

Characteristics of Benign and Malignant Bone Tumors Registered in the Hiroshima Tumor Tissue Registry, 1973-2012

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Background: Reported information on the characteristics of benign bone tumors is disjointed, and the long-term trends in the occurrence of malignant bone tumors by histological type have not been reported in Japan. Our aim was to describe the characteristics of both benign and malignant bone tumors as described in cases registered in the Hiroshima Tumor Tissue Registry from 1973 to 2012.

Methods: Cases were identified with the International Classification of Diseases for Oncology (ICD-O-3) topography code C40-C41 (bones, joints, and articular cartilage), and histological types were classified according to the World Health Organization 2013 system. We described the distribution of the cases by behavior, sex, skeletal site of tumor occurrence, histological type, period at diagnosis (in 10-year groups), and age at diagnosis (in 10-year groups).

Results: We observed 2,542 benign bone tumors, 272 intermediate bone tumors, and 506 malignant bone tumors. We confirmed that 81.6% of benign bone tumors were chondrogenic, consisting primarily of osteochondromas and enchondromas. Giant cell tumor of bone was the most dominant type of intermediate tumor, whereas osteogenic tumors and chondrogenic tumors were the most dominant types of malignant tumors. Among malignant bone tumors, 41.7% of tumors occurred in the long bones of the lower limb, and there were different peaks of age at the time of diagnosis for osteogenic tumors and chondrogenic tumors. A similar distribution of histological types was seen throughout the 40-year observation period.

Conclusions: Osteochondroma and enchondroma differed in terms of the age of the patient at the time of diagnosis and the skeletal sites where the tumors most frequently occurred. Giant cell tumor had a large impact on occurrence as a common type of intermediate bone tumor.

Clinical Relevance: The results of the present study, based on pathological tissue registry data, provide knowledge about the epidemiological and pathological features of bone tumors in Japan.

Benign and malignant bone tumors are relatively rare. Benign bone tumors comprise a wide variety of different histological types¹, occur most frequently between the ages 5 and 25 years, and can occur in any part of the skeletal system². They usually do not affect life expectancy, but several histological types of intermediate bone tumors such as osteochondromatosis and giant cell tumor of bone have a risk of malignancy. The information on the characteristics of benign bone tumors that has been reported to date is disjointed, and a long-term trend of benign bone tumors by histological type has not been reported in Japan. The Swedish

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TABLE I Number of Bone Tumor Cases by Behavior and Histological Type as Recorded in Hiroshima Tumor Tissue Registry, 1973-2012* ►

Histological Group†	Benign		No. of Cases
	ICD-O-3-M	Morphology	
1. Chondrogenic tumors			
	9210/0	Osteochondroma	1,057
	9220/0	Chondroma, NOS; enchondroma; synovial chondromatosis	952
	9221/0	Periosteal chondroma	19
	9230/0	Chondroblastoma, NOS‡	23
	9241/0	Chondromyxoid fibroma	23
2. Osteogenic tumors			
	9180/0	Osteoma, NOS	254
	9191/0	Osteoid osteoma	83
	9200/0	Osteoblastoma	18
3. Fibrogenic tumors			
	8810/0	Fibroma, NOS	13
	8823/0	Desmoplastic fibroma	2
4. Fibrohistiocytic tumors			
	8830/0	Benign fibrous histiocytoma/non-ossifying fibroma (metaphyseal fibrous defect)	10
	8831/0	Histiocytoma, NOS	2
5. Hematopoietic tumors			
6. Osteoclastic giant cell rich tumors			
7. Notochordal tumors			
8. Vascular tumors			
	9120/0	Hemangioma, NOS	16
	9121/0	Cavernous hemangioma	14
	9122/0	Venous hemangioma	2
	9131/0	Capillary hemangioma	6
9. Myogenic tumors	8890/0	Leiomyoma of bone	1
10. Lipogenic tumors			
	8850/0	Lipoma of bone	11
	8861/0	Angiolipoma, NOS	1
11. Tumors of undefined neoplastic nature			
	8811/0	Fibromyxoma	2
	8840/0	Myxoma, NOS	1
	9262/0	Ossifying fibroma	28
12. Miscellaneous tumors			
	8711/0	Glomus tumor, NOS	1
	8800/0	Soft tissue tumor, benign	1
	8824/0	Myofibroma	1
	9530/0	Meningioma, NOS	1
13. Other rare tumors			
14. Unclassified tumors			
Total			2,542

*ICD-O-3-M = International Classification of Diseases for Oncology morphology code, NOS = not otherwise specified. †The histological group was based on the WHO 2013 classification. ‡Chondroblastoma is regarded as demonstrating intermediate behavior according to the WHO 2013 classification; however, it is included as a benign tumor here because its ICD-O-3 behavior code is 0.

TABLE I (continued)

Intermediate			Malignant		
ICD-O-3-M	Morphology	No. of Cases	ICD-O-3-M	Morphology	No. of Cases
9210/1	Osteochondromatosis, NOS	40	9220/3	Chondrosarcoma, NOS; Conventional chondrosarcoma (grade 2, grade 3); Secondary chondrosarcoma	124
9220/1	Multiple chondromatosis	3	9221/3	Periosteal chondrosarcoma (juxtacortical chondrosarcoma)	1
			9231/3	Myxoid chondrosarcoma	3
			9243/3	Dedifferentiated chondrosarcoma	2
			9240/3	Mesenchymal chondrosarcoma	4
			9242/3	Clear cell chondrosarcoma	1
9200/1	Aggressive osteoblastoma	1	9180/3	Osteosarcoma	176
				Osteoblastic osteosarcoma	
			9181/3	Chondroblastic osteosarcoma	7
			9182/3	Fibroblastic osteosarcoma	4
			9183/3	Telangiectatic osteosarcoma	6
			9185/3	Small cell osteosarcoma (round-cell osteosarcoma)	1
			9192/3	Parosteal osteosarcoma	7
8821/1	Aggressive fibromatosis	1	8810/3	Fibrosarcoma	4
8823/1	Desmoplastic fibroma of bone	7	8830/3	Malignant fibrous histiocytoma	33
8830/1	Atypical fibrous histiocytoma	3			
9250/1	Giant cell tumor of bone	212	9250/3	Malignancy in giant cell tumor of bone	14
			9370/3	Chordoma	43
			9371/3	Chondroid chordoma	4
9130/1	Hemangioperithelioma, NOS	2	9120/3	Angiosarcoma	7
9133/1	Epithelioid hemangioperithelioma, NOS	1	9130/3	Hemangioperithelioma, malignant	1
9136/1	Spindle cell hemangioperithelioma	1			
			8890/3	Leiomyosarcoma of bone	4
			9040/3	Synovial sarcoma, NOS	7
			9041/3	Synovial sarcoma, spindle cell	1
			9043/3	Synovial sarcoma, biphasic	1
9150/1	Hemangiopericytoma, NOS	1	8800/3	Sarcoma, NOS	21
			8801/3	Spindle cell sarcoma	1
			9260/3	Ewing sarcoma	25
			9261/3	Adamantinoma of long bones	4
		272			506

Cancer Registry reported a longitudinal incidence rate of giant cell tumor³. Conversely, the characteristics of malignant bone tumors are well known^{4,6}. Such tumors occur frequently in teenagers and constitute 3% to 4% of childhood cancer in Hiroshima and all of Japan^{7,8}. Recently, an increased proportion of elderly patients with osteosarcoma has been reported in Japan⁶.

The goal of the present study was to describe the characteristics of bone tumors according to behavior and histological type on the basis of surgical resection and biopsy procedures that were registered in the Hiroshima Tumor Tissue Registry from 1973 to 2012.

Materials and Methods

The Hiroshima Tumor Tissue Registry is a population-based pathological tissue registry that was initiated in 1973 by the Hiroshima Prefecture Medical Association with the cooperation of the Radiation Effects Research Foundation. It encompasses the entire Hiroshima Prefecture (population in 2012, 2.86 million, representing 2.6% of the Japanese population) in Japan. Pathologists voluntarily report the pathological diagnosis of all tumors and provide sample slides of resected malignant tumors, including biopsy specimens. When there are

multiple tumor records for the same patient, such as biopsy and surgery records, the pathologist panels decide whether the records are reports of the same primary tumor or of multiple primary tumors by examining pathological reports or by performing a histological examination, if necessary. All tumors are coded with use of the first, second, or third revision of the International Classification of Diseases for Oncology (ICD-O). The Hiroshima Tumor Tissue Registry has provided all data on malignant tumors to the Hiroshima Prefecture Cancer Registry, which is a population-based cancer registry, and the Hiroshima Tumor Tissue Registry has contributed to improving the Hiroshima Prefecture Cancer Registry data quality since its inception in 2002. Details have been described elsewhere⁹.

The subjects in the present study were patients who were diagnosed with primary bone tumors of all types that were registered in the Hiroshima Tumor Tissue Registry from 1973 to 2012. Cases were identified with the ICD-O-3 topography code C40-C41 (bones, joints, and articular cartilage) and were assigned as bone tumors according to the World Health Organization (WHO) 2013 classification system¹⁰. Hematopoietic tumors, including malignant lymphoma, were excluded. Histological types were classified according to the WHO 2013

TABLE II Number of Bone Tumor Cases by Behavior, Sex, and Skeletal Site as Recorded in Hiroshima Tumor Tissue Registry, 1973-2012*

Skeletal Sites (ICD-O-3-T)	Benign			Intermediate			Malignant		
	Male	Female	Total	Male	Female	Total	Male	Female	Total
C40.0: Long bones of upper limb, scapula	98 (7.8%)	66 (5.1%)	164 (6.5%)	13 (8.9%)	10 (7.9%)	23 (8.5%)	22 (7.7%)	16 (7.3%)	38 (7.5%)
C40.1: Short bones of upper limb	387 (30.7%)	473 (36.9%)	860 (33.8%)	3 (2.1%)	10 (7.9%)	13 (4.8%)	2 (0.7%)	3 (1.4%)	5 (1.0%)
C40.2: Long bones of lower limb	369 (29.3%)	312 (24.3%)	681 (26.8%)	95 (65.1%)	69 (54.8%)	164 (60.3%)	126 (43.9%)	85 (38.8%)	211 (41.7%)
C40.3: Short bones of lower limb	192 (15.3%)	171 (13.3%)	363 (14.3%)	8 (5.5%)	7 (5.6%)	15 (5.5%)	5 (1.7%)	4 (1.8%)	9 (1.8%)
C40.9: Bone of limb, NOS*	6 (0.5%)	6 (0.5%)	12 (0.5%)	1 (0.7%)	2 (1.6%)	3 (1.1%)	1 (0.3%)	1 (0.5%)	2 (0.4%)
C41.0: Bones of skull and face	84 (6.7%)	137 (10.7%)	221 (8.7%)	2 (1.4%)	3 (2.4%)	5 (1.8%)	29 (10.1%)	25 (11.4%)	54 (10.7%)
C41.1: Mandible	19 (1.5%)	54 (4.2%)	73 (2.9%)	0 (0%)	2 (1.6%)	2 (0.7%)	12 (4.2%)	15 (6.8%)	27 (5.3%)
C41.2: Vertebral column	29 (2.3%)	21 (1.6%)	50 (2.0%)	4 (2.7%)	5 (4.0%)	9 (3.3%)	18 (6.3%)	14 (6.4%)	32 (6.3%)
C41.3: Rib, sternum, and clavicle	39 (3.1%)	29 (2.3%)	68 (2.7%)	3 (2.1%)	6 (4.8%)	9 (3.3%)	17 (5.9%)	22 (10.0%)	39 (7.7%)
C41.4: Pelvic bones, sacrum, and coccyx	29 (2.3%)	11 (0.9%)	40 (1.6%)	7 (4.8%)	10 (7.9%)	17 (6.3%)	48 (16.7%)	34 (15.5%)	82 (16.2%)
C41.9: Bone, NOS	7 (0.6%)	3 (0.2%)	10 (0.4%)	10 (6.8%)	2 (1.6%)	12 (4.4%)	7 (2.4%)	0 (0%)	7 (1.4%)
Total	1,259 (100%)	1,283 (100%)	2,542 (100%)	146 (100%)	126 (100%)	272 (100%)	287 (100%)	219 (100%)	506 (100%)

*All skeletal sites include associated joints except for "mandible" and "vertebral column." The values are given as the number of tumors, with the percentage in parentheses. ICD-O-3-T = International Classification of Diseases for Oncology topography code, and NOS = not otherwise specified.

system¹⁰ (Table I). When there was uncertainty about whether the behavior was benign or malignant (ICD-O-3 behavior code, 1), as in cases of osteochondromatosis and giant cell tumor, the tumor was classified as intermediate according to the WHO 2013 system. Malignant fibrous histiocytoma has been classified as a miscellaneous tumor since 2013; however, we classified it as a fibrohistiocytic tumor in the present study. We described the number, registration rate (per million population, standardized by age-class of the Segi's World Standard Population), and proportion of bone tumor cases by behavior, sex, skeletal site of tumor occurrence, histological type, period at diagnosis (in 10-year groups), and age of diagnosis (in 10-year groups). Bone tumor skeletal sites were classified according to the ICD-O-3 topography code. The present study was approved by the Data Usage Committee of the Hiroshima Tumor Tissue Registry.

Results

Benign Bone Tumors

We observed 2,542 benign bone tumors over a period of 40 years. Most benign tumors occurred in 3 sites, such as short bones of the upper limb (33.8%), long bones of the lower limb (26.8%), and short bones of the lower limb (14.3%) (Table II). The registration rates for benign bone tumors at the first period were 18.4 for males and 14.8 for females; thereafter, the rates increased and became stable around 28 for males and around 26 for females (Table III).

Among the benign tumors, the most common histological type was chondrogenic tumors (2,074; 81.6%) and the distribution of histological types was uniform and similar for both sexes for the entire observation period (Table III). A primary peak for benign chondrogenic tumors occurred in patients 10 to 19 years of age and then rapidly decreased. Thereafter, the number of patients >20 years of age gradually decreased among men, whereas a secondary peak in patients 30 to 49 years of age was observed in women (Fig. 1).

Among benign chondrogenic tumors, there were 1,057 osteochondromas (51.0%, ICD-O-3-M (morphology code)/behavior: 9210/0) and 952 enchondromas (45.9%, ICD-O-3-M/behavior: 9220/0). The number of osteochondromas peaked in teenagers for both sexes, whereas the number of enchondromas peaked in patients 30 to 49 years of age for both sexes (Fig. 2). Therefore, a secondary peak of benign chondrogenic tumors in patients 30 to 49 years of age among women was due to the peak of enchondroma. The peak of enchondroma in patients 30 to 49 years of age among women was enhanced compared with men, because the peak of osteochondroma in teenagers among females was relatively lower than that among males. Regarding the skeletal sites, osteochondromas occurred frequently in the lower limbs (long bones, 46.7%; short bones, 19.1%), whereas enchondromas occurred frequently in the short bones of the upper limbs (70.8%) (Fig. 3). Tumor distributions by skeletal site for osteochondroma and enchondroma were similar for both sexes.

Benign osteogenic tumors were the second most common benign tumor (355; 14.0%) (Table III) and occurred in the skull and face (48.5%) as well as mandible (14.9%) (Fig. 3). The number of patients with osteogenic tumors peaked at 10 to 19

years of age for both males and females, with an apparent secondary peak at 50 to 59 years of age among women (Fig. 1).

Intermediate Bone Tumors

We observed 272 intermediate bone tumors, including 212 giant cell tumors (77.9%) and 43 chondrogenic tumors (osteochondromatosis) (15.8%). The registration rates for intermediate bone tumors were 2.9 for males and 2.3 for females and remained stable over the observation periods (Table III). A primary peak of giant cell tumor was seen in patients 20 to 29 years of age, whereas a secondary peak was observed in patients 50 to 59 years of age (Fig. 1). Among the giant cell tumors, 64.6% of cases occurred in the long bones of the lower limb (Fig. 3).

Malignant Bone Tumors

We observed 506 malignant bone tumors over a period of 40 years. The registration rates from the first to the fourth decade were 3.5, 5.6, 4.6, and 5.5 for males and 3.0, 3.1, 3.2, and 4.8 for females, respectively (Table III). Malignant bone tumors occurred in the long bones of the lower limb (41.7%); in the pelvis, sacrum, and coccyx (16.2%); in the skull and face (10.7%); and in the rib, sternum, and clavicle (7.7%) (Table II). The numbers of malignant bone tumors were 287 for males and 219 for females, and the male:female ratio was 1.31:1. A primary peak in malignant bone tumors occurred in patients 10 to 19 years of age and then rapidly decreased. A plateau was observed in patients 20 to 50 years of age, with a secondary peak observed for patients 60 to 69 years of age and a decline observed in elderly individuals.

Tumor distributions by age were similar for both sexes. Among malignant bone tumors, the most frequent tumor types were osteogenic tumors (201; 39.7%) and chondrogenic tumors (135; 26.7%) (Table III). These 2 major histological groups covered approximately two-thirds of all malignant bone tumors. There was only a peak in teens for malignant osteogenic tumors, which occurred in the long bones of the lower limb (58.7%) (Figs. 1 and 3). There was a primary peak in teenagers and a secondary peak in middle-aged patients for malignant chondrogenic tumors, which were distributed in the long bones of lower limb (25.9%); in the bones of the trunk of the body such as the rib, sternum, and clavicle (20.0%); and around the pelvis (20.0%) (Figs. 1 and 3).

Time trends of the number of cases and registration rates were stable for entire period, particularly for female patients (Table III). However, in the last decade, the number of malignant cases increased because of an increase in the number of notochordal tumors in subjects aged 50 to 79 years.

Among the 51 miscellaneous tumors, 25 Ewing sarcomas were observed (14 in males and 11 in females) (Table I). Most cases of Ewing sarcoma occurred in children and adolescents (including 2 in patients 0 to 9 years of age and 13 in patients 10 to 19 years of age), and the other 10 cases occurred in patients 20 to 39 years of age.

Discussion

We presented the statistics—by sex, skeletal site, and histological type—on bone tumors of all behavior types

TABLE III Number and Registration Rates of Bone Tumors by Behavior, Histological Type, Sex, and Period at Diagnosis as Recorded in the Hiroshima Tumor Tissue Registry, 1973-2012*

Behavior and Histological Type	Male									
	1973-1982		1983-1992		1993-2002		2003-2012		1973-2012	
	No. of Tumors	Rate	No. of Tumors	Rate	No. of Tumors	Rate	No. of Tumors	Rate	No. of Tumors	Rate
Benign										
1. Chondrogenic tumors	198 (85.0%)	15.7	323 (86.6%)	24.4	283 (82.7%)	24.1	252 (81.0%)	24.0	1,056 (83.9%)	21.7
2. Osteogenic tumors	24 (10.3%)	1.9	38 (10.2%)	2.7	46 (13.5%)	3.4	44 (14.1%)	3.9	152 (12.1%)	3.0
3. Fibrogenic tumors	1 (0.4%)	0.1	3 (0.8%)	0.2	4 (1.2%)	0.4	1 (0.3%)	0.1	9 (0.7%)	0.2
4. Fibrohistiocytic tumors	1 (0.4%)	0.1	1 (0.3%)	0.1					2 (0.2%)	0.0
8. Vascular tumors	5 (2.1%)	0.3	3 (0.8%)	0.2	4 (1.2%)	0.2	7 (2.3%)	0.4	19 (1.5%)	0.3
9. Myogenic tumors							1 (0.3%)	0.2	1 (0.1%)	0.0
10. Lipogenic tumors	1 (0.4%)	0.1	1 (0.3%)	0.1	2 (0.6%)	0.1	1 (0.3%)	0.1	5 (0.4%)	0.1
11. Tumors of undefined neoplastic nature	3 (1.3%)	0.2	4 (1.1%)	0.3	1 (0.3%)	0.1	3 (1.0%)	0.2	11 (0.9%)	0.2
12. Miscellaneous tumors					2 (0.6%)	0.1	2 (0.6%)	0.2	4 (0.3%)	0.1
Subtotal	233 (100%)	18.4	373 (100%)	27.9	342 (100%)	28.5	311 (100%)	29.1	1,259 (100%)	25.6
Intermediate										
1. Chondrogenic tumors	1 (2.6%)	0.1	5 (20.0%)	0.5	13 (33.3%)	1.4	5 (11.4%)	0.6	24 (16.4%)	0.6
2. Osteogenic tumors							1 (2.3%)	0.0	1 (0.7%)	0.0
3. Fibrogenic tumors					1 (2.6%)	0.1			1 (0.7%)	0.0
4. Fibrohistiocytic tumors	1 (2.6%)	0.1	3 (12.0%)	0.2	1 (2.6%)	0.0			5 (3.4%)	0.1
6. Osteoclastic giant cell rich tumors	35 (92.1%)	2.7	17 (68.0%)	1.3	22 (56.4%)	1.5	38 (86.4%)	2.8	112 (76.7%)	2.1
8. Vascular tumors					2 (5.1%)	0.2			2 (1.4%)	0.0
12. Miscellaneous tumors	1 (2.6%)	0.1							1 (0.7%)	0.0
Subtotal	38 (100%)	2.9	25 (100%)	1.9	39 (100%)	3.3	44 (100%)	3.5	146 (100%)	2.9
Malignant										
1. Chondrogenic tumors	6 (13.3%)	0.4	27 (31.8%)	1.6	17 (23.3%)	0.9	22 (26.2%)	1.0	72 (25.1%)	1.1
2. Osteogenic tumors	23 (51.1%)	1.9	33 (38.8%)	2.5	31 (42.5%)	2.3	27 (32.1%)	2.5	114 (39.7%)	2.3
3. Fibrogenic tumors			1 (1.2%)	0.1	1 (1.4%)	0.0			2 (0.7%)	0.0
4. Fibrohistiocytic tumors	2 (4.4%)	0.2	2 (2.4%)	0.1	12 (16.4%)	0.6	7 (8.3%)	0.2	23 (8.0%)	0.3
6. Osteoclastic giant cell rich tumors	2 (4.4%)	0.1	6 (7.1%)	0.4					8 (2.8%)	0.1
7. Notochordal tumors	4 (8.9%)	0.3	7 (8.2%)	0.4	5 (6.8%)	0.2	14 (16.7%)	0.5	30 (10.5%)	0.3
8. Vascular tumors			3 (3.5%)	0.1			1 (1.2%)	0.0	4 (1.4%)	0.0
9. Myogenic tumors					1 (1.4%)	0.1			1 (0.3%)	0.0
11. Tumors of undefined neoplastic nature	3 (6.7%)	0.2	2 (2.4%)	0.1					5 (1.7%)	0.1
12. Miscellaneous tumors	5 (11.1%)	0.4	4 (4.7%)	0.3	6 (8.2%)	0.4	13 (15.5%)	1.2	28 (9.8%)	0.5
Subtotal	45 (100%)	3.5	85 (100%)	5.6	73 (100%)	4.6	84 (100%)	5.5	287 (100%)	4.9
Total	316		483		454		439		1,692	

*The values in the "Rate" columns indicate the age-standardized registration rate per million population according to the Segi's World Standard Population. Patients whose age was unknown were excluded.

that were diagnosed between 1973 and 2012. We confirmed that 81.6% of benign bone tumors were chondrogenic tumors, primarily consisting of osteochondromas and enchondromas. The most dominant types of malignant tumors were osteogenic tumors and chondrogenic tumors. Approximately 40% of the malignant bone tumors occurred in the long bones of the lower limb, with different age peaks at the time of diagnosis for each major histological type. A similar distribution of histological types was seen during the 40-year observation period. We observed only 25 cases of Ewing sarcoma over 40 years.

Few cancer registries routinely collect data on both benign and malignant tumors. The Bone and Soft Tissue Tumor (BSTT) Registry in Japan, which is a nationwide and organ-specific

registry, collects data on both benign and malignant bone tumors⁶. A recent report from that registry¹¹ demonstrated that 8,979 benign bone tumors were registered between 2006 and 2013. With the exclusion of lesions that were not recognized as benign bone tumors in the present study (i.e., giant cell tumors [1,187], neurilemmomas [51], neurofibromas [2], and tumors of an unknown histological type [150]), the number of benign bone tumors decreased to 7,589. Of those, the most dominant type was chondrogenic tumors (80.4%; 6,100 of 7,589) and the second most common type was osteogenic tumors (10.1%; 768 of 7,589). The distribution of histological types among benign tumor cases reported by the BSTT Registry was consistent with the benign tumors in the present study. The BSTT Registry also

TABLE III (continued)

1973-1982		1983-1992		1993-2002		2003-2012		1973-2012		Total
No. of Tumors	Rate	No. of Tumors	Rate	No. of Tumors	Rate	No. of Tumors	Rate	No. of Tumors	Rate	No. of Tumors
159 (81.1%)	12.2	295 (81.9%)	20.8	298 (78.4%)	22.3	266 (76.7%)	21.4	1,018 (79.3%)	19.1	2,074 (81.6%)
24 (12.2%)	1.7	45 (12.5%)	2.9	64 (16.8%)	3.5	70 (20.2%)	4.2	203 (15.8%)	3.1	355 (14.0%)
1 (0.5%)	0.1	1 (0.3%)	0.1	2 (0.5%)	0.1	2 (0.6%)	0.1	6 (0.5%)	0.1	15 (0.6%)
2 (1.0%)	0.2	4 (1.1%)	0.3	3 (0.8%)	0.2	1 (0.3%)	0.0	10 (0.8%)	0.2	12 (0.5%)
3 (1.5%)	0.2	7 (1.9%)	0.4	4 (1.1%)	0.2	5 (1.4%)	0.2	19 (1.5%)	0.3	38 (1.5%)
										1 (0.0%)
1 (0.5%)	0.1	1 (0.3%)	0.1	4 (1.1%)	0.2	1 (0.3%)	0.0	7 (0.5%)	0.1	12 (0.5%)
6 (3.1%)	0.4	7 (1.9%)	0.6	5 (1.3%)	0.3	2 (0.6%)	0.1	20 (1.6%)	0.4	31 (1.2%)
										4 (0.2%)
196 (100%)	14.8	360 (100%)	25.1	380 (100%)	26.9	347 (100%)	26.2	1,283 (100%)	23.3	2,542 (100%)
		4 (16.0%)	0.3	10 (27.8%)	0.9	5 (14.7%)	0.5	19 (15.1%)	0.4	43 (15.8%)
										1 (0.4%)
										1 (0.4%)
		4 (16.0%)	0.3	1 (2.8%)	0.1			5 (4.0%)	0.1	10 (3.7%)
31 (100%)	2.2	17 (68.0%)	1.1	24 (66.7%)	1.7	28 (82.4%)	2.1	100 (79.4%)	1.8	212 (77.9%)
				1 (2.8%)	0.1	1 (2.9%)	0.1	2 (1.6%)	0.0	4 (1.5%)
										1 (0.4%)
31 (100%)	2.2	25 (100%)	1.7	36 (100%)	2.7	34 (100%)	2.7	126 (100%)	2.3	272 (100%)
16 (36.4%)	1.1	16 (34.0%)	0.9	13 (25.0%)	0.6	18 (23.7%)	0.9	63 (28.8%)	0.9	135 (26.7%)
13 (29.5%)	0.9	20 (42.6%)	1.4	26 (50.0%)	1.8	28 (36.8%)	2.6	87 (39.7%)	1.6	201 (39.7%)
1 (2.3%)	0.1					1 (1.3%)	0.0	2 (0.9%)	0.0	4 (0.8%)
2 (4.5%)	0.1			2 (3.8%)	0.1	6 (7.9%)	0.3	10 (4.6%)	0.1	33 (6.5%)
2 (4.5%)	0.1	4 (8.5%)	0.2					6 (2.7%)	0.1	14 (2.8%)
				1 (1.9%)	0.0	13 (17.1%)	0.7	17 (7.8%)	0.2	47 (9.3%)
				2 (3.8%)	0.1	2 (2.6%)	0.1	4 (1.8%)	0.0	8 (1.6%)
						3 (3.9%)	0.1	3 (1.4%)	0.0	4 (0.8%)
2 (4.5%)	0.1			2 (3.8%)	0.1			4 (1.8%)	0.1	9 (1.8%)
5 (11.4%)	0.4	7 (14.9%)	0.6	6 (11.5%)	0.5	5 (6.6%)	0.2	23 (10.5%)	0.4	51 (10.1%)
44 (100%)	3.0	47 (100%)	3.1	52 (100%)	3.2	76 (100%)	4.8	219 (100%)	3.5	506 (100%)
271		432		468		457		1,628		3,320

showed that a primary peak of osteochondroma occurred in teenagers and that a primary peak of enchondroma occurred among men 30 to 34 years of age and among women 35 to 44 years of age¹¹. The age distributions of osteochondroma and enchondroma were in accordance with our results.

The Swedish Cancer Registry, the Bone Tumor Registry of Western Australia, and the BSTT Registry collect information on giant cell tumor, which is recognized as an intermediate tumor. Liede et al. reported that the giant cell tumor-to-osteosarcoma ratio, based on the data from the BSTT registry in Japan as well as the registries of Sweden and Mexico, ranged from 0.49 to 0.79¹². The giant cell tumor-to-osteosarcoma ratio from the Hiroshima Tumor Tissue Registry was 1.05, which was slightly higher than that reported in other registries.

Osteochondromatosis has a risk of malignant transformation into secondary chondrosarcoma, particularly in cases with multiple exostoses¹³. We observed 43 cases of osteochondromatosis, which has been reported to have a probability of malignant transformation of 1% to 5% among all primary osteochondromas^{14,15}. As the patients with osteochondromatosis in the Hiroshima Tumor Tissue Registry had had tissue resected during biopsy or surgery, we carefully reviewed their data individually to determine whether there were any cases in which osteochondromatosis had transformed into malignant chondrosarcoma, but we did not find any cases of malignant transformation. We will continue to consider the possibility of malignant transformation among patients with osteochondromatosis who are registered in the Hiroshima Tumor Tissue Registry.

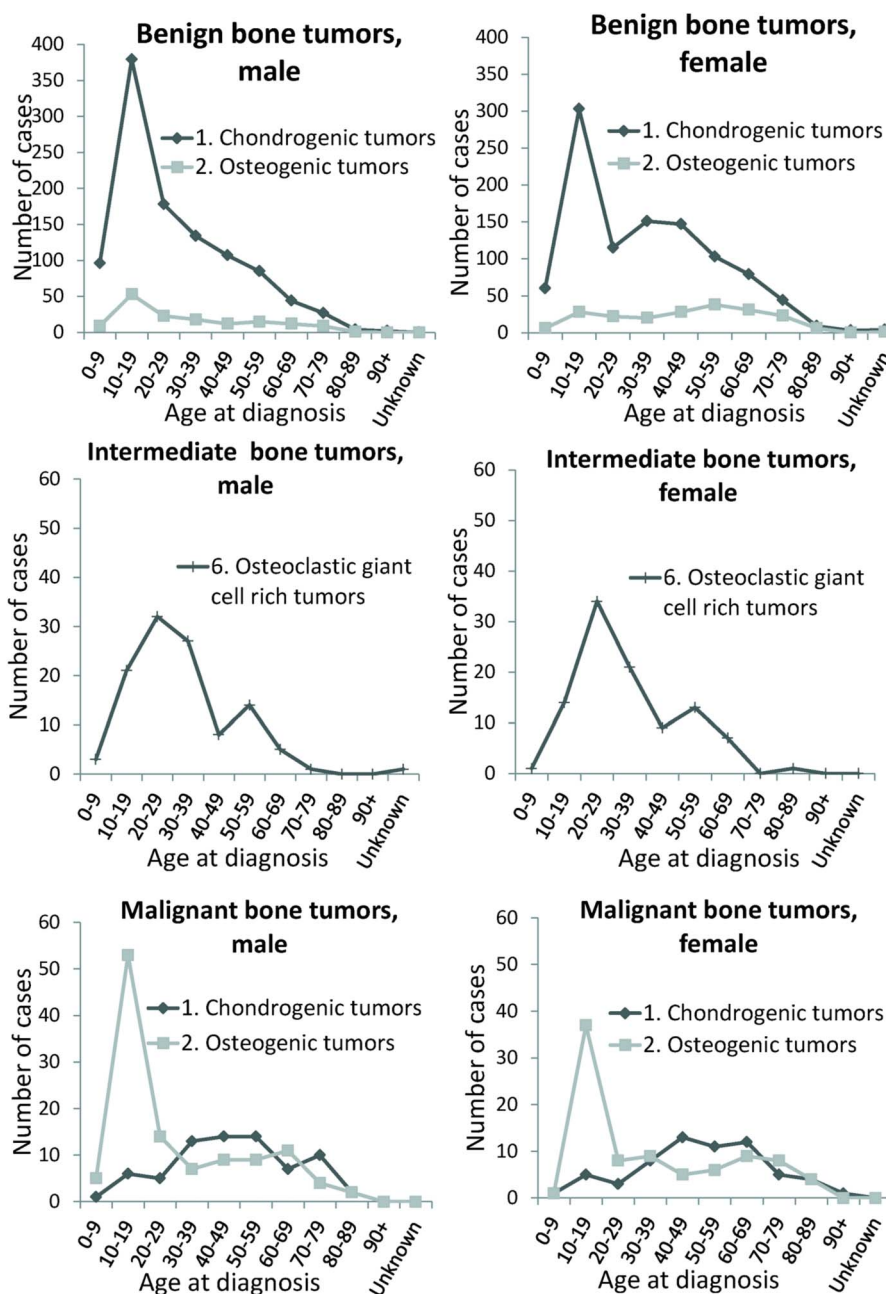


Fig. 1 Line graphs illustrating the age distribution for major histological groups of bone tumors by sex and behavior as recorded in the Hiroshima Tumor Tissue Registry between 1973 and 2012.

A peak in the incidence of osteosarcoma has been observed in elderly Caucasian individuals as a result of the relatively high prevalence of osteosarcoma in patients with Paget disease⁴. In addition, Ogura et al., in a report from the BSTT Registry, reported an increasing proportion of osteosarcoma cases among the elderly in Japan⁶. However, we found neither a peak of osteosarcoma in the elderly nor any case of osteosarcoma with Paget disease. These findings are attributed to the lower prevalence of osteosarcoma with Paget disease.

Hashimoto et al.¹⁶, on the basis of a mail survey, reported that the prevalence of Paget disease was 2.8 per million in Japan during the period between 1990 and 2002. This prevalence was extremely low when compared with the prevalence of 0.1% to 5% among individuals in high-prevalence countries¹⁷. Furthermore, Hashimoto et al. reported that half of the cases in their report were not confirmed by histological diagnosis¹⁶. Therefore, osteosarcoma in patients with Paget disease may not have been registered in the Hiroshima Tumor Tissue Registry.

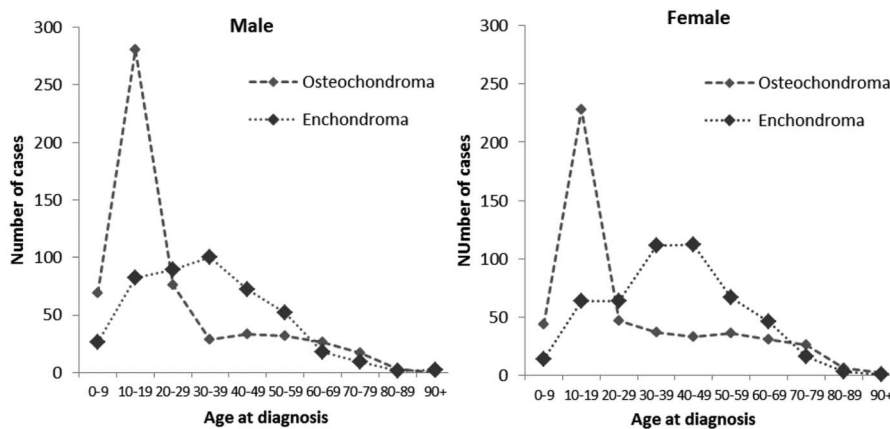


Fig. 2 Line graphs illustrating the age distribution for osteochondroma and enchondroma in patients with benign chondrogenic tumors as recorded in the Hiroshima Tumor Tissue Registry between 1973 and 2012.

We found that giant cell tumor represented a considerable proportion of bone tumors. Giant cell tumors primarily appeared in the long bones of the lower limb in patients 10 to

40 years of age. Giant cell tumor previously was considered to be benign, but recurrence after excision has been reported in 20% to 50% of patients, with 10% of cases becoming

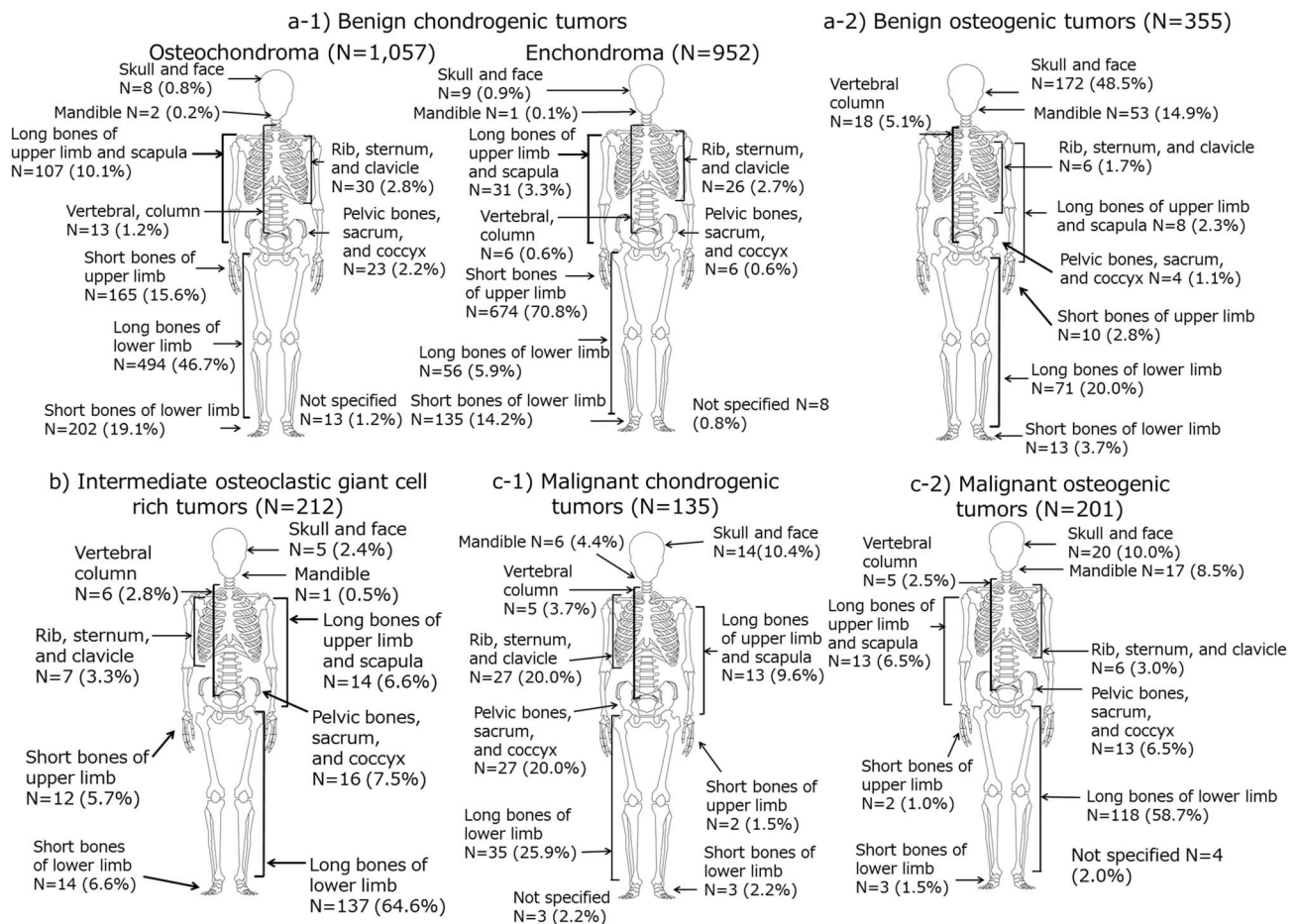


Fig. 3 Diagrams illustrating the skeletal site distribution for bone tumors by behavior and histological group as recorded in the Hiroshima Tumor Tissue Registry between 1973 and 2012.

malignant upon recurrence^{18,19}. Histologically benign giant cell tumor rarely occurs in cases of lung metastases²⁰. Therefore, giant cell tumor has been classified as intermediate since the latest WHO 2013 classification¹⁰. Although the first choice of treatment is curettage followed by filling with bone cement^{21,22} and additional treatment with adjuvants, the rate of recurrence is still high^{1,18}. Chemotherapy with denosumab, a monoclonal antibody that inhibits the osteoclastic activity of giant cell tumor, recently has emerged as another choice of treatment²¹. Active treatments are necessary in cases of giant cell tumor because of the risk of recurrence and malignant metastasis; however, the safety of long-term denosumab use has not yet been reported²³, although it was approved for use in giant cell tumor treatment in Japan in May 2014²⁴. We will continue to carefully observe the cases of giant cell tumor and the associated characteristics.

The present study had several limitations. First, our data were based on patients with tumors that had been resected during surgery or biopsy and registered in the Hiroshima Tumor Tissue Registry. Patients who did not undergo therapeutic or diagnostic resection were not registered in the database. According to *Cancer Incidence in Five Continents*, the incidence of malignant bone tumors in Hiroshima City from 1978 to 1999 and the rate in Hiroshima Prefecture per 100,000 population in the period 2003 to 2007 were reported to be 0.5 to 0.8 for males and 0.4 to 0.6 for females^{9,25-29}; in comparison, the registration rates per 100,000 population for malignant bone tumor in the Hiroshima Tumor Tissue Registry were 0.35 to 0.56 for males and 0.30 to 0.48 for females. Second, we observed 2,542 benign bone tumors over a period of 40 years; however, this number is most likely an underestimation because the majority of benign bone tumors are asymptomatic³⁰ and are not usually detected or resected for diagnosis. Conventional radiology such as radiographs, computed tomography, and magnetic resonance imaging are used to diagnose chondroid tumors¹. Among the benign bone tumors registered in the Hiroshima Tumor Tissue Registry and diagnosed after 1993, 95.6% were in patients who underwent surgery.

The Hiroshima Tumor Tissue Registry is a population-based tumor tissue registry that collects information on all tumors that are diagnosed pathologically in hospitals and clinical laboratories in Hiroshima Prefecture. In 2012, 88 institutions, including all designated cancer care hospitals, hospitals, clinics, and clinical laboratories, reported their tumor diagnoses to the Hiroshima Tumor Tissue Registry. Of the cancer cases registered in the Hiroshima Prefecture Cancer Registry, which is a regional cancer registry, 75% of the cases were also covered by the Hiroshima Tumor Tissue Registry³¹. Moreover, at the time of registration, all patients reported by local pathologists to the Hiroshima Tumor Tissue Registry are confirmed to not already be registered in the database with use of personal identifying information such as name, date of birth, address, etc. Therefore, there is no duplication of patients, even if the tumor information is reported by different hospitals (e.g., following biopsy and surgical diagnosis). The diagnoses associated with all tumors

registered in the Hiroshima Tumor Tissue Registry are confirmed histologically. If a patient with a benign bone tumor needed medical treatment, the diagnosis should be confirmed pathologically and the tumor information is registered in the Hiroshima Tumor Tissue Registry. Despite these limitations, we believe that the information on all benign, intermediate, and malignant bone tumors in the present study is valuable, and we have been able to show the variation of histological type and age distribution of bone tumors by behavior in Hiroshima Prefecture.

This report described characteristics of benign, intermediate, and malignant bone tumors with regard to frequency of cases, registration rate, age distribution, and skeletal site by pathological type. There were differences between osteochondroma and enchondroma in terms of the number of patients and skeletal sites where the tumor most frequently occurred, although both tumor types were originated from chondrogenic tumors. Giant cell tumor has a high frequency and was the most dominant type of intermediate bone tumor. These findings shed light on the epidemiological and pathological features of bone tumors. ■

NOTE: All authors are members of the Hiroshima Tumor Tissue Registry Working Committee. This study was administrated by the Committee. The tabulated numbers in this paper were based on the annual report of Hiroshima Tumor Tissue Registry No. 41, published in March 2017. The authors thank all pathologists who cooperated and submitted the pathological information and specimens to the Hiroshima Tumor Tissue Registry. They also thank the staff of the Hiroshima Prefecture Medical Association, the staff of the Tumor and Tissue Registry Office, the Radiation Effects Research Foundation, and Ms. Mikiko Hayashi for their help with data collection and analysis. The Radiation Effects Research Foundation, Hiroshima and Nagasaki, Japan, is a public interest incorporated foundation funded by the Japanese Ministry of Health, Labour and Welfare (MHLW) and the U.S. Department of Energy (DOE). This publication was supported by Radiation Effects Research Foundation Research Protocol 18-61. The views of the authors do not necessarily reflect those of the 2 governments.

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