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Skeletal Radiology

Primary leiomyosarcoma of bone

A clinical, radiographic, pathologic-anatomic, and prognostic study of 16 cases

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Abstract. Sixteen cases of primary leiomyosarcoma of bone are described. The patients, 11 males and 5 females, ranged in age from 9 to 74 years. The annual incidence of this tumor in Sweden was calculated to be 0.09 cases per million. This figure was obtained by reviewing a Swedish series of spindle cell sarcomas of bone of which one quarter (11/44) were diagnosed by us as primary leiomyosarcoma. The diagnosis was based on light- and electron-microscopic examinations using the same criteria as for leiomyosarcoma of soft tissues. Thirteen tumors were located in a long bone of an extremity (nine close to the knee joint) and three in the central skeleton. Radiographically, all the tumors presented as a purely osteolytic lesion, and three patients had sustained a pathologic fracture. In four of six cases angiography suggested malignancy by revealing hypervascularity, irregular tortuous vessels, and diffuse contrast opacification. Contrast-enhanced computed tomography, performed in two cases, showed hypervascular areas within the tumors. Scintigraphy showed a marked increase in radionuclide uptake in all five cases studied. The clinical behavior indicates that primary leiomyosarcoma of bone is highly malignant. Eight patients had died of the tumor and, of the eight patients who were alive at follow-up, two had metastases, and one had been operated on three times for a cutaneous metastasis, which had recurred locally twice. The remaining five patients had been continuously free of disease for 6.5 to 12.3 years.

Key words: Bone neoplasms – Leiomyosarcoma

Fibrosarcoma has been used indiscriminately as a term in the diagnosis of spindle cell sarcoma of bone. During the last two decades, however, malignant fibrous histiocytoma and leiomyosarcoma have been described and defined as separate entities among spindle cell sarcomas of bone. Until 1985 only 25 cases of primary leiomyosarcoma of bone had been reported in the literature. Sixteen of the tumors were located in the long bones of the extremities [4, 17, 20, 27, 31, 35, 41, 43, 46, 54, 55] and nine in the jaw bones [1, 10, 14, 29, 33, 37, 39, 52]. In 1980 we published a series of five patients with primary leiomyosarcoma of bone, all located in the long bones of the extremities [4]. The smooth muscle differentiation of the tumor cells was documented by light- and electron-microscopic studies using the same criteria for the diagnosis as for leiomyosarcoma of the soft tissues. Radiographically leiomyosarcoma of bone has been described as an osteolytic lesion. The angiographic appearance is little known [4], as is knowledge of the prognosis.

We report a series of 16 cases of primary leiomyosarcoma of bone with a description of the clinical, radiographic, and pathologic-anatomic findings and the results of a follow-up study.

Patients and methods

All the spindle cell sarcomas of bone reported to the Swedish Cancer Registry 1964–1979 were reviewed, a total of 44 cases. The review did not include tumors diagnosed and registered as osteosarcoma, chondrosarcoma, and Ewing sarcoma. Of the spindle cell sarcomas, 11 were accepted by us as primary leiomyosarcoma of bone; three of them had been reported from our institution. The other eight tumors were regarded as primary fibrosarcoma. Five cases of primary leiomyosarcoma of bone from our files, diagnosed before or after that period, have been added to these 11 cases. Five of the 16 cases have been described previously [4].The eight patients still alive at the time of follow-up (July 1986) were examined clinically, and chest radiographs were performed within 6 months of the follow-up examination. The clinical files were reviewed in all cases as were autopsy records and histologic material in five of eight deceased patients.

Radiographic methods

Plain radiographs (16 cases), angiograms (6 cases), and computed tomograms (2 cases) were reassessed. The radiographs were evaluated in relation to the tumor's general appearance and its effect on cortical and medullary bone and soft tissues. The presence of any tumor-related pathologic fracture was noted. The grade of vascularity of the tumors was rated as absent, slight, moderate, or marked hypervascularity in comparison to surrounding tissues. These four ratings were based on the presence or absence of hypertrophic supplying arteries, intratumoral tortuous vessels, intratumoral contrast opacification, and rapid filling of dilated draining veins. Computed tomography with and without contrast enhancement was performed in cases 15 and 16. A 100 ml bolus of contrast medium (240 mg iodine/ml) was injected intravenously; in case 15, an additional 100 ml was injected more slowly during the remainder of the examination.

Light- and electron-microscopic methods

Formalin-fixed specimens embedded in paraffin were cut in 5 μm-thick sections and stained according to the hematoxylin-van Gieson trichrome method and with hematoxylin-eosin (H&E). Gordon and Sweet's silver impregnation was used for the demonstration of reticulin fibers. The material used for electron-microscopy was, in five cases, primarily fixed in 3% glutaraldehyde and, in three cases, reprocessed from paraffin blocks. The electron-microscopic techniques have been described previously [4, 44].

Histologic grading and estimation of mitotic activity

We used four grades for the histologic malignancy grading of the tumors as we do for soft tissue sarcomas [5]. These related primarily to cellularity, cellular atypia, and mitotic activity, but also took account of cell differentiation. Moreover, the mitotic activity was estimated by counting the number of mitoses in 20 randomly selected high power fields (objective ×25, ocular ×10). After measuring the area of the visual field the mitotic activity per mm^2 could be estimated (Table 1).

Results

The clinical findings are summarized in Table 1.

Incidence

Upon review of the 44 spindle cell sarcomas of bone registered in the Swedish Cancer Registry during the period 1964–1979, 11 tumors were diagnosed by us as primary leiomyosarcomas. With a population of approximately 7.5 million, this gives an annual incidence in Sweden of 0.7 cases or 0.09 cases per million and year.

Age and sex

The median age was 50 years, with a range of 9 to 74. Of the 16 patients, 11 were males and five were females, resulting in a sex ratio of 2.2:1.

Anatomic location

Thirteen of the 16 tumors were located in a long bone of an extremity: three in the upper extremity (two in the proximal humerus and one in the clavicle) and 10 in the lower extremity (seven in the distal femur, two in the proximal tibia, and one in the distal tibia). Three tumors were located in the axial skeleton: one in the acetabulum, one in the sacroiliac region, and one in a rib.

Symptoms

The time interval between the onset of symptoms and diagnosis ranged from 5 weeks to 3 years. The duration of symptoms was 6 months or more in 10 patients. All but one of the 16 patients experienced pain in the tumor-bearing region. A palpable mass was noted in nine patients.

Plain radiography

The plain radiographic findings in the 16 cases of leiomyosarcoma of bone are summarized in Table 2. All 16 tumors presented as an osteolytic lesion involving cortical and medullary bone (Figs. 1–5). Of the 13 tumors located in a long bone, eight had a mainly metaphyseal location, five of them extending into the epiphysis and three into the diaphysis. Two tumors had a purely metaphyseal and three tumors a purely diaphyseal location. Nine of the 16 tumors had an indistinct cortical margin, while five had a distinct and two a fairly distinct cortical margin. Ten tumors had an indistinct medullary margin, while three had a distinct and three a fairly distinct medullary margin.

Eleven tumors had penetrated the cortical bone and a soft tissue extension was noted in six cases. Five tumors showed erosion of the internal aspect of the cortical bone, and four showed cortical expansion. Periosteal new bone formation was noted in six cases, either in the shape of a cortical thickening, a single lamellar layer, or a Codman triangle. Multilayered onion-skin appearances or spicular formations were not noted.

Three patients (cases 1, 4, and 12) presented with a pathologic fracture through the osteolytic lesion (Fig. 1), and one patient (case 6) sustained such a fracture two months after primary treatment. There were two fractures in the proximal part of the tibia, one in the proximal part of the humerus and one in the lateral end of the clavicle. One patient (case 5) was operated on for a giant cell tumor in the medial femoral condyle 31 years prior to the occurrence of a leiomyosarcoma imme-

Table 1. Diagnostic, therapeutic, histopathologic, and prognostic data in 16 patients with primary leiomyosarcoma of bone

Case	Age (years) Sex	Location[b]	Symptoms (duration in months)	Biopsy[c]	Primary treatment
1[a]	46/M	Proximal humerus D Right	Pain (7)	FNB(b), trephine, and incisional (twice)	Curettage and bone grafting
2[a]	68/M	Distal femur D Right	Pain (3)	FNB(m)	Marginal excision, AO-condylar plate, bone cement, RT: 65 Gy
3[a]	24/F	Distal femur M + E Right	Pain (6)	Trephine	Preop RT: 42 Gy
4	37/F	Lateral clavicle M + D Left	Pain (6)	None	–
5	47/M	Distal femur M + E Right	Pain Mass (2)	Incisional	–
6	9/M	Proximal tibia M + D Left	Pain Mass (3)	(1) Incisional (2) Trephine	(1) RT: 40 Gy + regional perfusion (30 mg Alkeran/54 min)
7[a]	29/M	Distal femur M Right	Pain (1)	Incisional (frozen section)	Curettage
8[a]	74/F	Distal femur M Right	Pain (5)	Incisional (twice)	–
9	34/M	Distal femur M + D Left	Pain Mass (9)	Trephine	–
10	53/F	Acetabulum Left	Pain Mass (12)	Incisional	–
11	69/M	Eleventh rib Left	Mass (12)	None	–
12	26/M	Proximal tibia M + E Right	Pain Mass (7)	Incisional	–
13	70/M	Proximal humerus M + E Left	Pain Mass (12)	Incisional	–
14	70/F	Sacroiliac region Left	Pain Mass (5)	Incisional	–
15	69/M	Distal tibia D Right	Pain Mass (10)	Incisional (frozen section)	–
16	71/M	Distal femur M + E Right	Pain (40)	Trephine	–

[a] Previously reported case [4]
[b] D = Dia-, M = Meta-, E = Epiphysis
[c] FNB = fine-needle (aspiration) biopsy, (b) = benign lesion, (m) = malignant lesion at cytologic examination
[d] Time given in months after final treatment
[e] Radiation therapy

diately lateral to the previous lesion (Fig. 2). The giant cell tumor was treated by curettage and postoperative irradiation (25.1 Gy).

Angiography

Angiography was performed in six patients (Table 3). Two tumors showed marked hypervascularity in comparison to the surrounding tissues (cases 6 and 9) (Fig. 3), two tumors showed moderate hypervascularity (cases 1 and 14), and two tumors showed no hypervascularity (cases 2 and 3). All four tumors showing hypervascularity were supplied by hypertrophic arteries. They also showed irregular tortuous vessels and diffuse contrast opacification. In case 9, the irregular vessels and the diffuse opacification were only apparent in the extraosseous part of the tumor and, in case 14, the diffuse opacification was limited to the peripheral parts of the tumor indicating central necrosis. In cases 6 and 9, in which the tumors showed marked hypervascularity, the contrast medium passed rapidly to dilated draining veins. In case 1, in which the tumor was moderately hyper-

Table 1 (continued)

Final treatment	Size (cm)	Histologic Grade (I–IV)	Mitotic activity per mm^2	Local[d] recurrence	Metastasis[d]	Tumor-related[d] death	Alive[d] (7/1986)
Radical interscapulothoracic amputation (29 months later)	7×2×2	III	7.1				132
Radical hip disarticulation (18 months later)	7×2×2	III	9.5				82
Wide resection +custom-made prosthesis	8×4×3	III	2.0		79		96
Wide resection of lateral 2/3 of clavicle	2×2×1	II	0.7				78
Wide thigh amputation	6×4×3	III	3.1				94
Radical thigh amputation (12 months later)	5×4×3	III	7.5				148
Wide thigh amputation (20 days later)	7×5×3	II	0.7		12	18	
Wide thigh amputation	6×5×4	II	1.6		45	81	
Radical hip disarticulation	6×5×3	III	9.5		22	48	
Marginal pelvic resection	8×6×5	III	4.6	37	8	39	
Marginal excision	7×5×4	II	3.0	26[c]	78	115	
Radical thigh amputation	9×6×5	III	4.6		15	18	
RT: 53+28 Gy (18 months interval)	7×3×2	III	4.6		12	26	
RT: 40 Gy	12×12	III	10.9			20	
Wide B-K amputation	10×5×4	III	10.0		3		38
Wide resection +custom-made prosthesis	8×6×5	II	1.2		27		30

vascular, the patient sustained a pathologic fracture 4 days before the angiography [4].

Computed tomography

Two patients (cases 15 and 16) were examined by computed tomography. In case 15 (Fig. 4), CT revealed a central lytic lesion in the distal portion of the tibial diaphysis. The cortex was eroded from the inside, while it had been partially thickened on the outside by new bone formation. Moreover, the CT showed cortical penetration and a wide extension of the tumor into adjacent soft tissue, which was not apparent on plain radiograms. With contrast enhancement, parts of the tumor, both within and outside the tibia, clearly increased in density. In case 16 (Fig. 5), CT revealed a lytic lesion in the distal metaphysis and epiphysis of the femur. The proximal border of the tumor was difficult to assess. The cortex of the diaphysis adjacent to the tumor was thinner on the affected side than on the healthy side, presumably because of disuse atrophy; at this level the medullary canal showed no gross pathology. With contrast enhancement, some parts of the tumor increased in density while others remained virtually unchanged.

Table 2. Plain radiographic and scintigraphic findings in 16 patients with primary leiomyosarcoma of bone

Case	Type	Margins		Effects on		Scintigraphy (Tc-99)	Remarks
		Cortical	Medullary	Bone[b]	Soft tissue		
1	Lytic	Indistinct	Indistinct	Penetration Expansion PNBF	Extension		Pathologic fracture
2[a]	Lytic	Distinct	Indistinct	Penetration PNBF		+ + +	
3[a]	Lytic	Indistinct	Indistinct	Erosion		+ + +	
4	Lytic	Distinct	Fairly distinct	Erosion Expansion PNBF			Scalloping Pathologic fracture
5	Lytic	Indistinct	Indistinct	Penetration			Giant cell tumor 31 years preop: Curettage + bone graft + RT: 25.1 Gy
6	Lytic	Fairly distinct	Fairly distinct	Erosion Expansion			Scalloping, reactive sclerosis in diphysis and metaphysis. (Pathologic fracture)[c]
7	Lytic	Distinct	Distinct	Erosion			
8[a]	Lytic	Indistinct	Indistinct	Penetration	Extension	+ + +	
9	Lytic	Fairly distinct	Fairly distinct	Penetration			
10	Lytic	Indistinct	Indistinct	Penetration PNBF	Extension		
11	Lytic	Distinct	Distinct	Penetration			
12	Lytic	Indistinct	Indistinct	Penetration	Extension		Pathologic fracture
13	Lytic	Indistinct	Indistinct	Penetration	Extension		
14	Lytic	Indistinct	Indistinct	Penetration		+ + +	
15	Lytic	Distinct	Distinct	Penetration Expansion PNBF	Extension		
16	Lytic	Indistinct	Indistinct	Erosion PNBF		+ + +	

[a] Radiograph published previously [4]
[b] PNBF = Periosteal new bone formation
[c] Two months after primary treatment

Scintigraphy

Five patients (cases 2, 3, 8, 14, and 16) were examined by scintigraphy using technetium-99 polyphosphonate (Table 2). A markedly increased uptake corresponding to the tumor site was noted in all cases. In case 16, scintigraphy was superior to computed tomography in delimiting the proximal border of the tumor (Fig. 5E).

Diagnostic and surgical procedures

The final surgical treatment was amputation in nine patients (Table 1). In seven of these (cases 1, 5–8, 12, and 15), the diagnosis was obtained by an incisional biopsy, in one (case 9) by a trephine biopsy, and in one (case 2) by a fine-needle aspiration biopsy. The amputation was radical in five patients and wide in four patients. One patient (case 10) underwent a marginal pelvic resection after an incisional biopsy had confirmed the diagnosis, and two patients (cases 3 and 16) had a wide resection of the distal femur and replacement with a custom-made prosthesis after a trephine biopsy had disclosed the diagnosis. Two patients had a local operation based on clinical diagnosis alone. One (case 4) had a wide resection of the lateral two-thirds of the clavicle, and the other (case 11) had a marginal excision of the left eleventh rib. Two patients (cases 13 and 14) were treated exclusively with radiation after the diagnosis had been confirmed by an incisional biopsy.

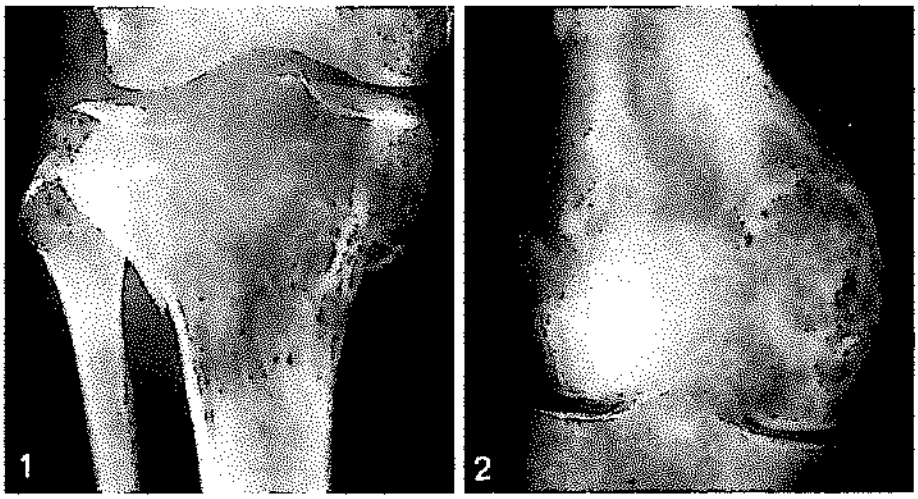

Fig. 1. *Case 12.* Leiomyosarcoma in proximal tibia. Pathologic fracture

Fig. 2. *Case 5.* Leiomyosarcoma in distal femur. Giant cell tumor in the medial condyle treated by curettage and postoperative irradiation 31 years previously

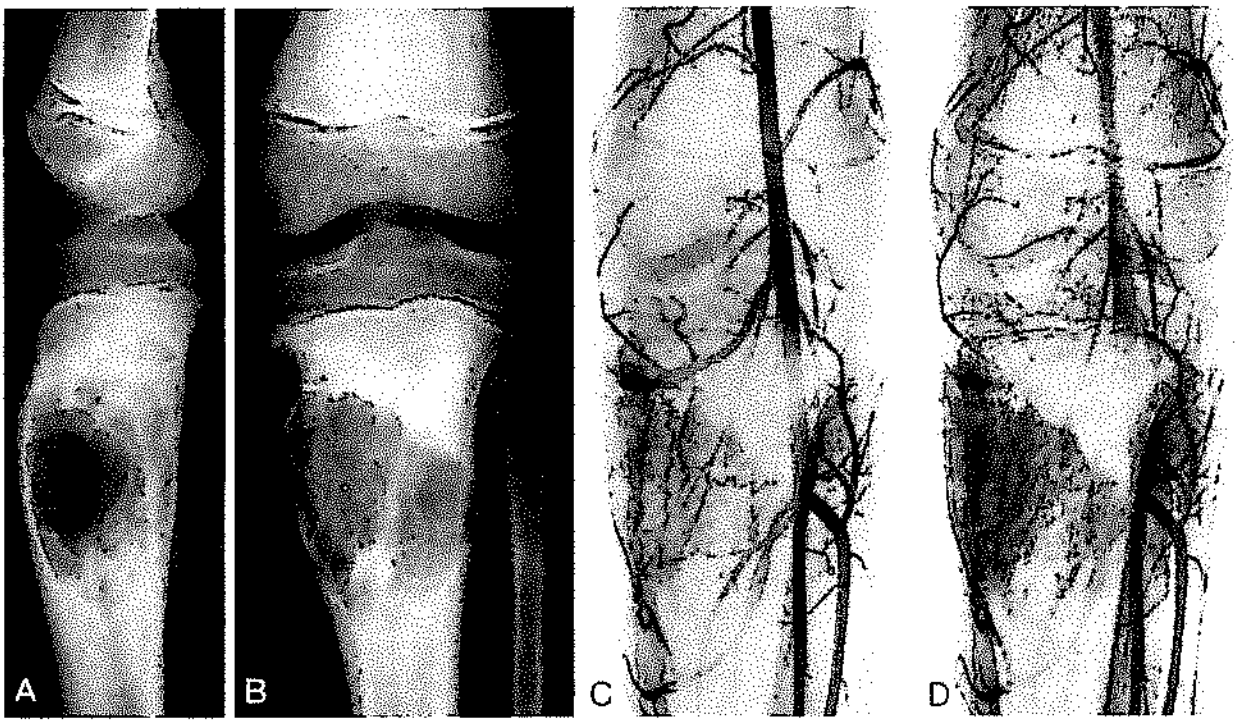

Fig. 3A–D. *Case 6.* Leiomyosarcoma in proximal tibia. **A** and **B** Plain radiography. Sclerosis adjacent to the osteolytic lesion. **C** and **D** Angiography. **C** Inferior medial genicular artery hypertrophic. Tortuous vessels at the site of the lesion. **D** Marked hypervascularity

Gross appearance and tumor size

The cut surface of the tumors had a greyish-white, meat-like appearance. The tumors usually eroded the bone from the inside, and cortical penetration was noted in 11 tumors (10 radiographically). The smallest tumor (2 cm) was found in the lateral end of the clavicle, and the largest tumor (12 cm) in the sacroiliac region. All of the remaining lesions exceeded 5 cm in maximum diameter. The tumors usually grew in an infiltrative manner, and soft tissue extension outside the bone was noted in nine cases (six radiographically).

Light-microscopic appearance

The 11 new cases had a light-microscopic appearance similar to that of the five previously described tumors [4]. All the tumors were predominantly intramedullary, and nine had invaded the soft tissues. Spindle-shaped tumor cells with elongated, often cigar-shaped, dense nuclei with eosinophilic

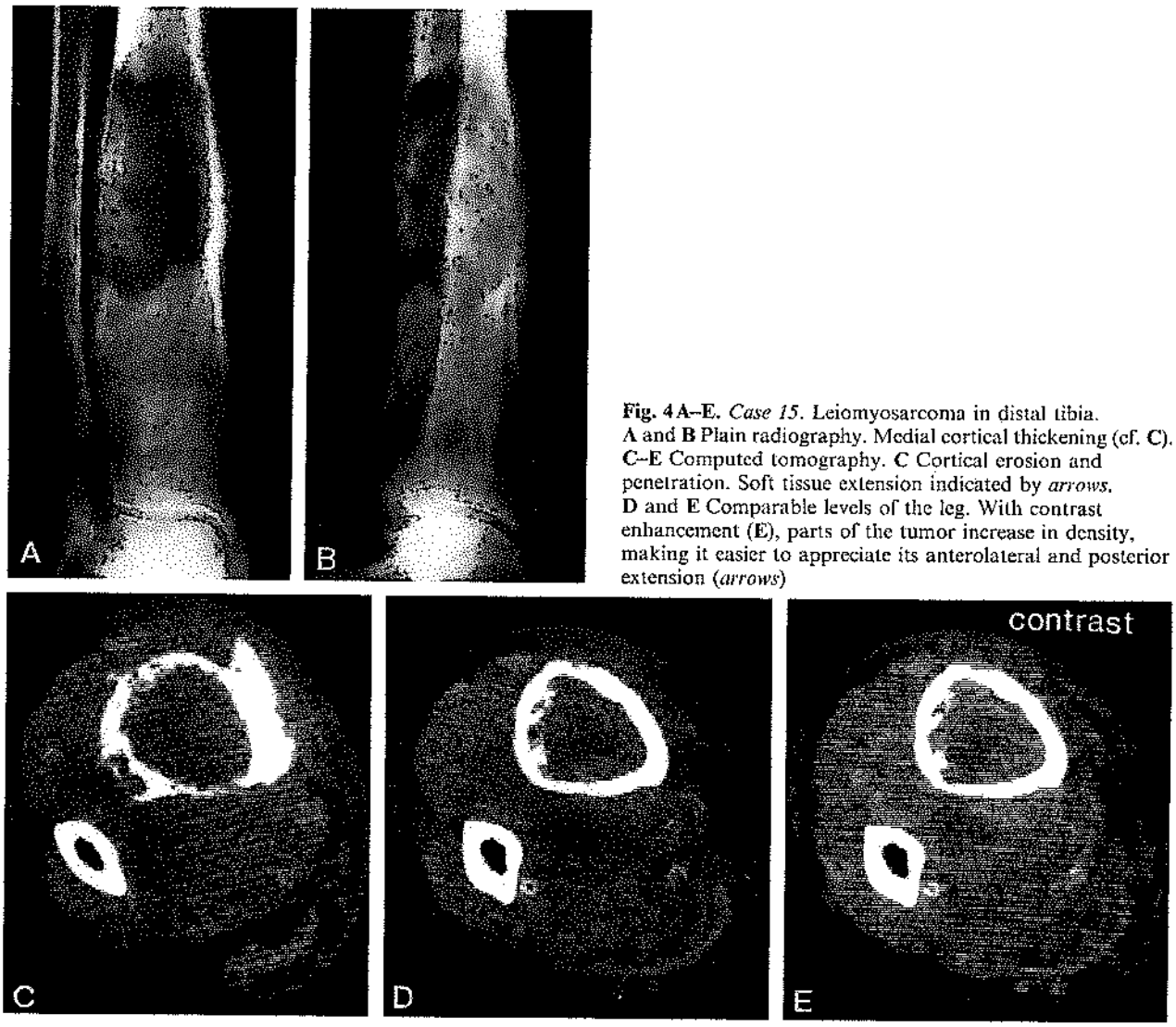

Fig. 4 A–E. *Case 15.* Leiomyosarcoma in distal tibia. **A** and **B** Plain radiography. Medial cortical thickening (cf. **C**). **C–E** Computed tomography. **C** Cortical erosion and penetration. Soft tissue extension indicated by *arrows*. **D** and **E** Comparable levels of the leg. With contrast enhancement (**E**), parts of the tumor increase in density, making it easier to appreciate its anterolateral and posterior extension (*arrows*)

and picrinophilic cytoplasm were a common and characteristic feature. The spindle-shaped tumor cells formed sharply demarcated fascicles, crossing each other at wide, sometimes right angles (Figs. 6A and B). All the tumors contained varying amounts of collagen. The tumors were rich in reticulin fibers which encircled individual tumor cells and bundles of cells. Focal hyalinized areas were a common finding, while necrosis was never a prominent feature. Five tumors were of grade II (cases 4, 7, 8, 11, and 16), and 11 tumors were of grade III. The mean number of mitoses was 1.4 per mm^2 for grade II tumors and 6.7 per mm^2 for grade III tumors. There was no grade I or grade IV tumor in the series.

The examined metastases had an appearance similar to that of the primary leiomyosarcomas of bone. Cutaneous metastases occurred in three patients; these were excised in two of them and diagnosed by fine-needle aspiration cytology in one. All the cutaneous metastases were small, less than 1 cm in diameter, superficially located in the dermis, and well-circumscribed.

Electron-microscopic appearance

Eight tumors were studied by electron microscopy, three of the five tumors previously described [4] and 5 of the 11 tumors not previously described. All eight tumors showed a picture characteristic of leiomyosarcoma – fusiform tumor cells arranged in a parallel fashion with elongated nuclei often with blunt ends, an abundance of fine cytoplasmic filaments of the actin type, arranged in bundles parallel to the longitudinal axis of the cells and containing elongated densities, pinocytotic vesicles along a cytoplasmic membrane, and segments of external laminae (Figs. 6C and D).

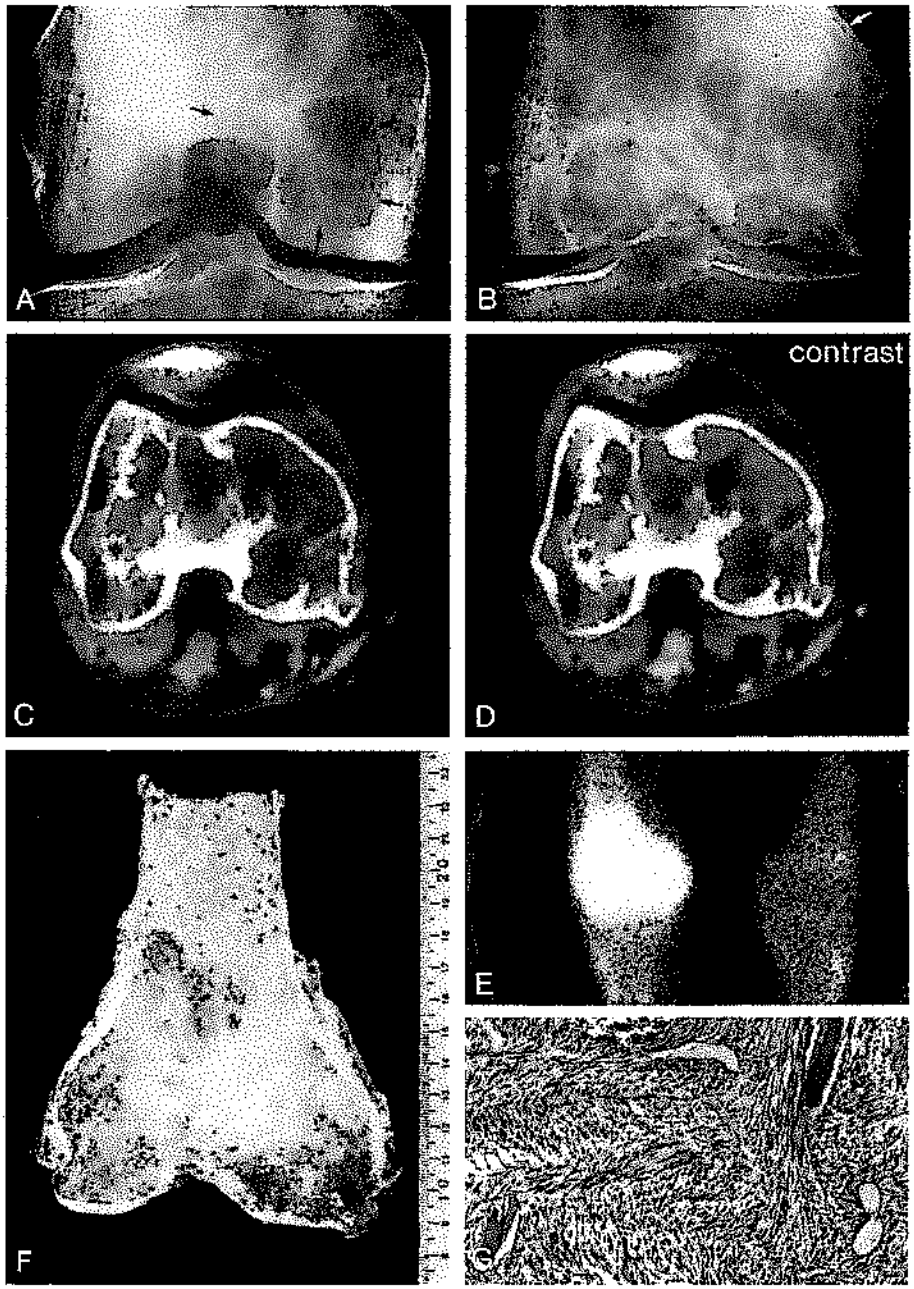

Fig. 5A–G. *Case 16.* Leiomyosarcoma in distal femur. **A** In retrospect it is apparent that the tumor was already present in the medial condyle 3 years prior to diagnosis (*arrows*). **B** The tumor now affects the lateral condyle as well. *Arrow* indicates periosteal new bone formation. **C** and **D** Computed tomography. With contrast enhancement (**D**) parts of the tumor increase in density. **E** Scintigraphy demonstrating the proximal extension of the tumor (cf. **F**) **F** Coronal section through the resected distal part of the femur. Scale in cm. **G** Photomicrograph of tumor tissue with remaining bone (H E, ×80)

Table 3. Angiographic findings in six patients with primary leiomyosarcoma of bone

Case	Grade of vascularity[b]	Hypertrophic supplying arteries	Intratumoral irregular tortuous vessels	Diffuse intratumoral contrast opacification	Rapid filling of dilated draining veins	Remarks
1[a]	2	+	+	+		Pathologic fracture
2	0					
3	0					
6	3	+	+	+	+	
9	3	+	+	+	+	
14	2	+	+	+		Central necrosis

[a] Angiograms published previously [4]
[b] 0 = No, 1 = Slight, 2 = Moderate, 3 = Marked hypervascularity in comparison to surrounding tissues

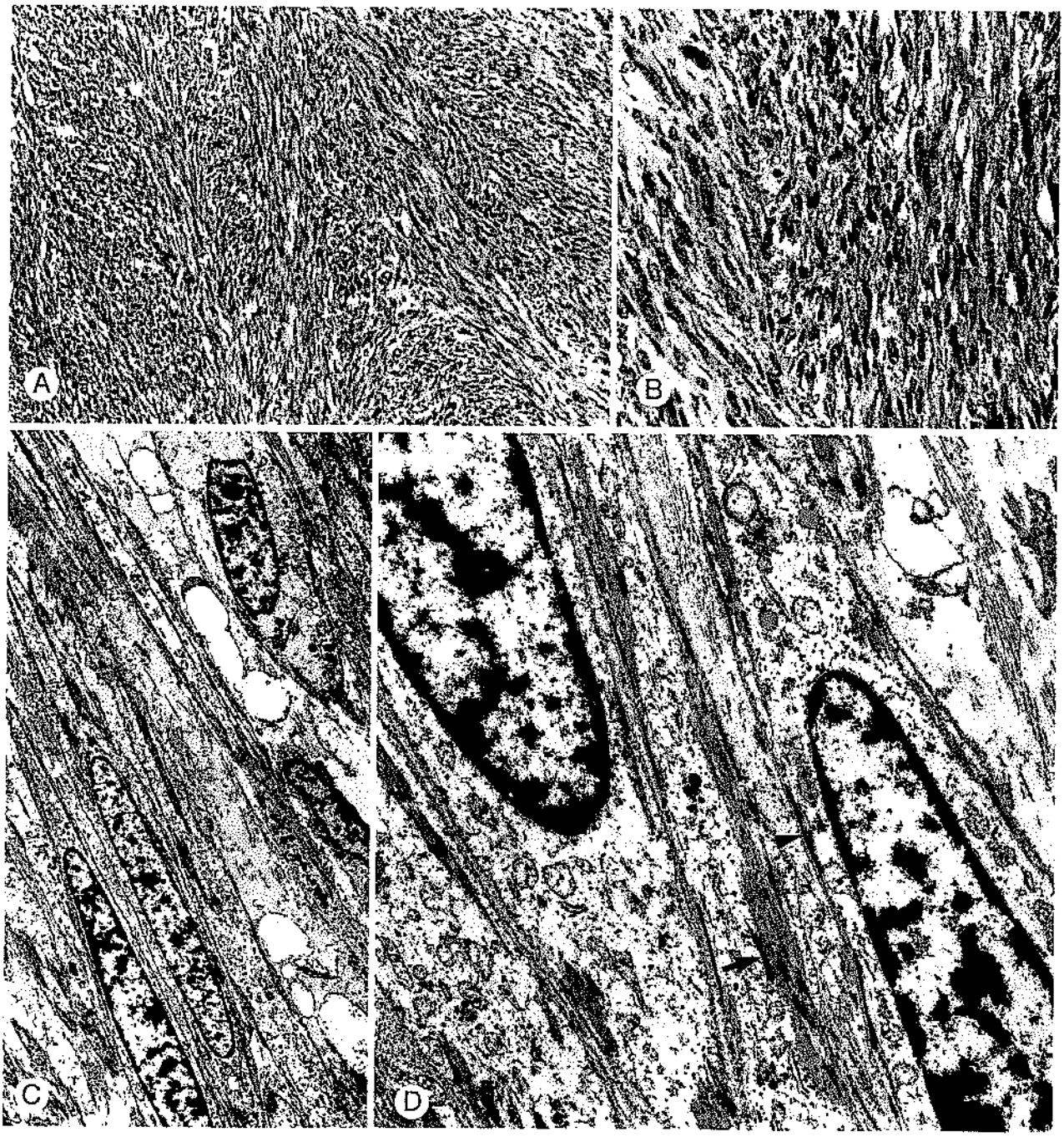

Fig. 6A–D. Bundles of fusiform cells arranged in parallel intersect at wide angles (van Gieson ×90). **B** Parallel arrangement of elongated cells with dense, cigar-shaped nuclei (van Gieson ×225). **C** and **D** Ultrastructurally the elongated tumor cells are partly separated by collagen. Abundant thin cytoplasmic filaments are arranged in a parallel fashion along the axis of the cells and form dense elongated condensations (*arrow*). Attachment sites are seen along the cytoplasmic membrane (arrowhead). The tumor cells are enclosed by external laminae. (**C** ×2100, **D** ×8500)

Follow-up

All the 16 patients with leiomyosarcoma of bone were followed for 2.5 years or more, or until death (Table 1). Of the eight patients still alive, six (cases 1, 2, 4–6, and 15) show no evidence of disease; for them, the median follow-up period after the final treatment was 7.3 years (range 3.2 to 12.3). One of the eight living patients (case 1) has undergone a radical interscapulothoracic amputation because of a local recurrence occurring 22 months after intralesional surgery. He is without evidence

of disease after 132 months. One patient (case 3) is alive after 96 months with multiple pulmonary metastases occurring 79 months postoperatively. The metastases had slowly progressed despite treatment with interferon, and the patient is now receiving chemotherapy (the sixth cycle of CY-VADIC treatment) with partial response to the treatment. In case 15, a cutaneous metastasis was noted three months postoperatively. It was treated with a marginal excision followed by chemotherapy (Adriamycin). Two local recurrences of the metastasis have occurred, both treated by local excision. The patient is without evidence of disease 38 months after treatment of the primary tumor (wide below-knee amputation). One patient (case 16) has a metastatic lesion in his first lumbar vertebral body diagnosed by fine-needle aspiration cytology and is currently under observation in a hospital with no further treatment planned.

Of the six patients with no evidence of disease at follow-up, five were treated by amputation; three radical (cases 1, 2, and 6) and two wide (cases 5 and 15); one patient (case 4) had a wide resection of the lateral two-thirds of the clavicle. The patient who was alive with pulmonary metastases (case 3) had undergone a resection of the distal femur and replacement with a custom-made prosthesis, as had the patient who was alive with a skeletal metastasis (case 16). Of the 14 patients followed for more than 5 years, or until death, six (cases 1–6) were without evidence of disease at 5 years postoperatively (43%); one of them (case 3) developed pulmonary metastases 19 months later.

Eight patients died from the effects of the tumor with a median survival time of 33 months (range 18–115 months). Autopsy was performed in five of these patients (cases 7, 9, 10, 12, and 13). All five had developed pulmonary metastases. At autopsy there were no signs of any retroperitoneal or uterine tumors or other possible primary sites for the skeletal leiomyosarcoma. Two of the patients not examined by autopsy (cases 8 and 11) had radiographic evidence of pulmonary metastases. The eighth patient who died (case 14) had a large sacroiliac tumor which had grown through the skin. She was not examined by autopsy, but she was clinically free from metastasis.

Three patients had cutaneous metastases (cases 10, 13, and 15), appearing 18, 24, and 3 months after the final treatment of the skeletal lesion. The two patients with cutaneous metastases who died (cases 10 and 13) were found at autopsy to have widespread metastases. The third patient (case 15), who was symptom-free at follow-up, had undergone excision of a cutaneous metastasis three times; it had recurred locally twice. Three patients had metastases to the lumbar spine (cases 8, 13 and 16). Two of these metastases were diagnosed by fine-needle aspiration cytology (cases 8 and 16), and one by autopsy. Three patients had metastases to the liver (cases 7, 10, and 13) and two to the adrenal glands (cases 9 and 10). Metastases to the mediastinum (case 12), the kidneys (case 10), inguinal lymph nodes (case 7), and supraclavicular lymph nodes (case 8) each occurred once.

Of the eight deceased patients, four were treated by amputation; two radical (cases 9 and 12) and two wide (cases 7 and 8). In two patients who underwent a marginal local excision (cases 10 and 11), the tumor recurred locally after 37 and 26 months respectively. Two patients had radiation therapy only; one elderly patient had massive soft tissue extension (case 13), and one had an inoperable tumor site (case 14). Both patients died, 26 and 20 months respectively after the commencement of the treatment.

Discussion

The 16 tumors in this report had a light- and electron-microscopic appearance with cellular and tissue features characteristic of leiomyosarcoma of soft tissues [7, 11, 56]. Ultrastructurally, abundant cytoplasmic filaments were seen arranged in parallel along the axis of the cells and formed dense structures some of which ended in marginal patches on the cytoplasmic membrane, a further indication of a leiomyomatous differentiation. The light- and electron-microscopic features of the leiomyosarcomas make it possible to distinguish them from other spindle cell sarcomas of bone, particularly fibrosarcoma and malignant fibrous histiocytoma .

Immunohistochemistry has been widely used in the diagnosis of myogenic tumors. The intermediate muscle filament desmin has been studied in particular and found to be a useful marker of rhabdomyosarcoma [2]. The expression and distribution of desmin in smooth muscle of various types has been found to vary and the few reported studies of desmin in leiomyosarcoma of varying origin have also produced very varied results [16, 21, 38]. In the largest series studied, 9 of 19 cases of leiomyosarcoma of the soft tissues were positive to desmin [21]. In a study of desmin in leiomyomatous tumors of the gastrointestinal tract, benign tumors were found to be positive to desmin, while all leiomyosarcomas were found to be negative. It was even suggested that a negative desmin reac-

tion in a leiomyomatous tumor may be used to support its malignancy [16]. In an ongoing study of desmin in leiomyosarcomas of the bone and soft tissues, using several mono- and polyclonal antibodies as previously performed on rhabdomyosarcomas [45], we have also found varying results.

The varying results by ourselves and others may be related to the tissue of origin and differentiation of the leiomyosarcoma, but may also partly be explained by the influence of various fixatives and methods for processing the tissue. A lack of desmin positivity does not exclude the diagnosis of leiomyosarcoma, especially in retrospective studies of routinely formalin-fixed and processed material, as was used in the present series of leiomyosarcomas of bone, and we therefore consider desmin immunohistochemistry to be of limited value for the diagnosis and the definition of leiomyosarcoma of bone. The diagnosis of leiomyosarcoma still remains essentially a light-microscopic diagnosis and, so far, electron-microscopy seems to make the most valuable contribution to the diagnosis. In all the cases where electron-microscopic examination was performed in the present series, the tumor cells revealed leiomyoblastic features.

When a leiomyosarcoma appears in the skeleton the possibility of a metastasis should be considered. In none of the cases in this series did the clinical findings, the follow-up, or autopsy findings indicate any other primary tumor. It is noteworthy that cutaneous metastases developed in three patients. Cutaneous leiomyosarcomas rarely metastasize [11], and it is unlikely that the skeletal tumor in these patients represented a metastasis of a primary cutaneous leiomyosarcoma. All cutaneous tumors were small and well-circumscribed in contrast to primary leiomyosarcoma of the skin [11]. In two patients, they developed late as a part of disseminated disease. The third patient had only one cutaneous lesion; it appeared after 3 months, but radiographic signs indicated that the skeletal leiomyosarcoma had been present for a long time before diagnosis (Fig. 4).

Leiomyosarcoma of bone is apparently more common than has been reported in the literature since it is evident that it has previously not always been distinguished and recognized as a separate entity. The difficulty in recognizing even benign leiomyomatous tumors using hematoxylin and eosin staining has been previously emphasized [50]. The use of the van Gieson trichrome stain as a routine method is undoubtedly of great help in diagnosing tumors of smooth muscle origin. Malignant fibrous histiocytoma of bone may contain areas which are difficult to distinguish from leiomyosarcoma of bone [3, 13]. In none of the present cases did the tumor cells show histiocytic differentiation.

In the present study we used four grades of histologic malignancy, following in principle the Mayo Clinic system which has been used both for bone and soft tissue sarcomas for several decades. This grading system has proved meaningful when studying the prognosis for bone sarcomas [53]. We have similar experience when studying soft tissue sarcomas. Using multivariate statistical analysis we have shown that the histologic grade is one of the most important independent prognostic factors [28, 32, 36]. The mean number of mitoses per mm^2 was nearly five times higher in grade III tumors than in grade II tumors. However, three of the five patients with a grade II tumor have died with metastasis. The present series is too small to evaluate the relationship between the grade of histologic malignancy (including mitotic activity) and survival.

Including our 16 cases, 36 leiomyosarcomas of bone have been reported in the literature [1, 4, 10, 14, 17, 20, 27, 29, 31, 33, 35, 37, 39, 41, 43, 46, 52, 54, 55]. Twenty-four of them were located in the long bones of the extremities, most often involving the metaphysis, and nine were located in the jaw bones. The remaining three tumors, all included in our series, were located in the axial skeleton (rib, sacroiliac region, acetabulum). Leiomyosarcoma of bone shares clinical features with fibrosarcoma of bone [8, 9, 12, 24, 26, 30, 40, 51] and malignant fibrous histiocytoma of bone [13, 15, 18, 19, 22, 23, 34, 48, 49]. Like these tumors, it usually presents as a painful osteolytic lesion, and a palpable mass often develops before diagnosis. The age distribution is fairly even from the first to the eighth decade of life, and the tumor seems to have a male preponderance, two to one in our 16 cases and three to one in the 20 cases reported by others.

The plain radiographic appearance of our leiomyosarcomas of bone certainly suggested malignancy. All the tumors were osteolytic, as were those reported previously. They exhibited aggressive radiographic characteristics, with penetration of cortical bone in most cases (11/16), and a pathologic fracture had occurred before diagnosis in three cases. Four tumors had caused cortical expansion as a sign that the surrounding bone was able to remodel along with the tumor growth. The plain radiographic appearance is not specific for leiomyosarcoma of bone since other primary and secondary malignant tumors can give rise to similar destruction of bone. In four out of six cases

angiography showed moderate or marked hypervascularity, irregular tortuous vessels, and diffuse contrast opacification; in two of the four cases, dilated draining veins filled rapidly with contrast medium. In two cases, computed tomography helped to determine the type and amount of bone destruction and, in one of these cases, it demonstrated an extraosseous extension of the tumor which was not detectable on plain radiographs. Contrast enhancement showed hypervascular areas in both tumors. Scintigraphy gave no clue to the diagnosis in the five cases studied, but in one of them, it was superior to computed tomography for determining the boundaries of the tumor.

One of our patients developed a leiomyosarcoma in close proximity to the site of a giant cell tumor removed 31 years previously. This tumor was located in the medial femoral condyle and had been treated postoperatively with radiation. Both irradiation and preceding bone disease, such as benign tumors, bone infarct, and Paget disease, are known to increase the risk of bone malignancies [3, 6, 9, 12, 13, 25, 30, 34, 42, 47].

The diversity of the treatments in our cases precludes any definite conclusions as to efficiency and importance to the prognosis. All eight patients still alive (six after more than 5 years) underwent either a radical or a wide operation, as indeed did four of the eight patients who died because of the tumor. Of the other four patients who died, two underwent a marginal operation and two only had radiation therapy. Pulmonary metastasis has occurred in eight of the 16 patients. This indicates that leiomyosarcoma of bone is a highly malignant tumor.

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