ACTA ORTHOPAEDICA SCANDINAVICA
SUPPLEMENTUM No. 111

From the Departments of Orthopaedics (Head, Professor S. Friberg, M. D.) and Radiopathology (Act. head: Professor G. Moberger, M. D.), Karolinska Institutet, Stockholm, Sweden.

Synovial sarcoma

HISTOLOGIC FEATURES AND PROGNOSIS

BY GUNNAR MOBERGER, ULF NILSONNE AND STEN FRIBERG JR.

MUNKSGAARD COPENHAGEN 1968

Introduction

Synovial sarcomas constitute a rare but interesting clinicopathologic entity among the malignant soft tissue tumors. These tumors are reported to comprise about 8% (*Ariel and Pack* 1963) of all malignant neoplasms of the soft somatic tissues. In Sweden only a few cases (5—10) occur annually according to the Cancer Registry of the National Board of Health 1958—1963 (*Ringertz and ass.* 1963)

Although the histologic features of synovial sarcoma have been adequately described, a considerable number of tumors are still erroneously classified as synovial sarcomas. Cases of proliferative inflammatory processes may also be misdiagnosed as synovial sarcoma with due risk to the patient of unnecessary therapeutic measures such as amputation of an extremity. As pointed out by *Cade* (1962), the comparative rarity of the tumors in any one hospital, and hence the limited experience of individual histopathologists add to the diagnostic difficulties.

The number of publications on synovial sarcoma is great, but there are only a few reports of series with sufficient number of cases and adequate follow-up to permit reliable clinicopathologic considerations. Thus factors influencing prognosis have not been well established, and a possible relationship between the histologic features of the tumors and the clinical course still remains controversial.

The main purpose of the present investigation has been three-fold:

1. To elucidate the morphologic characteristics of synovial sarcomas with special emphasis upon the differential diagnosis in regard to non-neoplastic or benign lesions and other types of mesenchymal sarcomas,
2. To make proper a correlation between the microscopic appearence of the tumors and the clinical course in a sufficient number of cases with adequate follow-up,
3. To study other factors which may influence prognosis.

Previous investigations.

Tumors arising from joint capsules, tendon sheaths and serous bursae were described as early as 1852 when *Chassignac* first reported a tumor of the tendon sheath. The tumor frequently ascribed to be the first published case of synovial sarcoma, however, was a lesion of the joint capsule, described by *Simon* in 1865. Due to the intraarticular location and the histologic features of this lesion, however, it can be assumed to have been a case of villonodular synovitis. *Stüer* in 1893 described a tumor of the elbow joint which was diagnosed as an *adenosarcoma,* with likely origin in the synovial membrane. This metastasizing tumor thus deserves to be referred to as the first published case of a true synovial sarcoma of the joint capsule. A similar case in the knee joint was also reported by *Hardie and Salter* in 1894, and was diagnosed as a *spindle cell sarcoma.* Thorough reviews of the early publications on synovial tumors were presented by *Jönsson* (1938), *Moll* (1960) and *Geiler* (1961).

The first adequately described case of synovial sarcoma was published by *Lejars and Rubens-Duval* in 1910. They described characteristic spaces lined with "l'endothelium synoviale" in the tumor tissue and hence adopted the term *synovial endothelioma. Tourneux* (1913) reviewed and described sarcomas of tendon sheaths and joint capsules as a distinct entity and recognized that the presence of giant cells indicated a benign course. He also observed two types of tumors, fusiform and "pseudoepithelial", designated both as *endotheliomas.*

In 1927 *Smith* introduced the term *synovioma* and considered tumors originating in tendon sheaths, joint capsules and bursae as an entity derived from synovial cell elements. The similarity between the tissue spaces found in synovial tumors and those in synovial membranes was emphasized by *King* in 1931. *Sabrasèz and de Grailly* (1931) suggested the term *synovialoma* and the next year *Sabrasèz and associates* published a comprehensive rewiew on primary articular sarcomas, in which they recognized benign as well as malignant synovialomas ("Synovialome malin polykystique"). Reporting three cases, *Knox* (1936) introduced the term *synovial sarcoma* which was adopted by *Berger* (1938) in a review of 21 cases collected from the literature, included 5 of his own. He presented the cumulative knowledge of the disease to that date. *Berger* also drew attention to the presence of "pseudo-synovio spaces" and areas of mucoid tissue in the tumors. The same year *Jönsson* (1938) published a monograph on malignant soft tissue tumors and presented detailed histologic descriptions and clinical course in 22 cases of synovial sarcoma. The histologic analysis in this comprehensive publication (mostly overlooked in the literature) was made by *Reuterwall,* the former chief pathologist at the Ra-

diumhemmet. According to Reuterwall's suggestions, *Jönsson* designated 8 of his 22 cases as *synovial fibrosarcomas.* These cases were shown to have better prognosis than the synovial sarcomas with their characteristic "pseudo-epithelial" structures, and *Jönsson* emphasized the relationship between histologic and clinical features.

De Santo and associates (1941) published 16 cases of synovial sarcoma and correlated the specific histologic characteristics of the tumors with their clinical course. They emphasized the fact that tumors with round or oval cells tended to be more malignant than others. *Fisher* in 1942 reviewed 43 previously reported cases and two of his own. He stressed the importance of the "bimorphic microscopic appearance" of the tumor structure and payed special attention to the "epitheliallike" tissue lining small cystic spaces or clefts. In 1944 *Haagensen and Stout* of Columbia University, New York, presented the most important current critical analyses of 104 cases, including 9 of their own and 95 collected from the literature that they regarded as satisfactorily documented. They emphasized the poor over-all therapeutic results since only 3 of the patients were known to have been from evidence of recurrence or metastasis more than five years after treatment. *Bennet* (1947) presented 32 cases registered at the Armed Forces Institute of Pathology from 1941—1945 and described in detail the common histologic patterns formed by the synovial sarcomas. In an extensive clinicopathologic report on 60 cases from Memorial Center, New York, *Pack and Ariel* (1950, 1958) emphasized the histologic appearence of the tumors in relation to their clinical course, and reported an absolute 5-year survival rate of 19% (therapeutic 5-year survival rate in 42 cases 23.5%). The authors concluded that the clinical course is usually determined by the degree of malignancy noted microscopically. *Tillotson and associates* (1951) reviewed 222 cases from the literature including 28 cases from the Mayo Clinic. These authors confirmed the poor prognosis of the tumors and reported only one patient alive without recurrence or metastasis out of 24 patients that were followed more than 5 years. *Wright* (1952) reported 47 cases from the Department of Pathology, University of Leeds, in which 5 cases of what he termed "malignant giant cell synoviomas" were included. The author stated that the existence of such tumor as an entity admits no doubt. He also claimed that prognosis is more related to histologic structure than to the mode of surgical treatment. In a report on 21 cases *King* (1952) claimed that the tumors are not derived from special synovial cells but from connective tissue cells, and that the classification of synovial tumors should be histologic rather than histogenetic. He found no correlation between degree of differentiation of the tumors and prognosis. The histologic features of 38 cases of synovial sarcomas from Columbia University were described in

detail by *Stout* (1953). In 1955 *Lichtenstein* published an important review of synovial sarcoma with a careful consideration of the differential diagnosis between this tumor and other lesions arising from the synovia of joints, bursae and tendon sheaths. Tumorlike lesions such as "benign synovioma", "giant cell synovioma" and pigmented villonodular synovitis represent, according to the author, peculiar hyperplastic granulomas rather than genuine neoplasms. *Craig and associates* (1955) presented the roentgenologic manifestations of 24 cases of synovial sarcoma. Fortythree cases of synovial sarcoma in children were reviewed by *Crocker and Stout* (1959). Clinically 22.5% of the children were tumor-free at periods more than 5 years after treatment, and thus the prognosis seemed to be better in children than adults. The number of cases however was considered too small to permit any correlation between histologic differentiation and biological course. Differentiation cannot, according to the authors, be regarded as a reliable guide to the degree of malignancy.

Vincent (1960) gave strong support to the concept of *King* (1952) that the synovial sarcomas arise from specialized mesenchymal cells near or distant to a joint, bursa or tendon sheath and that the tumor rarely enters a joint cavity. *Moll* (1960) reviewed 209 cases including 13 of his own series and 28 cases which were not later listed by *Aurich* (1965). In 1961 *Geiler* presented a comprehensive study of 433 cases from the literature and added 13 of his own. The problems encountered in the differential diagnosis towards benign neoplastic and inflammatory processes related to synovial tissues were particularly emphasized. The occurrence of synovial sarcomas at unusual sites was discussed by *Harrison and associates* (1961), who reviewed 4 cases presenting in the neck, and added another of their own.

Remarkable good therapeutic results were reported by *Cade* (1962) in a presentation of 100 cases of synovial sarcoma at the Westminster Hospital, London, arising from 1950 to 1960. Of 46 patients who could be assessed for 5 years or more, 50% were alive and free from disease for a minimum of 5 years (5 year survival rate 56%). The prognosis was said to depend partly on the adequacy of the initial treatment and equally on the degree of malignancy of the tumor. Some tumors of the "hurricane"-type were, according to the author, so malignant that the patient was unlikely to be saved regardless of early and adequate therapy. The author claims: "To improve the survival rate with freedom from recurrence, radical surgery should be undertaken at an early stage of the disease and the ancillary methods of treatment by radiotherapy and chemotherapy should be used". The less favourable results recorded in the series of cases collected before 1950 are said to depend partly on the inadequacy of the initial treatment.

Ariel and Pack (1963) completed their earlier study on synovial sar-

coma (1950) with a review of an additional 25 cases from the years 1950—1960. A 5 year absolute survival rate of 29% was reported and 60% of the patients were less than 40 years old. *Smolak* (1963) in a study of 15 cases, found that tumors of a more malignant course were characterized by the presence of epitheloid cells. *Weinreich* (1963) reviewed the clinical features of 370 cases collected from the literature and added 5 of his own. A delay of radical surgery was shown to be associated with an unfavourable prognosis. A survey of the literature on synovial sarcomas up to that date was also presented by *Aurich* (1965), who listed publications on 592 cases. The differential diagnostic aspects in regard to other synovial lesions were discussed and the importance of early and radical surgery for improved therapeutic end results were emphasized. The clinical and pathologic features and the results of treatment in 134 cases of synovial sarcoma at the Mayo Clinic during the years 1905 through 1960 was presented by *Cadman and associates* in 1965. Seventeen of these cases had earlier been published by *Tillotson and associates* (1951). The combined histologic and clinical investigation revealed that prognosis could not be correlated with the histologic appearance of the tumors, and no histologic feature could be found which could be related to the clinical outcome. The difficulties involved in the histologic diagnosis of tumors of a monophasic type were pointed out. In the more subtle varieties of synovial sarcoma the character of the cells was important in establishing the diagnosis. In opposition to these conclusions *Enzinger* (1965), reporting on 75 cases collected at the Armed Forces Institute of Pathology, found a certain correlation between tumor type and prognosis. The tumors were grouped into 3 different histologic categories: pseudoglandular, fibrosarcoma and endothelioid. The 5 year survival rate in the latter group was 36% whereas in the first 2 categories the prognosis was more favourable (50% and 59% respectively). Histologic type, encapsulation and the relative mitotic frequency seemed to be significant in the evaluation of the clinical behaviour of the tumors. The clinical aspects and results of treatment in 38 cases of malignant synovioma collected from the records of the Bone Service of the Department of Surgery at Memorial Hospital, New York, were reported by *Raben and associates* (1965). Based upon a critical discussion of the therapeutic results in their own and other case series, the authors conclude that a 50 per cent disease free 5 year survival rate is usually obtainable by a combination of surgery and radiation therapy. In a recent publication, *Mackenzie* (1966) has reviewed 58 cases treated at the Westminster Hospital in London from 1945 through 1965. The cases represent those in which the diagnosis of synovial sarcoma in the authors opinion was considered acceptable on histologic grounds. It seems reasonable to assume that the majority of these 58 cases were included in the 100 case series earlier reported by

Cade (1962). Thus it can be assumed that a number of the cases published by *Cade* have been excluded from this series as a result of a reassessment of the histology. The extraordinarily good therapeutic results reported by Cade (56% 5 year survival rate) would therefore be thrown into question. *Mackenzie* found no correlation between survival rates and the histologic features of the tumors.

In the past numerous reviews of previously published case series have been presented (e.g. *Tourneux* (1913) 93 cases, *Haagensen and Stout* (1944) 95 cases, *Tillotson* (1951) 222 cases, *Moll* (1960) 209 cases, *Geiler* (1961) 446 cases, *Weinreich* (1963) 370 cases, and lately *Aurich* (1965) 592 cases. Besides these 592 cases we have found reports on additional 519 cases through 1966 (Table I.)

The total number of published cases of synovial sarcoma at present thus somewhat exceeds one thousand. Only 9 publications, however, report on

Year	Author	No. of cases
1937	von Rosen	1
1937	Mouchet and ass.	1
1948	Ambros	1
1948	Knutsson	2
1951	Cade	11
1951	Martin and ass.	3
1954	Oota and ass.	3
1956	Mc Cormack and ass.	2
1958	Vinogradowa	6
1960	Moll[1]	41
1962	Cade	100
1963	Ariel and Pack	25
1963	Hare and ass.	5
1963	Smolak	15
1963	Weinreich	5
1964	Varret	1
1965	Cadman and ass.	117
1965	Enzinger	75
1965	Fievez and ass.	7
1965	Kehne	1
1965	Raben	38
1966	Cachin and ass.	1
1966	Mackenzie	58
	Total	519

Table I. Published cases of synovial sarcomas exclusive of those listed by *Aurich* (1965).

[1] Twentyeight cases from the literature, 13 of his own.

series of more than 25 previously unpublished cases with adequate follow-up (Table II).

Year	Author	No. of cases
1947	Bennett	32
1950	Pack and Ariel	60
1951	Tillotson and ass.	31
1952	Wright	47
1962	Cade	100
1963	Ariel and Pack	25
1965	Cadman and ass.	117
1965	Raben	38
1966	Mackenzie[1]	58

Table II. List of publications on case series of synovial sarcomas comprising more than 25 previously unpublished cases.

[1] Mostly included in the case series of *Cade* (1962). See text.

Reports on synovial sarcomas occurring in Sweden have been comparatively few. A total of 30 cases have been published (*von Rosen* 1937, 1 case, *Jönsson* 1938, 22 cases, *Silfverskiöld* 1940, 3 cases, *Karlén* 1942, 1 case, *Knutsson* 1948, 2 cases and *Fluur and associates* 1967, 1 case). *Nilsonne* (1965 and 1966) presented preliminary clinical data on the cases included in the present series.

Material.

A survey was made of cases diagnosed and/or treated as malignant synovial tumors in Sweden during the years 1925 through 1963. Altogether 160 cases could be traced, the cases occurring 1958—1963 with the aid of the Swedish Cancer Registry. Material was available for a histologic reassessment in 143 cases, and fresh sections could be cut from stored paraffin blocks in most of these. Special staining such as PAS, Alcian blue and reticulin stain (Laidlow) could therefore be utilized in numerous cases. All histologic examinations and evaluations were performed without knowledge of the later clinical course of the disease.

The reclassification led inevitably to the exclusion of a great number of cases. The results of the histologic reassessment in the 143 cases are presented in Table III, and 90 cases were considered to fulfil the criteria of synovial sarcomas. As a result, no less than 53 cases (37%) which were initially diagnosed as malignant synovial tumors were rejected.

Diagnosis	No. of cases		Per cent
SYNOVIAL SARCOMA		90	63
OTHER MALIGNANT TUMORS		37	26
Fibrosarcoma	4		
Neurofibrosarcoma	6		
Rhabdomyosarcoma, embryonal	3		
pleomorphic	6		
Angiosarcoma	10		
Mesenchymal sarcoma, indeterminate	8		
BENIGN TUMORS		4	3
PIGMENTED VILLONODULAR SYNOVITIS		12	8
Total		143	100

Table III. Histologic diagnosis after reclassification of 143 cases diagnosed and/or treated as malignant synovialomas in Sweden 1925—1963.

Differential diagnosis.

In 4 cases the tumor was rediagnosed as *fibrosarcoma;* in two of these because of a tendency toward collagen formation. Six other cases were *neurofibrosarcomas.* Three rapidly fatal tumors were reclassified as *embryonal rhabdomyosarcomas,* and cross striations could be demonstrated in the fibrillary cytoplasm of the tumor cells in 2 of these cases. Six tumors exhibited marked pleomorphism and scattered tumor giant cells and were therefore designated as *pleomorphic rhabdomyosarcomas.* The other tumors were composed of closely packed, fairly uniform cells with round nuclei. Vascular spaces were demonstrable and these tumors were rediagnosed as *angiosarcomas* of different types, hemangioendotheliomas and pericytomas. Eight tumors showed either specific and highly varying structures or were so poorly differentiated that no specific diagnosis was possible. They were grouped as *indeterminate mesenchymal sarcomas.* Most of the malignant tumors excluded from the synovial sarcoma series were distinguished by obvious cellular features not found in the latter group. In particular, a marked cellular pleomorphism was considered to militate against the diagnosis synovial sarcoma.

Among the cases erroneously classified as synovial tumors, 4 *benign tumors* were also diagnosed, such as one glomus tumor and one sweat gland adenoma. The reclassification also revealed 12 cases of *pigmented villonodular synovitis.* This diagnosis was based upon the granulomatous appearance of the cell proliferation, numerous phagocytic cells containing considerable amounts of hemosiderin pigment and scattered multinuclear giant cells (Fig. 1). There was also an increased tendency toward dissociation

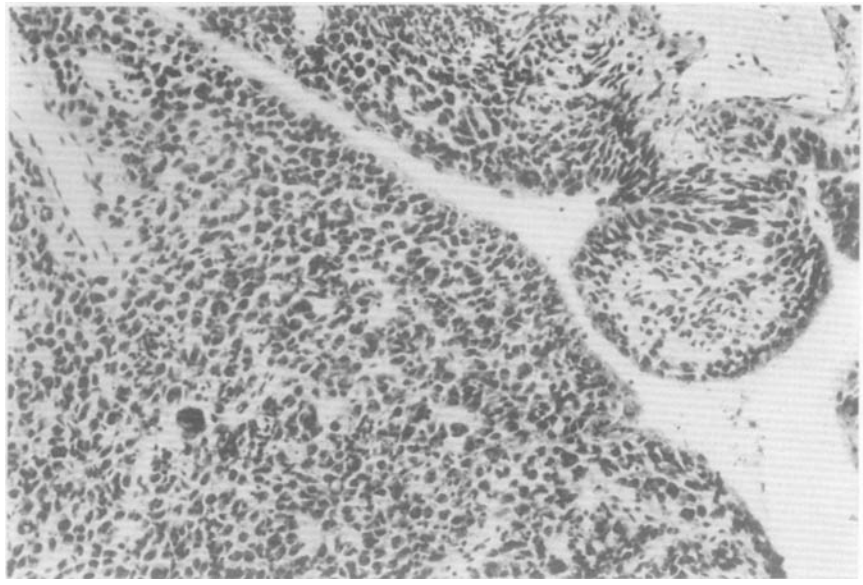

Fig. 1. Pigmented villonodular synovitis. Photomicrograph ×150 Cellular granulomatous tissue with scattered giant cells and synovial proliferations.

of the individual cell elements (Fig. 2) and areas with macrophages containing lipid granula.

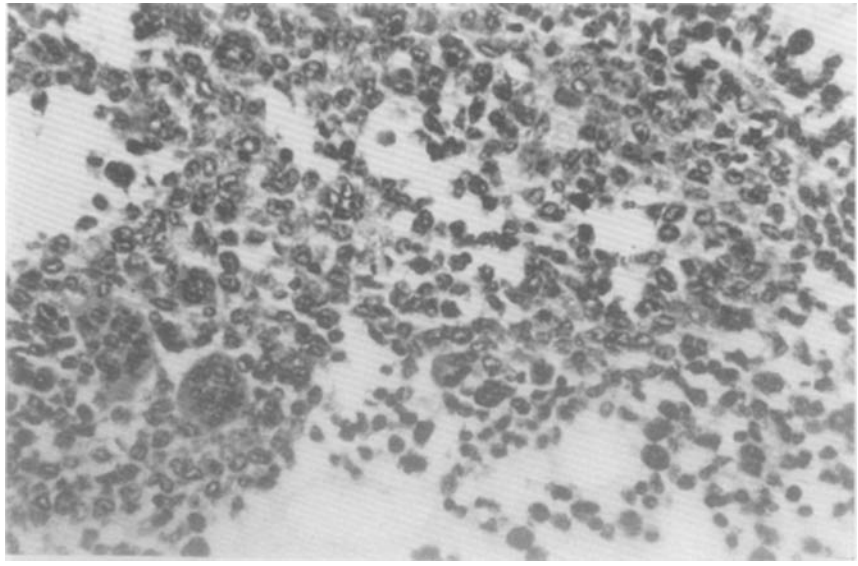

Fig. 2. Pigmented villonodular synovitis. Photomicrograph ×400. Dissociation of individual cells and numerous giant cells.

In 4 of these 12 cases of pigmented villonodular synovitis amputation had been performed. Two of these patients died 7 years after treatment with pulmonary lesions which clinically were considered metastasis from the synovial tumors. Autopsies in both cases however revealed that the lung tumors actually were primary epidermoid carcinomas.

Synovial sarcomas in present series.

As a result of the reassessment, 90 cases were diagnosed as synovial sarcomas. Ten of these cases were included in the case series published by *Jönsson* (1938), 4 of which were synovial fibrosarcomas.

Histologic features.

The histologic appearance of the tumors corresponded well with the excellently documented cases in earlier publications (e.g. *Stout* 1953, *Pack and Ariel* 1958, *Cadman* 1965). Thus the tumors were composed of either one or both of two histologically differing tissue types, often intermingled in varying proportions. One component which is generally referred to as "epithelioid" *(Cadman* 1965) or endothelioid *(Enzinger* 1965) could be better designated as *synovioblastic (Stout* 1958). This cell type is fairly large, polygonal, sometimes cylindrical with oval, palestaining nuclei (Fig. 3). The cells exhibit moderate pleomorphism, and may form solid nests or sheaths with indistinct cytoplasmic borders. They may be oriented around slits (so called clefts) or form more or less irregular tubes giving the structure a glandlike pattern.

The other cellular component often referred to as a fibrosarcomatous spindling or spindle-shaped cell element *(Stout* 1953) but better termed *fibrosarcomatoid,* is composed of elongated fibrillary cells forming reticulin fibers (Fig. 4). The cells often form dense bundles and the nuclei are thin and elongated with little atypia.

The varying types of synovial sarcomas in relation to the two cellular components are demonstrated in fig. 5. The term *synoviocytic sarcoma* has been chosen to represent the classical bimorphic type of tumors in which both cellular components appear more or less differentiated.

Synovioblastic sarcomas

In this type of tumor the synovioblastic elements entirely dominate, giving a rather homogeneous character to the lesion (Fig. 6). Tubular or glandlike structures may be formed, but numerous sections often need to be

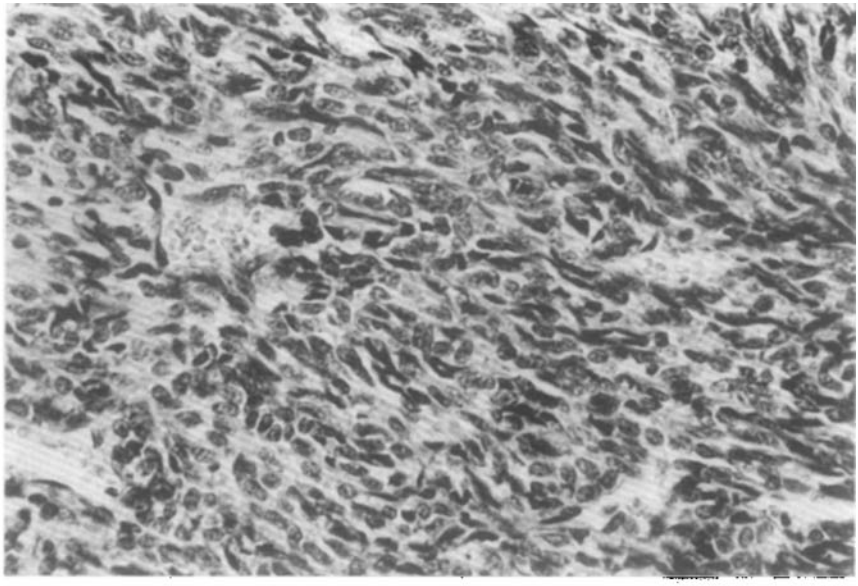

Fig. 3. Synovioblastic synovial sarcoma. Photomicrograph ×400. Monomorphic synovioblastic tumor cells exhibiting moderate pleomorphism. Knee joint tumor in a patient who died of pulmonary metastasis less than 1 year after amputation.

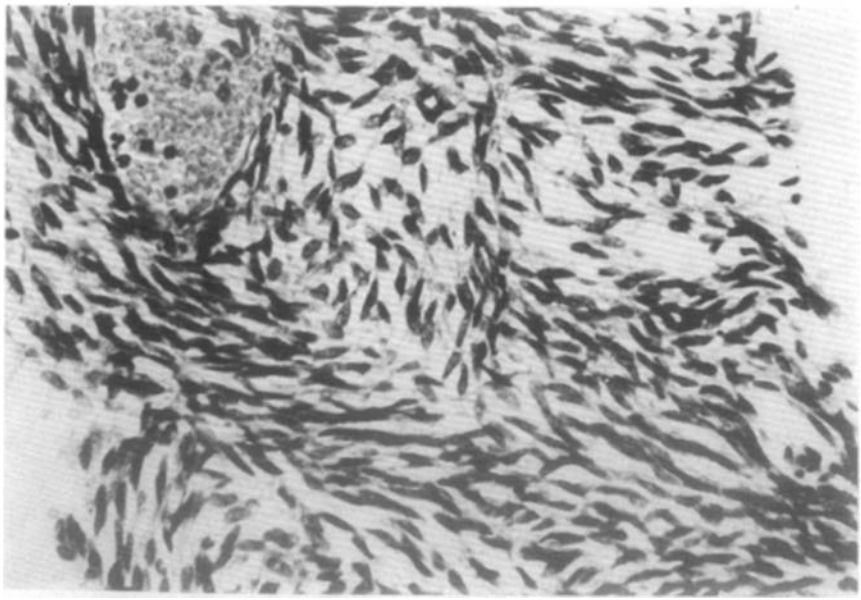

Fig. 4. Synoviocytic synovial sarcoma. Photomicrograph ×400. Fibrosarcomatoid component with well differentiated "spindle-shaped" tumor cells showing little pleomorphism. The tumor was located in the shoulder of a patient who died of pulmonary metastasis less than 3 years after local excision and postoperative irradiation.

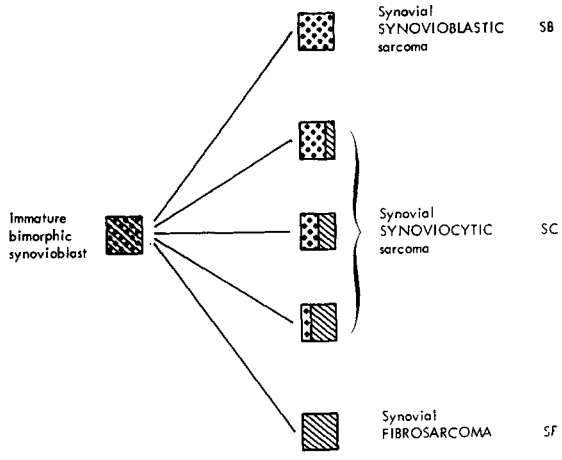

Fig. 5. Schematic presentation of the different types of synovial sarcomas with regard to the mutual relation between the two morphologic components.

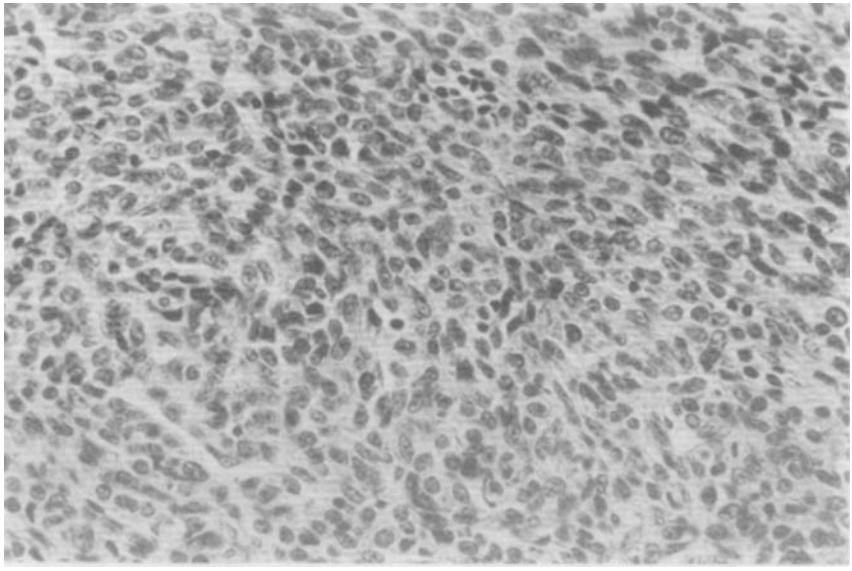

Fig. 6. Synovioblastic synovial sarcoma. Photomicrograph ×400. Homogeneous tumor structure composed of synovioblastic tumor cells. Section from a tumor in the foot. Amputation 16 months after repeated excisions of 2 recurrencies. The patient died of pulmonary metastasis 6 years after amputation.

examined to register such findings. The synovioblastic proliferations may exhibit varying degrees of differentiation and may occasionally appear fibrillar, resembling a fibrosarcoma (Fig. 7). The individual cells in the

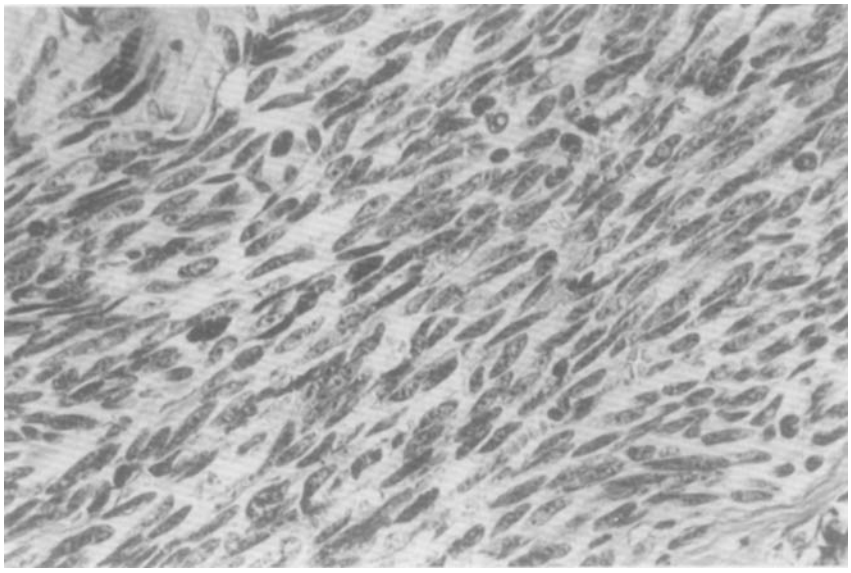

Fig. 7. Synovioblastic synovial sarcoma. Photomicrograph ×400. Fibrillar, poorly differentiated synovioblastic tumor cells masquerading fibrosarcoma. Moderate pleomorphism. Small distinct nucleoli. Tumor in the foot of a patient who died of generalized metastasis 14 months after amputation.

synovioblastic proliferations are, however, somewhat larger, and the nuclei less elongated. In the present series, tumors of this kind were considered rather monomorphic. A true fibrosarcomatoid component may be hard to exclude but we would rather agree with the statement by *Stout* (1953) that "it may be that cells of the supposed fibrosarcomatous areas are in reality synovioblasts masquerading as fibroblasts".

Synoviocytic sarcomas.

The classical bimorphic type of synovial sarcoma usually exhibits highly varying structures in different areas. The histologic pattern is complicated by the existence of two independent variables. First: The quantitative relationship between the two components. Second: The degree of differentiation (maturation) of the components. This is particularly valid for the synoviocytic component, and in tumors in which this component is highly differentiated, the picture resembles an adenocarcinoma ("pseudoglandular") (Fig. 8). In less differentiated tumors, the synoviocytic component may be more or less solid (Fig. 9), or forming strands or cords within the fibrosarcomatoid tumor tissue (Fig. 10).

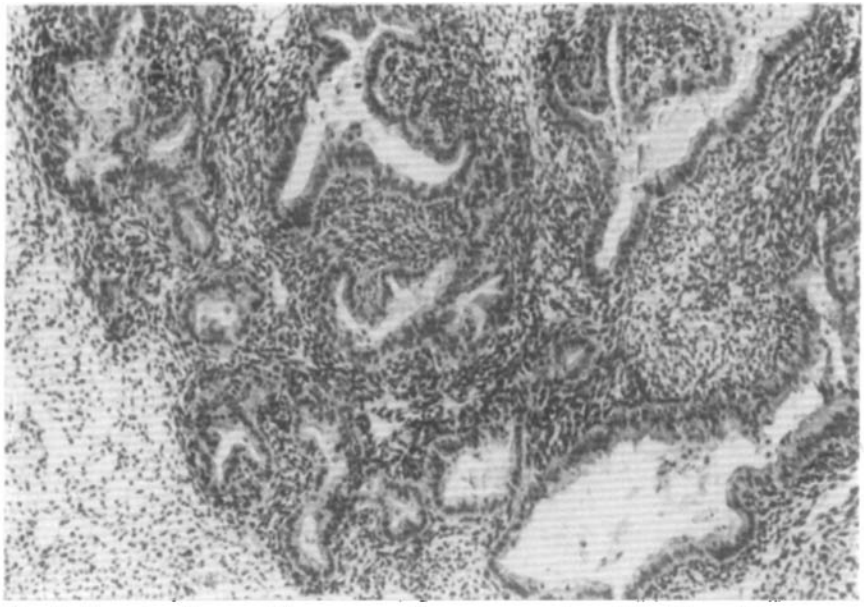

Fig. 8. Synoviocytic synovial sarcoma. Photomicrograph ×150. Bimorphic type of tumor with characteristic "pseudoglandular" synoviocytic structures and sparse fibrosarcomatoid component. Tumor in the ankle. Amputation 3 weeks after local excision. The patient died 2 years after amputation with pulmonary metastasis.

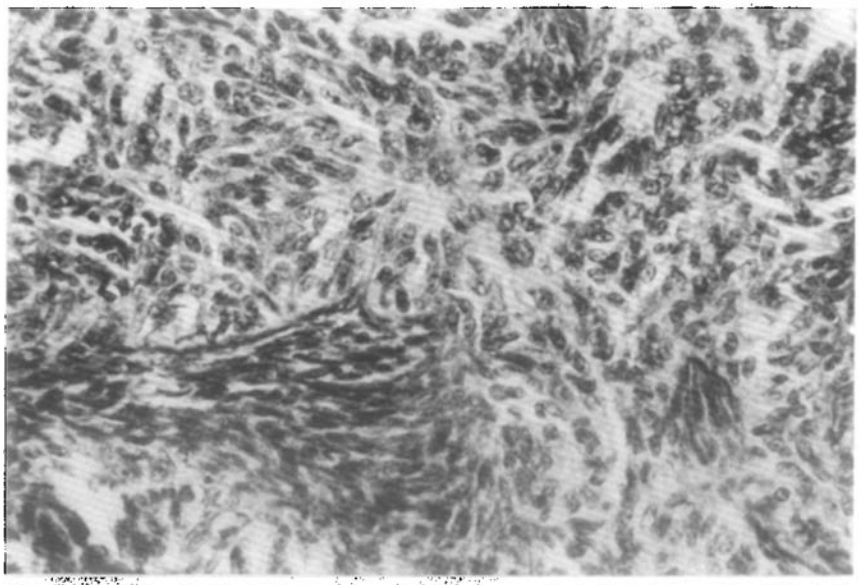

Fig. 9. Synoviocytic synovial sarcoma. Photomicrograph ×400. Bimorphic histologic pattern. Moderately differentiated synoviocytic component with predominance of solid structures. Large tumor in the thigh. Radical local excision. The patient is alive free from disease 20 years after treatment.

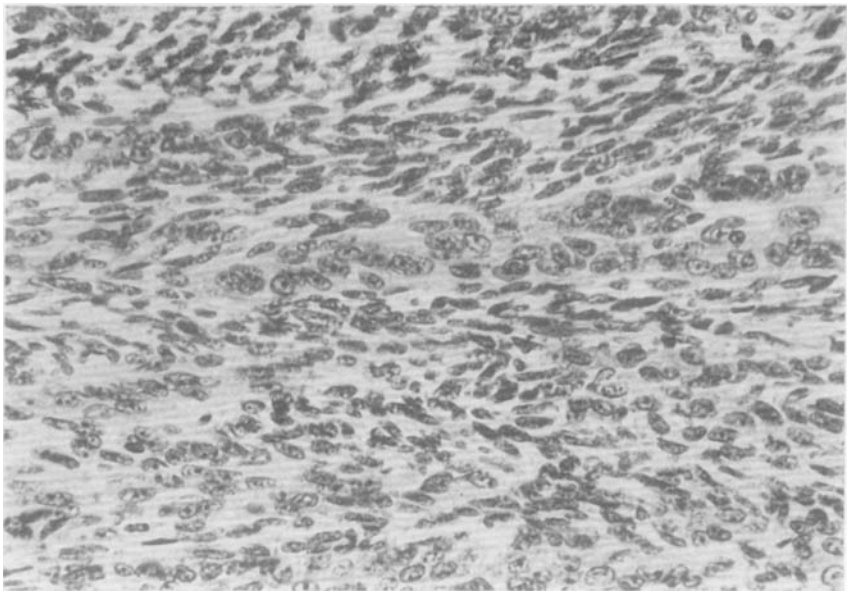

Fig. 10. Synoviocytic synovial sarcoma. Photomicrograph ×400. Bimorphic structure. Predominance of fibrosarcomatoid component with strands of synoviocytic tumor cells. In other areas the tumor developed "pseudoglandular" structures. The tumor was located in the foot. Local excision and postoperative irradiation was administered. No recurrencies. The patient died of intercurrent disease 4 years after treatment free from disease.

In most of the differentiated tumors mucoid material (hyaluronic acid) is secreted in the lumina of the glandlike tubes, and PAS-positive granules can frequently be demonstrated in the cytoplasm of the synoviocytes. In the present series, however, this was not a constant phenomenon, and in the opinion of the authors the demonstration of mucoid substance in the tumor cells cannot be regarded as pathognomic for synovial sarcoma.

The fibrosarcomatoid component in the synoviocytic tumors may show a highly varying degree of cellularity, and within wide areas it may dominate the picture (Fig. 11).

Synovial fibrosarcomas.

These tumors closely resemble fibrosarcomas on other locations (Fig. 12), and probably cannot be separated from such tumors on histologic grounds only. The relationship of the tumors to synovial tissues and a high degree of cellularity may be of importance in the differential diagnosis. A synoviocytic type of tumor can only be excluded by careful analyses of numerous sections.

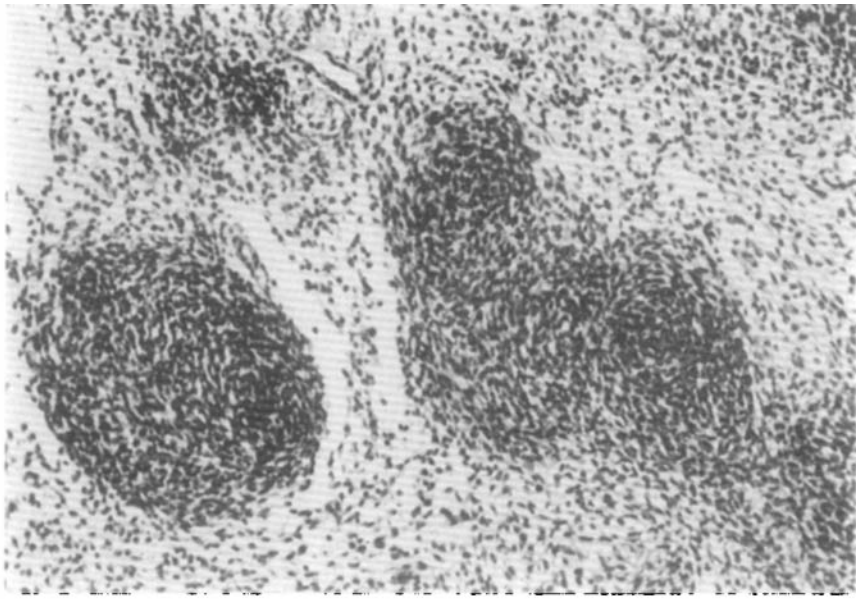

Fig. 11. Synoviocytic synovial sarcoma. Photomicrograph ×150. Fibrosarcomatoid component forming dense bundles of "spindle-shaped" tumor cells. In other areas typical "clefts". Tumor in the foot of a patient who died of pulmonary metastasis within 2 years after treatment.

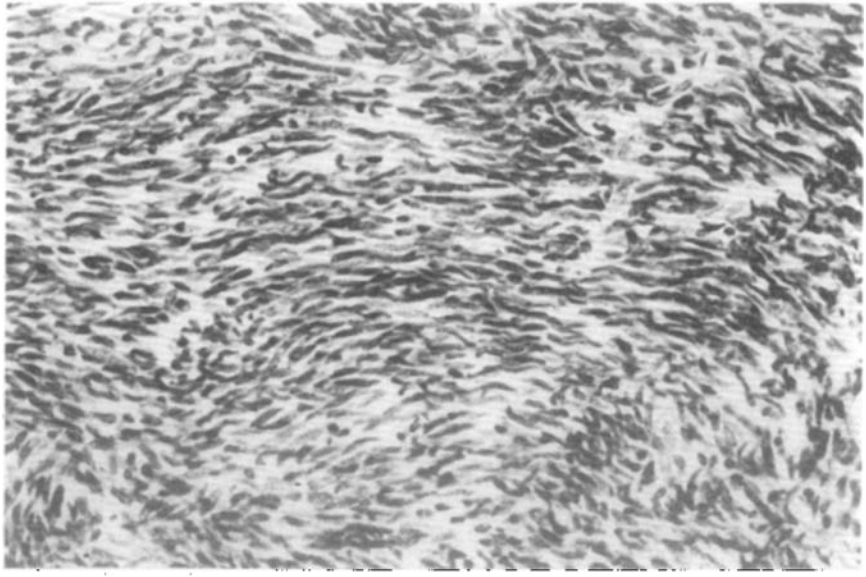

Fig 12. Synovial fibrosarcoma. Photograph ×400. Tumor structure resembling fibrosarcomas on other locations. Small sized tumor in tendon sheath in the hand. Two recurrencies after local excisions. Amputation 4 years after initial treatment. The patient died of pulmonary metastasis 5 years after amputation.

Clinical features.

Full follow-up records were available in all 90 cases of the present series and no patient was lost in the follow-up study.

Sex and age.

The distribution of the 90 patients according to sex and age is shown in fig. 13. There were 43 females and 47 males, indicating no obvious sex preponderance in this series.

Synovial sarcomas is essentially a disease of younger adults, and in the present series 75.6% (68 cases) occurred in patients younger than 50 years and 58.9% (53 cases) before 40 years of age.

Location.

Most of the lesions (93%) were located on the extremities (Table IV). Compared to other case series (e.g. *Pack and Ariel* 1950, *Cadman and ass.* 1965) the number of tumors arising in the foot is extraordinarily high. This site was followed in order of decreasing frequency by the knee, hand, ankle and thigh.

Clinical course.

Of the 90 patients 19 were alive and free of disease at the end of the study with a minimum observation time of 5 years after treatment. The *absolute survival rate* of the whole series to the date of expiration of the investigation is thus 21%. Since no patient was lost from the follow-up study and 7 patients died of intercurrent disease, the relative and *determinate survival rate* (D.S.R.) is 23% (19 of 83 patients alive). Table V shows the continous

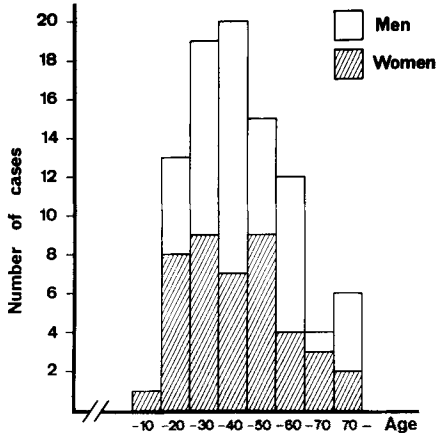

Fig. 13. Diagram illustrating age and sex distribution of 90 patients with synovial sarcomas.

Location	No. of cases	Per cent
LOWER EXTREMITY	62	69
foot	25	
ankle	8	
foreleg	3	
knee	16	
thigh	7	
hip	3	
UPPER EXTREMITY	22	24
hand	9	
wrist	3	
forearm	3	
elbow	3	
arm and shoulder	4	
OTHER LOCATIONS	6	7
abdominal wall	2	
thoracic wall	2	
neck	2	

Table IV. Location of 90 synovial sarcomas.

decrease in determinate survival rate with the time between the date of histologic diagnosis (biopsy or initial treatment) and the end of the investigation. Twelve patients died of their tumor within the first year after diagnosis. After 5 years 33 patients were alive and 5 had died of intercurrent disease. Thus the *absolute 5 year survival rate was 37%* and the *determinate 5 year survival rate* 39%. Four of the 85 patients received

Duration from diagnosis years	DEAD						ALIVE		D. S. R.[2]	
	of tumor			of i. d.[1]						
	no.	tot. no.	%	no.	tot. no.	%	no.	%	ratio	%
< 1	12	12	13	1	1	1	77	86	77/89	87
< 5	40	52	58	4	5	6	33	36	33/85	39
< 10	8	60	67	—	5	6	25	27	25/85	29
< 20 >	4	64	71	2	7	8	19	21	19/83	23

Table V. Clinical course and determinate survival rates in relation to duration from date of histologic diagnosis (initial treatment) in 90 patients with synovial sarcoma. Average follow-up time for the survivals 10 years.

[1] intercurrent disease

[2] determinate survival rate

only palliative radiation treatment since they suffered from extensive pulmonary metastasis when admitted to hospital. The total number of patients who received definite therapy was 86. Exclusion of the 5 patients who died of intercurrent disease leaves a total of 81 patients for whom therapeutic survival rates can be determined. Since 33 patients survived, the *therapeutic 5 year survival rate* is thus 41%. Ten years after biopsy or initial treatment of the 90 patients 60 (67%) had died of tumor and another four patients died of their tumor 10 to 20 years after diagnosis. The average follow-up time for the survivals was 10 years.

The clinical course of the 90 patients is presented graphically in fig. 14. From the diagram it is obvious that an observation period of 5 years is a fairly accurate measure of the malignancy of the disease.

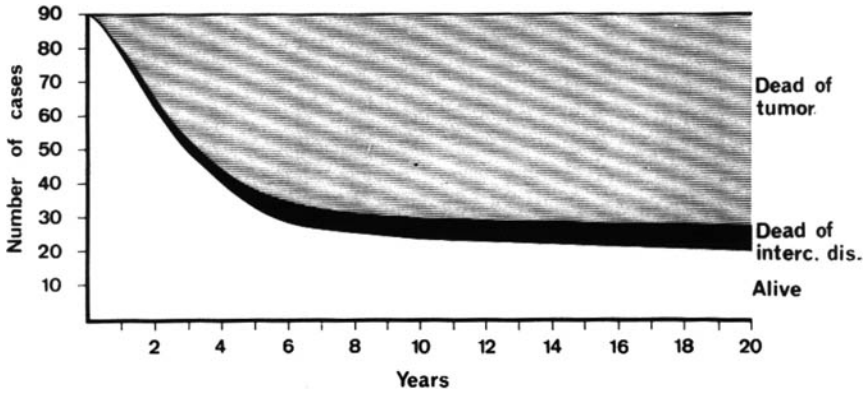

Fig. 14. Diagram illustrating the clinical course of 90 patients with synovial sarcoma.

Evaluation of factors influencing prognosis.

Histologic factors.

Type of tumor.

The histologic classification of the tumors was compiled without access to the clinical records, and the tumors were grouped according to the principles described above. The synoviocytic tumors were easily recognized whereas problems arose in the diagnosis of the synovioblastic sarcomas. In some cases a fibrosarcomatoid component could not be entirely excluded. The cytologic criteria by which a poorly differentiated synovioblastic lesion is distinquished from a fibrosarcomatoid one involves some subjective evaluation by the pathologist. Careful analysis of the cell character

was most helpful (compare *Cadman and associates* 1965), and a few doubtful cases were classified as synovioblastic tumors. When differentiated synoviocytic structures with tubular formation could be demonstrated, the case was registered as a synoviocytic sarcoma. In the diagnosis of synovial fibrosarcomas, the problem was mostly in deciding whether the tumor should be designated as a synovial tumor, or be excluded from the series. Careful scrutiny of numerous sections was in such cases necessary to exclude the presence of synoviocytic structures.

The clinical course of the patients with the three kinds of tumors is presented in Table VI. The determinate survival rates were significantly different in the three groups. Thus, the *synovial fibrosarcomas* (SF) had almost five times better prognosis (D.S.R. 56%) than the *synovioblastic* types (SB) (D.S.R. 12%). The *synoviocytic* sarcomas (SC) fell in between. The correlation between tumor type and survival rates is thus highly significant.

Type of tumor	No. of cases	Dead of tumor	Dead of i. d.	Alive	D. S. R. %
SB	44	38	1	5	12
SC	34	22	3	9	29
SF	12	4	3	5	56
Total	90	64	7	19	23

Table VI. Clinical course and determinate survival rates in relation to type of tumor in 90 cases of synovial sarcoma.

Cellular composition of the tumors.

An attempt was made to determine if any correlation existed between the relative proportion of the two components (synoviocytic and fibrosarcomatoid) and prognosis in the synoviocytic tumors. No such correlation could, however, be demonstrated. Of the 34 cases of synoviocytic sarcoma, 18 tumors exhibited a predominance of the synoviocytic component and 16 tumors showed a predominantly fibrosarcomatoid pattern. Of the 18 patients in the first group, 5 were alive at the end of the study, and of the 16 patients in the second group, 4 were alive. The determinate survival rates were 29% and 28% respectively (1 patient had died of intercurrent disease in the first group and 2 in the latter).

Histologic grade of malignancy.

A histologic grading of malignancy (based upon generally accepted cytologic criteria of tumor pathology) was possible in all the tumors. Such

criteria included the degree of maturation of individual tumor cells, the degree of cellular and nuclear polymorphism, loss of polarity, frequency of mitoses and degree of nuclear hyperchromatism. The grading was performed on the most malignant component found in the tumor tissue, independent of type or pattern. It must be confessed that the fibrosarcomatoid cell types rarely exhibited any marked polymorphism. A majority of the cytologic analyses on which the grading was based consequently refer to synovioblastic or synoviocytic cell elements. During the grading, the authors came to the conclusion that most of the mainly fibrosarcomatoid tumors exhibiting cellular immaturity were in reality poorly differentiated synovioblastic tumors.

The results of the correlation of the histologic grade of malignancy and clinical course is presented in Table VII. A highly significant difference was found between tumors with different grades of malignancy. Since the grading was made without knowledge of the clinical course in individual cases, we are of the opinion that the grading of malignancy according to the above principles is a reliable method to prognosticate a given case of synovial sarcoma. Such grading may also play an important role in the choice of therapy.

The survival time (from date of diagnosis) of 64 patients who died of tumor in relation to the different grades of malignancy is presented in fig. 15. Whereas all patients with grade 4 tumors died within 5 years, the survival time of patients with less malignant tumors was considerably longer. Only one patient with a grade 1 tumor had died of his disease 20 years after the initial treatment.

	GRADE OF MALIGNANCY											
	I			II			III			IV		
	SB	SC	SF	SB	SC	SF	SB	SC	SF	SB	SC	SF
No. of cases	—	7	4	7	10	7	30	15	1	7	2	—
Dead of tu.	—	1	—	5	7	3	26	12	1	7	2	—
Dead of i. d.	—	—	1	—	2	2	1	1	—	—	—	—
Alive	—	6	3	2	1	2	3	2	—	—	—	—
Total no. of cases	11			24			46			9		
D. S. R. %	90			25			11			0		

Table VII. Clinical course and determinate survival rates in relation to type of tumor and histologic grade of malignancy in 90 patients with synovial sarcoma.

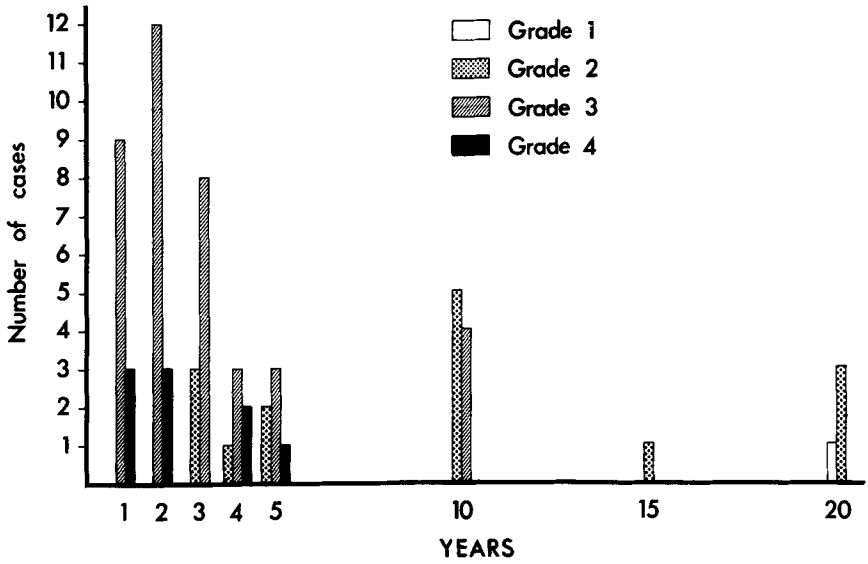

Fig. 15. Diagram illustrating the survival time with regard to histologic grade of malignancy of the tumors in 64 patients dead of synovial sarcoma.

Cellularity.

Synovial sarcomas may be extremely cellular and it is a common experience among pathologists that some of the most cellular tumors are also the most malignant. The cellularity of the tumors in this series was therefore estimated in order to find a possible correlation between cellularity and survival rates. It was found hard if not impossible to group synovial fibrosarcomas or fibrosarcomatoid components according to cell density. Only synovioblastic and synoviocytic components were therefore regarded. Extremely cellular and poorly cellular tumors were sorted out from the remaining lesions which formed an intermediate group with moderate cellularity.

Table VIII shows the relation between degree of cellularity and the

	Degree of cellularity		
	poor	moderate	high
Dead of tu.	19	33	8
Dead of i. d.	2	1	1
Alive	9	5	—
Total no. of cases	30	39	9
D. S. R. %	32	13	0

Table VIII. Clinical course and determinate survival rates in relation to degree of cellularity in 78 patients with synovioblastic and synoviocytic synovial sarcomas.

survival rates of 78 patients. The cellular tumors appeared to be the most malignant varieties with no survivals out of 9 cases. The difficulties in accurately estimating the cellularity of tumors with two cellular components intermingled should, however, not be underestimated. The number of poorly differentiated, high grade malignant synovioblastic tumors was naturally high among the tumors in the cellular group. Though cellular alterations indicating a high grade of malignancy may parallell cellullar density, the latter is often a more obvious histologic sign of a highly malignant tumor.

Clinical factors.

The authors recognize the difficulties involved in evaluating the influence of clinical factors on prognosis. In this series it was found difficult to obtain accurate information from the records on the duration of illness from the first symtom to the date of instituted therapy. The results of *Pack and Ariel* (1950, 1958) indicate that early radical surgery influences prognosis. The time which elapses from onset of disease to the date of surgery may certainly be critical for the clinical outcome.

Sex.

From Table IX it would seem that tumors in women had better prognosis than those in men. At the end of the investigation, 14 out of 43 women were alive and free from disease, whereas only 5 out of 47 men had survived. The relative number of different types of tumors in women and men respectively can hardly explain the difference in prognosis, and it may be possible that women are more observant than men, and hence will receive earlier treatment in the course of their disease.

Type of tumor	MEN				WOMEN			
	No. of cases	Dead of tu.	Dead of i. d.	Alive	No. of cases	Dead of tu.	Dead of i. d.	Alive
SB	21	21	—	—	23	17	1	5
SC	18	15	2	1	16	7	1	8
SF	8	2	2	4	4	2	1	1
Total	47	38	4	5	43	26	3	14

Table IX. Influence of sex and type of tumor on the clinical course in 90 patients with synovial sarcoma.

Age.

Table X demonstrates that there was no obvious difference in the determinate survival rates between younger and older age groups. The relative number of synovioblastic sarcomas was somewhat higher in the younger age groups. Thus, there were 29 synovioblastic tumors out of 44 cases in patients under 40 (66%), whereas only 17 out of 34 synoviocytic sarcomas (50%) occurred in this age group.

Age	Type SB	SC	SF	Tot. no of cases	Dead of i. d.	of tu.	Alive no.	D. S. R. %
—10	1	—	—	1	1	—	—	0
10—20	9	3	1	13	10	1	2	17
20—30	8	9	2	19	—	—	6	32
30—40	11	5	4	20	14	1	5	26
40—50	9	3	3	15	11	1	3	21
50—60	5	6	1	12	10	—	2	17
60—70	—	4	—	4	3	—	1	25
70—	1	4	1	6	2	4	—	0
Total	44	34	12	90	64	7	19	23

Table X. Clinical course and determinate survival rates in relation to age distribution and type of tumor in 90 patients with synovial sarcoma.

Location.

There was no difference in determinate survival rates between the 62 patients with tumors in the lower extremity and the 22 patients with tumor in the upper extremity (25% and 24% respectively). All 6 patients with tumors at other locations died of their disease. There was tendency, however, for peripheral tumors to have a better prognosis than those occurring more centrally (e.g. hip and shoulder).

Treatment	No. of cases tot.	irrad.	Dead of tu.	of i. d.	Alive	D. S. R. %
Biopsy only	4	3	4	—	0	0
Local excision	43	38	28	4	11	28
Amputation	43	22	32	3	8	20
Total	90	63	64	7	19	23

Table XI. Clinical course and determinate survival rates in relation to therapy in 90 patients with synovial sarcoma.

Treatment.

Table XI illustrates the type of therapy instituted in the 90 patients with synovial sarcomas. Four patients had pulmonary metastases when admitted to hospital and received only palliative treatment.

It is interesting to note that the determinate survival rate was somewhat higher in patients who were treated by local excision than those in whom amputation had been performed. Similar observations were made by *Cadman and associates* (1965). The surprisingly low cure rate following amputation could not be explained by a relative larger number of high grade malignant tumors in this group, because the number of synovioblastic sarcomas was the same among patients treated by excision and amputation respectively (table XII). No less than 38 of the 43 patients treated by excision received post-operative irradiation which may explain the fairly good therapeutic results in this group (table XI). It was, however, not possible to evaluate the curative effect of irradiation in the present case series since most of the patients were treated in different hospitals with highly varying doses.

Type of tumor	LOCAL EXCISION					AMPUTATION				
	no. of cases	Dead of tu.	Dead of i. d.	Alive	D. S. R. %	no. of cases	Dead of tu.	Dead of i. d.	Alive	D. S. R. %
SB	19	15	1	3	17	21	19	—	2	10
SC	20	12	1	7	37	14	10	2	2	17
SF	4	1	2	1	50	8	3	1	4	57
Total	43	28	4	11	28	43	32	3	8	20

Table XII. Clinical course and determinate survival rates in relation to type of tumor and therapy in 86 patients with synovial sarcoma.

Since a number of the amputations were performed after one or several recurrencies following local excisions, the question arose whether the amputated patients represented the most extensive cases. The clinical course in relation to the number of recurrencies following excision and prior to amputation respectively, are presented in Table XIII. Of the 43 patients who were treated with local excision, 23 had no recurrencies, and 20 had recurrence once or several times after repeated removal. Ten patients died of tumor in the former group and 18 in the latter. The determinate survival rates were 47% and 10% respectively. It could thus be demonstrated in this series *that patients which are free from recurrencies after local excision have almost five times better prognosis than those with one or several recurrencies.* A corresponding difference in survival rates could not be shown in the group of cases who had amputation.

	LOCAL EXCISION		AMPUTATION	
	0 Recurrence	One or several recurrencies	0 recurrence	One or several recurrencies
No. of cases	23	20	21	22
Dead of tumor	10	18	15	17
Dead of i. d.	4	—	3	—
Alive	9	2	3	5
D. S. R. %	47	10	17	23

Table XIII. Clinical course and determinate survival rates in relation to number of recurrencies and therapy in 86 patients with synovial sarcoma.

Of the 64 patients in the series who died of tumor, no less than 60 had pulmonary metastases. The remaining 4 died of generalized metastases. Lymph node metastases were registered in 15 cases (23%).

Discussion.

The synovial sarcomas have attracted special interest for many reasons. The relationship of the tumor to the synovial tissue in joint capsules, bursae and tendon sheaths, and hence the histogenetic origin of the tumors have long remained obscure. The morphologic appearance of the tumors with their strongly varying, biphasic histologic pattern has raised interest among pathologists. Probably the ability of this tumor of mesenchymal origin to mimic an adenocarcinoma has played a role in this respect. Furthermore different opinions have been presented as to the degree of malignancy of the tumors and the cure rates that could possibly be obtained by different methods of therapy. The question as to whether a correlation exists between histologic appearance and prognosis remains controversial. Thus the synovial sarcomas offer a number of unsolved problems of interest both to the pathologist and the clinician.

Histogenesis.

Synovial sarcomas have been defined by many authors as malignant tumors of synovial origin, arising from either joint capsules, bursae or tendon sheaths *(Jönsson* 1938, *Pack and Ariel* 1950, *Tillotsson and ass.* 1951). Such tumors can also be produced experimentally by the introduction of carcinogens into joint cavities *(Ghadially and Roy 1966)*. The occurence

of numerous synovial sarcomas outside of these structures, although often in close proximity to them, has, however, made such exclusive origin questionable *(Haagensen and Stout* 1944). The biphasic histologic pattern of the synovial sarcomas, more or less reminiscent of synovium, strengthens the opinion that these tumors are derived solely from synovial structures. In the adult organism this organ is composed of 2 identifiable components, an inner synovial layer and an outer connective zone which may be fibrous. *Luse* (1960) using electron microscopy, found no basement membrane between the 2 layers and considered that the synovial cells were the same type as those of the deeper zone. *Causey* (1962), on the other hand, found an amorphous basement membrane separating the synovial cells from the underlying fibrous cell elements. Tissue culture studies *(Vaubel* 1933, *Murray and ass.* 1944) have demonstrated that the synovial cells undoubtedly possess special properties which distinguish them from other mesenchymal cells. Thus, the synovial cells secrete mucinous substances, notably mucopolysaccharids (hyaluronic acid). Although 2 cell types were distinguishable in tissue culture, it was suggested (*Murray and ass.* 1944) that they were morphologically interconvertable. Thus it appears that synovial membranes are composed of 2 interchangeable cell types which may occur and undergo differentiation at sites distant from normal synovial tissue (*Mackenzie* 1966). The development of "synovial" tumors in mesenchymal tissue distant from synovial membranes *(Cadman and ass.* 1965) has an important bearing on the nature and origin of these tumors *(King* 1952).

The material in the present series permitted no conclusions as to the origin of the tumors in relation to synovial tissues. Although a majority of the tumors grew in close vicinity to joint capsules, bursae, and tendon sheaths, only 4 tumors in the series extended into joint cavities. This figure is lower than that reported e.g. by *Enzinger* (1965) who found intraarticular growth in 10% out of 75 cases.

Differential diagnosis.

A reassessment of the present series of 143 cases, previously diagnosed and/or treated as malignant synovial tumors, revealed that only 90 (63%) could be accepted as true synovial sarcomas. Similar experience has been reported by other authors (e.g. *Mackezie* 1966). This emphasizes the importance of acquiring further information about the histologic characteristics of synovial proliferations.

Of special interest and importance in the diagnosis of synovial tumors is the recognition of non-neoplastic lesions such as *pigmented villonodular synovitis,* which has occasionally been misinterpreted as a malignant tu-

mor. *Haagensen and Stout* (1944) have pointed out that synovial hyperplasias, giant cell tumors and other nonmalignant lesions usually involve the synovial tissues. *Lichtenstein* (1955) emphasized that proliferative lesions of the joints, showing phagocytic properties and giant cells are unlikely to represent true neoplasms. The term "benign synovioma" *(Wright* 1952 and others) or "giant cell tumor" of the tendon sheath is best avoided. In the present series, in agreement with *Cadman et al* (1965), no significant number of giant tumor cells were found in the synovial sarcomas. Thus the existence of a true malignant giant cell synovioma *(Geiler* 1961, *Wright* 1962) remains doubtful. The results of the present study support the opinion of *Cadman et al* (1965), that many of the diagnosed synoviocytic sarcomas, are in reality xantomata, pigmented villonodular synovitis and similar lesions. In our series all cases of villonodular synovitis were rather characteristic. Although rather cellular, the proliferation had a granulomatous character and deposits of hemosiderin in cell foci with evidence of phagocytosis were found in all cases. The presence of multinucleated giant cells was also obvious, and there was a tendency toward increased dissociation of the individual proliferating cells. Along with these features concomittant proliferation of synovial lining cells may occasionally cause some diagnostic difficulty.

In this study the histologic diagnosis of the differentiated, bimorphic synoviocytic sarcomas presented in general no major problem. The separation of poorly differentiated synovial tumors from other mesenchymal sarcomas may, however, cause difficulties. The cellular structures of the synovial sarcomas are, however, rather characteristic, and any marked degree of cellular pleomorphism militates against this diagnosis (*Cadman and ass.* 1965.) Thus in this series a few such tumors on other morphologic grounds could be classified as *rhabdomyosarcomas.* The documentation of cross striations in the elongated, fibrillar cytoplasm of the tumor cells in 2 cases established the diagnosis of embryonal rhabdomyosarcoma. In other lesions, the presence of tumor giant cells and fibrous areas of collagen formation suggested pleomorphic rhabdomyosarcomata. In a few cases no diagnosis was possible, and the tumors were simply designated as *indeterminate mesenchymal sarcomas.* The separation of poorly differentiated synovial sarcomas from *angiosarcomas* was in some cases considered difficult. In particular the authors found it difficult to interpret small slits, tissue spaces and similar structures in the tumor tissue, as indicative of a "clefting" synovial tumor. Vascular spaces or simply artefacts in the sectioned tissue are common features in various neoplasms and might easily be misinterpreted as "synovial spaces". In doubtful cases it is the cellular structure that is of prime importance in the diagnosis *(Cadman and ass.* 1965).

Synovial cells have the ability to secrete hyaluronic acid *(Murray and*

ass. 1944) and the periodic acid-Schiff (PAS) reaction was therefore applied in numerous cases of this series. It failed, however, to demonstrate positive granules in numerous tumor cells. Stainable *mucin* was, on the other hand, frequently found in the "pseudo-glands" of the synoviocytic tumors. In disagreement with *Pack and Ariel* (1950, 1958) we did not find that intracellular droplets of mucin served as a pathognomic and diagnostic feature. Moreover, several of the tumors excluded from the series for other reasons also exhibited stainable mucin substances.

Foci of *calcification* were found in 11 out of the 90 cases in this series. Such deposits were not restricted to any one type of tumor in particular. None of the tumors exhibited considerable *collagen* production. On the contrary, we would hesitate to designate a tumor as a synovial sarcoma when large amounts of intercellular collagen can be demonstrated. Abundant *reticulin* could be demonstrated in fibrosarcomatoid areas, but was of little help in the diagnosis and classification of these tumors.

Histologic classification.

Synovial sarcomas have been mostly described as bimorphic, composed of "epithelioid" and "fibrosarcomatous" structures intermingled in varying proportions. Whereas most authors require the presence of "pseudoglandular" structures or "clefts" for the diagnosis (e.g. *Cadman and ass.* 1965), others recognize tumors with entirely solid "epithelioid" components mixed with spindle cell elements *(Pack and Ariel* 1950). *Enzinger* (1965) classified one type of tumor as "endothelioid", but considered that in the absence of any distinct biphasic area, distinction of a synovial sarcoma from a malignant hemangioendothelioma or a poorly differentiated tumor of nerve origin may become exceedingly difficult, if not impossible. *Mackenzie* (1966) classified the tumors according to the predominance of either structure, and *Cadman and ass.* (1965) distinguished between "adenoid" and "clefting" types.

In this series, bimorphic tumors have been designated as *synoviocytic sarcomas.* The authors, however, designate a poorly differentiated tumor as a synovioblastic sarcoma, in which the structure is entirely solid, somewhat resembling a fibrosarcoma. We agree with *Stout* (1953) that a great number of synovial sarcomas which have been described by many authors as fibrosarcomas, are in reality poorly differentiated high grade malignant synovioblastic tumors. From a clinical and therapeutic point of view this is a most important consideration. *Cadman and ass.* (1965) also favour the above conclusion when they consider tumors consisting entirely of small spindle cells to "in all probability represent a monomorphic type of syno-

vial sarcoma". Such tumors are often said to "masquerade as a locally recurring low grade fibrosarcoma, only to manifest its lethal nature eventually". These authors, however, were unable to arrive at a firm classification in the absence of clefting and "epithelial-like" cells. In the present series, the histologic classification of the tumors was made without knowledge of the clinical courses of the cases. The high grade malignancy of the tumors classified as synovioblastic sarcomas manifested itself in low survival rates. Therefore we consider that the results of the clinico-pathologic study in the present series serve as confirmation that tumors with homogeneous small cell composition resembling fibrosarcomas may in reality be highly malignant synovioblastic tumors. These tumors have a distinctivly different pattern from *synovial fibrosarcomas,* in that the cells of such tumors are well differentiated, markedly fibrillar and threadlike. The differential diagnosis between fibrosarcomas of other origin may however, cause difficulties.

Clinical features.

The *sex* distribution of the 90 patients with synovial sarcoma showed no obvious preponderance. In most groups studied there has been a preponderance of male patients *(Berger* 1938, 13:8; *Haagensen and Stout* 1944, 62:41). However, *Pack and Ariel* (1950) found no predilection for either sex. It can thus be concluded that a sex difference is not of great significance *(King* 1952).

The *age* distribution of the present series confirms the fact that synovial sarcoma is essentially a disease of younger adults. In our series 59% of the cases occurred in patients before 40 years of age. *Pack and Ariel* (1950) had 60% and *Tillotsson and ass.* (1951) 71% of their cases occurring before the 40ies. Single cases may also occur in early childhood *(Crocker and Stout* 1959).

The *location* of the tumors in this series closely coincides with the figures presented by other authors. *Pack and Ariel* (1950) reported 57% of their tumors in the lower extremity (69% in this series). *Cadman and ass.* (1965) also found that most of the lesions were located on the lower extremity (71%) and reported the thigh as the most frequent site. In our series the foot and knee were the most common sites of origin.

Survival rates.

In the present series of 90 patients the absolute 5-year survival rate was 37%. *Haagensen and Stout* (1944) emphasized the poor over-all results of

therapy, and reported only 3 out of 104 survivals. In the well documented series presented by *Pack and Ariel* (1950) the 5-year survival rate was 23.5%. In children, *Crocker and Stout* (1959) reported that 22.5% of the patients were alive and tumorfree 5 years after treatment. Later publications have revealed improved results (*Cade* 1962, 56%, *Ariel and Pack* 1963, 29%, *Raben and ass.* 1965, 33% *Enzinger* 1965, 26% and *Mackenzie* 1966 51% 5-year survival rates). It would thus appear that *Raben and ass's* (1965) prediction of a 50% disease-free 5-year survival rate is certainly obtainable by adequate therapy. The highly varying therapeutic results reported in the past may to some extent depend on the relative number of different types of tumors included in the case series.

Factors influencing prognosis.

The influence on prognosis of varying *histologic factors* have been analysed in the present series. It could be demonstrated that tumors of different *types* have substantially different survival rates. The synovioblastic sarcomas thus had considerably lower determinate survival rates than synoviocytic sarcomas or synovial fibrosarcomas.

On the other hand, no such correlation could be registered with tumors containing different proportions of the morphologic components. Thus, the survival rates were the same whether the synoviocytic ("epithelioid") or fibrosarcomatoid components predominated in the tumor structure. This may explain the controversial results reported in the literature as to whether prognosis can be correlated with the histologic appearance of the tumors. According to *Pack and Ariel* (1950), "the clinical course is determined usually by the degree of malignancy noted microscopically". *De Santo and ass.* (1941), found that tumors with round or oval cells were more malignant. *Wright* (1952), reported that the differentiation of the tumor is related to prognosis. *Cade* (1962), considered some tumors of the "hurricane"-type to be extremely malignant and others (e. g. *Smolak* 1963, *Enzinger* 1965) found a positive correlation between certain histologic features and prognosis. On the other hand, several authors have failed to find any correlation between the appearance of the tumors and the course of the disease (*King* 1952, *Crocker and Stout* 1959, *Cadman and ass.* 1965 and *Mackenzie* 1966).

In the present series a grading of the histologic *degree of malignancy* of the tumors was performed. The analysis was made without knowledge of the future clinical course of the disease, and was performed on the most malignant component of the tumor. A highly significant correlation could be demonstrated between the histologic grade and survival rates. We find

these results so obvious that in our opinion *a histologic grading of the malignancy of synovial sarcomas is a most essential factor in evaluating the prognosis of a given case.*

Among the *clinical factors* influencing prognosis, neither *sex* and *age* of the patients nor the *location* of the tumor had any major prognostic significance. Women had somewhat higher survival rates than men, and peripheral tumors had a better prognosis than those occurring more centrally.

An analysis of the influence of therapy on prognosis was made. It is generally accepted that early, radical surgery is the treatment of choice for curative therapy *(Ariel and Pack* 1958, 1963, *Cade* 1962). Conclusive evidence to support this general opinion is, however, lacking in the literature. In this study, it could be demonstrated that *patients which are free from recurrencies after local excision have an almost five times better prognosis than those with one or several recurrencies.* Consequently, to achieve improved therapeutic results, it is essential that on patients with tumors that cannot be adequately removed by local excision, amputation should be performed at the earliest date. Radiation therapy with a supervoltage technique may improve therapeutic results.

Conclusions.

Synovial sarcomas constitute an entity among the malignant soft tissue tumors and frequently occur outside the synovial membranes of joint capsules, bursae or tendon sheaths.

A review of the literature has revealed that factors influencing prognosis have not been well established.

A reassessment of 143 cases of malignant synovial tumors occurring in Sweden during the years 1925—1963 has led to the exclusion of 53 cases (37%), illustrating the need for improved diagnosis of this lesion.

The differential diagnostic difficulties encountered in the histologic diagnosis of synovial sarcomas have been emphasized and special regard has been given to the differential diagnosis in regard to pigmented villonodular synovitis.

The histologic features of 90 cases of synovial sarcoma have been presented and the tumors have been classified into three types; synovioblastic sarcoma, synoviocytic sarcoma and synovial fibrosarcoma.

The clinical features of the case series have been briefly described and the survival rates have been presented. The absolute 5-year survival rate of the 90 cases was 37% and 19 patients were reported alive, and free from disease at the end of the study.

Histologic and clinical factors influencing prognosis were evaluated. It could be demonstrated that the histologic type of tumor and the grade of histologic malignancy had a highly significant influence on prognosis.

Of the 90 patients, 43 were treated by local excision and 43 were subjected to amputation. One or several recurrencies following local excison occurred in 42 out of 86 patients who received definite treatment (49%).

It has been demonstrated that the prognosis of patients who are free from recurrencies following local excison is almost 5 times better than those with one or several recurrencies.

Acknowledgements.

The authors wish to express their gratitude to the many Swedish collegues who kindly have given us access to their material. We also wish to thank the Swedish Cancer Registry for valuable aid in tracing some of the cases. We are indebted to Guy Masson, Radiumhemmet, for his able technical assistance in preparing the tables, diagrams and photomicrographs.

This work has received financial support from Cancerföreningen, Stockholm, which is gratefully acknowledged.

References.

Ambros, Z.: maziówczaku (synovioma) — nowotworze zlośliwym torebki stawowej (Sur les synoviomates-néoplasmes malignes des sacs d'articulations). Chir. Narzadów Ruchui Ortoped. Polska 13: 379, 1948.

Ariel, I. M. and Pack, G. T.: Synovial sarcoma New England J. of Med. 268: 1272, 1963.

Aurich, G.: Über maligne Synovialome Arch. für Geschwulstforschung 26: 156, 1965.

Bennett, G. A.: Malignant neoplasms originating in synovial tissues. J. Bone Jt. Surg. 29: 259, 1947.

Berger, L.: Synovial sarcomas in serous bursae and tendon sheaths Am. J. Cancer 34: 501, 1938.

Cachin, Y., Gérard—Marchant, R., Schweisguth, O., Richard, J. and Varret, D.: Les synovialomes malins parapharyngés Ann. oto-laryng. 83: 41, 1966.

Cade, S.: Proc. R. Soc. Med. 44: 13, 1951.

Cade, S.: Synovial Sarcoma. J. Royal Coll. Surg. Edinburgh 8: 1, 1962.

Cadman, N. L., Soule, E, H. and Kelly, P. J.: Synovial sarcoma Cancer 18: 613, 1965.

Causey, G.: Electron microscopy. Edinburgh, E & L. Livingstone Ltd. 1962 p. 51.

Chassaignac, M.: Cancer de la gaine des tendons.

Gaz. Hop. Paris 1852 p. 185.
Craig, R. M., Pugh, D. G. and Soule, E. H.: The roentgenologic manifestations of synovial sarcoma.
Radiology 65: 837, 1955.
Crocker, D. W. and Stout, A. P.: Synovial sarcoma in children
Cancer 12: 1123, 1959.
De Santo, D. A., Tennant, R. and Rosahn, P. D.: Synovial sarcomas in joints, bursae and tendon sheaths: A clinical and pathological study of sixteen cases.
Surg. Gyn. & Obst. 72: 951, 1941.
Enzinger, F. M.: In Tumors of bone and soft tissue.
Year Book Medical Publ. Inc. Chicago 1965 p. 315.
Fievez, M. and Haas, F.: Les sarcomes de la synoviale.
Ann. d'Anat. pathol. 10: 351, 1965.
Fisher, H. R.: Synovial sarcomesothelioma (sarcoendothelioma).
Am. J. Path. 18: 529, 1942.
Fluur, E., Moberger, G. and Nylén, B.: Terapeutiska synpunkter på synoviala sarcom.
Nord. Med. 78: 1523, 1967.
Geiler, G.: Die Synovialome.
Springer Verlag, Berlin 1961.
Ghadially, F. N. and Roy, S.: Experimentally produced synovial sarcomas.
Cancer 19: 1901, 1966.
Haagensen, C. D. and Stout, A. P.: Synovial sarcoma.
Ann. Surg. 120: 826, 1944.
Hardie, J. and Salter, S. C.: Primary sarcoma of knee joint.
Lancet 1: 1619, 1894.
Hare, H. F. and Cerny, M. J.: Soft tissue sarcoma. A review of 200 cases.
Cancer 16: 1332, 1963.
Harrison, E. G., Black, B. M. and Devine, K. D.: Synovial sarcoma primary in the neck.
Arch. Pathol. 71: 137, 1961.
Jönsson, G.: Malignant tumors of the skeletal muscles, fasciae, joint capsules, tendon sheaths and serous bursae.
Acta Radiol. Suppl. 36, 1938.
Karlén, A.: Fall av synovialom i knäleden.
Nord. Med. 16: 3705, 1942.
Kehne, H.: Zur Klinik der malignen Synovialome.
Z. Bl. Chir. 90: 930, 1965.
King, E. S. J.: Concerning the pathology of tumours of tendon sheaths.
Brit. J. Surg. 18: 594, 1931.
King, E. S. J.: Tissue differentiation in malignant synovial tumours.
J. Bone Jt. Surg. 34: 97, 1952.
Knox, L. C.: Synovial sarcoma.
Am. J. Cancer 28: 461, 1936.
Knutsson, F.: Two synovial fibrosarcomas (Jönsson).
Acta Radiol. 29: 4, 1948.
Lejars, F. and Rubens—Duval, H.: Les sarcomes primitifs des synoviales articulaires.
Rev. Chir. 41: 751, 1910.
Lichtenstein, L.: Tumors of synovial joints, bursae and tendon sheaths.
Cancer 8: 816, 1955.
Luse, S. A.: A synovial sarcoma studied by electronmicroscopy.

Cancer 13: 312, 1960.
Mackenzie, D. H.: Synovial sarcoma.
Cancer 19: 169, 1966.
Martin, J.-F., Noel, R., Guichard, A. and Feroldi, J.:
Les synovialosarcomes extra-articulaires.
J. Méd. Lyon 32: 155, 1951.
Mc Cormack, L. J. and Parker, W.: Malignant synovioma.
Cleveland Chir. Quarterly 23: 260, 1956.
Moll, P. J.: Synoviosarcoma. Utrecht 1960.
Mouchet, A. and Vincent, D. et J.: Tumeur de la synoviale genou.
Ann. Anat. Path. 14: 252, 1937.
Murray, M. R., Stout, A. P. and Pogogeff, I. A.: Synovial sarcoma and normal synovial tissue cultivated in vitro.
Ann. Surg. 120: 843, 1944.
Nilsonne, U.: Synovialom.
Nord. Med. 72: 1084, 1964.
Nilsonne, U.: Synoviala fibrosarkom.
Nord. Med. 74: 1120, 1965.
Oota, K., Aoki, T. and Tanaki, M.: On synovial sarcoma: Report of three cases and survey of Japanese literature.
Gann, Tokyo 45: 246, 1954.
Pack, G. T. and Ariel. I. M.: Synovial sarcoma (Malignant synovioma).
Surgery 28: 1047, 1950.
Pack, G. T. and Ariel, I. M.: Tumors of the soft somatic tissues.
Paul B. Hoeber, New York, N. Y. 1958 p. 507.
Raben, M., Calabrese, A. C., Higinbotham, N. L. and Phillips, R.:
Malignant synovioma.
Amer. J. Roentgenol. 93: 145, 1965.
Ringertz, N., Ericsson, J., Sjöström, Å., and Swenson, D.:
National Board of Health. The Cancer Registry. Cancer Incidence in Sweden 1963, Stockholm 1967.
Sabrazès, J. and de Grailly, R.: Synovialome.
Compt. Rend. Soc. Biol. (Paris) 106: 1158, 1931.
Sabrazès, J., Loubat, E., de Grailly, R. and Magendie, J.: Les tumeurs articulaires. Synovialomes malins polykystiques.
Gaz. Sci. Méd. Bordeaux 53: 481, 1932.
Silfverskiöld, N.: Three operated cases of malignant synovial tumours; synovialoma, synovial fibrosarcoma.
Nord. Med. 8: 910, 1940.
Simon, G.: Exstirpation einer sehr grossen, mit dickem Stiele angewachsenen Kniegelenkmaus mit glücklichem Erfolge.
Arch. Klin. Chir. 6: 573, 1864—65.
Smith, L. W.: Synoviomata.
Am. J. Path. 3: 355, 1927.
Smolak, K. and Szczygiel, K.: Malignant synovioma (an attempt of histoclinical correlation).
Nowotory 23: 11, 1963.
Stout, A. P.: Tumors of the soft tisseus.
Atlas of Tumor Pathology. A. F. I. P. Sect. II fasc. 5, Washington D. C. 1953 p. 111.

Stüer, J.: Eine ungewöhnliche Geschwulst der Ellenbogengelenksgegend. Mang. Diss. Würzburg 1893.
Tillotson, J. F., Mc Donald, J. R. and Janes, J. M.: Synovial sarcomata. J. Bone Jt. Surg. 33: 459, 1951.
Tourneux, J. P.: Les sarcomes des gaines tendineuses. Rev. Chir. 47: 817, 1913.
Varret, D.: Les synoviosarcomes hypopharynges. Thèse pour le doctorat en Médicine. R. Foulon & Co. Paris 1964.
Vaubel, E.: The form and function of synovial cells in tissue culture. J. Exp. Med. 58: 63, 1933.
Weinreich, M.: Zum klinischen Bild des malignen Synovialoms. Z. Orthop. 97: 353, 1963.
Vincent, R. G.: Malignant synovioma. Ann. Surg. 152: 777, 1960.
Vinogradova, T. P.: On malignant synoviomas. Arch. Pathol. 1: 23, 1958.
von Rosen, S.: Ein Fåll von Synovialem Sarco-endotheliom des Kniegelenks. Acta. Orthop. Scand. 8: 191, 1937.
Wright, C. J. E.: "Malignant synovioma". J. Path. Bact. 64: 585, 1952.