Exposure to Ionizing Radiation and Development of Bone Sarcoma: New Insights Based on Atomic-Bomb Survivors of Hiroshima and Nagasaki

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Background: Radiation-induced bone sarcoma has been associated with high doses of ionizing radiation from therapeutic or occupation-related exposures. However, the development of bone sarcoma following exposure to lower doses of ionizing radiation remains speculative.

Methods: A cohort analysis based on the Life Span Study (n = 120,321) was performed to assess the development of bone sarcoma in atomic-bomb survivors of Hiroshima and Nagasaki followed from 1958 to 2001. The excess relative risk per gray of ionizing radiation absorbed by the bone marrow was estimated. Additional subject demographic, survival, and clinical factors were evaluated.

Results: Nineteen cases of bone sarcoma (in eleven males and eight females) were identified among the 80,181 subjects who met the inclusion criteria, corresponding to an incidence of 0.9 per 100,000 person-years. The mean ages at the time of the bombing and at diagnosis were 32.4 and 61.6 years, respectively. The mean bone marrow dose was 0.43 Gy. Osteosarcoma was the most commonly identified bone sarcoma. The most common bone sarcoma site was the pelvis. The overall unadjusted five-year survival rate was 25%. A dose threshold was found at 0.85 Gy (95% confidence interval, 0.12 to 1.85 Gy), with a linear dose-response association above this threshold. The linear slope equaled an excess relative risk of 7.5 per Gy (95% confidence interval, 1.34 to 23.14 per Gy) in excess of 0.85 Gy.

Conclusions: On the basis of what we believe is one of the longest and largest prospective studies assessing the development of bone sarcoma in individuals exposed to ionizing radiation, it appears that the development of radiation-induced bone sarcoma may be associated with exposure to much lower doses of ionizing radiation than have previously been reported. Such new insights may potentially improve bone sarcoma prevention measures and broaden our understanding of the role of ionizing radiation from various sources on the development of malignant tumors. This study stresses the need to become increasingly aware of the various health risks that may be attributable to even low levels of ionizing radiation exposure.

Level of Evidence: Prognostic Level I. See Instructions to Authors for a complete description of levels of evidence.

Bone sarcoma is relatively uncommon, accounting for 0.5% to 1% of malignant neoplasms[1-5]. Various causative agents, including exposure to ionizing radiation[6], have been associated with the development of bone sarcoma.

The development of bone sarcoma in adults and children following therapeutic or occupational exposure to high-dose ionizing radiation has been reported[7-22]. Other studies have also demonstrated an association between exposure to relatively

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A commentary by Charles M. Turkelson, PhD, is linked to the online version of this article at jbjs.org.

high levels of internal sources of radiation and the development of an excess of bone sarcomas[23-25]. However, an increase in the risk of bone sarcoma following exposure to lower doses of ionizing radiation is speculative. In fact, various authors have reported no increase in the risk of bone sarcoma following exposure to low doses of ionizing radiation in occupational settings[26,27], from prenatal x-rays[28], or from radiation therapy for benign conditions[29-32]. High-dose radiation, ranging from 10 to 290 Gy, for cancer therapy has been associated with an increased risk of bone sarcoma[33-40]. According to reports from the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR)[41] and the International Agency for Research on Cancer (IARC)[42], an increase in bone sarcoma incidence following exposure to ionizing radiation has rarely been reported at doses below 5 Gy and the appropriate predictive dose-response model for the risk of bone sarcoma due to ionizing radiation is uncertain[16,19,21,23,25,35,43].

The age distribution of individuals with bone sarcoma is dependent on the type of lesion[44]. Moreover, estimates of the latency period for radiation-induced bone sarcoma have ranged from 2.8 to fifty-five years[33,34,36,39,45-48] and are potentially influenced by the age at the time of radiation exposure[49]. Although some authors have postulated an inverse relationship between the latency period and the radiation dose[50,51], other authors have questioned the existence of such a relationship[1,13,46,52]. In addition, bone sarcoma is associated with a relatively poor clinical prognosis and a low survival rate, and some authors have suggested that radiation-induced bone sarcoma has a more aggressive nature than typical bone sarcoma does[47,53,54].

The Radiation Effects Research Foundation's Life Span Study (LSS), consisting of Japanese atomic-bomb survivors of Hiroshima and Nagasaki, is a longitudinal population-based study performed to characterize radiation-associated risks of cancer and other diseases[55-59]. Utilizing the data provided by the Life Span Study, we investigated the development of bone sarcoma associated with exposure to low to moderately high levels of ionizing radiation. As a secondary objective, we attempted to investigate the role of age at exposure as well as the association of other factors with anatomical location, morphological type, latency period, and survival.

Materials and Methods

With use of the Life Span Study (n = 120,321), we identified cases of bone sarcoma among atomic-bomb survivors of Hiroshima and Nagasaki in Japan. For the purpose of this study, cartilage sarcomas were also included in the category of bone sarcomas. The characteristics of the Life Span Study have been previously described in the literature[55-57]. Tumor registries were established in Hiroshima and Nagasaki on January 1, 1957, and January 1, 1958, respectively. The subjects who were included in the Life Span Study were individuals who were in Hiroshima or Nagasaki at the time of the atomic bombings, who were alive and not known to have cancer before January 1, 1958, and for whom bone marrow radiation dose estimates were calculated.

The time of sarcoma development was considered to be the date on which the individual was initially diagnosed by the physician irrespective of the time of onset of symptoms, the date of original consultation and medical treatment for tumor-related symptoms, or tumor identification based on the death certificate. Tumors discovered at the time of autopsy were considered clinically diagnosed. Thus, cases of bone sarcoma were identified with use of the Hiroshima and Nagasaki Tumor Registries and verified with use of additional information from death certificates, autopsy reports, and Tissue Registry records[60]. According to the scheme proposed by the World Health Organization's International Classification of Diseases for Oncology (ICD-O) (first, second, and third editions), bone sarcomas were classified on the basis of anatomical site (ICD-O code 170 [1st edition] and codes C40 and C41 [2nd and 3rd editions]) and morphological type. Tumors diagnosed outside of the tumor registry catchment area were excluded from this study.

Additional information of interest regarding the bone sarcoma cases included sex, city of exposure, age at the time of the bombing, age at diagnosis, time from exposure to diagnosis, survival period, survival status at the time of the latest follow-up, and cause of death. Furthermore, a review of the clinical records was also conducted to determine the exact tumor location, the treatment type, the presence of metastatic disease, and any other relevant clinical characteristics. In addition, the bone marrow dose (in grays) was estimated, with the neutron dose given a weight of 10 and the gamma radiation dose given a weight of 1 to adjust for biological effectiveness[61]. The estimated radiation dose to the bone marrow was based on an average skeletal dose calculated with the Dosimetry System 2002 (DS02)[61]. With the DS02, which was developed by an international scientific working group, the dose to the skeleton was determined with use of an anthropometric model and information on each survivor's location in relation to the hypocenter of the bomb as well as proximity to external shielding structures, age, position, and orientation, through a series of detailed calculations based on a large body of theoretical and empirical work[61].

Pearson correlation tests (version 15.0; SPSS, Chicago, Illinois) were conducted for bivariate analysis of continuous data. For parametric analysis, independent-sample t tests were conducted for two independent samples, whereas, for nonparametric analysis, the Mann-Whitney U test was performed. Kaplan-Meier survival analysis was conducted to determine the cumulative survival rate following diagnosis. The AMFIT function of the Epicure statistical software program (version 1.4; HiroSoft International, Seattle, Washington) was used to perform Poisson regression of grouped survival data to compute rates[62]. Person-year observations for the subjects included in the study were calculated from January 1, 1958, to the time of tumor diagnosis, the date of death, or the December 31, 2001, Life Span Study update. Various predictive dose-response models (i.e., linear, linear-quadratic, quadratic, spline, and threshold) were assessed to determine the best fit for bone sarcoma development, adjusted for sex and age at diagnosis (age at risk), and radiation dose. Radiation effects were modeled, accounting for background incidence rates, with use of the excess relative risk (ERR). The excess relative risk, which is equal to the relative risk (RR) minus 1 (ERR = RR – 1), allows for analysis of the radiation-related excess incidence separately from the background incidence and is the standard model used in radiation epidemiology[61]. Likelihood ratio tests were performed to make nested model comparisons. All p values were two-sided, with a threshold of significance set at $p < 0.05$.

The conduct of the Life Span Study was approved by the Human Investigation Committee of the Radiation Effects Research Foundation. The use of death

TABLE I Characteristics of Bone Sarcoma Cases That Fulfilled the Inclusion Criteria

Variable	Mean and Standard Deviation (Range)
Bone marrow dose *(Gy)*	0.43 ± 0.90 (0-2.86)
Ground distance from hypocenter *(km)*	3.1 ± 1.6 (0.8-5.9)
Age at time of the bombing *(yr)*	32.4 ± 18.4 (0-61)
Age at diagnosis *(yr)*	61.6 ± 15.2 (18-81)
Time from exposure to diagnosis *(yr)*	29.3 ± 12.1 (13-53)
Survival from time of sarcoma diagnosis *(yr)*	2.5 ± 4.3 (0-14.3)

TABLE II Bone Sarcoma Rates by Bone Marrow Dose

Bone Marrow Dose (Mean Weighted by Person-Years) *(Gy)*	Person-Years	No. of Cancer Cases	No. of Observed Bone Sarcoma Cases (No. Expected)*	Sarcoma Rate per 100,000 Person-Years	Excess Relative Risk (95% CI)
<0.005 (0.001)	930,039	2614	12 (8.2)	1.3	0
0.005-0.1 (0.030)	756,014	6078	3 (6.5)	0.4	–0.7 (–0.93 to –0.02)
0.1-0.2 (0.14)	159,445	4323	0 (1.4)	0	–1.0 (–∞ to –0.01†)
0.2-0.5 (0.32)	162,648	3489	0 (1.4)	0	–1.0 (–∞ to –0.01†)
0.5-1 (0.71)	92,560	2290	0 (0.8)	0	–1.0 (–∞ to 0.72†)
1-2 (1.36)	50,086	3718	2 (0.5)	4.0	2.0 (–0.54 to 10)
>2 (2.67)	19,887	2221	2 (0.2)	10.0	7.0 (0.25 to 29)

*The expected number of cases is derived from the Poisson regression model adjusted for sex and log(age) but not for the radiation dose (i.e., no excess relative risk). †The 95% confidence interval (CI) could not be computed directly because the upper and lower bounds did not converge when the estimated relative risk was calculated from the linear form of the model. In this case, calculations were performed by using the log-linear (log[relative risk]) form of the model for the dose group and subtracting 1 to obtain the excess relative risk. (For an individual dose group, the estimated relative risks [and confidence interval] for the log-linear model and for the linear model are identical except for the constant 1.)

certificates of the Life Span Study subjects was approved by the Ministry of Internal Affairs and Communications. The respective committees of the Hiroshima City Cancer Registry, Hiroshima Prefecture Tissue Registry, and Nagasaki Prefecture Cancer Registry approved the use of cancer registry data for the present study.

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Results

The Life Span Study cohort consisted of 120,321 subjects. However, 8368 subjects were excluded because they had died, were diagnosed with cancer, or lost to follow-up before January 1, 1958. In addition, 6525 subjects were excluded because the radiation dose was unknown, and 25,247 subjects who were not in the cities at the time of the bombing were also excluded. Thus, 80,181 subjects fulfilled the inclusion criteria and were included for further assessment (Fig. 1 and Table I). Throughout the course of follow-up, 24,733 of the subjects who fulfilled the inclusion criteria developed cancer, including nineteen cases of bone sarcoma. (In addition, ten bone sarcoma cases were documented among subjects who did not meet the inclusion criteria.) The total number of person-years, based on the 80,181 subjects who met the inclusion criteria, was 2,170,679. Table II illustrates the observed and expected bone sarcoma incidence rates for various radiation doses. The overall incidence rate for the development of bone sarcoma in our study population was 0.9 per 100,000 person-years.

Eleven of the subjects with bone sarcoma were male and eight were female. Nine were in Hiroshima at the time of the bombing, and ten were in Nagasaki. The incidence rate per 100,000 person-years for the development of bone sarcoma in our study population was 1.4 for males and 0.6 for females. The overall mean bone marrow radiation dose (and standard deviation) of individuals with bone sarcoma was 0.43 ± 0.90 Gy (range, 0 to 2.86 Gy). There was no significant relationship between the radiation dose and the city or sex ($p > 0.05$).

The mean age of the patients with bone sarcoma was 32.4 ± 18.4 years (range, zero to sixty-one years) at the time of the bombing and 61.6 ± 15.2 years (range, eighteen to eighty-one

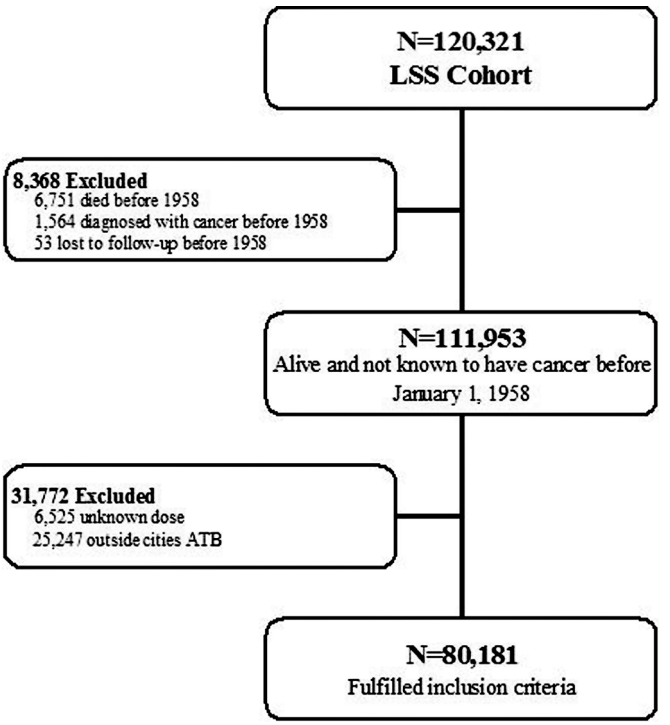

Fig. 1

Flow diagram illustrating the study population, which was derived from the Life Span Study (LSS) cohort population of Hiroshima and Nagasaki. ATB = at the time of the bombing.

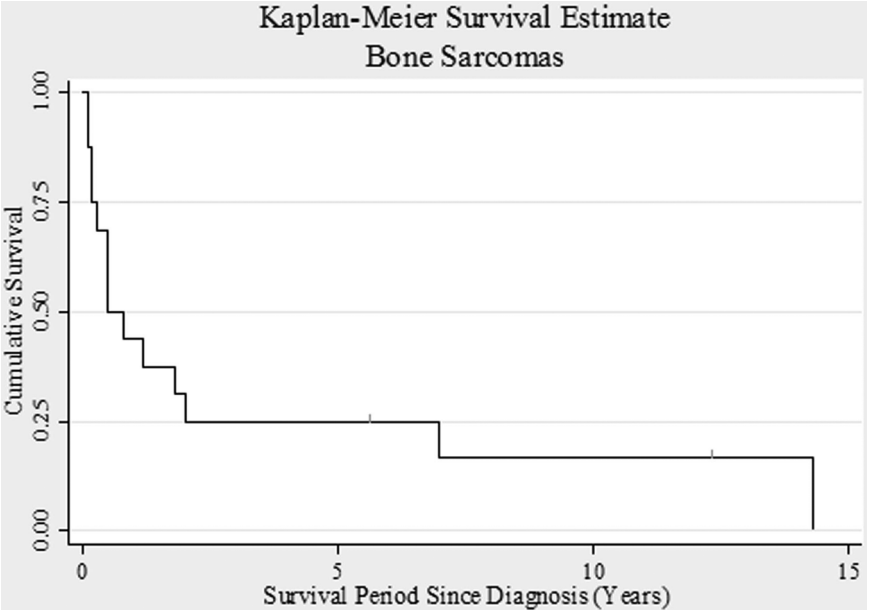

Fig. 2

Kaplan-Meier survival analysis. Tick marks on the survival estimate represent subjects who remained alive at the time of the final follow-up assessment.

years) at the time of diagnosis. The mean time from exposure to diagnosis was 29.3 ±12.1 years (range, thirteen to fifty-three years). A negative correlation was found between the time from exposure to diagnosis and the age at the time of the bombing ($r = –0.57$, $p = 0.011$), but no association was noted between the time to diagnosis and the bone marrow dose ($r = 0.11$, $p = 0.670$). However, our study had insufficient power to properly investigate these factors.

The most commonly identified type of sarcoma was osteosarcoma (five cases). The most common sarcoma site was the

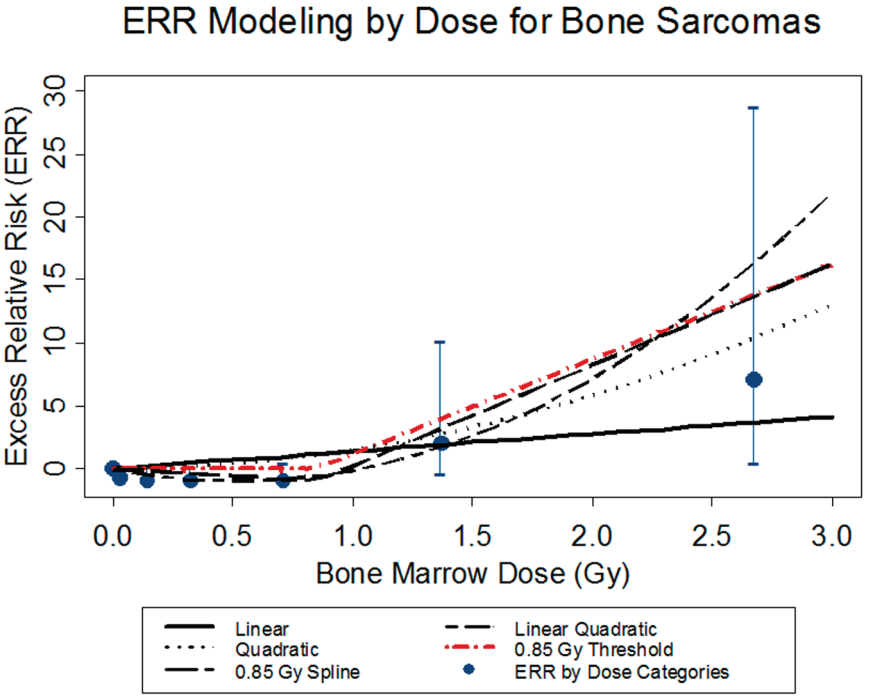

Fig. 3

Excess relative risk (ERR) of bone sarcoma as a function of the radiation dose in grays (Gy) to the bone marrow. The error bars indicate the 95% confidence interval. The five curves represent the dose-response models tested. The baseline incidence in each model was adjusted for sex and age at diagnosis (age at risk).

pelvis (six cases), followed by the lower extremities (five), the spinal column (five), the head (two), and the ribs (one). The subjects who developed ameloblastoma (n = 1; 1.21 Gy) or chondrosarcoma (n = 2; 1.43 ± 2.02 Gy; range, 0.002 to 2.86 Gy) were exposed to the greatest radiation dose at the time of the bombing. No significant association was noted between bone marrow dose and sarcoma location or morphological type ($p > 0.05$).

Of the nineteen patients with sarcoma identified at the time of the 2001 Life Span Study update, two remained alive. Kaplan-Meier survival analysis indicated a 25% overall five-year survival rate (45% for males and 0% for females) (Fig. 2). Although the mean survival time was longer for males (3.8 years; 95% confidence interval [CI], 0.71 to 8.31 years) than for females (0.8 years; 95% CI, 0.21 to 1.31 years) during the entire follow-up period, this difference did not reach significance ($p > 0.05$). Stratification of survival by treatment type was not possible because of insufficient clinical information. Although chart review revealed the development of metastasis in six of the subjects, it could not be determined if metastasis occurred in the remaining nine. Of the seventeen deaths, ten were the direct result of the bone sarcoma. No information regarding genetic or syndromic factors, occupation, or smoking status was available for assessment.

The excess relative risk due to radiation exposure was modeled with adjustment of the background incidence for sex and age at risk. After examination of the fit of the various models (linear [deviance = 221.9], linear-quadratic [deviance = 212.3], quadratic [deviance = 218.3], spline [deviance = 214.1], and linear-threshold [deviance = 216.70]) relating bone sarcoma incidence to bone marrow radiation dose, it was determined that a linear-threshold model exhibited a good fit to the data (Fig. 3). Assessment of the likelihood profile and its bounds showed the best fit to be a linear model with a threshold at 0.85 Gy (95% CI, 0.12 to 1.85 Gy). The model showed a linear dose response, with an excess relative risk of 7.5 (95% CI, 1.34 to 23.14; $p = 0.002$) per Gy in excess of the threshold of 0.85 Gy (Fig. 3).

Discussion

The role of ionizing radiation as a potential environmental risk factor for the development of bone sarcoma was initially reported in 1922 by Beck[63] in his account of sarcomas arising from the radiation treatment of tuberculous arthritis. Shortly thereafter, in 1929, the causal relationship between ionizing radiation and bone sarcoma was confirmed by Martland and Humphries[64] in their report noting an excessive frequency of bone sarcoma occurring in American radium dial painters, who ingested large quantities of ^{226}Ra and ^{228}Ra by licking the tips of paintbrushes containing radium used to color the faces of watches to obtain a fluorescent glow. Radium was found to cause bone necrosis, anemia, osteitis, and osteosarcoma. In studies of 1474 women employed in the radium dial industry before 1930, sixty-one cases of bone sarcoma were noted with a mean radiation dose to bone of 17 Gy[9,12]. In subsequent studies of 2383 women, no bone sarcoma occurred in individuals with a radiation exposure of <10 Gy[50]. Throughout the years, various accounts have confirmed that bone sarcoma is associated with radiation exposure, primarily at very high doses[7-22,65].

Our current understanding of the impact of radiation exposure on the risk of bone sarcoma has been aided by studies such as those of patients in various countries who had been administered Thorotrast (a contrast medium containing thorium); Mayak nuclear facility workers exposed to plutonium; individuals who received internal or external radiation for the treatment of ankylosing spondylitis, cervical cancer, Hodgkin disease, childhood cancers, retinoblastoma, and benign gynecological disease; and the atomic-bomb survivors of Hiroshima and Nagasaki[7-25,56,65]. The Life Span Study cohort of atomic-bomb survivors, comprising more than 120,000 individuals followed since 1958, constitutes one of the best populations for assessing the risk of sarcoma due to low-to-moderate radiation doses. In the recent cancer incidence report involving atomic-bomb survivors of Hiroshima and Nagasaki in the Life Span Study cohort, Preston et al. found that, on the basis of a linear model, sarcomas as a group exhibited an excess relative risk per Gy of 0.48 (90% CI, 0.07 to 1.4), with an excess absolute risk of 0.39 (90% CI, 0.08 to 1.04) per 10,000 person-years per Gy at age seventy in individuals exposed at age thirty[56].

The current analysis, which did not involve any new design or data collection but rather was based on all available data from the already ongoing Life Span Study cohort follow-up, was performed to explicitly investigate bone sarcoma. Among the explored models, all of which gave similar overall fits to the data, the linear model with a threshold at 0.85 Gy appeared the most plausible from a statistical and biological perspective. More specifically, the spline and, in particular, the linear-quadratic model yielded lower degrees of deviance than did the linear-threshold model, but if these models were acceptable they would have produced an unexplained reduction of risk (e.g., excess relative risk = –1.0 at 0.5 Gy and –0.6 at 0.85 Gy for the linear-quadratic model), which does not seem plausible. The evidence suggests that the fit of the linear non-threshold model is poorer than that of the other models (Fig. 3). Therefore, the current study suggests that acute exposure to a radiation dose in excess of 0.85 Gy results in an increased risk of development of bone sarcoma. Furthermore, a significant excess relative risk of 7.5 per Gy in excess of the threshold of 0.85 Gy was noted. This study provides further confirmation that radiation-associated bone sarcoma appears to follow an overall threshold dose-response relationship, substantiating the findings of previous studies involving radium dial painters in the United States[50] and United Kingdom[66] as well as various studies of animals; however, our findings differ, in some respects, from those of other reports that support the use of linear or quadratic dose-response models[16,19,21,43].

The prognosis for radiation-associated bone sarcoma is influenced by the type, size, and location of the lesion, which may determine its growth, aggressiveness, and potential for recurrence[67-70]. Survival rates may improve and are dependent on the time of detection, tumor size, tumor grade, and nature of surgical and other oncological treatments. In a study of

forty-two patients presenting with radiation-induced bone sarcoma (mean radiation dose, 50 Gy), Kalra et al.[53] reported that, although the overall five-year survival rate was 35%, the survival rate was 0% for patients treated with a palliative intent and 41% for patients treated with a curative intent. The authors further noted that the most common site of bone sarcoma development was the pelvis (in 33% of their patients). Our study also showed the pelvis to be the most common bone sarcoma site. The five-year survival rate of subjects in our study was 25%, with a clear distinction between males (45%) and females (0%). However, the sex difference in survival rate did not reach significance, and may have been due to differences in the therapeutic care received. Additionally, various authors have noted that a tumor located on the periphery of the bone is associated with a longer survival period than one that is more centrally located or is incompletely resected[53,71,72]. Further analysis to investigate the effects of treatment type on survival could not be done because of the lack of available clinical information.

Previous studies of atomic-bomb survivors have not focused on the increased risk of bone sarcoma induced by radiation[56]. The current finding of a linear model with a 0.85 Gy threshold and a ninefold excess relative risk of bone sarcoma induction at 2 Gy has certain implications for radiation therapy techniques. However, because of the very low absolute risk, the very wide confidence limits on the risk estimate, and the long latency period between radiation exposure and clinical detection of radiation-induced sarcoma, the full implications of this new finding are uncertain.

A review of the Surveillance, Epidemiology and End Results (SEER) database by Brenner et al.[73] demonstrated a 35% increase in second cancers over a ten-year period following radiation therapy to the prostate; 8% of these cancers were sarcomas. In three-dimensional conformal radiation therapy, as the central-axis dose increases, the adjacent, normal, in-field tissues also receive a higher dose[74]. In a large pelvic field, a substantial portion of such tissue, including a large portion of the osseous pelvis and proximal portions of the femora, may be subjected to a dose higher than the threshold for bone sarcoma induction.

Additionally, with intensity-modulated radiation therapy, there is some evidence that the integral dose is increased and that adjacent volumes receiving a low dose may also be increased[75-77]. This effect may be attributed to the entry and exit of the greater number of beams used to achieve the greater target conformality in intensity-modulated radiation therapy than in conventional conformal therapy. There is also increased leakage from the gantry head and through the multileaf collimator due to the greater number of monitor units required to deliver the dose[78]. Treatment of deep-seated pelvic tumors with use of higher-energy beams in intensity-modulated radiation therapy for dose escalation[79] and the sparing of normal tissue[80,81] can also be accompanied by an increased exposure of normal tissue to radiation due to secondary neutrons[82,83]. Particularly with prostate cancer, diagnosis is being made at younger ages and earlier stages, and long-term control of the cancer is common. In this setting, the benefit of the increased ability to sculpt the dose around target tissues and avoid organs in the pelvis that are at risk with higher-energy intensity-modulated radiation therapy beams must continue to be weighed against the potential for increased short-term and long-term risk of harm to the patient, specifically induction of second malignant tumors, including sarcomas.

Although this is one of the largest and longest longitudinal population-based studies assessing the occurrence of radiation-associated bone sarcoma, it has inherent limitations. Complete, detailed information was not available regarding any underlying genetic susceptibilities, occupational hazards, smoking status, or history of radiation treatment that may have predisposed individuals to the development of bone sarcoma. However, because of the proper sampling methods involved in our large population, we believe that such variables may be assumed to be randomly distributed among the cohort. Also, because of the small size of our group of subjects with bone sarcoma, it is difficult to discern the effect, if any, of radiation dose on the development of specific morphological types of sarcoma, age at diagnosis, and time from exposure to diagnosis. However, our study did suggest that the time from exposure to diagnosis was greater in children. This is in agreement with a previous study by Weatherby et al.[48], although others have suggested that the latency period is shorter in children than in adults[3], or that no difference exists between these age groups[84]. Alternately, the inverse correlation of the age at the time of the bombing to the age at diagnosis may be an artifact of the longer time that individuals exposed at an earlier age will live before reaching middle or older age—i.e., the age when people may be more likely to develop sarcoma. A final limitation resulting from our sample size is the inability to determine how the time from exposure to diagnosis and the prognosis depend on the sarcoma type.

In conclusion, this investigation involving the Life Span Study cohort of atomic-bomb survivors of Hiroshima and Nagasaki suggests that the development of bone sarcoma is associated with exposure to lower doses of ionizing radiation than those previously reported in the literature. In this study, a linear-threshold dose-response model with an estimated threshold of 0.85 Gy and a significant excess relative risk of 7.5 per Gy in excess of the threshold level was found to be preferable to several other models in describing the risk of radiation-induced bone sarcoma. Associations between factors other than the radiation dose and the sarcoma type or the time from exposure to diagnosis could not be discerned from this study. The findings of this study may help to further clarify concerns about radiation exposure associated with medical diagnostic procedures or occupational hazards, and may aid in the design of adjustments to radiotherapeutic techniques to minimize the risk of developing radiation-induced bone sarcoma. ■

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