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Epithelioid sarcoma

Diagnosis, prognostic indicators, and treatment*,†

ABSTRACT A retrospective review of 241 cases of epithelioid sarcoma reaffirmed the propensity of this tumor to occur in the distal extremities of young adults. The tumor was generally firm and nontender, and involved the dermis, subcutis or deeper soft tissues, particularly fascial planes, aponeuroses, and tendon sheaths. Follow-up data, available in 202 cases (84%), showed a 77% recurrence and a 45% metastatic rate. The most common initial sites of metastasis were lymph nodes (48%) and lungs (25%). A more aggressive course was associated with a proximal or axial tumor location, increased size and depth, hemorrhage, mitotic figures, necrosis, or the presence of vascular invasion. More favorable behavior was observed when the tumor arose in younger individuals, in distal extremities, or in females between the ages of 10 and 49. (The last observation calls for further work with steroid receptors.) Radical excision or amputation still appears to be the initial treatment of choice, though adjunctive high-dose radiotherapy to the excision site may prove to be of additional value.

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INTRODUCTION

Since its first detailed description in 1970,[6] epithelioid sarcoma has been accepted as a unique soft tissue sarcoma which typically pursues an indolent, relentless clinical course with numerous recurrences, and frequently culminates in regional lymph node or pulmonary metastasis. Its microscopic appearance may frustrate the surgical pathologist, often mimicking necrobiotic granuloma, nodular fasciitis, benign and malignant fibrous histiocytoma, synovial sarcoma, "amelanotic" melanoma, ulcerated squamous cell carcinoma, and other benign or malignant processes.

Epithelioid sarcoma usually occurs in the soft tissues of young adults, particularly involving the hands and forearms, and produces multinodular masses of epithelial-appearing cells having a tendency to grow along fascial planes, aponeuroses, and tendon sheaths. It involves the viscera only secondarily. Unusual primary sites include the penis[15,27] and vulva.[11,13] Many case reports and review articles have been written, stressing different features of the tumor.[1–3,6–15,17–23,25–37] Medenica has observed damage to tumor cells immediately adjacent to surrounding cuffs of lymphocytes and proposed that the slow growth of the neoplasm might be related to the high efficacy of lymphocyte-mediated defenses.[23] Another report shows a poorer prognosis in recurrent cases or in those showing vascular invasion or lymph node metastasis.[30] Still other papers have detailed the tumors cytologic and radiologic features.[1,20] Al-

though published results of chemotherapy and radiotherapy are few, Shimm et al. have recently reported that radiation therapy, combined with surgery, may achieve a low rate of local recurrence.[35]

The ultrastructural, immunohistochemical, and biochemical features of epithelioid sarcoma have been examined particularly for the presence of intracytoplasmic filaments.[2,6,8,10,12,18,20,21,23,25,26,29] Based on the ultrastructural and electrophoretic characteristics, Mills et al. felt that the 7- to 10-nm-diameter intracytoplasmic filaments represented vimentin.[26] We recently reported that 75% of our cases contain intermediate filament cytokeratins, present in both the epithelial-like and spindle cell elements.[4]

Regarding histogenesis, several reports have indicated similarities between epithelioid sarcoma and normal synovium, or synovial lesions.[5,10,12,18,21,25,29,32] Machinami et al. studied the tumor enzymatically, demonstrating 5′-nucleotidase in the tumor cell membranes as well as in normal synovium and endothelial cells.[21] Others have suggested fibrocytic, histiocytic, or fibrohistiocytic origins.[6,8,36]

Despite these accounts, published data on prognostic indicators and therapy remain meager,[30,35] and many physicians still find epithelioid sarcoma a difficult diagnosis to make. It is with this background that we review our experience with the tumor and present our findings and observations.

MATERIALS AND METHODS

The 241 cases included in this study were selected from consultation material submitted to the AFIP from 1943 to 1983. Most had been coded as epithelioid sarcoma, and many had been included in other reports.[2,4,6,17,20,32,34,36] Cases reviewed prior to 1970 were usually coded as acidophilic fibrosarcoma, fibrosarcoma of myotendinous origin, fascial fibrosarcoma, or fascial sarcoma. Only those cases having glass slides and clinical data available were accepted for re-examination and review. Cases in which the tumor was too poorly differentiated to make an unequivocal histologic diagnosis of epithelioid sarcoma were eliminated from the study.

Each tumor was examined for the presence and degree of calcification, ossification, necrosis, hemorrhage, lymphocytic infiltrate, and vascular or neural invasion. Mitotic rates were counted per 10 high-power fields (HPF) in the more cellular regions of the tumor. The depth of the tumors, as related to skin structures, superficial fascia or skeletal muscle, was also recorded. In selected cases, immunoperoxidase staining for cytokeratins (CK), S-100 protein, Human Factor VIII-associated antigen (HFVIII), carcinoembryonic antigen (CEA), alpha-1-antitrypsin (AAT), alpha-1-antichymotrypsin (ACT), and lysozyme (LYS) were performed. Additionally, more traditional stains were available in many cases, including reticulin, trichrome and PAS stains, with and without diastase predigestion.

Follow-up data were obtained through several mail solicitations, most recently in 1977 and 1983. The acceptable follow-up interval was defined as a period of at least 1 year from the initial surgical procedure (or less than 1 year if the tumor metastasized), even though in many cases the tumor had clinically been noted for several years. Two hundred two cases (84%) met these criteria and have been analyzed for trends in behavior.

CLINICAL FINDINGS

Age, sex and race

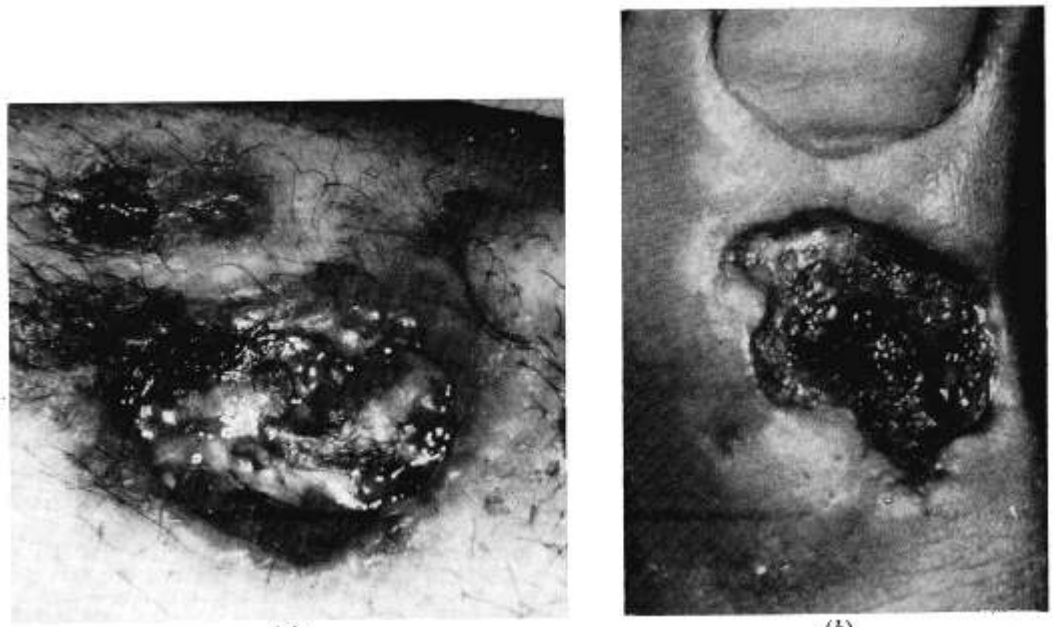
Although the age at presentation (initial surgical procedure) ranged from 4 to 90 years, 74% of the patients presented between the ages of 10 and 39 (Table 1). The average (mean) age at presentation was 27 years, 11 months. The sex was indicated in 239 of the 241 cases, showing a male preponderance of 1.8:1 (155:84). Tumors from 19 different countries were reviewed, and showed no geographic or racial predisposition.

Location

The distal upper extremities were most frequently involved (58%), particularly the hands and forearms. Next in frequency were the distal lower extremities (15%), the proximal lower extremities (12%), proximal upper extremities (10%), trunk (3%), and head and neck (1%). The tumor microscopically involved the skin in 24% of the cases and skeletal muscle in 28%. The remaining neoplasms involved fascia, tendons, or the interlobular septa of the subcutis. The left side was involved in 102 cases and the right in 96 cases.

Presentation signs and symptoms

Most of the tumors presented as firm to hard palpable masses in the deep soft tissues, subcutis, or dermis. They were generally invasive, rarely described as protuberant. Several hand tumors caused "diffuse swelling" whereas others mimicked ganglion cysts. The average (mean) duration



(*a*) (*b*)

FIGURE 1
(*a*) Twelve percent of the cases reported ulceration at the time of initial presentation. This tumor was present for 1 year as a painless ulcerated mass on the leg of an 18-year-old female. Note the smaller, satellite lesions. (AFIP Neg. 84-7462.) (*b*) This ulcerated tumor was on the dorsum of the right great toe of a 21-year-old male. Although the toe was amputated, tumor recurred in the stump 20 months later and eventually metastasized to lung and scalp. (AFIP Neg. 84-7461.)

of symptoms before the initial surgical procedure was 2 years, 5 months (range: "1 week" to 25 years).

Although the majority of the patients were otherwise asymptomatic, pain or tenderness was a complaint of 54 (22%). Only one patient presented with severe, debilitating pain. Contractures were present in 11% of the patients with hand tumors. Ten patients (4%) registered with complaints attributable to nerve compression, including muscular weakness, numbness, and paresthesias. Three patients with deeply seated tumors complained of chronic sinus tracts in the shoulder, paravulvar area, and abdominal wall, respectively. The last of these had been draining for 20 years.

Twenty-eight patients (12%) suffered from tumor ulceration at the time of presentation; many had been unsuccessfully treated with antibiotics for months to years (Fig. 1). Ulceration was especially noted in the metastatic tumors. One patient

TABLE 1.

Epithelioid Sarcoma: Age Distribution (241 Cases)

Age at First DX	No.	Percent by Decade	Males		Females	
			No.	Percent	No.	Percent
0–9	11	(5%)	6	(2%)	5	(2%)
10–19	66[a]	(27%)	40	(17%)	25	(10%)
20–29	70[a]	(29%)	55	(23%)	14	(6%)
30–39	43	(18%)	29	(12%)	14	(6%)
40–49	21	(9%)	13	(5%)	8	(3%)
50–59	19	(8%)	10	(4%)	9	(4%)
60–69	4	(2%)	0	(—)	4	(2%)
70–79	3	(1%)	1	(1%)	2	(1%)
80–89	3	(1%)	1	(1%)	2	(1%)
90–99	1	(1%)	0	(—)[b]	1	(1%)
Total	241		155	(65%)[b]	84	(36%)[b]

[a] Includes case where sex of patient was not given.
[b] Percentages (in totals) reflect rounding error.

with widespread ulcerating skin metastases bled extensively from the open wounds, requiring blood transfusions.

TRAUMA

Unsolicited reports of antecedent trauma to the area which developed tumor were given in 20% of the cases (48/241). The time interval from the incident to presentation with tumor varied from "immediately" to 20 years (mean: 2 years, 5 months). Males predominated 3.7:1 over females. All of the tumors occurred in the extremities; the left side in 21 cases and the right in 17. Forty-two percent (20/48) of these were superficial lesions and involved the dermis, while 21% (10/48) were deeper, microscopically contiguous to striated muscle.

The reported incidents included crush injuries, bruises, lacerations, bone fractures, and muscle tears. Several tumors were associated with sports injuries, whereas others seemed related to foreign-body-type injuries, including shrapnel, fiberglass, and embedded glass fragments. Tumors also developed in the site of a tattoo and in a region of numerous heroin injections. One tumor developed as a "callus" under a ring, while another developed following electric fulguration of a "wart" and the topical use of a wart remover.

ROENTGENOGRAPHIC CHARACTERISTICS

There were no consistent radiologic changes diagnostic of epithelioid sarcoma. The x-rays occasionally showed speckled patterns of calcification, reflecting the microscopic presence of calcifications or ossification in 28% of the cases (68/241). Although the tumor sometimes involved the periosteum, it rarely caused changes in adjacent bones. If present, these changes usually consisted of localized demineralization or cortical thinning. One case, however, showed changes suggestive of rheumatoid arthritis, while another had localized osteomyelitis-like changes. One of the patients had a bone scan which reportedly showed uptake in the region of the tumor. No cases of primary, intraosseous epithelioid sarcoma were encountered.

GROSS APPEARANCE

The usual appearance was of one or more firm, tan-white, nonencapsulated nodules with indistinct, infiltrating margins (Fig. 2). Necrotic regions were sometimes identified which were softer and gray to yellow. Occasional communication with the surface was noted in the form of sinus tracts.

FIGURE 2
Epithelioid sarcoma involving the finger of a 16-year-old male. Nodular masses are evident in the subcutaneous and peritendinous tissues of the amputated finger. Tumor recurred after amputation and presented as a line of nodules on the volar aspect of the forearm. (AFIP Neg. 66-8008.)

When a primary tumor involved skin, it usually grew in a distinctly nodular or multinodular configuration in the deep dermis (Figs. 3 and 4). As the nodule or nodules enlarged they became confluent, forming irregular tumor masses (Fig. 5). A number of tumors arose within tendons or within muscular compartments, probably from myotendinous connections or muscle septa. Occasional tumors compressed, obliterated, or invaded small peripheral nerves or even large nerve trunks.

MICROSCOPIC APPEARANCE

The appearance varied after recurrence or metastasis, generally becoming less recognizable. The individual cells usually displayed a striking eosino-

FIGURE 3
This tumor was taken from the hand of the oldest patient in the study, a 90-year-old female. The mass had been present for 25 years. Notice the multinodular pattern of growth. (AFIP Neg. 84-6648.)

philia and grew as nodular proliferations of plump, epithelial-appearing cells blending with fusiform cells (Fig. 6). Transition between the two cell types was always subtle, never abrupt. Intercellular collagen was prominent in most cases. Many tumors contained avascular clefts, probably resulting from unequal fixation-shrinkage of the tumor cells and the collagenous stroma. Intracytoplasmic vacuoles were seen in many tumor cells, sometimes mimicking lipoblasts, or the primitive lumina formed by endothelial cells in certain vascular neoplasms.[38]

The pattern of growth seemed to depend on the amount of necrosis that was present. The most common and most recognizable pattern was a "pseudogranulomatous" proliferation of polygonal cells forming broad, undulating collars around central, relatively acellular or necrotic zones (Figs. 3–6). These central regions contained hyalinized collagen, necrotic debris, or occasionally a loose bluish matrix of acid mucopolysaccharides with scattered erythrocytes. Tumors showing little or no necrosis seemed to grow more diffusely and generally lacked the "geographic" effect (Fig. 7).

Five percent of the cases (12/241) contained multinucleated giant cells, usually comprising only a minor and inconspicuous component of the tumor. These multinucleated cells generally lacked the bizarre pleomorphism seen in giant cells of malignant fibrous histiocytoma. An additional but separate 5% of the cases (13/241) showed regions of storiform growth (Fig. 8). Neither xanthoma cells nor significant phagocytic activity were observed.

Calcification without bone formation was observed in 19% (45/241) of the cases. Mineralization occurred largely in the necrotic regions but occasionally involved viable cellular elements as

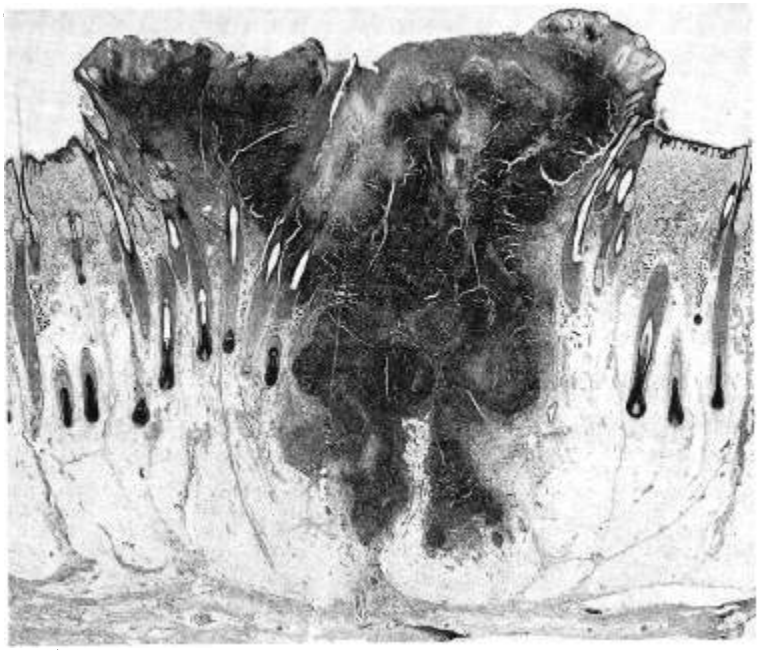
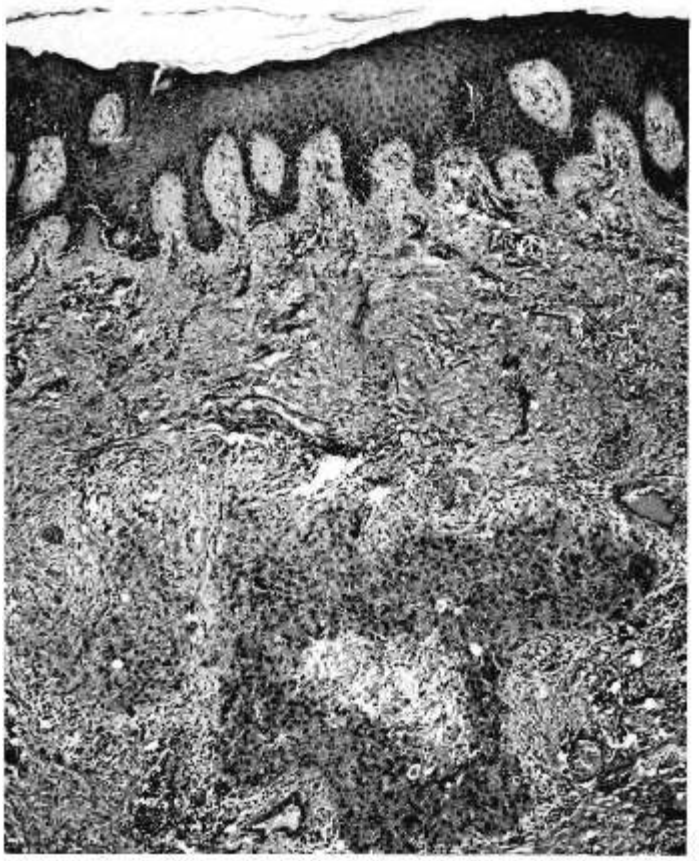


FIGURE 4
This tumor, shown involving the scalp, arose in the leg of a 16-year-old male and metastasized 3 years later. (AFIP Neg. 84-7402.)



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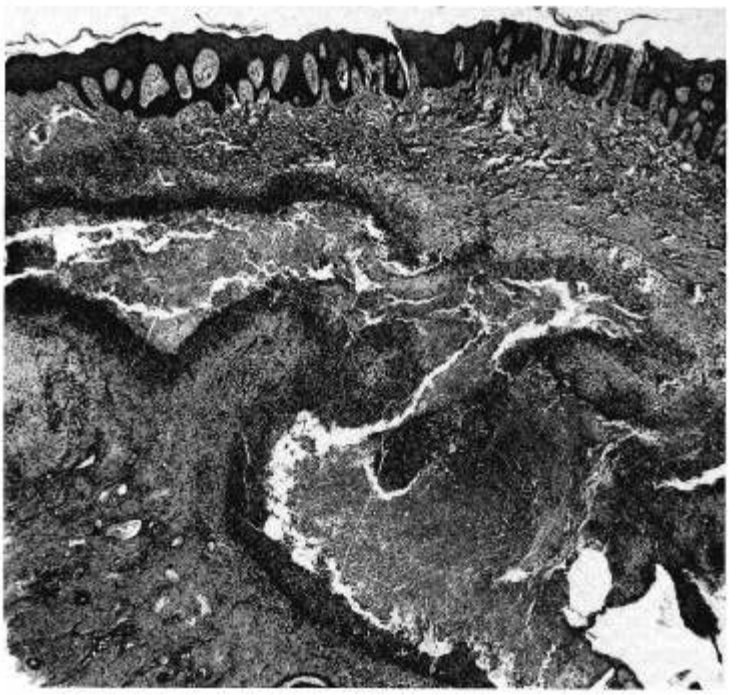
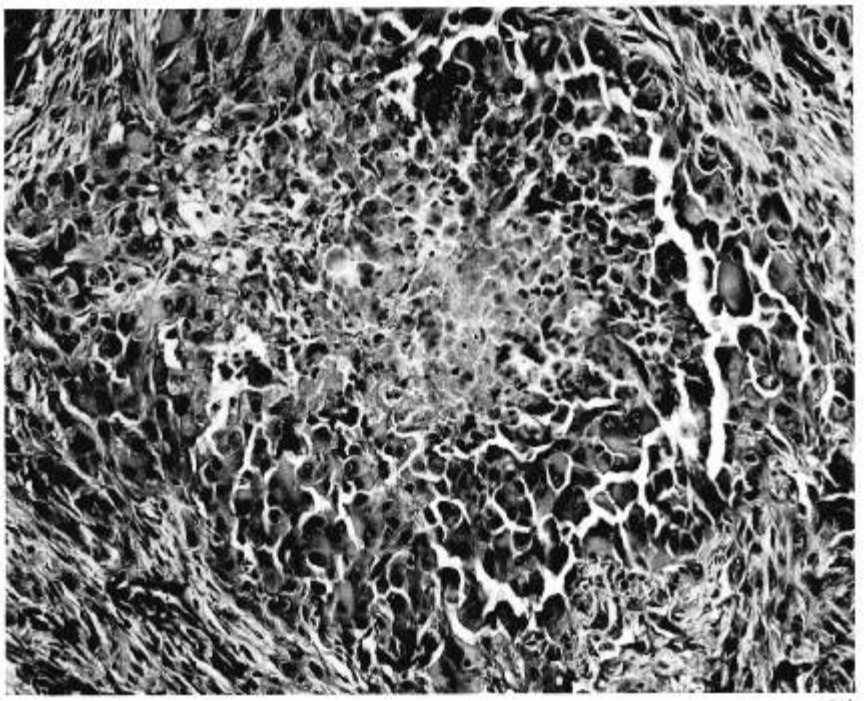


(*b*)

FIGURE 5
(*a*) This tumor involved the anterior abdominal wall of a 54-year-old female. It was associated with a wound dehiscence that had been draining for 20 years. Note the collar of tumor cells around the necrotic central region. (AFIP Neg.84-6641.) (*b*) Same tumor showing coalescence of nodules into a large, serpiginous mass. (AFIP Neg. 84-6642.)



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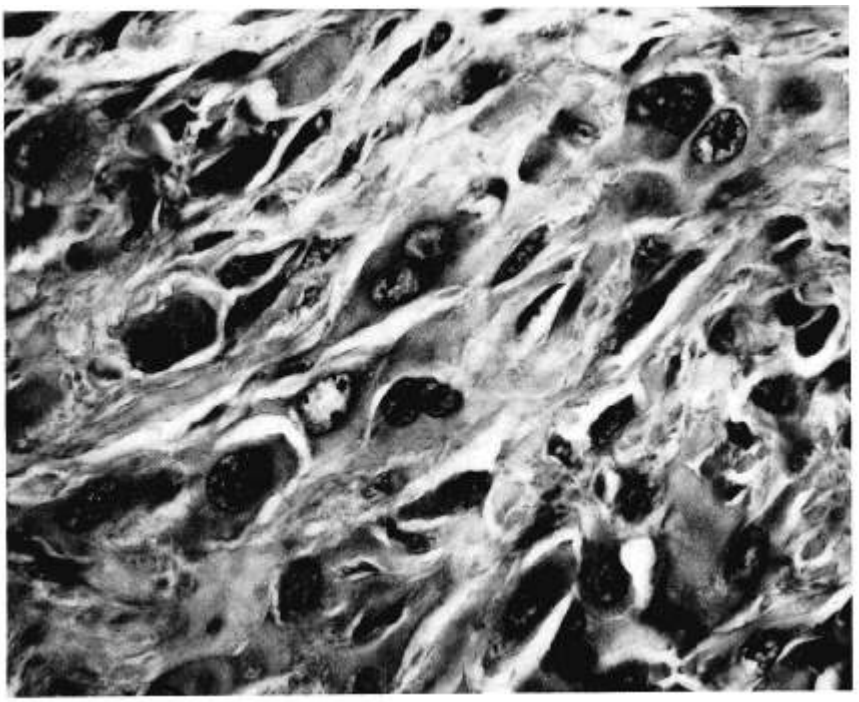
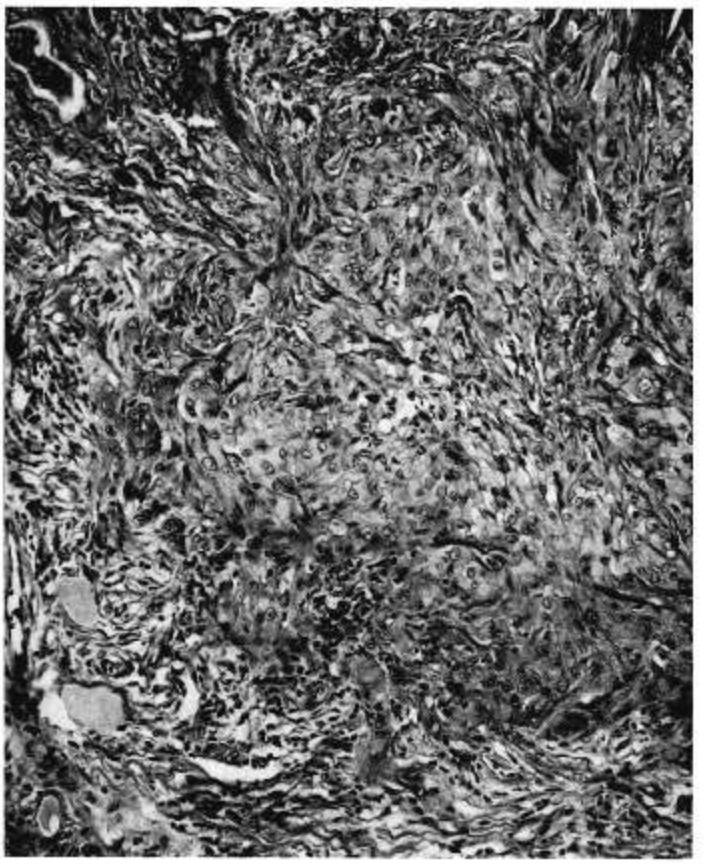


(*b*)

FIGURE 6
(*a*) Tumor from the forearm of a 21-year-old male. Note the plump epithelial-like cells, intercellular collagen and central necrosis. (AFIP Neg. 84-6628.) (*b*) Same tumor showing spindled and polygonal cell elements separated by a collagenous stroma. Although tumor cells sometimes mimicked rhabdomyoblasts, cross-striations were not encountered. (AFIP Neg. 84-6630.)

well. Never was it present to the degree seen in calcifying variants of synovial sarcoma. Osseous metaplasia was present in 10% of the tumors (23/241) (Fig. 9*a*), usually occurring in the larger ones (5.2 cm mean diameter). In only one case was it a prominent feature. Cartilaginous metaplasia occurred in only one tumor, a re-excision specimen from an ankle tumor of a 15-year-old girl (Fig. 9*b*).

Many tumors showed a chronic inflammatory-cell infiltrate sometimes reminiscent of the reac-



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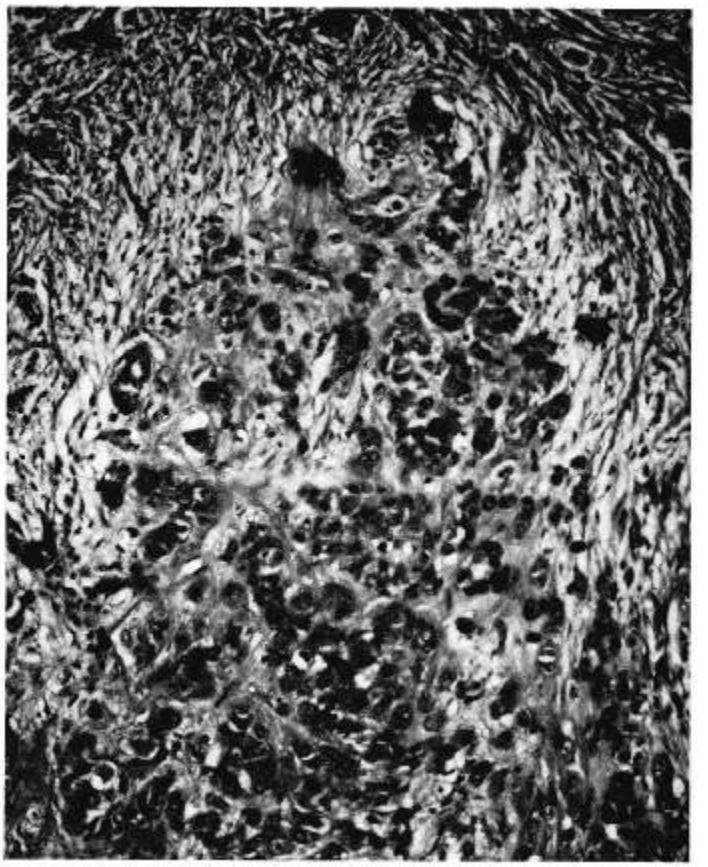
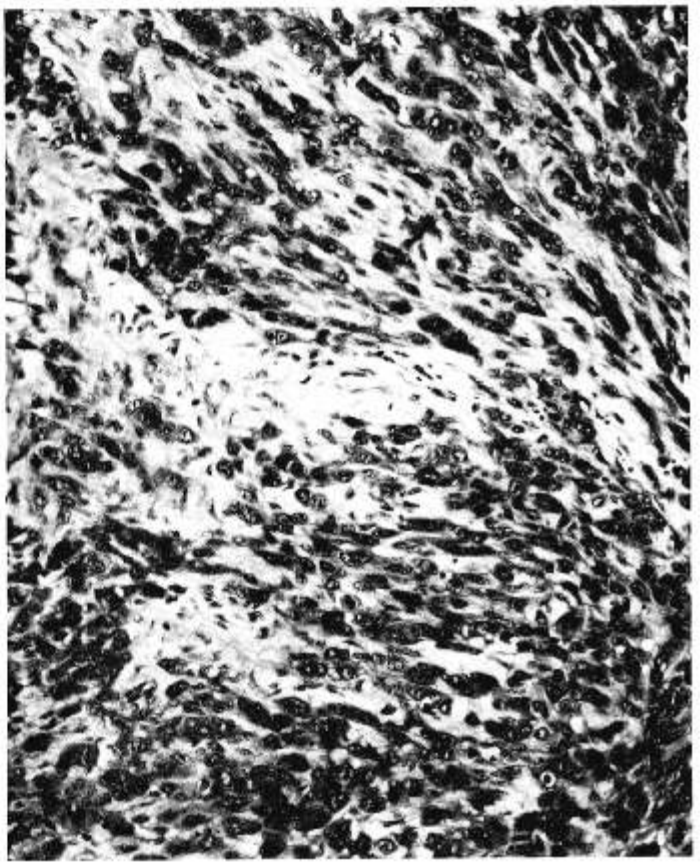


(b)

FIGURE 7
Portions of the tumor may imitate other neoplastic processes, emphasizing the need to examine all available material. All of these tumors showed typical histology in other areas. (*a*) Tumor from the knee of a 21-year-old male showing epithelial-appearing and spindled cells without regional necrosis. (AFIP Neg. 84-6646.) (*b*) Polygonal cells and collagenous stroma in a tumor arising in the ring finger of a 13-year-old male. The tumor had been present for 10 years. (AFIP Neg. 84-6643.) (*c*) Same tumor as in Fig. 3, showing prominent cording. (AFIP Neg. 84-6635.) (*d*) This tumor, taken from the shoulder of a 37-year-old female, focally produced an acid mucopolysaccharide matrix. Note the prominent intracytoplasmic vacuoles. (AFIP Neg. 84-7393.)



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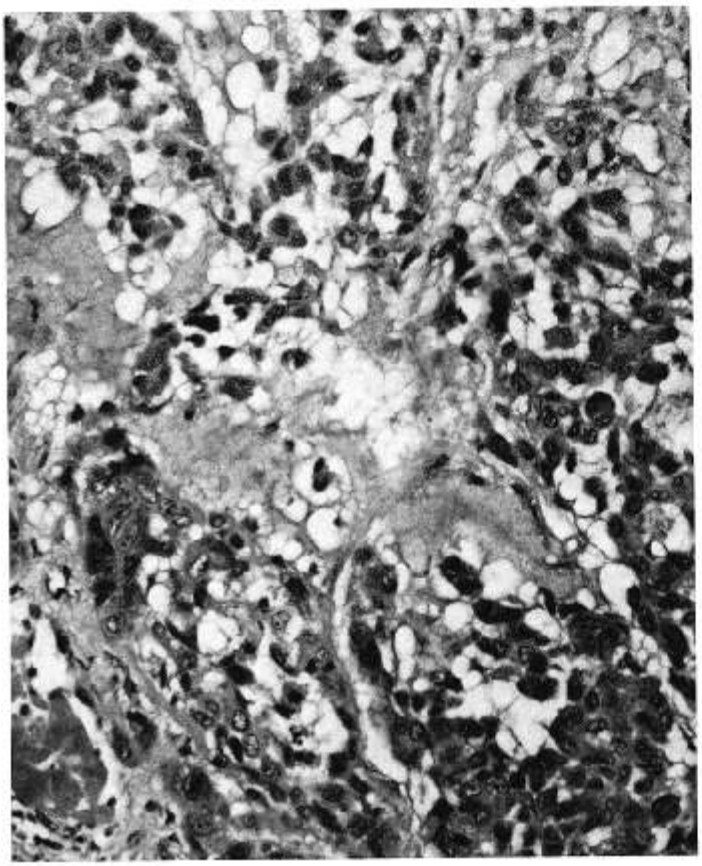
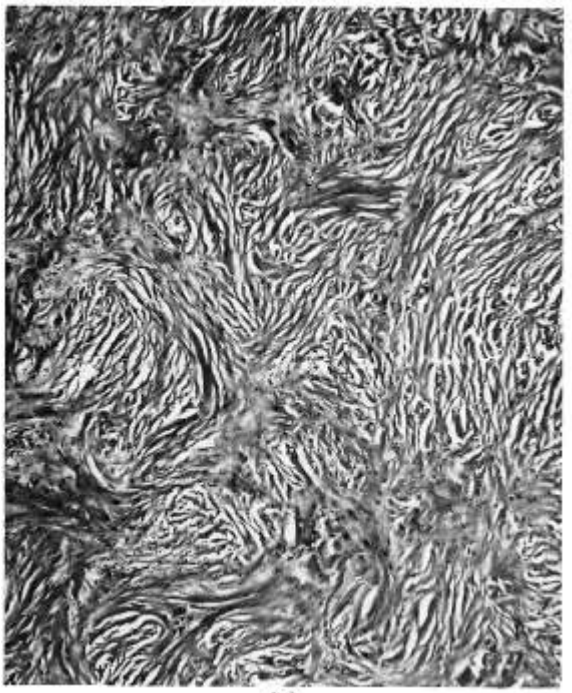


(d)



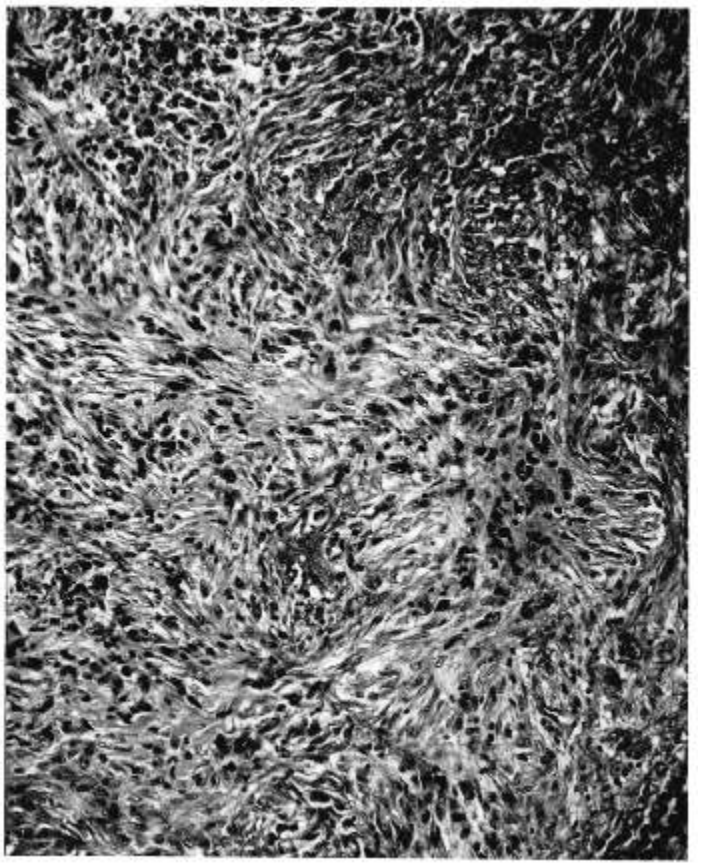
(*a*)

tion incited by invasive squamous carcinoma of skin origin. In one exceptional case, the infiltrate was so intense that it mimicked a lymph node.

SPECIAL STAINS

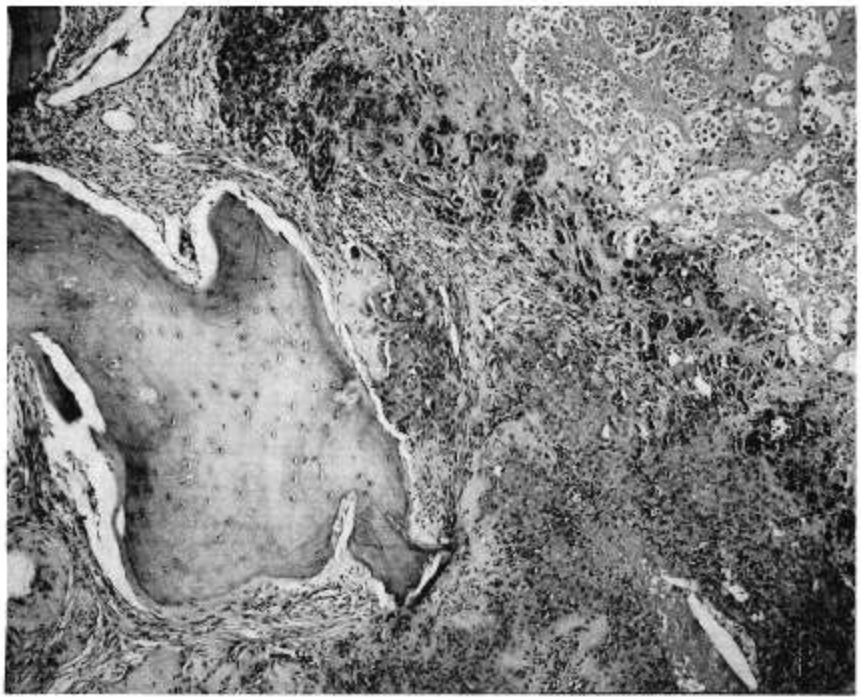
Routine stains

Although a correct diagnosis could generally be made with hematoxylin and eosin stains, other preparations were helpful in demonstrating certain features of the tumor or in excluding other diagnostic considerations. Reticulin and trichrome stains highlighted the nodular growth pattern and emphasized the intercellular collagen. Many tumors contained glycogen and showed PAS positivity (Fig. 10). Although extracellular acid mucopolysaccharides (hyaluronidase-sensitive) were present, intracellular mucin production was conspicuously absent. Occasional tumors contained neutral lipid. Iron stains helped identify the pigment, found in many tumors, as hemosiderin. Aldehyde fuchsin, Fontana and Warthin–Starry (pH 3.2) melanin stains, and preparations for acid-



(*b*)

FIGURE 8
Storiform growth patterns were focally seen in 5% of the cases. (*a*) Lesion from the foot of a 21-year-old male showing tight fascicular arrangements and artifactual retraction spaces. Other regions were classic for epithelioid sarcoma. (AFIP Neg. 84-7388.) (*b*) Tumor from the knee of a 21-year-old male showing prominent spindling and intercellular collagen. (AFIP Neg. 84-6647.)



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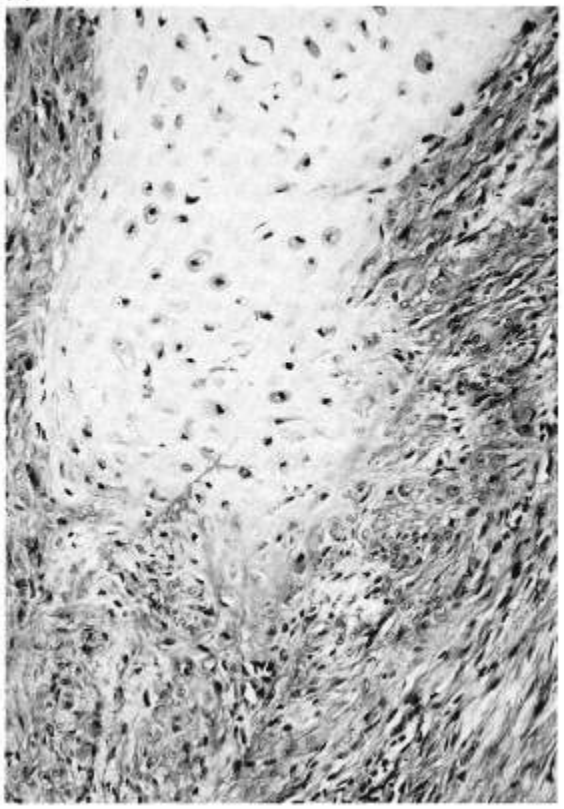


(b)

FIGURE 9
Metaplastic elements. (*a*) This tumor, from the calf of a 51-year-old male, showed bone formation, a feature displayed in 10% of the tumors. Generally, osseous metaplasia was not a bad prognostic sign. (AFIP Neg. 84-6639.) (*b*) Cartilaginous differentiation occurred only in this case, a tumor from the ankle of a 15-year-old female. The tumor recurred three times before metastasizing. (AFIP Neg.84-7391.)

fast or fungal organisms were all uniformly negative.

Immunohistochemical stains

Table 2 depicts our immunohistochemical experience with epithelioid sarcoma. Over 75% of the cases demonstrated the presence of cytokeratins (34/44), reacting to polyclonal antibodies directed against human plantar callus (Fig. 10).[4] Initially we were perplexed when several of the cases stained positively for HFVIII, but repeat studies using trypsin predigestion were uniformly negatively. Stains for S-100 protein helped in the elimination of several melanomas; however, one of the cases that we included was weakly positive, a finding we cannot explain at this time. Stains for CEA protein were positive in 38% of the tumors that were addressed (5/13). Stains directed against the so-called histiocytic markers, LYS, AAT and ACT, showed positive reactions in 17% (3/18), 53% (10/19), and 73% (8/11) of the cases, respectively.

DIFFERENTIAL DIAGNOSIS

Necrobiotic granuloma

Although the pattern of necrosis may mimic that of epithelioid sarcoma, a necrobiotic granuloma

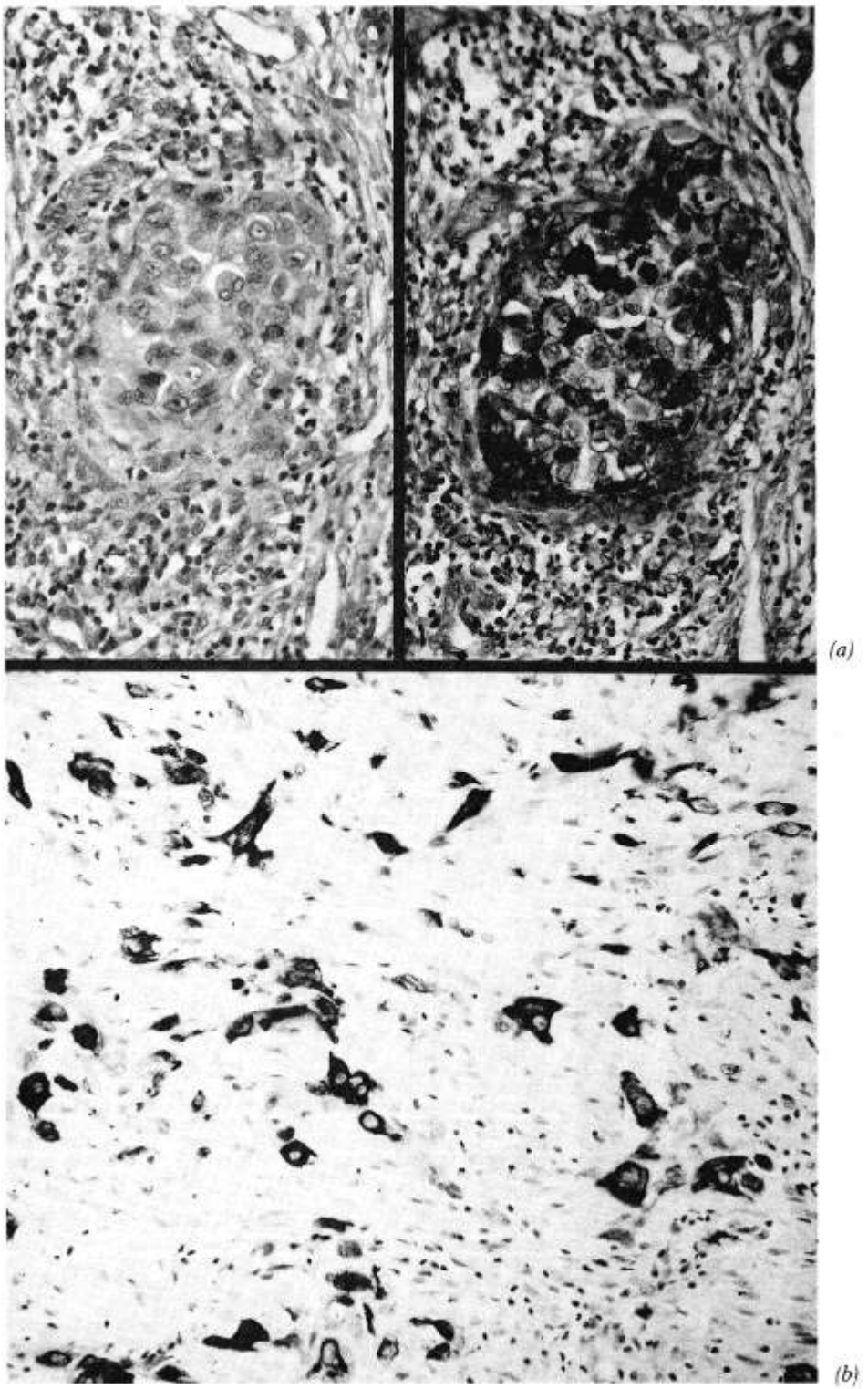


FIGURE 10
Special stains. (*a*) This tumor, resected from the palm of a 10-year-old male, was PAS-positive (left view H&E, right view PAS). (AFIP Neg. 84-6621, 84-7397.) (*b*) Over 75% of our cases have shown cytokeratin positivity. This tumor was from the palm of a 24-year-old male. Note immunoreactivity in both the polygonal and spindle cells. (AFIP Neg. 83-9603.)

TABLE 2.

Epithelioid Sarcoma: Immunohistochemical Staining Patterns

Stain[a]	Total	Positive Cases	Negative Cases	Percent Positive
CK	44	34	10	77%
CEA	13	5	8	38%
S100	12	1	11	8%
HFVIII	11	0	11	—
LYS	18	3	15	17%
AAT	19	10	9	53%
ACT	11	8	3	73%

[a] Predigestion with trypsin was performed on all HVIII and ACT stains. Most of the CK, LYS, and ATT stains also utilized predigestion. Trypsinization was not done on the CEA or S-100 stains.
Abbreviations: CK = cytokeratins; CEA = carcinoembryonic antigen; HFVIII = human factor VIII; LYS = lysozyme; AAT = alpha-1-antitrypsin; ACT = alpha-1-antichymotrypsin.

TABLE 3.

Diagnoses Suggested (Other than Epithelioid Sarcoma)

Benign (91 Cases)	Malignant (57 Cases)
Fibrous histiocytoma—18	Synovial sarcoma—18
Fasciitis—9	Fibrosarcoma—11
Other reactive processes—9	Sarcoma not classified—10
Fibromatosis—8	Carcinoma—4
Synovioma—6	Clear cell sarcoma—3
Atypical fibroxanthoma—5	Rhabdomyosarcoma—3
Giant cell tumor of tendon sheath—5	Malignant fibrous histiocytoma—2
Fibroma—4	Angiosarcoma—2
Tenosynovitis—2	Dermatofibrosarcoma protuberans—1
Proliferative myositis—2	Other—3
Juvenile aponeurotic fibroma—1	
Granuloma annulare—1	
Foreign-body granuloma—1	
Neurofibroma—1	
Hemangiopericytoma—1	
Other—18	

(NG) usually contains more inflammatory elements and displays less distinct cells with little cellular pleomorphism. Giant cells are much more common in NG, as are zones of capillary proliferation. Although both processes may contain iron pigment and varying numbers of mitotic figures, NG usually contains more hemosiderin and displays fewer mitotic figures than does epithelioid sarcoma.

Giant cell tumor

The cell populations of the two tumors are different: a GCT usually displays more multinucleated giant cells as well as uniform, rounded uninuclear cells with amphophilic or basophilic cytoplasm and minimal spindling. Epithelioid sarcoma, however, appears more acidophilic and shows more spindled elements, increased pleomorphism, and active nuclear features. The presence of cytokeratins, and a "geographic" pattern of necrosis, if present, are more in keeping with epithelioid sarcoma.

Malignant fibrous histiocytoma

In the cases where a storiform pattern is focally present, the presence of necrosis and cellular pleomorphism may lead to a diagnosis of malignant fibrous histiocytoma. The pleomorphism of epithelioid sarcoma, however, usually falls short of that seen in a MFH, and bizzare tumor giant cells are virtually never seen. Also of importance is the multinodular pattern and absence of xanthoma cells in the epithelioid sarcomas of this study, as well as the presence of immunoreactive cytokeratins and, in many cases, glycogen.

Squamous carcinoma

Because of the epithelial-like character of the cells and the tendency to ulcerate, a diagnosis of infiltrating squamous carcinoma might be contemplated. Epithelioid sarcoma, however, completely lacks epidermal hyperplasia or atypia, and though both tumors may contain immunoreactive cytokeratins, there are no keratin pearls in epithelioid sarcoma.

Malignant melanoma

Although the more common pigmented variety of melanoma is not usually mistaken for epithelioid sarcoma, by light microscopy "amelanotic" forms may present a problem. Abnormal junctional activity was not observed in any epithelioid sarcoma. If epithelioid sarcoma contains pigment, it is invariably iron, stainable with the Prussian blue reaction. A Fontana stain or the more sensitive Warthin-Starry (pH 3.2) preparation may help exclude a melanocytic origin, although we have found that the S-100 protein reaction is a more reliable indicator of neuroectodermal origin. Furthermore, melanomas do not usually produce an acid mucopolysaccharide matrix, as may be seen in epithelioid sarcoma (Fig. 7*d*).

Synovial sarcoma

Although both tumors may contain epithelial and spindled elements, we have never observed the abrupt transition in epithelioid sarcoma that is

seen in biphasic synovial sarcoma. The spindled elements of synovial sarcoma are usually more fusiform and have a tendency to grow in whorls or long fascicles, similar to a fibrosarcoma. This long fascicular growth is not seen in epithelioid sarcoma. Although both tumors may express cytokeratins and extracellular mucin, in our experience the presence of intracytoplasmic mucin droplets is a feature exhibited only by synovial sarcoma. Additionally, CEA reactivity seems to be more common in epithelioid sarcoma (5/13) than in synovial sarcoma (1/7).

Epithelioid hemangioendothelioma

These recently described vascular neoplasms have been mistaken in the past for epithelioid sarcoma, since both tumors consist of plump, polygonal cells having an epithelial appearance.[39] The cells of epithelioid sarcoma, however, are usually deeply eosinophilic, whereas those of epithelioid hemangioendothelioma are more pale, amphophilic, and are surrounded by a hyalin matrix. Although intracytoplasmic vacuoles are a feature common to both tumors, only the vacuoles in EH contain erythrocytes. Furthermore, EH generally shows HFVIII immunoreactivity and is cytokeratin-negative, in contrast to epithelioid sarcoma which is HFVIII-negative, and usually demonstrates cytokeratins. Additionally, the presence of necrosis with a surrounding "geographic" cellular proliferation is much more in favor of epithelioid sarcoma.

CLINICAL BEHAVIOR

Following the initial surgical procedure,the tumor recurred in 77% of the cases with follow-up (155/202). Thirty-one percent of the tumors recurred only once (63/202), 27% recurred twice (55/202), 8% recurred three times (17/202), and 10% recurred more than three times (20/202). The recurrences generally occurred proximal to the initial primary site and averaged (mean) 2.3 additional resections.

Ninety of the patients in the follow-up group sustained metastasis (45%). In this group, metastatic sites were specified in 83 cases (Table 4), and the initial site of metastasis mentioned in 63. Of these, the most frequent initial sites were lymph nodes (48%) and lungs (25%). Less common initial sites included scalp (10%), skin other than scalp (6%), and mediastinum, dural space, liver, bone, and brain. Although pulmonary spread was reported as the first site of metastasis in only 25% of the cases that metastasized, lung involvement was ultimately reported in 51% of the metastatic cases (42/83).

TABLE 4.

Epithelioid Sarcoma: All Metastatic Sites (83 Cases)

Site	Cases	Percent
Lung	42	51%
Lymph nodes[a]	28	34%
Scalp	18	22%
Bone	11	13%
Brain	11	13%
Liver	10	12%
Pleura	9	11%
Others[b]		

[a] Since lymph nodes were not examined in many of the cases, the actual number may be higher than indicated.

[b] In decreasing frequency: diaphragm (4), kidney (3), mediastinum (3), epidural space (2), pericardium (2), adrenal (2), deep striated muscle (2), pancreas, thyroid, hard palate, optic nerve, myocardium, dura, periosteum, duodenum, esophagus.

PROGNOSTIC INDICATORS

Site

In general, the more proximal or axial the primary site,the worse the outcome (Table 5). Regions with an increased risk of metastasis were the proximal upper extremities, 71% (15/21), and the trunk, 57% (4/7). A somewhat decreased metastatic rate was noted in the most common region, the distal upper extremity, where tumors metastasized in 38% of the cases (44/116).

Sex

Tumors in 67 females with follow-up averaged 3.4 cm in greatest diameter compared to those of 134 males which averaged 3.7 cm. They also had fewer mitotic figures per 10 HPF (2.3 vs. 3.2) and exhibited less hemorrhage. We found that not only did epithelioid sarcoma occur less frequently in females, it behaved more favorably (Table 6). It presented in slightly older patients; the mean age at diagnosis in females was 30 years, 9 months, compared to 26 years, 7 months in males. With similar follow-up periods of 6 years,10 months, we found that 78% of the females were alive and 64% of the males. Although both had comparable local recurrence rates (females 79%, males 75%), females averaged "only" 1.8 additional resections compared to 2.6 in males. Additionally, the local recurrence rates differed following amputation. In females only 7% (2/27) of the tumors recurred locally following amputation, compared with 26% (17/66) in males. Whereas 30% of the tumors

TABLE 5.

Epithelioid Sarcoma: Behavior by Site (202 Cases)

Site of Primary	No.	Sex M:F	Mean Follow-up	Alive	Local Recur.	No. of Recur.	MET	DOD
Head and Neck								
Scalp	2	2:0	2y 5m	2/2	2/2	3.5	1/2	0/2
Ear	1	1:0	7y 1m	1/1	0/1	—	0/1	0/1
Subtotal	3	3:0	4y 0m	3/3	2/3	3.5	1/3	0/3
Trunk								
Chest wall	1	1:0	18y 0m	0/1	1/1	7.0	1/1	1/1
Abd. wall[a]	2	0:1	8y10m	0/2	2/2	4.5	1/2	2/2
Sacral	1	0:1	9y 9m	1/1	1/1	2.0	1/1	0/1
Ishiorectal	1	1:0	9y 9m	0/1	1/1	1.0	0/1	0/1
Vulva	2	0:2	8y 1m	1/2	2/2	2.5	1/2	1/2
Subtotal	7	2:4	10y 3m	2/7	7/7	3.4	4/7	4/7
Proximal Upper Extremity								
Shoulder	5	4:1	5y 6m	2/5	2/5	1.0	4/5	3/5
Axilla	1	1:0	1y 0m	0/1	0/1	—	1/1	1/1
Upper arm	10	7:3	4y11m	3/10	6/10	2.3	8/10	7/10
Elbow	5	4:1	8y 8m	3/5	5/5	1.2	2/5	2/5
Subtotal	21	16:5	5y 8m	8/21	13/21	1.7	15/21	13/21
Distal Upper Extremity								
Forearm	30	20:10	6y 2m	24/30	22/30	1.7	14/30	6/30
Wrist	9	6:3	5y 0m	4/9	8/9	1.9	7/9	5/9
Hand/Palm	33	18:15	6y 9m	28/33	29/33	2.0	8/33	5/33
Fingers	41	28:13	7y11m	31/41	33/41	3.1	2/41	9/41
Thumb web	3	2:1	7y 0m	3/3	3/3	1.3	3/3	0/3
Subtotal	116	74:42	6y10m	90/116	95/116	2.3	44/116	25/116
Proximal Lower Extremity								
Hip	2	1:1	6y 6m	2/2	0/2	—	0/2	0/2
Buttock	5	2:3	6y 0m	3/5	4/5	2.8	2/5	2/5
Thigh	10	9:1	7y 1m	6/10	4/10	1.3	4/10	4/10
Knee	8	7:1	6y 4m	5/8	6/8	1.8	4/8	3/8
Subtotal	25	19:6	6y 6m	16/25	14/25	1.9	10/25	9/25
Distal Lower Extremity								
Lower leg	18	11:7	7y 8m	13/18	13/18	2.6	9/18	5/18
Ankle	3	1:2	9y 5m	2/3	3/3	2.3	2/3	1/3
Foot/heel/sole	8	7:1	6y 6m	4/8	7/8	2.9	4/8	4/8
Toes	1	1:0	5y 1m	0/1	1/1	1.0	1/1	1/1
Subtotal	30	20:10	6y10m	19/30	24/30	2.6	16/30	11/30
Totals	202	134:67	6y10m	138/202 (68%)	155/202 (77%)	2.3	90/202 (45%)	62/202 (31%)

[a] The two abdominal wall tumors include one case where the sex of the patient was not given, and another case where the patient died of extensive local disease and an autopsy was not performed. Metastasis was not clinically evident.[2] MET = metastasis, DOD = dead of disease.

ultimately metastasized in females, 51% did so in males, accounting for a 21% female fatality compared to a 35% male fatality. Although metastatic sites appeared similar for both sexes, all six cases that initially spread to scalp occurred in males.

Age at first diagnosis

Although females presented with tumors at later ages than males (and doing better), we found that, in general, tumors diagnosed and treated at earlier ages behaved more favorably. The 140 nonfatal cases occurred an average of almost 5 years earlier than did the 62 fatal ones; 26 years, 6 months versus 31 years, 3 months. Tumors presenting in the first decade of life did very well. The neoplasms in this age group were generally small and dis-

TABLE 6.

Epithelioid Sarcoma: Differences by Sex (201 Cases)

	Mean Age First DX	Mean Follow-up	Alive	Local Recur.	No. of Recur.	MET	Recur. Post-Amputation	DOD
Males (no. = 134)	26y 7m	6y10m	86/134 (64%)	101/134 (75%)	2.6	69/134 (51%)	17/66 (16%)	47/134 (35%)
Females (no. = 67)	30y 9m	6y10m	52/67 (78%)	53/67 (79%)	1.8	20/67 (30%)	2/27 (7%)	14/67 (21%)
Totals (no. = 201)	27y11m	6y10m	138/201 (69%)	154/201 (77%)	2.3	89/201 (44%)	19/93 (20%)	61/201 (30%)

TABLE 7A.

Epithelioid Sarcoma: Behavior by Decade (202 Cases)

Age at First DX	No.	Sex M:F	Mean Follow-up	Alive	Local Recur.	No. of Recur.	MET	DOD
0–9	7	4:3	5y 1m	7/7	4/7	1.5	0/7	0/7
10–19	59[a]	37:21	6y 9m	44/59	47/59	2.0	22/59	15/59
20–29	63	50:13	6y 9m	39/63	49/63	2.7	31/63	23/63
30–39	38	25:13	5y11m	27/38	26/38	2.0	15/38	10/38
40–49	14	8:6	9y10m	9/14	12/14	1.4	9/14	5/14
50–59	13	8:5	5y 5m	7/13	11/13	2.7	9/13	6/13
60–69	4	0:4	11y 4m	4/4	4/4	2.0	0/4	0/4
70–79	2	1:1	1y 1m	0/2	0/2	—	2/2	2/2
80–89	2	1:1	4y 9m	1/2	2/2	1.0	2/2	1/2
90–99	0							

[a] Includes one case where sex of patient was not given.

TABLE 7B.

Epithelioid Sarcoma: Behavior by Sex and Decade

Age at First Surg.	No.	Local Recurrence	Metastasis	Dead of Disease
Males				
9–9	4	1/4 (25%)	0/4 (—)	0/4 (—)
10–49	120	92/120 (77%)	61/120 (51%)	43/120 (36%)
50+	10	8/10 (80%)	8/10 (80%)	4/10 (40%)
Females				
0–9	3	3/3 (100%)	0/3 (—)	0/3 (—)
10–49	53	40/53 (75%)	15/53 (28%)	9/53 (17%)
50+	11	10/11 (91%)	5/11 (45%)	5/11 (45%)

played little necrosis. Of the seven cases diagnosed before the age of 10, none metastasized (Tables 7A and 7B); however, there was a 57% recurrence rate (4/7).

Intervals

The fatal cases averaged 1 year, 6 months from the initial surgical procedure to the first recurrence and the nonfatal cases, 2 years, 1 month. No difference was noted in the interval from the first to the second recurrence, both averaging 1 year, 9 months. Curiously, the time to the first metastasis was greater in the fatal cases, averaging 4 years, 1 month, versus 3 years, 4 months in the nonfatal ones.

Local recurrence

Seventy-seven percent of the cases showed at least one tumor recurrence and averaged 2.3 additional resections. Of more interest, however, was the group that did not sustain recurrence (47/202). Seventeen of these 47 tumors metastasized (36%), killing 13 patients (Table 8). Primary tumors that metastasized most frequently without first recur-

TABLE 8.

Epithelioid Sarcoma: Behavior of Tumors without Local Recurrence (47 Cases)

	No.	Mean Age First Surg.	Mean Follow-up	Alive	Metastasis	Dead of Disease
Male	33	25y 6m	4y 6m	24/33 (73%)	13/33 (39%)	9/33 (27%)
Females	14	30y 8m	5y 8m	10/14 (71%)	4/14 (29%)	4/14 (29%)
Totals	47	27y 1m	4y10m	34/47 (72%)	17/47 (36%)	13/47 (28%)

ring included those in the axilla (1/1), shoulder (2/5), upper arm (3/10), thigh (3/10), forearm (4/30), and lower leg (2/18). Less likely to metastasize before recurring were tumors arising in the hand (1/33) or in the finger (1/41). Figure 11 illustrates that the number of recurrences was not an accurate prognostic harbinger of metastasis. Although the percentage of tumors that metastasized did increase with increased numbers of recurrences, the rising risk was smaller than expected.

Tumor size and depth

The tumor size at initial presentation was specified in 73 of the 202 tumors with follow-up. The indicated range was from 0.5 to 15 cm with a mean of 3.6 cm. In general, patients with tumors less than 2.0 cm did considerably better than did the patients with larger tumors (Fig. 12). No tumor smaller than 1.0 cm proved fatal, although one that size did metastasize. The smallest tumor to cause death was 1.5 cm in diameter. Deeply seated tumors shown microscopically to involve skeletal muscle did worse. When this was observed, 64% of the male patients and 67% of the female patients developed metastases. By contrast, the tumor behaved much better when it occurred in the superficial dermis or was confined in fascia or tendon; metastases were seen in 46% of the male and in 24% of the female patients.

Mitotic rates

Mitotic rates roughly paralleled the incidence of metastasis and ranged from 1 to 14/10 HPF in the initial biopsy material of the patients with follow-up. Thirty percent of these tumors had up to 1 mitotic figure/10 HPF and had a 27% metastatic rate. Tumors demonstrating 2 figures/10 HPF (23%) showed a 39% incidence of metastasis while

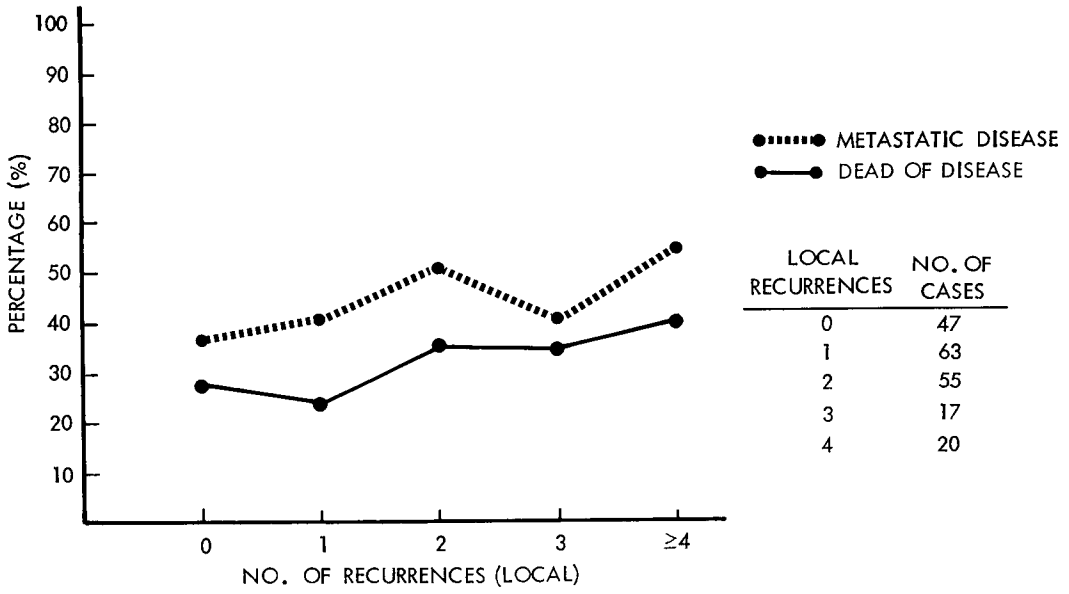
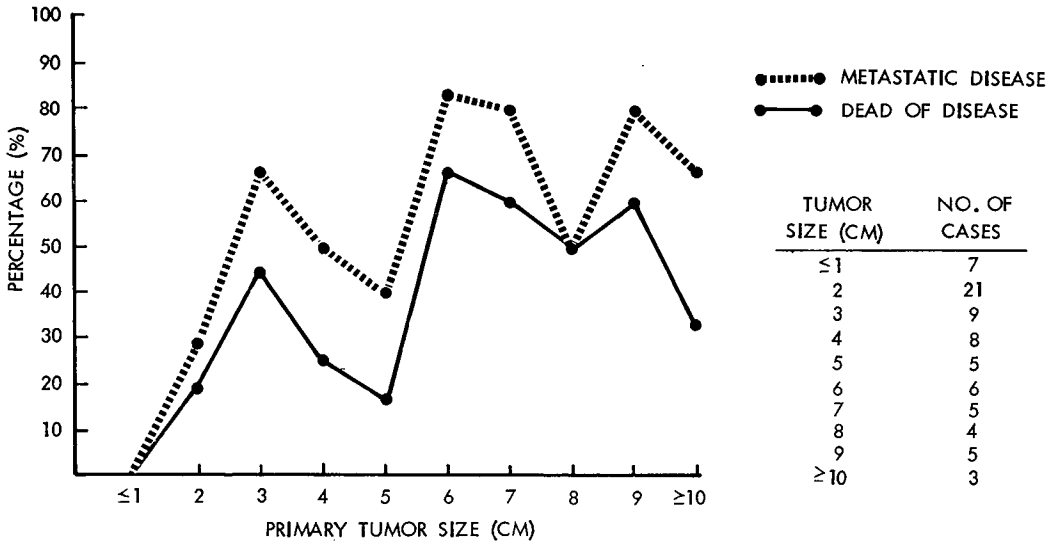


FIGURE 11

Number of recurrences plotted against tumor behavior in 202 patients with follow-up. The difference between the lines reflects patients who were alive but had sustained metastasis. Note the large number of cases that metastasized without recurrence. (AFIP Neg. 84-7782.)



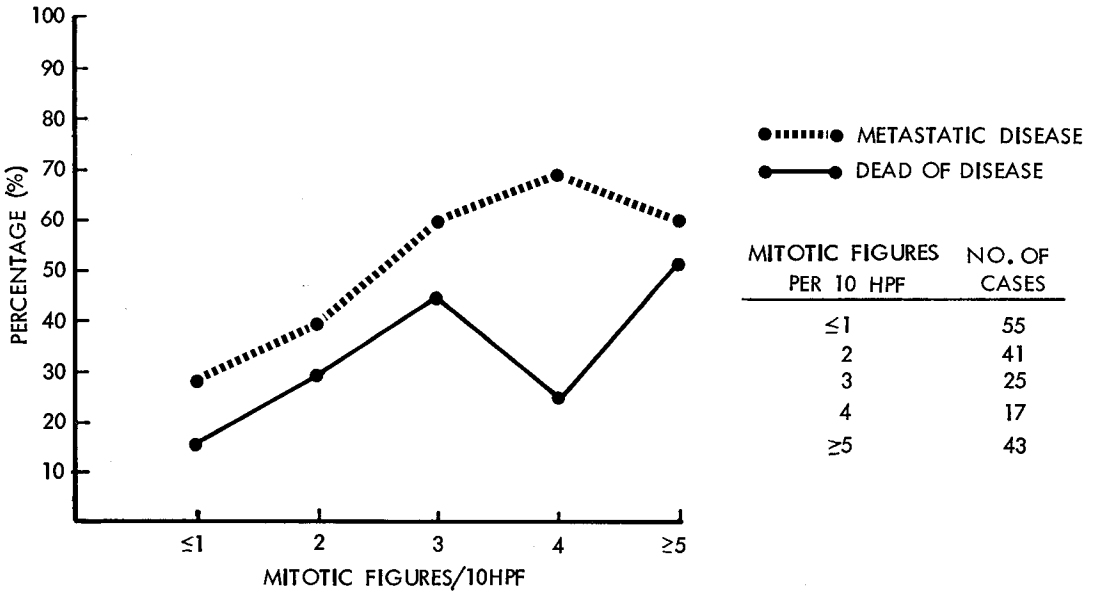
TUMOR SIZE (CM)	NO. OF CASES
≤1	7
2	21
3	9
4	8
5	5
6	6
7	5
8	4
9	5
≥10	3

FIGURE 12
Size of the primary tumor plotted against tumor behavior (73 cases). (AFIP Neg. 84-7779.)

the remaining tumors, with 3 or more mitotic figures/10 HPF, showed at least a 60% metastatic rate (Fig. 13).

Tumor necrosis and hemorrhage

As in most soft tissue tumors, the amount of tumor necrosis paralleled tumor metastasis (Fig. 14). In tumors with little or no necrosis (29 cases), 34% metastasized. In largely necrotic tumors (nine cases), 88% metastasized. Of interest was an inverse relationship of recurrence to necrosis; recurrences fell from 94% in those tumors with little necrosis to 64% in the highly necrotic tumors. The reason for the fall was perplexing, but might reflect more aggressive clinical treatment given highly necrotic tumors. In general, we found that



MITOTIC FIGURES PER 10 HPF	NO. OF CASES
≤1	55
2	41
3	25
4	17
≥5	43

FIGURE 13
Number of mitotic figures in initial biopsy or resection material plotted against tumor behavior (181 cases). (AFIP Neg. 84-7783.)

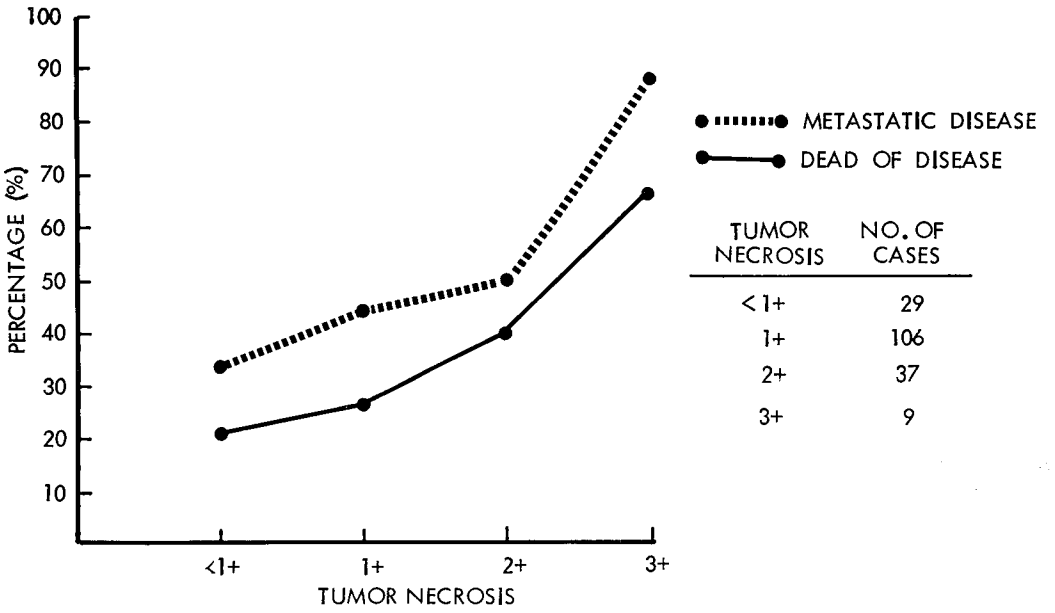


FIGURE 14
Degree of tumor necrosis in initial biopsy or resection material plotted against tumor behavior (181 cases). (AFIP Neg. 84-7784.)

hemorrhagic tumors behaved poorly. The tumor metastasized in 32% of the cases where hemorrhage was negligible (22/68) and in 81% when hemorrhage was considerable (22/27). As might be expected, the degree of hemorrhage paralleled tumor size, mitotic activity, and the degree of necrosis.

Invasion

The presence of vascular invasion (Fig. 15) herald-

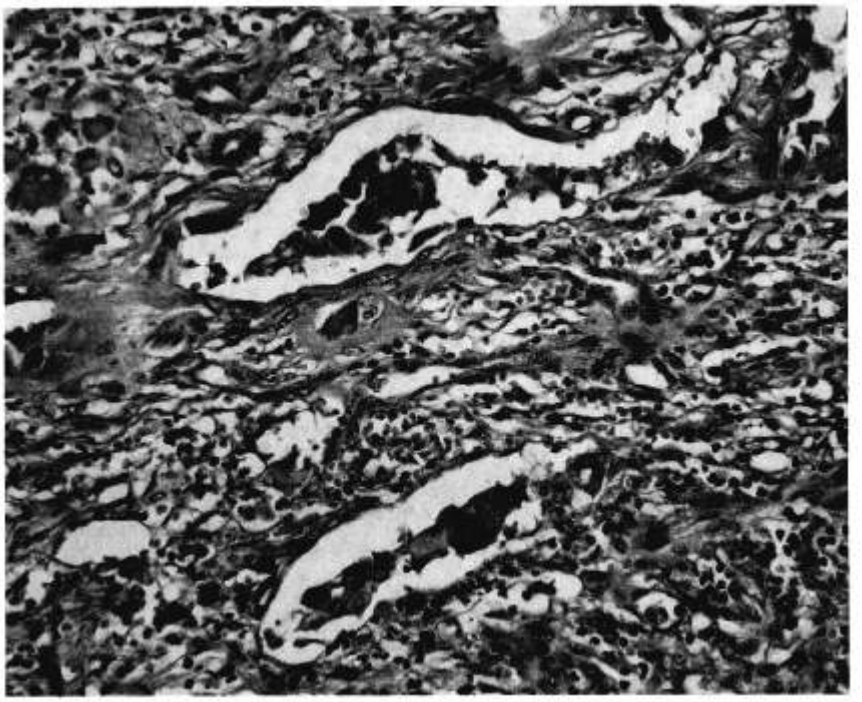


FIGURE 15
Vascular invasion was associated with metastasis in 96% of the cases in which it occurred. This tumor is from the leg of a 13-year-old male who died 8 years later with widespread metastatic disease. (AFIP Neg. 84-7387.)

TABLE 9.

Epithelioid Sarcoma: Invasiveness vs. Behavior

Invasion	No.	Alive	Recurrence	Metastasis	Dead of Disease
Vascular	23	8/23 (35%)	16/23 (70%)	22/23 (96%)	15/23 (65%)
Neural	14	8/14 (57%)	8/14 (57%)	6/14 (43%)	6/14 (43%)
Total	202	138/202 (68%)	155/202 (77%)	90/202 (45%)	62/202 (31%)

ed a 96% incidence of metastasis (Table 9). Neural invasion, however, was less ominous, associated with metastasis in 43%.

Lymphocytic infiltrate

Metastasis did not seem related to the degree of lymphocytic infiltration; however, when lymphocytes were absent or only minimally present, there was a 92% recurrence (24/26).

THERAPY

Although we are at a handicap in discussing therapy, since all the cases were tumors seen in consultation and treated elsewhere, our data indicate that it is important that "cure" not be claimed without long-term follow-up. Five percent (3/62) died as late as 18 and 19 years after the initial surgical procedure (Fig. 16). As chemotherapy and radiotherapy results have generally been dismal, early aggressive surgical management appears to be the treatment of choice. Though dependent somewhat upon the site of origin, this usually means radical surgery, or amputation if radical resection is not feasible. In support of such initial aggressive therapy are the high local recurrence rate and the poor results of chemotherapeutic agents. Also supportive of aggressive early treatment is the fact that the tumor may metastasize to distant sites without first involving regional lymph nodes.

Unfortunately, even amputation did not assure good results. Ninety-three patients were treated in this manner, and of these, 65% (60/93) were alive at the end of the follow-up period. Of interest is the high 20% recurrence following amputation. This probably reflects subtle tumor growth beyond the boundaries of clinically identifiable disease and implies the need for even wider surgical margins than is usually thought necessary. This probably also accounts for the high local recurrence rate in general (77%). It is interesting that the tumor recurred after amputation more commonly in males

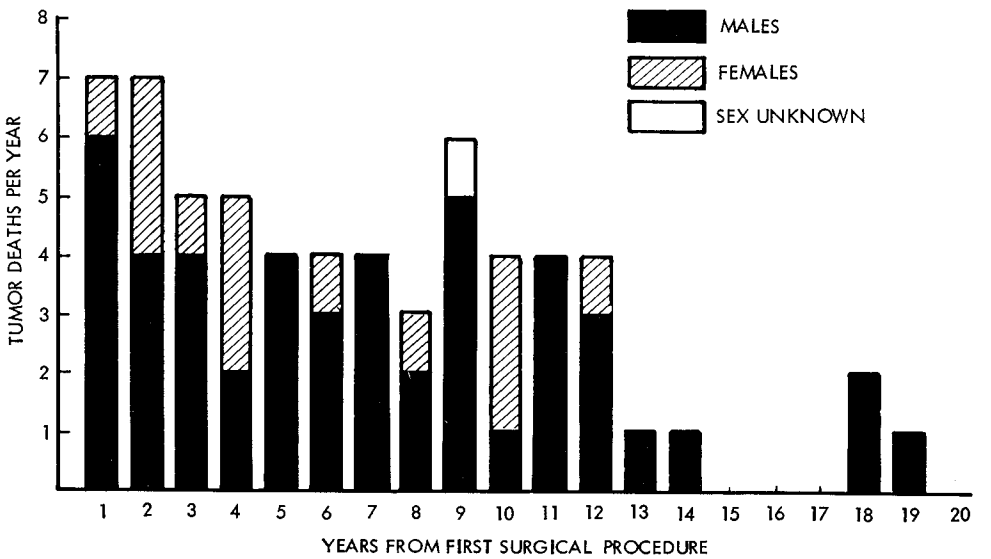


FIGURE 16
Years from first surgical procedure to death of disease. (AFIP Neg. 84-7780.)

than in females. This "curability" of females by radical procedures remains unexplained but might be explained by hormonal influences.

Because of the slow growth of the tumor, resection of solitary metastatic lesions may be considered in specific cases. One patient had segmental pulmonary resections on two different occasions for metastatic disease from a finger tumor (the finger had been previously amputated). Though only 2 years have elapsed since the second pulmonary resection, no additional disease has been noted.

Many of our patients had palliative radiation therapy (RT) to distant metastatic sites. These treatments seemed only to diminish the size of the tumor, without significantly altering the overall outcome. We found that in several cases, radical tumor excision combined with RT to the primary tumor site seemed to result in a more favorable outcome. The radiation in these cases was of high dose, usually 6,000 rads or more, given locally. Caution must be urged, however, as our numbers are still few and interpretation of favorable behavior with this treatment must be viewed in the light of the known, long, protracted natural history of the tumor.

The reported experience with chemotherapy in these tumors has not been very encouraging. The most commonly used agents were adriamycin, vincristine, cytoxan, actinomycin D, and methotrexate. Other agents included leucovoran factor, DPIC, platinol, phenylalanine mustard, oncovin, and interferon. Use of these agents was usually limited to cases with advanced metastases and no "cures" could be directly attributed to their use.

GENERAL DISCUSSION

Epithelioid sarcoma can be a difficult histologic diagnosis, especially with only a single surgical specimen which may not be diagnostic or representative of the neoplasm. Many of these tumors demonstrate different microscopic appearances with progression following recurrence or metastasis; in some, a correct diagnosis may be made only by thorough examination of the entire case. Because of this, review of all material is mandatory.

The elevated metastatic rate in this study (45%) probably reflects the length of follow-up, which was as long as 39 years in one patient. Prolonged follow-up appears mandatory in accurately evaluating the true behavior of this tumor. Indeed, it is difficult to talk of even a 10- or a 15-year survival period since several of the patients died of disease up to 19 years after their initial procedure. That the rate of tumor deaths (31%) is 14 percentage points lower than the metastatic rate merely emphasizes this indolent course. We might expect more deaths with an even longer follow-up period.

The sex incidence varies in different age groups. It is nearly equal in the first decade of life and in the years after 50, but there is a marked male predominance (120:53) in the middle years (10–49). As pointed out previously, during the middle years females appear to have a much better prognosis than males. These findings, in the decades of increased sex hormone levels, suggest that some factor, perhaps hormonal, may "protect" females from developing the tumor or from the more aggressive tumor behavior seen in males during this period. Certainly a study of hormonal influences, particularly receptor proteins, seems appropriate.

As with the vast majority of other soft tissue sarcomas, the reason the tumor develops remains unclear. The relatively high percentage of cases with unsolicited histories of trauma (20%) and the large numbers of primary tumors associated with nonhealing wounds and chronic sinus tracts leads to speculation that the tumor, at least in some cases, may begin as a florid reactive process in which proliferative control is lost, ultimately resulting in an autonomous, neoplastic proliferation. Such an interpretation, however intriguing, is difficult to prove.

The nature of epithelioid sarcoma has been debated since the first description of this tumor. We continue to feel that it is a mesenchyme-derived neoplasm, despite the cytokeratin positivity that it exhibits. Epithelial origin is doubted, as we have been unable to document dysplastic processes in the overlying epidermis or within skin adnexal structures. Additionally, many tumors arise in deep locations, in association with mesenchyme-derived tendons and fascia, far removed from epithelial-derived tissues.

Synovioblastic differentiation has been suggested by several authors; one suggested that epithelioid sarcoma be lumped together with chordoid sarcoma and synovial sarcoma under the term "tenosynovial sarcoma." [12] Although epithelioid sarcoma and synovial sarcoma do have similarities, we continue to feel that each represents a distinct entity. The anatomic distributions are different; epithelioid sarcoma affects the distal extremities and superficial locations much more commonly than does synovial sarcoma. The incidence of ulceration, recurrence, and lymph node metastasis is also greater in epithelioid sarcoma. Furthermore, the transition from epithelioid cells

to spindled elements in epithelioid sarcoma is always more gradual than in biphasic synovial sarcoma. Additionally, the spindled elements of epithelioid sarcoma rarely form the prominent fascicular or whorled growth commonly seen in synovial sarcoma. We have recently found that despite the fact that both tumors exhibited cytokeratin production, epithelioid sarcoma reacts to CEA protein antibodies more frequently. Intracytoplasmic mucin is frequently seen in synovial sarcoma but is not a feature of epithelioid sarcoma. □

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