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OCCURRENCE AND DISTRIBUTION OF BONE TUMORS IN BEAGLE DOGS EXPOSED TO ^{90}Sr

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Abstract

Radiation-induced bone tumors in beagle dogs exposed to ^{90}Sr have been evaluated in terms of their incidence, time of appearance, occurrence as multiple tumors, anatomic distribution, and the influence of sex on their development. Among dogs fed ^{90}Sr during skeletal development, the incidence of bone tumors was dose dependent. Tumors thus appeared in 10 of 19 dogs receiving average skeletal doses of 130 Gy, 15 of 60 receiving 97 Gy, 5 of 61 receiving 61 Gy, 2 of 65 receiving 26 Gy, and 1 of 40 receiving 1.3 Gy. No tumors appeared among 66 dogs who received 8 Gy, 78 who received 0.3 Gy, and 80 non-irradiated controls, all of which have been observed for life. Among dogs given a single intravenous injection of ^{90}Sr in early adulthood, tumor production was somewhat higher than among ^{90}Sr-fed dogs at the same radiation dose: bone tumors were present in 6 of 25 dogs who received 62 Gy and 1 of 20 dogs who received 7.5 Gy. Bone tumors appeared sooner and were more often multiple in animals receiving the higher doses. Long bones were the sites of most of the tumors appearing after the highest dose level. Bones of the head, particularly the mandible, were the predominant site of tumors in the next highest dose level group.

Key words: Radiations, injurious effects, neoplastic, ^{90}Sr, dogs, bone tumors.

^{90}Sr is an important fission-produced radionuclide and has received considerable attention as a potential environmental contaminant, early on as a component of fallout from atomic weapons testing, and later, as one of the 'short-lived' radioactive wastes that are part of the nuclear fuel cycle. Since ^{90}Sr is distributed in the body in a manner similar to calcium, any ^{90}Sr that is released into the environment and assimilated by people will be concentrated in bone—^{90}Sr in the bone mineral and its daughter ^{90}Y along bone surfaces—where their emitted beta particles may irradiate nearby cells.

Concern about the possibility of hazards to people from exposures to ^{90}Sr released to the environment has led to a number of animal studies on its radiobiologic effects. Beagle dogs have been the principle large animal model for the study of the toxicity of ^{90}Sr (1, 5). They have received exposures by injection (8, 14), inhalation (13), and ingestion, either ending in early adulthood, as described in this paper, or continuing for life (4).

Since ^{90}Sr is concentrated in skeletal tissues, its emitted particles irradiate cells in and around bone, where the effects are manifested. Primary bone tumors (mostly osteosarcomas) have been produced in ^{90}Sr-exposed dogs (4, 8, 12, 14, 15), monkeys (6), pigs (11), rabbits (26), rats (15) and mice (16–18).

Besides bone cancer, neoplasia or preneoplastic changes in hematopoietic tissues, referred to collectively as myleoproliferative syndrome (MPS), may result from ^{90}Sr, as reported in dogs (7), pigs (10), and rats (15). Another important ^{90}Sr-induced effect observed in mice (17) and in dogs given ^{90}Sr is squamous cell carcinoma of the jaw (22).

Bone tumors, MPS, and squamous cell carcinomas of the jaw are all important radiation-related causes of death among ^{90}Sr-fed beagles. Generally deaths from MPS occur earlier than deaths from osteosarcoma. Bone tumor deaths, in turn, happen at about the same time or slightly earlier than those from oral squamous cell carcinomas (3).

Recently, we presented the results of a careful analysis of the histopathology of ^{90}Sr-induced tumors in beagle dogs and described a model for the development of radiation-induced osteodysplasias (20). In this report we present data on the occurrence, time of appearance, and sketal distribution of fatal bone tumors induced by continued exposure to ^{90}Sr. Further, we show how factors such as sex and magnitude of radiation dose appear to influence the location of tumors.

Material and Methods

The bone tumors presented in this report were produced in beagle dogs given chronic exposures to ^{90}Sr. The

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Table 1

Experimental design of the ^{90}Sr toxicity study in dogs receiving the radionuclide in utero and up to 540 days of age

Treatment code	^{90}Sr/g dietary calcium (kBq)	Ingested kBq/day	Total ingested (kBq)	No. of dogs
D 00	0	0	0	80
D 05	0.259	0.740	370	77*
D 10	0.777	2.590	1 480	40
D 20	4.551	16.280	8 880	65*
D 30	13.690	48.100	25 900	65
D 40	41.070	148.000	81 400	61
D 50	123.210	444.000	240 500	60
D 60	370.000	1332.000	717 800	19

* One dog remains alive as of July 1984.

dogs were part of a 25-year experiment at the Laboratory for Energy-Related Health Research of the University of California at Davis. In that study, beagles from the outbred, closed colony maintained at the laboratory were exposed to varying levels of ^{90}Sr or ^{226}Ra, to describe the comparative toxicity of the two radionuclides in terms of dose, time, and effect, and to eventually use the data on dogs to predict effects in exposed human populations. Although that study is not yet completed, periodic updates of the entire study have been published (1–3, 23–25).

As described in the previous work of NILSSON et coll. (20), most of the tumors in this paper arose in dogs fed a ^{90}Sr-containing diet. Administration of ^{90}Sr to experimental animals (designated 'D') began when they were in utero, while their mothers received a diet containing one of several concentrations of ^{90}Sr, as $SrCl_2$ (Table 1). Feeding began on day 21 of gestation and continued through gestation and through lactation; at weaning, pups were placed on the same feeding regimen until 540 days of age. The beginning and ending times of ^{90}Sr feeding were chosen to correspond to the approximate times of beginning and completion of skeletal development. One of the tumor-bearing dogs was from a small group of animals which received the ^{90}Sr-containing diet beyond 540 days, for the duration of life (2).

In a small series, dogs were also given a single intravenous injection of ^{90}Sr in 0.1 N hydrochloric acid in saline at 540 days of age (Table 2).

All dogs were housed indoors to prevent environmental contamination during the time of ^{90}Sr feeding and injections. After the administration of radioactivity was completed and after allowing some time for the elimination of radioactivity not deposited in the skeleton, animals were moved to outside pens, where they remained for the duration of life.

Each dog received quarterly physical examinations and periodic whole-body counting for the determination of ^{90}Sr body burdens, from which the average dose in bone was calculated (24). Regularly scheduled hematologic and radiologic surveys were also performed. Throughout the study, veterinary medical care was provided as needed. Moribund dogs were euthanized. After death, each dog was subjected to a complete necropsy and histopathologic examination of tissues. The results will provide the basis for future reports upon the completion of the study.

Table 2

Experimental design of the ^{90}Sr toxicity study in dogs receiving a single intravenous dose at 540 days of age

Treatment code	^{90}Sr/kg (kBq)	Total injected (kBq)*	No. of dogs
S 20	136.900	1 369	20
S 40	1 221.000	12 210	26

* Assuming a 'typical' 10 kg beagle.

Results

Control material. In the non-irradiated control material no bone tumors have been observed. These dogs have been under observation for a mean life span of 13.8 years (median 14.7 years) (Table 3).

Doses. The cumulative skeletal doses from ^{90}Sr varied from an average of 0.3 Gy in the D05 dogs to 130 Gy in the D60 dogs (Table 3). The corresponding range of dose rates was 0.07 mGy/day to 160 mGy/day.

Survival. Dogs fed or injected with ^{90}Sr died sooner at higher exposure levels than they did at lower levels (Table 3). In most cases, dogs dying from bone tumors did so at an average time somewhat longer than the average survival time for the entire treatment group shown in Table 3, which includes animals that died from other radiation-induced diseases. Among the ^{90}Sr-fed animals, the mean age at death from bone tumors was 2.5 (range 1.6–3.0) years for the 10 D60 dogs, 7.9 (4.9–9.9) years for the 15 D50 dogs, 12.4 (8.4–14.5) years for the 6 D40 dogs, 12.7

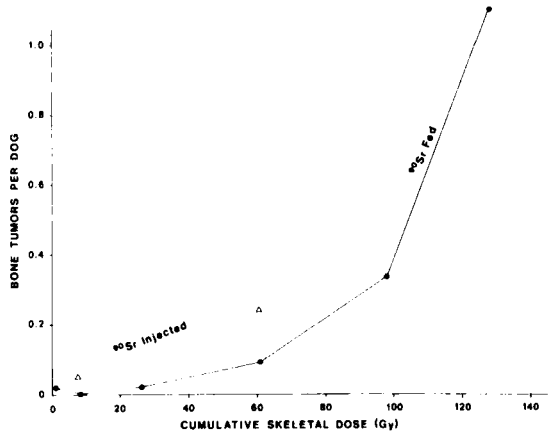

Fig. 1. Number of bone tumors per dog in relation to total cumulative irradiation dose to the skeleton.

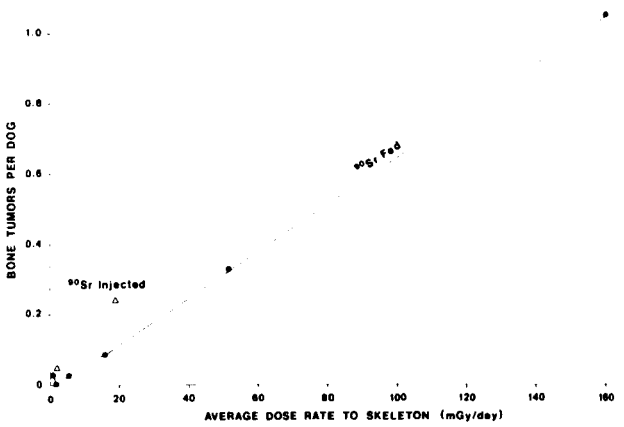

Fig. 2. Number of bone tumors per dog in relation to average irradiation dose rate per dog to the skeleton.

Table 3

Survival, average skeletal dose, dose rate, and bone tumors in dogs fed or injected with ^{90}Sr

Treatment code	No. of dogs	Mean survival (years)	Mean cumulative skeletal dose (Gy)	Mean skeletal dose rate (mGy/day)	No. of dogs with tumors	No. of tumors	Tumors per dog
D 00	80	13.8	0	0	0	0	0
D 05	78	13.3	0.30	0.07	0	0	0
D 10	40	13.2	1.30	0.28	1 (3 %)	1	0.03
D 20	66	13.2	8.00	1.70	0	0	0
D 30	65	13.3	26.30	5.50	2 (3 %)	2	0.03
D 40	61	10.9	61.40	16.00	6 (10 %)	7	0.08
D 50	60	5.5	97.20	51.60	15 (25 %)	19	0.33
D 60	19	2.2	127.50	160.20	10 (53 %)	20	1.05
S 20	20	12.5	7.50	2.1	1 (5 %)	1	0.05
S 40	26	11.5	61.60	18.5	5 (19 %)	5	0.24

(10.0–15.5) years for the 2 D30 dogs and 14.8 for a single D10 dog. Among the ^{90}Sr-injected animals, the mean age at death was 13.0 (10.6–14.6) years for the 5 S40 dogs and 10.3 years for a single S20 dog. The only continuously-fed D50 dog which succumbed to bone cancer died at 6.5 years.

Tumor incidence in relation to administered activity, total dose, and dose rate. Tumor production increased by approximately three-fold increments between treatment levels, reflecting the magnitude of the increases in administered activity presented in Tables 1 and 2. The tumor incidence in the various treatment groups, however, did not reflect proportionality to the total dose (Table 3). For example, the tumor yield at the D60 level, expressed in terms of percentage of dogs with tumors and number of tumors per dog, was roughly 2 and 3 times greater, respectively, than that at the D50 level. This difference exceeded the ratio of cumulative doses, 1.3, but approximated the ratio of the average dose rates, which was 3.1, especially for the number of tumors per dog. The relationship between these various values was even more evident at the D40 and D30 levels, which had tumor yields 13 and 35 times lower than the D60 level (and dogs with tumors 7 and 18 times lower), even though doses were only 2 and 5 times lower, respectively. Average dose rates, however, for D40 and D30 dogs were 10 and 30 times lower than for the D60 dogs; that the production of tumors was more linearly related to dose rate than cumulated dose is shown in Figs 1 and 2.

The injection of ^{90}Sr resulted in a greater production of bone tumors than ingestion of ^{90}Sr which gives the same skeletal dose or dose rate. The relationship of the two treatment modes is shown in Figs 1 and 2, but the injected material is too small for drawing a definitive general conclusion about its effectiveness as compared with that of ^{90}Sr-feeding.

Tumor multiplicity. The number of multiple tumors increased with higher radiation exposures. Half the tumors in the D60 dogs was found in 3 dogs, 2 having 3 tumors each, and one having 4 tumors. In the D50 group, half the

neoplasms was found in 5 dogs having 2 tumors each. In the lower dose levels, no animal had more than one tumor (Fig. 3). The histologic diversities of the tumors from the dogs with multiple malignancies are indicative of their primary origins.

Tumor rate in relation to sex. The number of fatal tumors in the population of nearly equal numbers of either sex was practically the same in males as in females, 18 versus 22, respectively (Table 4), or if the whole tumor material of all groups was taken into account, 27 versus 28 (Table 5). If all tumors, i.e. not only fatal ones, were considered a difference was found between the sexes on the D60 versus the D50 levels, being for males 13/20 (65±13%) and 5/19 (26±10%), respectively. Using non-parametric statistical analysis these values are significantly different ($p<0.05$). In the lower dose groups, there was a somewhat higher tumor incidence among males, but very few tumors were produced at these levels.

Anatomic localization. The anatomic distribution of the fatal tumors differed between the different dose groups and between the sexes (Table 4). There was a clear predominance of tumors in the long bones in the D60 group, with the humerus most often being affected; furthermore, most of these were in males. In the D50 level, 54 per cent of the fatal neoplasias were restricted to the head, particularly the mandible, where 43 per cent occurred. Seven tumors were localized in the pelvic bones, all in females. Overall, the bones of the head (skull and mandible) accounted for one-third of the fatal tumors. About one-fifth of the fatal tumors were in the long bones. If all tumors are taken into account (Table 5, Fig. 4) it seems clear that in this study a close association between dose and anatomic localization does exist, with a preponderance of tumors in the long bones, (60%) and scapulae (20%), the head (47.8%) and the vertebrae (35.7%) in the highest, the second highest and the lower dose groups, respectively.

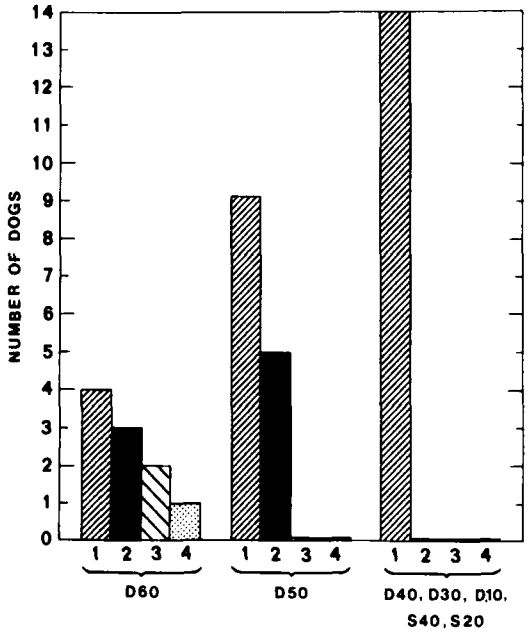

Fig. 3. Tumor multiplicity at different dose levels. In the pooled groups two tumors, anatomically not indicated, were excluded. Long bones (■), pelvi bones (■), vertebrae (▨), head (■).

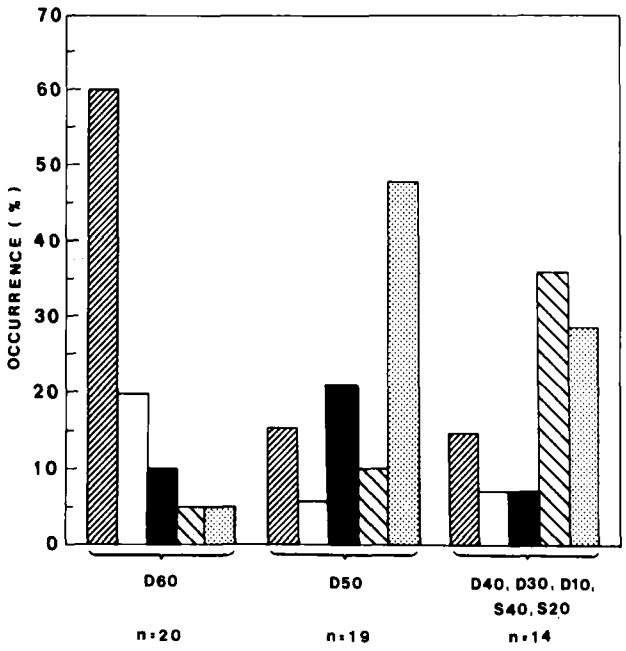

Fig. 4. Percentage location of tumors in different bones. In the combined group an additional tumor in a rib is not included. Scapulae (□). Other symbols as in Fig. 3.

Discussion

As shown by the data in this report, the crude bone tumor yield in dogs from ^{90}Sr exposure shows an almost linear correlation between tumors per dog and dose rate as well as administered dose. On the other hand the cumulative dose indicates some kind of threshold effect (Figs 1, 2).

The result obtained in the dogs are approximately in agreement with those found in mice with regard to the interrelationships between tumor incidence, accumulated dose, and dose rate (17), although the tumor yield per unit of radiation dose is much higher in mice than in dogs. The reasons for the increased effectiveness in mice may be many, and probably include factors such as species differences, different routes of administration and lack of mortality corrections although difficult to perform without objections. Above all, it may be because all parts of the mouse skeletons (other than the very smallest) were scrutinized histologically. In this context, it is pertinent to point out that considerable strain differences exist in mice with regard to the cancerogenicity of ^{90}Sr. Out of four strains investigated (CBA, C57Bl, Swiss Albino) and hybrids between them, the Albino strain was most sensitive and the CBA strain the most resistant, whereas the hy-

Table 4

Anatomic localization of fatal bone tumors in beagles fed or injected with ^{90}Sr

	Females						Males								
	D 60	D 50	D 40	S 40	Total	Per cent	D 60	D 50	D 40	D 30	D 10	S 40	S 20	Total	Per cent
Scapula		1	1		2	11									
Long bones	1	0.5*			1.5	8	5		1					6	27
Pelvic bones	2	4		1	7	39									
Spine		1	1		2	11	1			1	1	1	1	5	23
Mandible		2.5*			2.5	14		4	1					5	23
Skull		1		1	2	11	1	1	1			1		4	18
Ribs										1				1	5
Not indicated			1		1	6						1		1	5
Total	3	10	3	2	18		7	5	3	2	1	3	1	22	

* One dog died of osteosarcoma of the femur and mandible, so contributes 1/2 to each value.

Table 5

Anatomic localization of all bone tumors in beagles fed or injected with ^{90}Sr

	Females						Males								
	D 60	D 50	D 40	S 40	Total	Per cent	D 60	D 50	D 40	D 30	D 10	S 40	S 20	Total	Per cent
Scapula	3	1	1		5	19	1							1	4
Long bones	2	3	1		6	22	10		1					11	39
Pelvic bones	2	4		1	7	26									
Spine		2	1		3	11	1			1	1	1	1	5	18
Mandible		2			2	7		4	1					5	18
Skull		2		1	3	11	1	1	1			1		4	14
Ribs										1				1	4
Not indicated			1		1	4						1		1	4
Total	7	14	4	2	27		13	5	3	2	1	3	1	28	

brids between CBA and Albino had an intermediate tumor incidence (19).

It is well known that there is a close relationship in mice between dose and multicentric genesis (16). This is also in agreement with the findings of multiple tumors in dogs.

Why the majority of tumors appeared in males at the D60 level and in females at the D50 level is difficult to understand. Neither survival time nor dose factors seem to offer an explanation. Also, hormonal influences do not seem to help the interpretation, because if hormones play a role, the effects would be valid at both these high levels and not only at one. This finding is therefore confusing, particularly if the very clear sex differences that occur in mice are taken into consideration. In a series of mice from the above-mentioned strains and their hybrids, the tumor incidence was higher in females for all strains but C57Bl. The average tumor incidence when all the different strains were included was a factor of 1.54 greater in females than in males. In this context, it should also be noted that estrogenic hormone, irrespective of sex, when given in combination with ^{90}Sr, highly significantly increases the tumor rate, at least at high dose levels, although the survival time of the animals is shortened by a factor of almost two (21).

It is also difficult to explain why all the tumors located in the pelvic bones were found in female dogs, regardless of the dose level. Such differences have never been noted between males and females given ^{90}Sr or ^{90}Sr and estrogen in mice (21).

In the dogs, the bones most often affected with tumors were the long bones followed by the bones of the head, the spine, the pelvic bones and the scapulae. In mice, the long bones also were the most frequently affected with the tumor incidence inversely proportional to the dose. For increasing doses, the tumor yield decreased in the long bones but increased in others, particularly in the spine (17). This was a fairly regular pattern in mice, but not in dogs, where the predominance of tumors in the long bones

was lost with decreasing doses. Why bones of the head, particularly the mandibles, are the predominant sites of tumors in the dogs cannot be explained.

In mice it has been shown that the tumor rate as well as the tumor type within regions of the long bones (proximal, distal epiphysis-metaphysis, and mid-diaphysis) vary with the doses of ^{90}Sr employed (17). This seems to be related to doses delivered at the different regions (17), but has not been verified in the present dog material. It is known, however, that variable doses exist in regions of the humerus of ^{90}Sr-fed beagles (9).

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