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Radiation-Induced Sarcomas of Bone

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Abstract. Historically, the literature reveals that the incidence of radiation induced bone sarcomas is very low. Details related to epidemiology cannot be identified, however, because of the difficulty of identifying precisely the patient population at risk for development of the radiation induced sarcoma. The change in character of practice in cancer management with ever increasing numbers of patients receiving both radiation therapy and chemotherapy should alert physicians to the potential for increased incidence of this rare and unusual tumor.

Key words: Sarcomas – Bone – Neoplasms – Radiation induced.

The pathogenesis and etiology of human malignant tumors of bone remain obscure, although many etiologic agents are known to have direct relationships to the development of malignant tumors of bone in various experimental conditions (Table 1). Interest in the field is particularly keen for various reasons, including not only the unusual character of the radiographic findings, but also the interest in the etiology of malignant sarcomas of bone being intensified by the recognized late effects of cancer treatment and their increasing importance. This is of particular interest, since cancer therapy is becoming more effective and more successful. Radiation carcinogenesis, especially leukemia, is one of the well recognized late effects of successful cancer therapy. Table 2 identifies other late neoplastic changes following medical irradiation. Malignant tumors of other histologic types have been reported in the irradiated individual (Tables 3 and 4).

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Table 1. Etiologic agents for osteosarcoma

1. Chemical carcinogenesis	
Methylcholanthrene	
Beryilium oxide etc.	
2. Viral agents	
DNA viruses	includes polyoma virus
SV40 virus	(osteosarcoma in syrian hamsters)
RNA viruses	(Harvey and Maloney mouse sarcoma virus)
FBJ virus (C type)	isolated from spontaneous sarcoma
RFB	isolated from radiation induced osteosarcoma in x/Gf mouse
3. Radiation carcinogenesis	
External versus internal radiation	
Dose	
Fractionation	
Protraction	
NSD or TDF	
Latent period	
4. Other etiologic agents	
Subperiosteal sheathing with plastic trauma	

In spite of the great interest, the frequency of radiation induced malignant bone tumors is low. Because of the long latent period and low incidence, most clinical reports have been case studies, often with incomplete data on the radiation dosage to the target tissue, inadequate histologic evaluation of the area irradiated prior to radiation therapy and subsequently, as well as the lack of appropriate roentgenographic evaluation.

The radiobiologic effect of X or gamma radiation on an irradiated individual is mostly determined by the magnitude of the absorbed dose and its distribution within the tissues being irradiated. Thus, the absorbed dose and its distribution becomes one of the most important parameters in evaluating the biologic damages including late effects. The wide variation in absorbed dose is most dramatic in those patients treated with photon energies less than 500-KV.

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Table 2. Late neoplastic changes following medical irradiation

1. Adult leukemias following
   (A) Therapy for ankylosing spondylitis
   (B) Therapy for metropathia hemorrhagica
   (C) General diagnostic and therapeutic radiation
   (D) Radiation epilation for tinea capitis
2. Childhood malignancies following
   (A) In utero irradiation
   (B) Preconceptual irradiation
3. Malignancies in limited irradiated field
   (A) Carcinoma, thyroid, following irradiation of thymus
   (B) Cancer following therapy for ankylosing spondylitis
   (C) Carcinoma of certain organs in neck following irradiation for benign conditions of neck
   (D) Cancer of certain organs of head following radiation epilation
   (E) Carcinoma of intestine, rectum, uterus following therapy for metropathia hemorrhagica
4. Breast cancer following
   (A) Fluoroscopy of chest
   (B) Radiotherapy for acute postpartum mastitis
5. Hepatoma following thorotrast, diagnostic radiology
6. Bone sarcoma, cancer of sinuses of head following use of radium solutions in therapy of benign diseases
7. Cancer, general, following therapy for metropathia hemorrhagica

In those circumstances, there is a wide disparity in absorbed dose between soft tissue and the immediately adjacent bone tissues. The more superficial portions of the bone have higher dosage distributions than the deeper surfaces of the bone. This variation in dose distribution is directly related to the energy of the beam and the energy of the photons being used for treatment.

Most experimental work on the production of tumors by irradiation has been concerned with carcinomas and with superficial sarcomata. Tumors have been produced inadvertently in bones close to the areas of irradiated tissue. Marie, Clunet, and Raulot-Lapointe, in 1910, observed such a tumor while evaluating the relationship between radiation injuries and carcinoma [30]. Theirs was the first report of an experimental sarcoma of bone produced by irradiation. Lacassagne and Vinzent, in 1929, treated with 1,000 Roentgen units an abscess adjacent to the femur of a rabbit, noting the development of an osteogenic sarcoma some six and a half months later [27]. Lacassagne also produced a fibrosarcoma in the tibia 36 months after 1,980 Roentgen units had been delivered over an abscess near the bone. From these data he ascribed the relationship between chronic infection and radiation in the production of sarcomas of bone.

Table 3. Five groups of people whose exposure to various types of radiation has been the subject of investigation [51]

	Type of radiation	Period of exposure	Source	Approx. numbers	Follow-up (years)
1. Bomb survivors	Accidental	Minutes	External	100,000	15
2. American radiologists	Occupational	Years	External	3,500	4–40
3. British radiologists	Occupational	Years	External	1,300	5–60
4. Ankylosing spondylitics	Therapeutic	Months	External	14,000	9–25
5. Dial painters Radium chemists Therapeutic ^{226}Ra	Therapeutic				

Table 4. Ratio of observed to expected incidence of various diseases in the 5 groups of people described in Table 1 [51]

Disease	Bomb survivors	American radiologists	British radiologists	Ankylosing spondylitics	Dial painters, etc.
Leukemia	10:1	2:1	2:1	9:1	1:1
Aplastic anemia	2:1	NR	NR	30:1	1:1
Osteosarcoma	NR	NR	NR	2:1[a]	50:1
Carcinoma sinuses	NR	NR	NR	NR	100:1[b]

NR = nil recorded

[a] Observed
[b] Expected

In 1931, Schurch and Uehlinger implanted a one microgram radium needle periostally in the jaw of a rabbit, leaving it in place for some 20 days [38]. One and a half years later, a spindle cell sarcoma with areas of cartilaginous and osteoid tissue was found. Sabin, Doan, and Forkner, in 1932, studied the effects of intravenous injections of 5.1 micrograms of radium chloride and also 7.7 micrograms of mesothorium upon the bone marrow of rabbits [36]. Osteogenic sarcoma was found subsequently in two of the seven animals surviving 11 to 19 months.

Schurch and Uehlinger, 1935, placed vaseline impregnated with two to five micrograms of radium or mesothorium in the femora of 22 rabbits [39]. Eighteen to twenty-one months later, five animals had sarcomas at the site of the implantation. Three of these tumors were osteoblastic and two were polymorphic or spindle cell sarcomata. In 1936, Jentzer produced sarcoma in the skull of a rabbit by the application of radium [23]. Ross implanted platinum tubes containing 0.1 mg of radium in the thoracic wall of young rabbits and an osteogenic tumor of the rib resulted in one animal [33].

Hellner in 1937, in conjunction with his report of one clinical case of radiation induced sarcoma, also described a polymorphic sarcoma produced by repetitive exposure of the lower end of the femur of a rabbit to radium [21]. Ludin produced a chondrosarcoma in the tibia of a rabbit following 8,000 roentgen units delivered over a period of 6.5 months [29]. In 1937, Daels and Biltris introduced a mixture of radium, paraffin, diatomaceous earth, and arsenious acid into the skulls of guinea pigs and two bone sarcomata resulted [14]. Schurch and Uehlinger's third paper reported sarcomata in 50 percent of animals which survived exposure to radioactive materials for a long period [40]. The same authors in 1938 described osteogenic sarcoma in 14 of 21 rabbits in which 0.005 mg of mesothorium had been implanted 21 to 29 months previously [49]. Daels and Biltris, in 1938, implanted collodion strips impregnated with radium sulfate into the pectoral muscles of fowls, with osteogenic sarcomas being found in two of the birds four to five years later [14].

Dunlap, Aub, Evans, and Harris in 1944 reported osteogenic sarcomas appearing in the vertebrae or pelvic bones in nine to thirteen rats fed 100 micrograms of radium [16]. The average interval from the time of the radium ingestion to the discovery of the tumors was 365 days.

From a histopathologic point of view, the majority of specimens demonstrated radiation osteitis particularly at the periphery of the bone tumor. In the humans, this is present in about 50% of the cases. The histologic features of the bone tumors range from osteogenic sarcomas in about 50 to 60% of the cases to fibrosarcomas, chondrosarcomas, and aplastic spindle cell sarcomas and giant cell carcinomas constituting the remainder.

Table 5. Incidence of neoplasia in orbital tissues irradiated for treatment of retinoblastoma in 232 patients followed five years or more

Calculated dose	Incidence of radiation-induced neoplasia
6000 R or less	3/121 (2.5%)
6000 R to 10,999 R	4/73 (5.5%)
11,000 R to 15,000 R	12/38 (32%)

Sagerman (1969) [37]

Except for radiation induced leukemia which usually develops relatively shortly after radiation exposure (a latent period of three to four years), other histologic types for second malignant tumors tend to have a long latent period. Studies on survivors of atomic bomb casualties in Japan and sporadic case reports in the literature have provided useful data on the induction period.

In general, the median latent period for radiation induced bone sarcomas is 11 years. From data derived from animals experiments, it has been stated that the latent period is inversely related to the radiation dosage. This has been confirmed by the review of the incidence of neoplasia in orbital tissues irradiated for treatment of retinoblastoma by Sagerman in 1969 (Table 5) [37].

The radiobiologic mechanism in carcinogenesis at the dose level used in definitive radiotherapy is thought to be at least a product of two processes of cell kill probabilities and transformation rate. Dosages in the range of cancerocidal levels leave fewer reproductively capable cells to proliferate in a transformed state. Therefore, the high therapeutic dose would not only reduce the potentially transformable cells, but also impede doubling time of transformed cells due to poor vascularization and increased fibrosis. Experimental studies of carcinogenesis show a reduction in the frequency of second tumors and prolongation of latent periods following high doses of radiation. The extensive clinical studies by Hutchison also conclude that relatively high doses of radiation either are noncarcinogenic or follow a different quantitative relationship from that seen at low doses [22]. From data derived from a review of the literature, it is interesting to note that no radiation induced sarcomas were seen at dosages below 3,000 rads in three weeks.

The relationship of radiation carcinogenesis to the susceptability at different ages of the patients at the time of irradiation is not clear. It does tend to sup-

port, however, the concept that sensitivity to carcinogenesis is related to the age of the patient. Thus, the child is more sensitive to cancer induction in bone than the adult.

The induction of malignant tumors of bone is so serious a late effect of radiation therapy that an estimate of the magnitude of the risk is important. The problem does not arise in those patients treated palliatively for disseminated cancer. This is not only because the dose is usually below 1,100 rets minimum required for osteogenic sarcoma induction, but because the patients are not likely to live beyond the minimum latent period. It is also unimportant in curative radiation therapy of malignant disease because the hazard from the original tumor far outweighs that from a possible radiation induced second primary lesion. The hazard does, however, need to be considered in evaluating the desirability of elective radiation therapy in patients with long life expectancy. A valid estimate of the hazard obviously requires knowledge of the size of the population at risk, and the numbers of the sarcomas induced. Neither parameter is known in precise detail at this time. In 1977, 320,000 patients received radiation therapy as a part of a treatment program for cancer. This was administered for cure, as an adjunct to surgery or chemotherapy, or for palliation. It is estimated that about 50% of the patients treated by radiation are treated for cure. However, it is extremely difficult to determine the number of individuals who received elective radiation therapy in patients with long life expectancy.

Hatcher in 1945 reviewed the reports in the literature of 24 patients who had developed bone sarcomas following radiation exposure [19]. Seventeen of these tumors resulted from roentgen therapy for tuberculosis arthritis. The precise details of the treatment programs employed are not available making definitive conclusions difficult. Hatcher added three cases to the group with documentation as to the radiation therapy and with appropriate histologic documentation (two of the cases being chondrosarcomas and one a fibrosarcoma.) The three tumors reported by Hatcher regarded as sarcomata were produced by radiation therapy for earlier neoplasms in the same regions. The possibility that they represented recurrences or metastases of the original tumors was considered, but the long delay period between the original tumor, the treatment program, and the subsequent development of the bone sarcoma is in favor of the causal relationship. The radiation dosage was large in each instance and was administered in fractionated doses over long periods of time.

A number of documented studies have dealt with the potential incidence of radiation induced malignant tumors of bone illustrated in Tables 6 and 7.

The survey by Court-Brown and Doll of patients who had received radiation therapy for ankylosing spondylitis revealed a significant number of leukemias, but only a small excess of solid tumors in the irradiated areas [11]. Only three of the solid tumors were bone sarcomas in over 14,000 patients treated, two more than expected in the control population. Details of the radiation treatments were not given in the report, but dosages ranged from 800 to 1,500 rads over several day periods. This would usually be less than the 1,100 rets found by more recent data to be the effective threshold for the development of bone sarcomata. The low incidence of bone sarcoma in the spondylitis patients is in harmony with the hypotheses stated above. The other pertinent study is the induction of bone sarcomas by internally deposited radium-224. Repeated injections of radium-224 were given to about 2,000 German patients shortly after World War II with the intention to treat tuberculosis, ankylosing spondylitis, and other diseases. The well known effects of radium-226 in luminous dial workers are not comparable to the effects of therapeutic external beam irradiation since radium-226 radiation is delivered at a low dose rate for many years in areas of bone localization. In contrast, radium-224 which has a physical half-life of only 3.64 days delivers much more of this radiation to the osteoprogenitor cells on the bone surfaces in one to two weeks. While the quality of X-ray photons is very different from the alpha emission from radium-224, comparative biological effects may be useful. Latent periods range from 3.5 to 22 years in the radium-224 treated patients. Juveniles treated with radium-224 were only slightly more susceptible than adults. In these reports, the radiation dosages from radium-224 are given as the averages for whole bones. Doses to cells on bone surfaces are probably about ten times greater than the averages. Many of the reported dosages are very large, but of more importance is the fact that no tumors were seen in patients whose average bone dose was less than 90 rads corresponding to a surface dose of 900 rads. To date, the overall instances of bone sarcomata in the patients treated with radium-224 is 54 out of 897 patients or 6%. However, the incidence of bone sarcoma was six patients out of 470 patients or 1.3% when the span of repeated injections was less than five months, an estimated average surface dose range of 1,500 rads to 6,000 rads in five months.

Hatfield and Schulz estimated the risk of developing radiation induced bone sarcoma following radiation therapy for carcinoma of the breast to be about 0.2% of the patients surviving for ten years or more after therapy [20]. The risk would be doubled in 20 years. The long latent period, the difficulty of long

Table 6. Irradiation-induced sarcomas of bone reported since 1948

Authors	Year	Sarcomas of the Osteogenic Series[a]			
		Osteosarcoma	Chondrosarcoma	Fibrosarcoma	Other
Cahan et al. [4]	1948	10	1	–	–
Kaae and Glahn [25]	1949	–	–	1	–
Wolfe and Platt [52]	1949	2	–	–	–
Spitz and Higinbotham [47]	1951	1	–	–	–
De Young [15]	1952	1	–	–	–
Tebbet and Vickery [49]	1952	1	–	–	–
Jones [24]	1953	1	–	–	–
Skolnik et al. [44]	1956	2	–	–	–
Sabanas et al. [35]	1956	8	–	9	–
Carroll et al. [6]	1956	1	–	–	–
Cruz et al. [12]	1957	7	–	2	–
Cade [3]	1957	2	1	–	–
Raventos et al. [32]	1960	–	–	1	–
Bloch [2]	1962	1	–	–	–
Steiner [48]	1965	7	–	5	–
Soloway [45]	1966	5	1	–	–
Castro et al. [9]	1967	–	3	2	–
Schwartz and Rothstein [41]	1968	–	–	1	–
Sagerman et al. [37]	1969	5	–	–	–
Yoneama and Greenlaw [53]	1969	1	–	–	–
Senyszyn et al. [42]	1970	2	–	2	1
Hatfield and Schulz [20]	1970	5	1	3	–
Arlen et al. [1]	1971	25	2	1	–
Castleman et al. [7]	1972	–	–	–	1[b]
Castleman et al. [8]	1972	1	–	–	–
Sparagana et al. [46]	1972	1	–	–	–
Sim et al. [43]	1972	10	4	19	1
Fehr and Prem [17]	1973	3	1	–	–
Rushforth [34]	1974	1	–	–	–
Lee et al. [28]	1975	1	–	–	–
Fitzwater et al. [18]	1976	–	1	–	–
Totals		104	15	46	3
Percentage		61.9	8.9	27.4	1.8

[a] Following the classification of McKenna et al. [31]
[b] Reported as osteochondrosarcoma and cannot be classified further

term follow-up and possibly the failure to recognize and report sarcomas that occur in irradiated tissues, makes quantitative estimates of radiation carcinogenesis potential very difficult.

The criteria for the establishment of the diagnosis of radiation induced sarcoma have been outlined by Cahan and adapted for the purposes of this presentation (Table 8) [4]. With the changing contemporary management of malignant disease and with increasing numbers of patients being treated with combined radiation therapy and multiple drug chemotherapy, there may be an associated shortening of the period for cancer induction as well as an increase in the frequency of second malignant lesions or neoplasms. This has been reported by Canellos and Chabner [5, 10]. This is particularly apparent in patients with Hodgkin's disease where total nodal irradiation and intensive chemotherapy are often pursued.

Table 7. Radiation induced sarcomas of bone

	No. cases	Osteo-sarcoma	Chondro-sarcoma	Fibro-sarcoma	Other
Dates to 1945	28				
1945–1976	168	104	15	46	3
1976 Fitzwater et al. [18]	1		1		
1978 Kim et al. [26]	27	12			
Total	224				

The definitive diagnosis of radiation induced neoplasms of bone should be based on histologic proof. Careful examination of the original histologic material must be made to differentiate radiation induced

Table 8. Criteria for the diagnosis of radiation induced sarcomas of the bone

1. No microscopic or roentgenographic evidence of abnormalities in the bone at the time of the radiation therapy
2. Radiation applied in significant dosage to the field in which the sarcoma subsequently develops (threshold 1,100 rets)
3. A relatively long, symptom free, latent period (median 11 years)
4. Microscopic evidence of sarcoma
5. Exposure to carcinogens or co-carcinogens

sarcomas from recurrent or persistent sarcomas. Histologic comparison of the pretreatment lesion with the suspected radiation induced sarcoma is mandatory. Occasionally, the lesion (sarcoma) will be present originally when adequate and careful evaluation is done. This is illustrated by the broad histologic characteristics that are often associated with giant cell tumors of bone where areas of malignancy may be present initially, but missed on the initial histologic evaluation. If the lesion is present initially, these cases should not be included in studies of radiation induced bone sarcoma. Other clinical aspects of long latent periods and such late radiation stigmata as skin changes such as telangiectasia, atrophy, fibrosis, and discoloration should aid in the establishment of the diagnosis of the second malignant neoplasm.

In those individuals who develop radiation induced malignant lesions of bone in the extremities, careful evaluation of the patient should be carried out for evidences of dissemination. In the absence of distant dissemination, local aggressive therapy by surgical management can result in cure.

The incidence of radiation induced bone sarcomas is very low. The precise details relative to epidemiology cannot be identified at this point because of the difficulty of identifying precisely the patient population at risk for the development of the radiation induced sarcoma. However, the change in character of practice in cancer management with ever increasing numbers of patients receiving both radiation therapy and chemotherapy, should alert the physician to the potential for increased incidence for this rare and unusual tumor.

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