	24	287	4.7	679	11.1	1879	30.8	1176	1	0	0
Number of mice with tumor	1	8	0	12	0	1	4	14	1	17	0	0	40	0	0	3
Tumor incidence (%)[a]	5	40	0	60	0	5	16	56	4	68	0	0	82	0	0	3

[a]Number of tumors per number of mice.

γ-line at 269.6 keV was measured, together with that of its decay product ^{219}Rn at 271.2 keV. As in the case of ^{228}Th, no significant amounts of ^{227}Th were found outside the injection site.

We applied the following method for the calculation of doses after paratibial injection of 1 kBq per mouse.

Thorium-227

Initial systemic dose rate:

$$D_sR_o = 0.01385 \times 26.24\ \text{MeV} \times 0.27 \times \frac{1\ \text{kBq}}{2.7\ \text{g}} = 0.36\ (\text{Gy/day}),$$

$E_{227\text{Th}} = 5.95$ MeV, $E_{223\text{Ra}} = 26.24$ MeV (sum of α-particle energies of ^{223}Ra and decay products).

Total skeletal dose:

$$D_{s\,tot} = 0.036 \int_0^{Tms} e^{-\lambda_{eff}t}\,dt\ (\text{Gy}).$$

$\lambda_{eff} = 0.0379\ \text{day}^{-1}$ is nearly equal to λ_p (^{227}Th half-life = 18.72 days) since $\lambda_p >> \lambda_b$.

Local dose rate and total local dose:

$$D_LR_o = 0.01385\ (E_{227_{Th}} + 0.27E_{\text{Decay products}}) \times C_a = B_o = 1.81\ (\text{Gy/day}),$$

$$D_{L\,tot} = B_o \int_0^{Tms} e^{-\lambda_{eff}t}\,dt\ (\text{Gy}).$$

Cerium-144

For ^{144}Ce we found only about 0.8×10^{-4} of the injection site concentration in the skeleton. Because ^{144}Ce itself as well as its decay product ^{144}Pr are rare earth radionuclides, they stayed nearly completely in colloidal form at the injection site. Initial local dose rate of 1 kBq paratibially injected ^{144}Ce:

$$D_LR_o = 0.01385\ (E_{Ce} + E_{Pr}) \times C_a = C_o = 0.179\ (\text{Gy/day}).$$

Reference (*21*) gives the mean β-particle energies for ^{144}Ce and ^{144}Pr: $E_{144Ce} = 0.09$ MeV, $E_{144Pr} = 1.2$ MeV. The total local dose,

$$D_{L\,tot} = C_o \int_0^{Tms} e^{-(\lambda_p + \lambda_b)t}\,dt,$$

$\lambda_{eff} = 0.00338\ \text{day}^{-1}$; $\lambda_b = 0.00095\ \text{day}^{-1}$; $\lambda_p = 0.00243\ \text{day}^{-1}$ (^{144}Ce half-life = 284.5 days).

RESULTS

Table I shows the dosimetry and induction of osteosarcoma at three different dose levels of the thorium radiocolloids plus animals treated with one dose level of ^{144}Ce. The α-particle doses were selected on the basis of our observations from earlier experiments. Thus, for induction of systemic osteosarcoma, doses of between 0.9 and 20 Gy were found to be effective (*3*), with the highest absolute incidence of more than 50% at a mean skeletal dose of about 10 Gy. This systemic dose was included in both thorium series. The effectiveness of this dose has been confirmed, as shown in the last line of Table I, which demonstrates that this high yield can be achieved by the paratibial administration of thorium colloids. The systemic skeletal dose rates and doses as calculated in Table I result from the continuous build-up of the soluble radium isotopes that are the progeny of ^{228}Th or ^{227}Th, respectively, which were released from the injection site and distributed throughout the skeleton, where their radioactive daughter products are produced.

All tumor incidences are given as numbers of tumors per number of mice. In the case of thorium injected paratibially, induced systemic osteosarcomas are in competition with

TABLE II
Time Intervals of Tumor Incidences, Mean Tumor Appearance Times and Mean Survival

Injected activity (kBq/mouse)	^{227}Th						^{228}Th						^{144}Ce		Controls	
	2.9		8.9		25.0		1.03		3.02		9.66		29		0	
Number of mice	20		20		20		25		25		25		49		98	
Number of mice with bone tumor in 100-day intervals	Local	Systemic	Local	Systemic	Local	Systemic	Local	Systemic	Local	Systemic	Local	Systemic	Local	Systemic	Local	Systemic
<300 days	0	0	0	1	0	0	0	3	1	16[b]	0	0	3	0	0	1
300–400 days	0	1	0	9	0	1	4	9	0	1	0	0	10	0	0	0
400–500 days	1	1	0	1	0	0	0	2	0	0	0	0	17	0	0	0
500–600 days	0	3	0	1	0	0	0	0	0	0	0	0	7	0	0	1
>600 days	0	3[a]	0	0	0	0	0	0	0	0	0	0	3	0	0	1
Mean tumor appearance time (days)	463	631	—	382	—	357	356	350	285	252	—	—	446	—	—	580
Mean survival T_{ms} (days) (±SD)	590 (±127)		394 (±95)		313 (±40)		329 (±55)		249 (±54)		208 (±51)		429 (±115)		622 (±163)	

[a]One animal with two bone tumors.
[b]Two animals with two bone tumors.

local bone tumors, whereas ^{144}Ce caused only local effects, because after colloidal administration of ^{144}Ce only negligible systemic doses were produced. Consequently no systemic bone tumors were seen in the ^{144}Ce-treated mice due to the very low systemic skeletal dose. Thus all of the local bone tumors in the ^{144}Ce-treated mice must be considered to be induced by radiation.

The occurrence of local osteosarcomas in the case of the two thorium radiocolloids is complicated by a number of parameters, such as the competition with systemic osteosarcomas, apparently a certain minimum threshold of dose rate and dose and the mean survival time. The latter, as shown in the last row of Table II, reflects the life-shortening effect of higher thorium doses, which resulted in generalized atrophy, partly due to tooth damage, and diseases of the hematopoietic system. In some cases animals had to be euthanized because of debilitating local radiation dermatitis, which also led to atrophy.

A minimum post-treatment survival of about 250 days seems to be necessary for the development of bone tumors. If the incidence of systemic bone tumors is maximal, as seen at skeletal doses of 8–12 Gy, the simultaneous development of local bone tumors seems to be restricted. This is probably because the local induction of bone tumors requires a latent period which is longer than or at least equal to that of systemic bone tumors. This is demonstrated in Table II, where the incidence of all bone tumor cases with time is given in 100-day intervals. The appearance times of the two types of bone tumors overlap in all the experimental groups.

An increasing dose in the ^{227}Th experiments, as well as in those with ^{228}Th, shows a very clear trend to an earlier induction of systemic tumors if we compare tumor appearance times for the doses of 2.8–8.5 Gy in the case of ^{227}Th and 4.7–11.1 Gy for ^{228}Th. This type of acceleration has been observed in earlier experiments using protracted doses of ^{224}Ra (*3*). All these events could have masked the development of local bone sarcomas in our thorium experiments.

In the highest dose groups of both thorium isotopes no local tumor and only one systemic bone tumor was observed, most probably due to the early nontumor death of experimental animals as mentioned above.

According to Table I the following radiation conditions are required for the induction of local bone tumors: (a) α-particle doses of a minimum of 140 Gy and dose rates between 1–5 Gy/day; (b) much higher β-particle doses of about 1200 Gy and dose rates of about 5 Gy/day. The data for ^{144}Ce seem to be minimum conditions, since pilot studies in our laboratory using shorter-lived β-particle-emitting rare earths with lower β-particle energies such as ^{141}Ce and ^{177}Lu with local doses of 50–220 Gy (unpublished data) have not induced local bone tumors, although, analogous to the case of ^{144}Ce, no competition with systemic osteosarcomas occurred. In addition, the short duration of the irradiation itself may have contributed to this lack of effect.

DISCUSSION

Systemic Bone Tumors

Experiments with bone-seeking radionuclides (i.e. those distributed throughout the skeleton) have been carried out in many species and over a large dose range. A distinct dose–effect relationship, also shown in our current experiments, has been demonstrated (*3*). The following is a summary thereof: The incidence of systemic bone tumors increases with dose. In the case of dose protraction with short-lived α-particle emitters, higher incidences are observed compared to single doses. This phenomenon is seen over a large dose range (*4*, *22*). The local administration of

TABLE III
List of Systemic Tumors and Their Anatomical Location

Bone tumor location	^{227}Th 2.9 kBq	^{227}Th 8.9 kBq	^{227}Th 25.0 kBq	^{228}Th 1.03 kBq	^{228}Th 3.02 kBq	Sum (%)
Head	2	2	1	1	0	6 (11)
Vertebral column	3	4	0	5	10	22 (40)
Pelvis-sacrum	2	2	0	6	8	18 (33)
Ribs	0	2	0	1	0	3 (5)
Long bones	2	2	0	1	1	6 (11)
Total	9	12	1	14	19	55 (100)

the long-lived ^{228}Th isotope as a colloid by paratibial injection must be be considered as a protracted systemic application of ^{224}Ra, as this daughter nuclide is released continuously from the injection site (*22*). The average systemic doses achieved using this injection method are thus comparable to those reported in the past by multiple injections over long time spans (*3*, *5*, *22*, *24*). In these earlier studies it was shown that protracted doses of ^{224}Ra effected a much higher efficiency of induction of bone tumors (percentage tumors per gray) compared to single injections. This enhanced effect was observed with doses down to 1 Gy (*5*). While single injections with doses up to 15 Gy produced a maximum bone tumor incidence of 22%, the protracted application produced up to 90% tumors with 10 Gy. Even at a dose of 3 Gy, up to 50% incidence was observed (*3*). The same high efficiency was also seen after paratibial injection of the ^{228}Th colloid (Table I) with tumor incidence of more than 50% in the two groups with systemic doses of 4.7 Gy and 11.1 Gy. Thus, in all of these cases, there is a greater effect of protracted doses of high-LET radiation, which has been referred to in the literature as the "reverse protraction effect" or "reverse (inverse) dose-rate effect," respectively, and has been described for animals as well as for humans (*6*, *22*, *25–27*).

A remarkable observation from the studies of systemic bone tumors is their anatomical localization (shown in Table III). The preferential site of systemic radiation-induced osteosarcomas as well as spontaneous osteosarcomas was the axial skeleton of our mice, which has also been reported in earlier experiments (*3*). It has also been pointed out by Schlenker *et al.* (*28*) that, in general, the site of radiation-induced osteosarcomas corresponds to that of spontaneous osteosarcomas. Thus it seems that the number of systemic bone tumors increases with skeletal dose (within a certain range of radiation dose and dose rate); the anatomical distribution of these tumors, however, is not substantially different from normally (spontaneously) occurring tumors; i.e., it is governed by the natural predisposition of the particular species.

Local Bone Tumors

The induction of radiation-induced local osteosarcomas by β-particle-emitting ^{144}Ce was found to be very effective after injection of 185 kBq into Sprague-Dawley rats, causing an osteosarcoma yield of about 80% (*9–12*). Although local doses were not calculated, they seem to correspond to that of our experiments as shown in Table I.

The production of local bone tumors by external β-particle irradiation from a ^{90}Sr+^{90}Y source placed directly on the backs of mice has been described by Ootsuyama and Tanooka (*13–15*). A high yield of osteosarcomas was observed with local doses and dose rates that were comparable to our ^{144}Ce experiments described above. The conditions for the efficient production of local bone tumors can be defined as follows: (a) Relatively high β-particle energies are required, possibly because of the role of the endosteal dose. For instance, in the case of ^{144}Ce, about 30% of the target dose is received by the endosteal area, which is considered to be sensitive for bone tumor induction. (b) Dose rates must be above a certain threshold. For external ^{90}Sr+^{90}Y this is at least 1.5 Gy per exposure (*14*) and for internal ^{144}Ce several grays per day (ref. *9* and Table I). (c) The irradiation period must be protracted, at least 250 days. Even for very high dose ranges no local tumor formation was observed if a single dose was applied (*13*).

The dose–effect relationship for local osteosarcoma induction is not quite clear. Delbrück *et al.* (*11*) stated that in the case of ^{144}Ce treatment there was no connection between dose and the incidence of bone tumors within the range investigated. Our own experiments using the β-particle-emitter ^{144}Ce were performed at only one dose.

Local bone sarcomas developing after internal α-particle irradiation have not been reported previously. With respect to the local effects of the α-particle-emitting thorium colloids, we conclude that local osteosarcomas are induced at about one order of magnitude lower dose than β-particle doses.

Results with α-particle emitters, however, were impaired by some implications. The small number of animals that was

used could not show significant differences between the different dose groups. In addition, the competition between local and systemic effects did not allow a relationship between dose and effect to be established. The endosteal doses for the two thorium isotopes lie in the range of the systemic doses (due to the decay products) shown in Table I.

Comparability of Doses

The induction of two types of bone tumors by very different dose distributions raises the question of whether and how the doses can be compared. Since the origin of the doses is completely different, as pointed out above (physiological for the systemic dose and artificial for the local one), we must restrict the definition of dose to the released energy per unit mass. As the type of mass could not be defined in more detail the doses have been compared only arbitrarily and, in the case of local α-particle dose, are restricted to the periosteal surface only. For a discussion of the problems occurring in the dosimetry of internal α-particle emitters see refs. (*29*) and (*30*).

In the case of the mean systemic doses we also must consider that the doses are not distributed homogeneously throughout the skeleton. As pointed out by Marshall *et al.* (*31*), local doses may reach a level seven times higher at the bone surface than the mean dose for ^{224}Ra. Taking into account all these parameters, we may conclude that the induction of local bone tumors requires activity concentrations or doses at least one order of magnitude greater than that required for systemic bone tumors.

The origin of osteosarcomas from endosteal or periosteal surfaces, respectively, after internal and external irradiation has been discussed in detail by Vaughan (*32*). She concluded that osteosarcomas arose from the endosteal rather than from the periosteal surface, but in miniature swine fed ^{90}Sr continuously, a considerable proportion of osteosarcomas were found to arise from the periosteum at the highest dose levels (*33*). In our own experiment we have no direct proof for a pure periosteal origin of the locally induced bone tumors, since histology of the bone tumors was not performed in these cases. But considering the geometric situation of α-particle-radiation range, the dose to the endosteum cannot be significant.

CONCLUSIONS

The data for the two types of radiation-induced bone tumors show that we may be dealing with two different mechanisms. The occurrence of systemic bone tumors at certain sites in the skeleton, which starts at rather low doses, is governed not only by the specific doses at these regions but also by the natural skeletal distribution of spontaneous bone tumors in the respective species.

The induction of local tumors, however, requires very high doses concentrated at the injection site. In addition, high energies and long irradiation periods are needed. This, of course, represents a purely experimental event, though the biological properties of the local bone tumors (growth rates, development of metastases, etc.) are comparable to those of systemic bone tumors, as has been reported by Jasmin *et al.* (*9*).

However, these observations have important clinical consequences: The risk of local bone sarcoma as a consequence of high-dose therapeutic irradiation close to the bone is shown to be rather low. This means that the majority of radiation therapies are probably safe in this respect. Furthermore, this applies to both external and internal irradiation, the latter being in common use as in the intra-articular injection of insoluble radiocolloids in arthritic diseases, albeit here radionuclides with shorter half-lives are used (*34*, *35*). On the basis of our own results with the short-lived ^{141}Ce and ^{177}Lu, these treatments may be considered safe (up to relatively high doses) with respect to the development of local bone tumors.

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REFERENCES

1. T. F. Dougherty, Ed., *Some Aspects of Internal Irradiation*. Pergamon Press, Oxford, 1961.
2. C. W. Mays, W. S. S. Jee, R. D. Lloyd, B. J. Stover, J. H. Dougherty and G. N. Taylor, Eds., *Delayed Effects of Bone-Seeking Radionuclides*. University of Utah Press, Salt Lake City, 1969.
3. W. A. Müller, W. Gössner, O. Hug and A. Luz, Late effects after incorporation of the short-lived alpha-emitters ^{224}Ra and ^{227}Th. *Health Phys.* **35**, 33–55 (1978).
4. A. Luz, W. A. Müller, W. Gössner and O. Hug, The dependence of late effects in mice on the temporal distribution of skeletal alpha-doses from ^{224}Ra and ^{227}Th. In *Biological Effects of ^{224}Ra* (W. A. Müller and H. G. Ebert, Eds.), pp. 135–148. Martinus Nijhoff, The Hague, 1978.
5. W. A. Müller, A. Luz, A. B. Murray and U. Linzner, Induction of lymphoma and osteosarcoma in mice by single and protracted low alpha doses. *Health Phys.* **59**, 305–310 (1990).
6. H. Spiess and C. W. Mays, Bone cancer induced by ^{224}Ra (ThX) in children and adults. *Health Phys.* **19**, 713–729 (1970).
7. ICRP, A *Review of the Radio-sensitivity of the Tissues in Bone*. Publication 11, International Commission on Radiological Protection, Pergamon Press, Oxford, 1968.
8. ICRP, *Alkaline Earth Metabolism in Adult Man*. Publication 20, International Commission on Radiological Protection, Pergamon Press, Oxford, 1973.
9. C. Jasmin, M. Allouche, J. G. Jude, E, B. Klein, J. P. Thiery, B. Perdereau, R. Gongora, G. Gongora and A. Mazabraud, Un modèle expérimental d'ostéosarcome chez le rat. *La Semaine des Hopitaux de Paris* **58**, 1684–1689 (1982).
10. M. Allouche, H. G. Delbrück, B. Klein, R. Masse, A. Matar, M. Morin, J. LaFuma and C. Jasmin, Malignant bone tumours induced by a local injection of colloidal radioactive ^{144}Cerium in rats as a model for human osteosarcomas. *Int. J. Cancer* **26**, 777–782 (1980).
11. H. G. Delbrück, M. Allouche, C. Jasmin, M. Morin, F. Deml, L. Anghileri, R. Masse and J. Lafuma, Bone tumours induced in rats with radioactive cerium. *Br. J. Cancer* **41**, 809–815 (1980).

12. B. Klein, S. Pals, R. Masse, J. LaFuma, M. Morin, N. Binart, J. R. Jasmin and C. Jasmin, Studies of bone and soft-tissue tumours induced in rats with radioactive cerium-chloride. *Int. J. Cancer* **20**, 112–119 (1977).

13. A. Ootsuyama and H. Tanooka, One hundred percent tumor induction in mouse skin after repeated β irradiation in a limited dose range. *Radiat. Res.* **115**, 488–494 (1988).

14. A. Ootsuyama and H. Tanooka, Induction of osteosarcomas in mouse vertebrae by repeated external β-irradiation. *Cancer Res.* **49**, 1562–1564 (1989).

15. A. Ootsuyama and H. Tanooka, Threshold-like dose of local β irradiation repeated throughout the life span of mice for induction of skin and bone tumors. *Radiat. Res.* **125**, 98–101 (1991).

16. W. A. Müller, Präparative Arbeiten über ^{227}Ac und seine Folgeprodukte. *Radiochim. Acta* **9**, 181–186 (1968).

17. A. Luz, The range of incidence of spontaneous neoplastic and non-neoplastic lesions of the laboratory mouse. *Zeitschrift für Versuchstierkunde* **19**, 342–343 (1977).

18. W. A. Müller, Studies on short-lived alpha-emitters in mice and rats. Part I: ^{224}Ra. *Int. J. Radiat. Biol.* **20**, 27–38 (1971).

19. W. A. Müller, Studies on short-lived alpha-emitters in mice and rats. Part II: ^{227}Th. *Int. J. Radiat. Biol.* **20**, 233–243 (1971).

20. A. Rytz, Recommended energy and intensity values of alpha particles from radioactive decay. *Atomic Data Nucl. Data Tables* **47**, 205–239 (1991).

21. ICRP, *Radionuclide Transformations: Energy and Intensity of Emissions,* pp. 546–560. Publication 38, *Annals of the ICRP* **11–13**, Pergamon Press, Oxford, 1983.

22. W. A. Müller, A. Luz, U. Linzner and A. B. Murray, The oncogenic risk of alpha-doses from osteotropic radionuclides down to the mGy-range and the role of the reverse protraction factor. In *Joint Bone Radiobiology Workshop* (N. J. Parks, Ed.), pp. 2–5. U.S. DOE Report UCD-472-136, University of California, Davis, 1991.

23. W. A. Müller, A new experimental approach for the induction and evaluation of late effects from exposure to continuous low level alpha-radiation. In *Radiation Research. A Twentieth-Century Perspective*, Vol. I (J. D. Chapman, W. C. Dewey and G. F. Whitmore, Eds.), p. 163. Academic Press, San Diego, 1991. [Abstract]

24. W. A. Müller, A. Luz, E. H. Schäffer and W. Gössner, The role of time-factor and RBE for the induction of osteosarcomas by incorporated short-lived bone-seekers. *Health Phys.* **44** (Suppl. 1), 203–212 (1983).

25. H. Spiess and C. W. Mays, Protraction effect on bone sarcoma induction of ^{224}Ra in children and adults. In *Radionuclide Carcinogenesis* (C. L. Sanders, R. H. Busch, J. E. Ballou and D. D. Mahlum, Eds.), pp. 437–450. AEC Symposium 29, CONF-720505, NTIS, Springfield, VA, 1973.

26. D. Chmelevsky, H. Spiess, C. W. Mays and A. M. Kellerer, The Reverse Protraction Factor in the induction of bone sarcomas in ^{224}Ra patients. *Radiat. Res.* **124**, S69–S79 (1990).

27. M. M. Elkind, Enhanced neoplastic transformation due to protracted exposures of fission-spectrum neutrons: biophysical model. *Int. J. Radiat. Biol.* **59**, 1467–1475 (1991).

28. R. A. Schlenker, A. T. Keane and K. K. Unni, Comparison of radium-induced and natural bone sarcomas by histological type, subject age and site of occurrence. In *Risks of Radium and Thorotrast* (D. M. Taylor, C. W. Mays, G. B. Gerber and R. G. Thomas, Eds.), pp. 55–63. Report 21, British Institute of Radiology, London, 1989.

29. D. P. Fisher, M. E. Frazier and T. K. Andrews, Energy distribution and the relative biological effects of alpha emitters. *Radiat. Prot. Dosim.* **13**, 223–227 (1985).

30. J. L. Humm and L. M. Chin, A model of cell inactivation by alpha-particle emitters. *Radiat. Res.* **134**, 143–150 (1993).

31. J. H. Marshall, P. G. Groer and R. A. Schlenker, Dose to endosteal cells and relative distribution factors for radium-224 and plutonium-239 compared to radium-226. *Health Phys.* **35**, 91–101 (1978).

32. J. M. Vaughan, *The Effects of Irradiation on the Skeleton*. Clarendon Press, Oxford, 1973.

33. E. B. Howard, W. J. Clarke, M. T. Karagianes and R. F. Palmer, Strontium-90 induced bone tumors in miniature swine. *Radiat. Res.* **39**, 594–607 (1969).

34. K. Chlud, Therapieprinzipien bei entzündlichen und degenerativen mono- und oligoartikulären Gelenkerkrankungen. *Therapiewoche* **31**, 3248–3256 (1981).

35. C. Guaydier-Souquieres, J. Beguin, D. Ollivier and G. Loyau, Knee arthroscopy after yttrium or osmic acid injection. *Arthroscopy: J. Arthroscop. Relat. Surg.* **5**, 70–75 (1989).