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Review Article

Soft Tissue Sarcomas

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Abstract

Soft tissue sarcoma is a rare type of cancer that begins in the tissues that connect, support, and surround other body structures. This includes muscle, fat, blood vessels, nerves, tendons, and the lining of your joints.

More than 50 subtypes of soft tissue sarcoma exist. Some types are more likely to affect children, while others affect mostly adults. These tumors can be difficult to diagnose because they may be mistaken for many other types of growths. Soft tissue sarcoma can occur anywhere in your body, but the most common types occur in the arms and legs, and in the abdomen. Surgical removal is the most common treatment, although radiation and chemotherapy also may be recommended-depending on the size, type, location and aggressiveness of the tumor.

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Introduction

Soft tissue sarcomas are tumors that originate in the mesodermal tissue, which produces the body's connective tissue. There are also some types of epitheliums, which because they are of mesodermal origin, can also cause sarcomas. They can be classified according to the tissue that produces it. The common feature of these neoplasms is the spread, preferably by hematogenous route, unlike carcinomas that do so by lymphatic route. They are rare tumors and make up 1% of all male neoplasms and 0.6% of female neoplasms. They constitute 6.5% of tumors in children under 15 years of age. Due to the rarity of their presentation and their indolent character, most of the time they go unnoticed in their initial stage. Their growth is centrifugal, and they are often surrounded by a pseudo capsule with little reaction of normal tissue adjacent to the tumor lesion. (Figure 1).

Epidemiology

They are rare tumors in all regions. In the United States, currently, its incidence is 0.7% to 2% of the total population. About 6,000 new cases are reported annually with about

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1,500 deaths caused by these tumors. The most common varieties are fibrosarcomas, liposarcomas, rhabdomyosarcomas and synoviosarcomas.

Malignant fibrohistiocytoma has increased in frequency as new differential diagnoses have been made, as many of them were previously considered undifferentiated sarcomas.

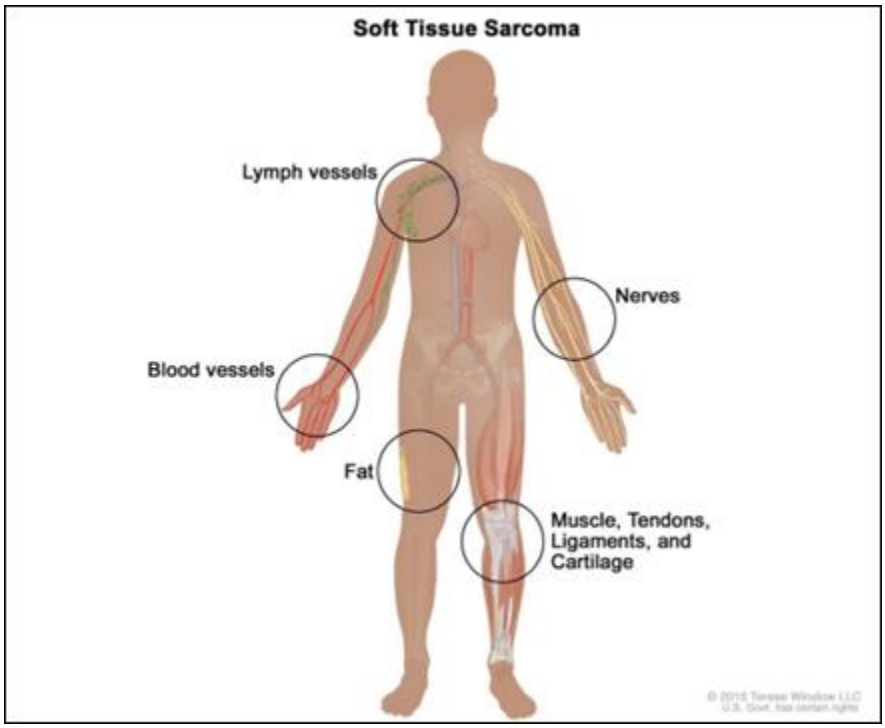

Figure 1: Soft tissue sarcoma.

Etiology

The origin of soft tissue tumors is unknown, but studies have been done trying to look for their cause. There are different factors involved in the development of sarcomas, among which are:

Environmental factors

Ionizing radiation

The history of previous radiant treatments in the area can cause sarcomas in these tissues in the 10 or 15 years after said treatment. Cases of appearance of chest wall fibrosarcoma, after a period of more than 10 years, irradiated by breast cancer have been described. The incidence is higher when the treatment was performed with Cobalt Therapy. Intrauterine fetal exposure to diagnostic x-rays doubles the risk of developing infantile rhabdomyosarcoma. Overall, a small proportion of sarcomas are induced using external radiation therapy. A cohort study in tumor registries showed a significant increase in connective tumors after breast, ovarian, testicular, cervical, and non-Hodgkin lymphoma cancers, not being significant in Hodgkin lymphoma. However, in hospital cohort studies of children and adults treated for Hodgkin lymphomas, higher than expected risks of 40 and 15 times respectively

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were found, with sarcoma originating over the irradiated region. Women irradiated for breast and ovarian cancer, during the first 10 years of evolution, have an 8 to 25 times higher than expected risk of developing sarcoma. The risk of developing uterine sarcoma is also increased in cervical cancer survivors who have received radiation therapy. In children diagnosed with bilateral or familial retinoblastoma and in family members with Li-Fraumeni syndrome, a very high risk of developing radiogenic sarcomas has been reported after brief latency periods of four to six years. In the various series of irradiated patients and in which a genetic alteration apparently does not coexist, sarcomas have occurred after a latency period of 2 to 40 years and with an average time of 8 to 10 years. Sarcomas secondary to radiotherapy are usually diagnosed in more advanced stages and with a worse histological degree than those that originate spontaneously. In post-radiotherapy sarcomas, all histological varieties have been described, but the most frequent is malignant fibrohistiocytoma.

Very few studies have been conducted to assess the risk of sarcoma based on the total dose of irradiation administered. In long-term follow-up of pediatric cancers, 60% of sarcomas originated within the field of radiation therapy and the risk was 50 times higher than expected when patients had received doses equal to or greater than 50 cGys. It has also been suggested that the level of risk of second tumors may be lower in patients treated with megavoltage than with orthovoltage. However, the total dose is more important than the radiation therapy modality used. Thorotrast (Thorium colloidal dioxide) was an alpha emitting radioisotope that was used to visualize the vascular system in the past. 17 It was abandoned in 1955 when its causal relationship with certain types of cancer became known, the most frequent being hepatic angiosarcoma. The risk of developing hepatoma, angiosarcoma and carcinoma was related to the total dose received in the liver tissue, being 30% at 40 years in the group that had received more than 20 cm^3 (equivalent to 30 rads per year). The number of thorotrast-induced angiosarcomas increased in the 70s-80s, due to the cumulative effect of low-dose diagnostic procedures and long latency times. Various histological types of sarcomas were also described in granulomas secondary to injection and/or extravasation of radiopharmaceuticals. The diagnostic or therapeutic administration of other radioactive substances can induce sarcomas in the anatomical sites near their deposit, describing laryngeal sarcomas after treatment of hyperthyroidism with iodine-125, which released higher extra thyroid doses of ionizing radiation than iodine-131 [1].

Non-Ionizing radiation

Some studies on exposure to low-frequency electromagnetic fields and childhood cancer have found a direct, though not significant, association between sarcomas and increased home exposure to such radiation. A cohort study of electrical workers potentially exposed to low-frequency electromagnetic radiation showed a higher-than-expected excess prevalence of sarcomas. The explanation suggested by the authors consists of immunosuppression and hormonal dysregulation caused by the modification of the circadian rhythm of melatonin. These

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findings have been documented and reproduced in experimental animals.

Occupational exposures

Carcinogenic chemicals such as 3 methylcholanthrene and certain viruses can cause sarcomas in animals, but the origin in humans has not been confirmed. Studies conducted in Sweden with exposure to phenoxy acetic acid (a class of herbicide) or chlorophenols (wood preservatives), showed that the risk of sarcomas was increased six times in that population studied. These studies were not demonstrated in a subsequent analysis of 350,000 farmers and carpenters exposed to these chemicals Herbicides derived from phenoxy acetic acid, chlorophenols and their derivatives, especially 2,3,7,8–tetradichlorodenzene-para-dioxin (2,3,7,8 TCDD) or dioxin, have been associated with an increased risk of sarcomas in agricultural populations, workers in manufacturing and plastics industries, geographic areas accidentally exposed to leaks, and among Vietnam War veterans.

In Sweden, clinical observations promoted a case-control study showing a six-fold increased risk of sarcomas associated with occupational exposure with phenoxy acetic acid and chlorophenols. Subsequently, other studies in different countries (Denmark, Scotland, Italy, England, etc), have found a direct relationship between agricultural and forestry workers, both men and women, exposed to these toxic substances and the development of sarcomas. Such relationships have also been documented in farmers and workers in manufacturing industries of phenoxy acetic acid, chlorophenols and dioxins. However, these data have not been reproduced in other studies on potentially exposed populations. The reasons for the inconsistency of results in the studies of populations exposed to phenotoxic herbicides and their contaminants may be due to the great diversity of phenotoxic derivatives (in the United States the agricultural use of 2,4-dichlorophenoxyacetic acid predominates, while in Sweden the main herbicide is 2-methyl-4-chlorophenoxyacetic), to the extent and intensity of exposure, to errors in memory when remembering cases, individual susceptibility, insufficient latency time, etc.

Conducting studies with the methodology and infrastructure necessary to solve these hypotheses are extremely difficult due to the complexity of the population, industrial, occupational, clinical, biological, toxicological, and evolutionary parameters. The relationship between dioxin exposure and sarcomas is more consistent.

A study in the United States with more than 5,000 workers showed a risk three times higher than expected, increasing to nine times among people with more than one year of exposure and with 20 or more years of latency. Another study of more than 19,000 workers from 10 countries found a six-fold increased risk between 10-19 years of exposure. An increased risk of developing sarcomas among populations exposed to dioxins because of accidental contaminations, such as those in Seveso (Italy) and Missouri (United States), has also been described.

During the Vietnam War, American troops used as an exfoliant the herbicide "Agent Orange" composed of 50% 2,4,5-T (2,4,5-

Trichlorophenoxyacetic acid) and the remaining 50% of 2,4-D (2,4-Dichlorophoxyacetic acid), a mixture of phenothiazines, herbicides and dioxin. Two studies conducted on Vietnam veterans exposed to Agent Orange used in the war have found an excess of sarcomas among the population exposed to the herbicide.

Other pesticides have also been linked to an increased risk of sarcomas, notably arsenical inorganic insecticides (especially with hepatic angiosarcomas), chlorohydrocarbon insecticides, hexachlorobenzene and organochlorine products. Exposure to vinyl chloride, during industrial plastics manufacturing processes, is also associated with an increased risk of hepatic angiosarcomas, preceded by liver fibrosis lesions.

Liver lesions also appeared in exposures to inorganic arsenical compounds and thorotrast (Thorium colloidal dioxide) Although the biological mechanisms underlying the association between sarcomas and chemicals are not sufficiently clarified, the available data suggest that they act by altering biochemical signals of intercellular communication, cell replication pathways, and inhibiting apoptosis.

Finally, other studies have linked sarcomas to other occupations: slaughterhouse workers, forestry workers, and formaldehyde exposure. Regarding the former, discerning the possible causes is very difficult due to the large number of exposures: manipulation of plastics to wrap meat, viruses and other potentially oncogenic zoonotic organisms, various chemical substances, including 2,4,6 trichlorophenol, used for the pretreatment of leather from the skin, etc.

Drugs

Administration of inorganic arsenical drugs, anabolic androgenic steroids and estrogenic compounds have been linked to the subsequent development of hepatic angiosarcoma. In cancer survivors, the appearance of a sarcoma as a second tumor is mainly caused by radiation, regardless of the use or not of chemotherapy. However, there is some evidence to suggest a possible link between sarcomas and some antineoplastic drugs. In experimental animals, regional arterial infusions of Adriamycin increase the risk of developing Rhabdomyosarcomas, this effect being dose dependent.

In patients treated for Hodgkin lymphoma, a higher-than-expected prevalence of sarcomas has been found after the exclusive use of polychemotherapy. In the occurrence of secondary cancers in children, a twofold increased risk of developing sarcomas has been observed among patients who had received alkylating chemotherapy plus radiotherapy, compared to those who had only been treated with radiation. Further studies are needed to classify whether alkylating agents and doxorubicin contribute to the development of secondary sarcomas. The use of immunosuppressive drugs in pathologies other than cancer and transplantation also increases the risk of developing various types of sarcomas, especially Kaposi's sarcoma.

Other environmental factors

Attempts have been made to establish a causal relationship between trauma and

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sarcomas, but the available evidence suggests that trauma only allows the pre-existing tumor to be discovered and may accelerate its growth. Cases of sarcomas have been reported in surgical scars, burns and in the vicinity of metal prostheses to fix fractures or bone implants. But epidemiological studies with large casuistries have not found an excessive risk of developing sarcomas or osteosarcomas after hip arthroplasty.

The risk of breast sarcoma in women with silicone prostheses is being evaluated. But given the low incidence of this tumor and the low prevalence of exposure, the value of such an observation is very limited to evaluate the hypothetical association.

The influence of dietary factors on these tumors has hardly been studied. A case-control study suggested a higher risk associated with high consumption of dairy products and seed oils, as well as a lower risk with the abundant intake of cereals, bread, and pasta. Another study found a higher prevalence of pediatric rhabdomyosarcomas among consumers of diets with animal organs (liver, brains, tongue, gizzard, etc).

Some authors have observed a higher prevalence of pediatric sarcomas in families with low socioeconomic status. The use of smokeless tobacco (chewed or aspirated) increases the risk of developing sarcomas especially in the upper gastrointestinal tract, respiratory tract, and neck-facial region. The interaction between smoking and occupational exposure 2,3,7,8-TCDD is synergistic with respect to the risk of sarcomas. The use of marijuana and cocaine in periods greater than 12 months prior to birth, increases from two to five times the risk of developing infantile rhabdomyosarcoma, associated with urogenital malformations and microcephaly.

Other causes

Thus, a history of chronic injuries, such as bedsores or sequelae of trauma with long and torpid evolution, have been reported as a possible cause of sarcomas. Other studies have shown that an important antecedent is chronic lymphedema, especially in patients with old breast cancer operations, who several years later developed Lymphangiosarcomas (Stewart-Treves syndrome).

It has not been possible to demonstrate genetic predisposition towards these neoplasms, except for young patients with Li-Fraumeni syndrome, in whom they have a higher incidence of soft tissue sarcomas than expected in the same age group.

This familial cancer syndrome is associated in addition to sarcoma, with osteosarcoma, breast cancer, brain tumors, leukemia, and adrenal carcinomas. In these patients there are alterations of the tumor suppressor gene p53. There have been reports of sarcomas in children associated with a higher incidence of other familial cancers, especially breast cancer in women younger than 30 years.

Soft tissue sarcomas are also associated with a variety of birth defects such as basal cell nevus syndrome, tuberous sclerosis, Werner syndrome, intestinal polyposis, and Gardner syndrome. In von Recklinghausen's multiple neurofibromatosis, neurofibrosarcomas may occur in 15% of patients. Table 1 for the genetic alterations that can occur in sarcomas.

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Frequent aberrations that arise in soft tissue sarcomas Histology	Chromosomal aberrations	Affected genes
Dermatofibrosarcoma	t(17;22) (q22;q13)	COL1A1-PDGFB
Childhood fibrosarcoma	t(12;15);+11; also +8,+17,+20	ETVG(TEL)/NTRK3
Neurofibrosarcoma	Suppression 17q11.2	
Malignant fibrous histiocytoma	19p+, ring chromosome	
Hemangiopericytoma	t(12,19) (q13;q13.3) y t(13,22)(q22;q13.3)	
Alveolar sarcoma of the soft parts	t(X;17) (p11.2; q25)	ASPL/TFE3]
Leiomiosarcoma	t(12;14)	
Synovial sarcoma	t(X;18) (p11.2; q11.2)	SYT/SSX
Chondrosarcoma extra skeletal myxoid	t(9;22) (q22;q12)	EWS-CHN
Clear cell sarcoma (MMSP)	t(12;22) (q13;q12)	ATF1/EWS
Well differentiated liposarcoma	Ring chromosome 12	
Myxoid liposarcoma	t(12;16) (q13;p11)	WT1/EWS
Pleomorphic liposarcoma	Complex	
Desmoplastic tumor	t(11;22) (p13; q12)	WT1/EWS
Alveolar rhabdomyosarcoma	t(2;13)	PAX3 fusíón with ALV
Embryonic rhabdomyosarcoma	+2q, +20	

Table 1: Frequent aberrations that arise in soft tissue sarcomas.

Prevention

Current knowledge of the risk factors associated with sarcomas, although very limited, has important implications for the primary and secondary prevention (early diagnosis) of these tumors.

People at higher risk from environmental or therapeutic exposures to ionizing radiation, primary or secondary immunosuppression, susceptible genetic syndromes, etc. need, after understandable and adequate information, the establishment of appropriate medical surveillance. The evolutionary control of tumors should include diagnostic imaging methods that avoid repeatedly performing studies with ionizing radiation, such as ultrasound and magnetic resonance imaging, due to the risk of second neoplasms.

In addition to these radiations, exposure to chemical compounds (herbicides, dioxins, vinyl chloride, etc.) without adequate protection will be avoided in all people who work with these substances. The

consumption of tobacco and other hallucinogenic drugs should be avoided, also implicated in some way in the development of these lesions and that on the other hand cause many other conditions as or more serious in the body.

In people with a causal genetic syndrome of sarcomas, all detection measures should be taken to achieve an early diagnosis and a rapid and adequate treatment of the lesions. It is to be hoped that in the future, with gene therapy, these conditions can be eliminated. All these recommendations should also be extended to all pediatric and adult populations, regardless of their Risk Factors. The scientific community should strive to design and conduct future studies to identify other risk factors associated with sarcomas, as they will undoubtedly bring new data to the biology, etiology, and prevention of cancer.

Biology

Each of the tissues of the body that make up the soft parts (fat, muscles, vessels, etc.) can cause sarcomas. Given the great variety of original tissues there is a wide variety of lesions that have their benign and malignant variant. There are also intermediate forms, which look like sarcomas but rarely metastasize, but are recurrent and cause local invasion (desmoid tumors or aggressive fibromatosis).

In general, each of the sarcomas resembles the cell that originated it, but sometimes it is very difficult to specify the original cell and therefore, to classify them. Thus, the same tumor may have different histological classification, depending on the pathologist performing the study.

Both puncture and freezing biopsy do not identify the type of sarcoma. In addition to conventional microscopy, Immunohistochemistry or electron microscopy techniques are required for its characterization. As a characteristic detail, these tumors produce reticulin. Stains with vimentin are very useful in these lesions, as well as the S-100 protein others of histiocytic and neural origin. By determining HER-2/NEU, C-KIT (CD117) and Vascular Endothelial Growth Factor (VEGF) a prognostic factor for sarcoma can be obtained.

Histological classification

The tissue that gave rise to the lesion gives its name and allows them to be classified. As the tissues originating in the mesoderm are varied, they cause a wide variety and lesions, many of them difficult to pin down in their original tissue.

Fibrous tissue

Pseudosarcomas

- Tumordesmoide
- Mesenteric fibromatosis (Gardner syndrome)
- Fibromatosis of the penis (Peyronie's disease)
- Fibromatosis palmo-plantar
- Fibromatoisi intraabdominal
- Fibromatosis extraabdominal
- Dermatofibrosarcoma protuberans

Fibrosarcoma

- Well differentiated
- Semi- differentiated
- Little differentiated

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Histiocytic tissue

- Malignant fibrohistiocytoma
- Pleomorphic
- Mixoide
- Giant Cell
- Angiomatoide
- Inflammatory

Adipose tissue

- Liposarcoma
- Well differentiated
- Mixoide
- Round cells
- Pleomorphic

Muscle tissue

- Leiomiosarcoma
- Leiomiosarcoma epitelioide
- Rhabdomyosarcoma
- Embryonic
- Alveolar
- Pleomorphic
- Mixed

Blood vessels

- Hemangiosarcoma
- Malignant hemangioendothelioma
- Sarcoma de Kaposi
- Linfangiosarcoma
- Malignant hemagiopericitoma
- Malignant gnomic tumor

Peripheral nerves

- Schwanoma
- Malignant tumor of granulosa cells
- Neurinomas
- Estesioneuroblastomas
- Neuroblastoma
- Ganglioneuroblastoma
- Melanocytic malignant schwanoma
- Paraganglioma maligno

Synovial tissue

- Biphasic tenosinovial sarcoma
- Sinoviosarcoma
- Biphasic: fibrous and epithelial
- Single phase: fibrous epithelial
- Clear cell sarcoma
- Choroid sarcoma

Bones

- Osteosarcoma
- Sarcoma de Swing
- Multiple myeloma

Cartilage

- Chondrosarcoma
- Well differentiated
- Mixoide (sarcoma cordoide)
- Mesenquimático

Mesothelial tissue

- Mesothelioma
- Epithelial
- Fibrous
- Biphasic

Of indeterminate origin

- Granulosa cell tumor
- Sarcoma alveolar
- Clear cell sarcoma
- Extra-skeletal Ewing sarcoma
- Sarcoma granulocíti
- Mesenquimoma

(de Enzinger FM, Weiss SW., 1988)

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Another important feature from the histological point of view is the degree of differentiation of the tumor, which can be:

G1: Well-differentiated tumors

G2: Moderately differentiated tumors

G3: Poorly differentiated tumors

The determination of gradation is based, among other factors, on the number of mitoses present, nuclear pleomorphism, degree of cellularity, neovascularization, vascular invasion and degree of necrosis.

Due to their origin in mesodermal tissue, they can originate a wide variety of connective and stromal elements [2].

Staging

Following the AJC (America Joint Committee) the staging of Soft Tissue Sarcomas includes in addition to T (Tumor) N (Node) and M (Metastasis), G (Histological Grade) to determine the stage (Tables 2 and 3).

Histological gradation has great relevance since it changes the stage regardless of the size of the lesion.
For the determination of the histological degree, pathologists rely on the rate of mitosis, the presence of necrosis, the degree of cellularity, nuclear pleomorphism, cell type, encapsulation and vascularization, among other parameters.

TNM	Characteristics
T1	Tumor up to 5 cm.
T2	Tumor larger than 5 cm.
No	No adenopathies
N1	With adenopathies
G1	Well-differentiated tumor
G2	Moderately differentiated tumor
G3	Poorly differentiated tumor
Mo	No metastasis
M1	With metastasis

Table 2: American Joint Committee Classification.

Stadium	T	N	G	M
She	T1	No	G1	MO
Ib	T2	No	G1	Mo
IIa	T1	No	G2	Mo
IIb	T2	No	G2	Mo
IIIa	T1	No	G3	Mo
IIIb	T2	No	G3	MO
VAT	Any T	N1	Any G	Mo
IVb	Any T	Any N	Any G	M1

Table 3: Stages.

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The prognosis is closely related between the stage. Thus, in a paper presented by Lawrence, et al. the results were as follows, according to Table 4. For stage I, 5-year survival was 79%, and for stage II it was 65%. From stage III less than half of the patients were alive at 5 years and only 10% of the patients with stage IV.

Stage	Number of patients	5-year survival
I	496	79%
II	191	65%
III	282	45%
IV	359	10%
Total	1328	

Table 4: Survival by stage.

The location of the sarcoma also has prognostic importance since it has an influence on the degree of resectability of the lesion and its possibility of cure. Lesions located in the trunk (mediastinum), retroperitoneum and head and neck are more difficult to resiccate with adequate margins and therefore with a worse prognosis.

Injuries to the limbs are also influenced by the fact that they are distal (better prognosis) or proximal (worse prognosis). Not so if they are upper or lower limbs since it has no influence on survival or the disease-free period.

Sarcomas rarely metastasize nodal, as their route of spread is preferably blood. Thus, in a review of 374 patients, out of 113 with nodal evaluation, only 3 patients (2.6%) presented nodal metastases.

In a review of more than 2,500 patients, Weingrad, et al. found that only 5% of patients had developed nodal metastases, with Sinoviosarcoma and Rhabdomyosarcoma being the two that did so most frequently.

The origin of sarcoma, regardless of its histological degree, is not in itself an important prognostic factor.

Clinic

Most soft tissue sarcomas cause a progressively growing tumor, being asymptomatic at the onset. As its volume increases, a tumor or lump begins to originate, and pain appears.

Neuralgia, paralysis, and edema can occur due to compression of the mass on other normal tissues. They can also cause restriction in joint movement or painful joint effusion Figure 2.

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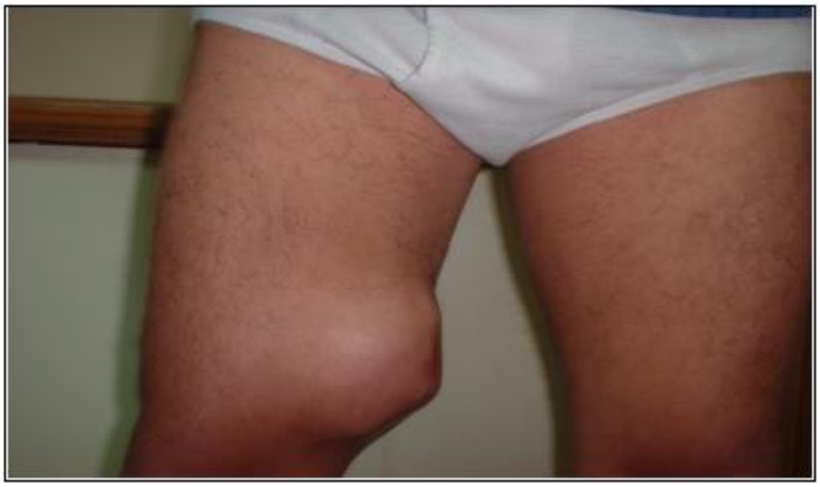

Figure 2: Bulky fibrosarcoma of the right member (courtesy of Dr. Hunis).

Pain is one of the characteristic symptoms of these injuries, as they increase their volume and compress neighboring structures, so when they are small, they often do not present pain. In the growth of abdominal masses, they can cause obstructive symptoms at the urinary and digestive level. When the location is thoracic, mediastinal growth can produce compression of vascular structures, causing edema and mediastinal syndrome. The speed of growth of lesions is closely related to the degree of differentiation and the variety of sarcoma. Thus, there are tumors with a slow and indolent growth that are discovered as large abdominal masses after a long evolution, and others of high growth rate, progress quickly causing early symptoms and spread of the lesion.

As the lesions grow, general symptoms such as weight loss, fever, asthenia, and progressive deterioration of the general condition appear. They can be associated with episodes such as severe hypoglycemia, or hormonal dysfunction caused by endocrine paraneoplastic syndromes.

Therefore, any tumor in the soft tissues that grows without a specific cause must be carefully studied, being necessary, most of the time, the study by means of a biopsy to confirm its origin.

Diagnostic methods

Faced with a tumor that grows without a proven cause, different diagnostic procedures are used.

- Radiology
- Echography
- Computed Tomography
- Nuclear Magnetic Resonance
- Arteriography
- Bone Scintigraphy
- PET (Positron Emission Resonance)

Using these methods, the characteristics of the lesion can be evaluated, as well as the invasion of neighboring structures. With radiology and ultrasound, it is possible to evaluate the lesion in the first instance. With tomography and resonance, you get more quantity and quality of information, and you can have details of the sarcoma. The data obtained are very useful to have a staging and then plan surgical treatment. With the Resonance the invasion of neighboring structures, the injuries of vessels and nerves

and of the affected muscular planes are appreciated. Arteriography allows to visualize the vascularization of the lesion, as well as the invasion to vascular structures. Bone scintigraphy is used on suspicion of bone invasion or metastasis. PET may be useful in angiosarcomas and other varieties of sarcomas, in patients who need to rule out the presence of metastases, before performing tumor surgery. It is with a puncture or incisional biopsy that cytological or histological confirmation of sarcoma is obtained. The larger the sample size, the more details the pathologist can give us about the tumor lineage. Many times, you can only have a confirmation of the variety with the complete resection of the tumor mass and after having performed Immunohistochemistry techniques.

Treatment

For the most appropriate treatment of these injuries, a multidisciplinary team is needed that includes both the Surgeon, the Radiation Therapist, and the Clinical Oncologist. The most appropriate therapeutic procedure for each case must be agreed upon based on a correct prior staging. Treatments used for sarcomas include:

Surgery

It is the treatment of choice for these injuries. Proper surgical resection is the most important prognostic factor in sarcomas. The high incidence of local recurrences forces the surgeon to have wide limits in his resections taking well-defined margins by neighboring healthy tissues. These criteria of broad resection in limb lesions can lead to the need for amputation if the margins are not safe, especially in lesions that in addition to the risk of local recurrence, have implicit the risk of distant metastasis. Any surgical procedure should be preceded by careful study to rule out systemic lesions from metastasis. At the beginning, the lesions are limited by a pseudo capsule and tend to respect the different anatomical planes. This pseudo capsule often contains viable tumor cells and is not a safe limit of resection. Margins may vary according to Table 5.

Type of Resection	Resection	Amputation	Dissection plane	Microscopic details
Intracapsular	Resection of intracapsular lesion	Intracapsular Amputation	Broad resection	Tumor in the margins
Marginal	Marginal excision in block	Marginal amputation	Including the extracapsular area	Reaction of neighboring tissues + microsatelitosis
Wide	Wide block resection of the lesion	Extensive resection including amputation of bone structure	Reaction of normal tissues of the anatomical compartment	Normal tissue + satellite lesions
Radical	Radical block resection	Disarticulation	Normal extra-compartmental tissues	Normal tissues

Table 5: Resection margins.

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In general, higher-grade lesions require broader resections, while small, low-grade, well-localized lesions require more limited limits. Adequate margins should be accompanied by the normal tissues of the structures of the affected compartment. In tumors located in the skin and subcutaneous tissue, radical resection includes a margin of up to 5 cm of healthy tissue neighboring the lesion. In high-grade patients, they often need, in addition to surgery, the use of radio and chemotherapy, being preferable to be more conservative in the margins of resection, especially for the preservation of vital structures such as nerves or vessels. The percentages of local recurrences vary greatly according to the different series and the different types of tumors treated. It is considered, in general, that there is a local failure (recurrence) in 30% of the tumors operated. The reoperation of these recurrent lesions is much more difficult than at the first opportunity since there is a profound alteration of the anatomical structures of the area with the first surgery.

With the combined use of radio and chemotherapy after surgery, the number of local recurrences is substantially reduced. Before performing the resection, not only the location, but also the histological variety and a correct staging of the lesion must be considered. If there are no proven metastases, the limit of resection of the tumor should be as wide as possible, often requiring study by freezing the margins to know that they are free of neoplastic cells.

In limb resections, distal compression is used to prevent intraoperative spread by embolization of tumor cells and facilitate more precise dissection with less blood loss. The resection of the tumor must be done in block, without seeing the lesion, that is, passing through healthy tissue, with a margin that varies according to the location between 1 and 5 cm. The ideal margin is 2 to 3 cm per healthy tissue. If you plan to irradiate the area later, especially in limbs, you should avoid damaging the lymphatic system of the area as little as possible, as this will cause severe post-radiation edema. Block resection should include the aponeurotic muscle structures of the anatomical region, as well as nerve structures. Neurological sequelae and deficits may appear that often require post-surgical orthopedic or kinetic treatment. Both the skin and the subcutaneous cell of the affected area should be thoroughly resected. They may require further treatments with plastic surgery to cover the area with musculocutaneous flaps that cover the operated region. If bone structures are involved, the bone should be resected with a wide margin or replaced by a prosthesis. If a joint is affected, resection of the injury can result in subsequent arthrodesis of that joint. The following should be considered for amputation:

1. Very large lesions that cannot have an adequate margin and that are not very sensitive to complementary treatments with radiation and/or chemotherapy.
2. Sarcomas that recurred to initial surgery.
3. Tumors that cause symptoms that are impossible to alleviate either by pain, bleeding or by recurrent and torpid infections.
4. Local recurrences of high-grade sarcomas when the first treatment was correct.
5. Involvement of the vascular axis of the limb: the resection and repair of the

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vascular axis entails a significant morbidity and the possibility of complications.

6. Important nerve involvement: In general, a major nerve can be sacrificed, but exeresis of two nerves makes amputation advisable. Nerve grafting may be assessed in some cases.
7. Bone and soft tissue involvement so that the application of a prosthetic device is not feasible.
8. Extensive local contamination from previous surgery or poorly planned biopsy.
9. Pathological fractures because the fracture hematoma spreads the neoplasm and makes conservative treatment impossible.

Amputations are subject to the same criteria of radicality as broad resections. Amputation is not indicated in those tumors that have spread or are at high risk of metastasis. Extensive limb resections can be done without the need for amputation. It should only be left for those cases where the resection is insufficient.

Amputations must be radical, which means that the proximal margin has to be wide. An amputation with a small margin would require irradiation of the residual limb and this, in general, is not recommended.

Major amputations must be regulated, with resection of all muscle groups from their origin.

Regulated amputations

- Hemipelvectomy and its variants with anteroposterior flap.
- Internal hemipelvectomy.
- Hip disarticulation.
- Amputation of the leg, above the knee.
- Interscapular amputation, with or without rib resection.
- Amputation above or below the elbow.

Other amputations: Any distal amputation can be done, but surgery should be considered including muscles, tendons, and possible routes of spread, removed with the part being amputated.

Compartment resections are indicated for grade 2 tumors and for grade 3 tumors up to 5 cm. These are rare indications since it is necessary that the tumor is well confined within the compartment, and it is difficult for this to occur.

It is not necessary to remove the muscles from their origin to insertion, but sometimes it is necessary to do so as not to leave muscle remains poorly vascularized and without function. It is essential to leave the skin in good condition so that it can be irradiated approximately one month after surgery.

Unless amputation is indicated, for any sarcoma extensive resection, plus radiation therapy, is recommended. This treatment is best suited for sarcomas of the upper extremity and those below the knee.

In the thigh, in tumors located between two compartments near the vascular axis and those neighboring the Scarpa triangle, the most appropriate treatment is broad resection plus radiotherapy.

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In sarcomas of the foot, ankle, distal third of the leg and knee, hands, wrist, distal third of the forearm and elbow, to perform a broad resection it is necessary to sacrifice skin and capsuloligamentous and tendon structures. If the resection is correct, the chances of closing the surgical wound by bringing the skin closer is quite difficult. The subsequent addition of radiation therapy to these areas, especially in the foot, ankle, knee, wrist, and elbow, means posterior fibrosis and problems of motility and skin instability. Amputation is often recommended in these cases. A treatment alternative is extensive local resection, the application of plastic tubes to perform brachytherapy and coverage with a free flap.

Another issue to consider is ganglion emptying or resection. Prophylactic emptying is not indicated in these tumors, except in those cases where the regional nodes are affected. Synovial sarcomas are the most frequent of lymphatic spread, as well as in rhabdomyosarcomas, myxoid liposarcoma and epithelioid sarcomas. In these tumors, the study of the regional nodes can have a prognostic and therapeutic result. However, the role of nodal resection in patient survival is controversial.

Resection of solitary metastases has improved the survival of operated patients. For these surgeries, it is a necessary condition that the primary lesion must be controlled, and no other residual lesions should remain. Candidates for these interventions are those patients with metastases who have little response to systemic treatments and have unique lesions of slow evolution.

In patients with a single metastasis, with an operated sarcoma, surgical resection is indicated, if it can be resectable.

Based on the above, sarcoma resections can be summarized according to Table 6.

Stage I:	**T1NoMoG1:**	Resection with adequate margin, then control Resection with a thin margin, then evaluate radiation therapy
	T2aNoMoG1	Resection plus radiation therapy
	T2bNoMoG1	Resection, then evaluate radio and/or chemotherapy
Stage II and III:		Resection with pre- or postoperative radiation therapy, then evaluate chemotherapy Unresectable preoperative radiotherapy
Stage IV Single		metastatic injury, evaluate surgery and then chemotherapy
		Multiple or single unresectable lesions, chemotherapy

Table 6: Therapeutic scheme according to the stage.

Radiant treatment

Radiation is used in soft tissue sarcomas to decrease the percentage of local recurrence after surgery and improve cosmetic results. They began from the 40s with the treatments performed by Cade. The replacement of the old cobalt irradiation techniques by the current techniques of irradiation with linear electron accelerator, has managed to improve the quality of the treatment and reduce the sequelae to tissue irradiation.

Irradiation can destroy residual lesions that may have remained after surgery. For this reason, the incidence of local recurrences is lower than in non-irradiated tissues and in those cases where the margins are scarce or

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doubtful. When irradiation is used as an initial treatment, it is much less effective since when the volume is greater, the sensitivity and therapeutic effect decreases. It can also be used with palliative criteria in those inoperable or metastatic lesions (especially at the bone level).

In cases where the margins of the surgery are not safe, the placement of metal clips on the edges of the areas to be irradiated helps in the planning of the therapeutic field. Irradiation, like surgery, should include the entire anatomical compartment of the lesion. After surgery there are changes in the area, which should be considered when planning the area to be irradiated. Neighboring nodal areas should not be irradiated unless nodal involvement is suspected. Irradiation of the nodal area can only be applied in a sinoviosarcoma or epithelioid sarcoma.

The irradiation technique is based on careful planning in three dimensions of the lesion or area to be treated. For this, studies carried out with computed tomography or magnetic resonance imaging on the lesion are very useful. The calculation of the dose depends on the area to be irradiated. The average dose is 45 to 50 cGy over the initial volume, to reach with boost to 65 cGy over the area of the lesion or scar. It is divided into 5 weeks and the ideal period to start it is after 20 or 30 days of surgery. In cases where the lesion has not been resected and in those locations that do not have the risk of irradiating radiosensitive organs (kidney, liver, etc.), it can reach up to 70 to 80 cGy. Devices not less than 6 MeV must be used to be able to arrive with an appropriate dose to the site to be irradiated, especially in abdominal or thoracic lesions, and other devices of lower power may be used for the irradiation of limbs.

Preoperative irradiation is performed with the aim of reducing the volume of the lesion and decreasing its vascularization, creating hypoxic zones in the tumor. This facilitates subsequent surgical resection by delimiting the tumor areas from the normal ones. In general, soft tissue sarcomas are poorly sensitive to irradiation. They have an inverse relationship between the sensitivity and the volume of the lesion: the greater the volume, the lower the sensitivity. The disadvantage of preoperative radiant treatment is the possibility of hindering the subsequent histopathological study, and the risk of favoring the appearance of post-surgical complications: infections, wound dehiscence, and necrosis. In the case of not responding to preoperative irradiation, surgical treatment may be delayed or made unfeasible.

A study by O'Sullivan showed that both preoperative and postoperative radiotherapy are equally effective and obtain similar local control and survival in sarcomas of the extremities. The results at 5 years in patients treated with pre-operative radiotherapy vs. those treated postoperatively were as follows: in local control: 93% vs 92%; in patients free of relapse or metastasis: 67% vs 69%; recurrence-free survival: 58% vs 59%; and overall survival: 73% vs 67% (P=0.48).

A study by M. D. Anderson Hospital - Houston, USA-, showed that patients treated with preoperative radiotherapy had a significantly lower incidence of local recurrence, compared to those not irradiated (7% vs 33%) (P=0.003).

In special cases, interstitial implants with Iridium192 or Iodine125 can be used. They are placed at the time of surgery by means of catheters and removed after a few days. It should be carefully planned before placing them, to avoid sequelae (fistulas, fibrosis, etc.).

Chemotherapy

The role of chemotherapy in these lesions presented significant advances in the last 20 years. The first drugs to demonstrate activity in advanced lesions were Adriamycin, Actinomycin D, Cyclophosphamide, Ifosfamide, DTIC, Methotrexate, Vincristine and Cisplatin (generally used in combinations, with responses between 25 to 40%, but with a short duration of responses). Studies conducted by ECOG (Eastern Cooperative Oncology Group), Cancer and Leukemia Group B and SWOG (Southwest Oncology Group) used Adriamycin in adjuvant schemes.

One of the combinations associates Adriamycin with Dacarbazine, which demonstrated synergistic activity in animal studies. The response rate in advanced lesions is 42 to 47% with 10% complete remissions. The average survival in responders reaches 15 months Table 7.

Scheme	% RC	% RP	Rank
A	01-Jun	16–27	19
To	Mar-14	18–44	28
ADCV	15–33	38–71	37
In	2	18	
MAID	12	49	

Table 7: Responses to different chemotherapeutic schemes in Soft Tissue Sarcomas. A: Adriamycin, AD: Adriamycin+dacarbazine; ADCV: Adriamycin+Dacarbazine+Cisplatin+Vincristine; IM: Ifosfamida+Metotrexato; MAID: Methotrexate+Adriamycin+Ifosfamide+Dacarbazine; CR: complete remission; PR: partial remission.

Another combination performed in several centers was the so-called CYVADIC, which included: Cyclophosphamide, Vincristine, Adriamycin and Dacarbazine, with a response of 50% and an average survival in the responders of 16 months. A study conducted by EORTC compared the CYVADIC scheme, versus Adriamycin alone and Adriamycin with Ifosfamide, showing no differences between either group.

Regarding studies with adjuvant chemotherapy, MD Anderson presented his experience in 122 patients treated with the CYVADIC regimen after surgical and radiant treatment, in sarcomas greater than 10 cm. and of high grade (G3). They showed a local control of 89% at 5 and 81% at 10 years, against 72% and 58% respectively, of the control groups without chemotherapy. In relation to survival, in the treated group it was 72% at 5 years and 58% at 10, compared to

47% and 44% respectively in the control group. There are a wide variety of studies that compared Adriamycin in different therapeutic schemes Table 8.

Group	Scheme	No.	% RC	% RP	Remarks
GOG	A	80	6	16	Uterine sarcomas only
	To	66	11	24	
ECOG	A	34	3	18	Only leiomyosarcomas
	To	32	3	44	
ECOG	Neither is c/3	93	6	19	A 70 mg/m²
	The sem	92	4	16	At 15 mg/m²/se
SWOG	ACVD	221	14	52	
	ACVAd	224	12	40	
ECOG	A	66	6	27	A 70 mg/m²
	ACV	70	4	19	A 50 mg/m²
	CVAd	64	2	32	A 0 mg/m²
SWOG	To	79	14	32	
	ADC	95	13	35	
	Adad	98	9	24	
GOG	A	30	1	19	
	And	34	2	20	
SWOG	To	135	7	10	Bolus
	To	143	10	18	Infusion cont.
SWOG	ADVV	27	15	67	A:30 C 300
	ADCV	24	33	71	A:80 C:800
EORTC	ADCV	71	20	38	Total dose
	ADCV	74	3	14	1/2 serving
EORTC	I	68	3	18	3 g/m²
	C	67	1	8	1,5 g/m²

Table 8: Use of Adriamycin in sarcomas. GOG: Gynocologic Oncologic Group; ECOG:Eastern Cooperative Oncology Group; SWOG: South West Oncology Group; EORTC: European Organization for Research and Therapy of Cancer; A: Adriamycin; C:Cyclophosphamide; V:Vincristine D:Dacarbazine; Ad:ActinomycinD; I: Ifosfamide: RC:complete remission; RP:partial remission.

The administration of preoperative chemotherapy has proven useful in limb lesions. A study carried out in Boston, comparing three different schemes, using Adriamycin, Ifosfamide and Platinum, showed 74% of responses in 23 patients, especially in intraarterial administration.

The response to chemotherapy also serves as a prognostic factor. According to Henshaw, the percentage of necrosis after neoadjuvant chemotherapy (>=95%) at the time of surgery shows a lower percentage of recurrences and greater survival.

High-dose chemotherapy regimens have been used, supported by colony-stimulating factors, especially with drugs such as Adriamycin, but without achieving the expected responses. Autologous bone marrow transplantation has also been used in cases of bone sarcomas or infantile rhabdomyosarcomas. In a study carried out at the Royal Marsden Hospital in Sutton, 6 courses of Vincristine, Doxorubicin and Cyclophosphamide were used, followed by high doses of Melphalan and bone marrow transplantation, in 36 patients.

The 5-year survival was 57%, 44% were free of disease, and there was a death from toxicity. In other work by Pinkerton of the European Bone Marrow Transplant Registry, of 95 patients, 64 received high-dose treatment, after a CR or RP. 20% maintained the response for more than 40 months and 35% of the 40 transplant patients remain disease-free. The results of a high-dose schedule of Ifosfamide, Carboplatin and Etoposide followed by TAMO were published. Of 55 patients treated, overall survival was 50% at 2 years and 26% at 5. The mean survival was 23 months with a mean follow-up of 21 months.

Among the new drugs, we can mention: Gemcitabine, Vinorelbine, Etoposide, Taxanes, Temozolomide and Irinotecan: All of them have shown activity in sarcomas.

Based on the determination of the C-Kit at the level of the cell membrane, a new therapy has emerged, which makes it possible to treat with modifiers of the biological response to sarcomas. GITS have been the neoplasms that have benefited the most from the use of these new drugs, such as Imatinib.

Benjamin presented 218 patients diagnosed with GIST, in whom the average survival was 63.8 months and the time to progression was 16.4 months, in those treated with Imatinib, being 5.1 months in patients with classic chemotherapy treatment.

There are studies using another compound: Bortezomib, in recurrent or metastatic lesions with 2 responses in 11 treated patients.

Specific types of sarcomas [3]

Fibrosarcoma

Fibrosarcomas, with all their varieties, constitute the most frequent group of sarcomas. They are derived from the fibrocytes and fibroblasts of connective tissue. Within this group of sarcomas are the following varieties:

Varieties of Fibrosarcomas

a) Pseudosarcomas

- Tumor desmoide
- Mesenteric fibromatosis (Gardner syndrome)
- Fibromatosis of the penis (Peyronie's disease)
- Fibromatosis palmo-plantar
- Fibromatoisi intraabdominal
- Fibromatosis extraabdominal
- Dermatofibrosarcoma protuberans

b) Fibrosarcoma

- Well differentiated
- Semidiferenciado
- Little differentiated

The most frequent age of presentation of these lesions is between 20 and 50 years, although there are cases in children and adolescents. It predominates in the male sex. The most frequent variety is that of well-differentiated fibrosarcomas Figure 3.

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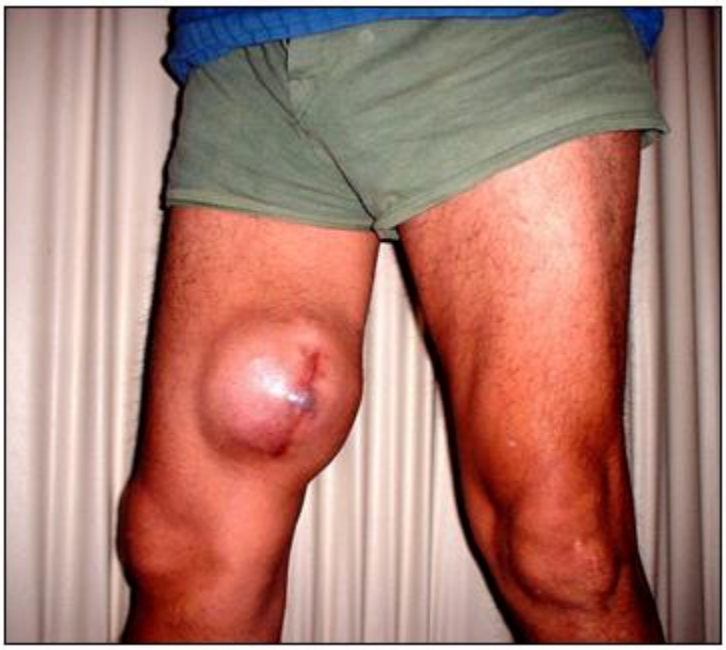

Figure 3: Well differentiated fibrosarcoma (courtesy Dr. Hunis).

There are cases derived from aggressive fibromatosis that must be differentiated from these lesions, which are called Pseudo sarcomas, since histologically they are benign fibroids, but their behavior is that of a sarcoma: they invade and infiltrate neighboring structures.

Certain fibrosarcomas have been reported as secondary in areas that received high doses of radiation therapy. Due to their location, those of the head and neck have a better prognosis than those of the extremities. The prognosis is closely related to its histological gradation.

The well-differentiated have a recurrence rate of 40% and a 5-year survival of 95%, while the poorly differentiated have a 75% local recurrence rate and a 5-year survival of 50%.

The treatment of choice for these lesions is wide or radical excision. They have a high incidence of local recurrence (up to 60%) if adequate surgery was not performed. If the margin is not adequate, it should be completed with postoperative irradiation to reduce the possibility of local recurrence. The higher the histological grade, the greater the chance of local recurrence. There is little chance of cure for non-operated fibrosarcomas, treated with radiation exclusively.

Desmoid tumor

They are aggressive fibromatosis that derive from the fascias and aponeurotic muscle structures anywhere in the body. Histopathologically these lesions are made up of normal-looking fibroblasts. They predominate in the tissues of the abdomen. They usually appear in women in the postpartum period. They differ from Fibroids by the infiltration of neighboring structures.

The treatment of choice, like all fibrosarcomas, is extensive resection of the

lesion. If the margin is adequate, they do not recur and are cured. If the margin is not adequate there is a local recurrence of 50 to 75%. In a review of 138 patients, Postner reported that inadequate margins or recurrent forms were the most important prognostic factor. The overall survival of these patients was 92% at 5 years.

Radiation therapy should only be done in cases where the margins are positive. 50 to 65 cGys are applied depending on the place to be irradiated. Wara reported on 12 patients treated with radiation therapy after surgery, of whom 2 died and the rest remained alive after 2 to 6 years of treatment.

In cases where the margin is doubtful or insufficient and reoperation is not possible, patients should be kept in strict control and only irradiated at the first sign of recurrence. Kiel reported 8 patients with doubtful or positive margins who were controlled and only 1 had relapse.

There are studies using hormone treatment in unresectable lesions, which achieved stabilization of the disease for a variable period. Lanari reported patients treated with progesterone, Kinzbrunner with Tamoxifen and Waddell administered indomethacin and ascorbic acid, causing tumor regression. There are works using Imatinib in tumors that express the c-kit. Of 22 evaluable patients at 4 months, 78% were disease-free. All expressed polymorphism and mutations of exon 18, proving to be a useful drug in patients with unresectable tumors.

Neurofibromatosis type 1

Another autosomal dominant inherited syndrome associated with an increased risk of sarcomas is neurofibromatosis type 1. In the pediatric population, rhabdomyosarcomas, fibrosarcomas and liposarcomas develop more frequently than expected. After the second decade of life there is a greater predisposition to neurogenic sarcomas.

Mesenteric fibromatosis Gardner syndrome

It is an aggressive fibromatosis, which affects the mesenteric tissues. It is part of a genetic association that causes multiple colonic polyposis, epidermoid lipomas, and fibroids.

Fibromatosis of the penis (Pyrone's disease)

It is a fibromatosis that affects the connective tissues that lie between the corpora cavernosa and tunica albuginea of the penis. It causes pain and curvature of the penis in erection. The recommended treatment is surgery, but there are also cases treated with irradiation.

Fibromatosis palm-plantar

They affect aponeuroses of the soles of the feet and hands. When it is located only in the hands, it constitutes Dupuytren's Disease. They have a hereditary tendency and appear preferably in people over 60 years of age, both in men and women. They are slow-growing lesions like nodules that invade the fascias and neighboring tissues. They are benign but tend to relapse if they are not resected with an adequate margin of healthy neighboring tissue.

Dermatofibrosarcoma protuberans

They predominate in patients between 30 and 40 years old. They are low-grade sarcomas

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and are preferably located in the skull and trunk, constituting 1.4% of all sarcomas. Its histogenesis is unknown and may be of fibrous or histiocytic origin. They may have slow growth that simulates a keloid scar, but at other times they have rapid growth. It has a high recurrence rate. If operated, the Mohs technique is used, with adequate margins at all ends. With this technique, recurrence is rare. In cases that occur, they can be reoperated. They are local recurrences but do not metastasize.

Glenn reported on 35 treated cases, of which 20 added postoperative radiation therapy and only 1 patient recurred. Survival was 12 to 97 months (average 36 months).

Treatment by a multidisciplinary team, together with the experience of the surgical and oncological team that must decide the most appropriate type of therapy, is considered the most important prognostic factor to avoid recurrence after surgery.

The relationship of dermatofibrosarcoma protuberans with fibrosarcoma is widely contemplated in the literature, being important the number of published cases of dermatofibrosarcoma protuberans with fibrosarcomatous transformation. However, the number of cases with transformation to malignant fibrohistiocytoma is much lower and is limited to some isolated case or included in the series of fibrosarcomas originated on dermatofibrosarcoma. There are times when the tumor expresses the tyrosine kinase receptor and there are studies that reported results to Imatinib.

In a study conducted by Chang, disease-free survival at 5 and 10 years was 86% and 76% respectively, with a recurrence of 16%. The mean time to recurrence was 38 months (range 1-100 months). In 30% of patients with recurrence, the same was after 5 years. Extensive local resection with good margins decreases the risk of recurrence. It is necessary to continue monitoring the patient annually for more than 5 years, due to the risk of recurrence.

Histiocytic tissue

Malignant fibrohistiocytoma

Malignant fibrohistiocytoma, also known as fibroxanthosarcoma or malignant fibrous xanthoma, is a rare soft tissue sarcoma whose histiogenesis has not yet been fully clarified. The malignant fibrohistiocytoma variety has increased in frequency with the review of biopsies previously classified as undifferentiated sarcomas. These tumors, most of them high-grade, show a mixture of histiocytic cells and fibroblast cells. There are different varieties of Fibrohistiocytomas:

- Pleomorphic
- Mixoide
- Giant cells
- Angiomatoid
- Inflammatory

Histologically, the main feature of this tumor is the variable degree of cellular pleomorphism. lnmunohistochemically, most of these tumors are expressed in Vimentin and presence of cytoplasmic immunoreactivity with alpha 1 antitrypsin of tumor cells.

They predominate in adults over 60 years of age. The primary location of malignant fibro histiocytoma can be hepatic (which is rare),

and also splenic (much rarer), both of mesenchymal lineage. Among the clinical manifestations, the following are reported: abdominal pain, masses in different locations of the body, weight loss, anemia, coagulopathy of consumption, among others.

Abdominal tomography or MRI describes a large mass with extensive areas of necrosis. The findings of these lesions are not specific. With selective arterial angiography, vascular irrigation can be demonstrated exactly, which can vary between highly vascularized to hypovascularized tumors.

The treatment of choice is extensive resection of the lesion.

Adipose tissue

Liposarcomas

Liposarcomas are those that follow fibrosarcomas in frequency. They can be located anywhere in the body that has fat.

Microscopically the cells are very similar to normal fat cells, especially in the well-differentiated or myxoid forms. The most frequent presentation is in the form of large masses, well delimited, pseudo encapsulated, mucoid surface, viscous, suggestive of myxoma, bright yellow color that imitates a lipoma or a surface similar to the cerebral gyrus, of indolent evolution, of yellowish appearance and consistency similar to fat.

They may present with satellite nodules or with multiple foci of injury. They are slow growing and, in the abdomen, can form voluminous masses of several kilos. Sometimes it is difficult to diagnose differentially with lipomas.

There are different varieties of Liposarcomas

- Well differentiated
- Mixoide
- From round cells to Lipoblastic.
- Pleomorphic

Although they can appear at any age, they predominate between 40 and 60 years. The incidence among men/women is 1.5 to 1 respectively.

In a series published by Scout, they predominated in lower limbs (45%), retroperitoneum (14%), trunk (14%), head and neck (6%), upper limbs (8%) and others (13%). Liposarcomas manifest S-100 immunoreactivity to varying degrees.

Liposarcoma mixoide

Myxoid liposarcoma is the most common of the liposarcomas, it is easily diagnosed in freeze cuts. It has a classic appearance and is a hypocellular myxoid lesion composed of small cells with a prominent vascular component. The nuclei of the cells are small and oval with a finely dispersed chromatin. Mitoses are uncommon except in the most cellular samples. Foci of round or pleomorphic cells may be found and are associated with a decrease in the survival rate. Extracellular mucoid material can accumulate in large lakes thus simulating a tumor originating in the lymphatic vessels. The treatment of choice is the broad resection of the lesion with adequate margins.

Round cell liposarcoma

Round cell liposarcoma is characterized by small tumor cells with clearly eosinophilic

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cytoplasm. The presence of lipoblasts scattered between them, establishes the diagnosis. Mitosis is more common than in the myxoid form, but the vascular plot is less prominent. Pseudo glandular arrangement of tumor cells is common. The natural history of this tumor is extremely aggressive.

The treatment of choice is the broad resection of the lesion with adequate margins. On certain occasions when the margins are doubtful, the treatment with irradiation of the surgical bed must be completed.

Liposarcoma pleomorphic

The Pleomorphic form is the most aggressive and the survival to 5 years is 20-25%. They can have any anatomical distribution, including the lower extremities in the popliteal fossa and inner thigh region, in the retroperitoneal, perirenal, mesenteric and shoulder region areas and in rare locations such as the pleura. Pleomorphic liposarcoma is characterized by being very cellular with a high mitotic index. Multivacuolated giant cells are observed. Vacuoles are characteristically small and numerous within giant tumor cells.

The treatment of choice is the broad resection of the lesion with adequate margins. After surgery, radiant treatment in the surgical bed and adjuvant chemotherapy should be added due to the high risk of metastasis.

Muscle tissue

These sarcomas originate from muscle tissue cells. They can be classified into:

- Leiomiosarcoma
- Leiomiosarcoma epitelioide
- Rabdomiosarcoma
- Embryonic
- Alveolar
- Pleomorphic
- Mixed

Leiomiosarcomas

Leiomyosarcomas are sarcomas that derive from smooth muscle. The origin is unknown, but several theories are discussed about it. They are likely to derive from soft tissues in the wall of small vessels, ectopic mesenchymal muscle tissue, or viscera that are released at some point in their growth.

They are in muscular structures of the retroperitoneum, skin, subcutaneous cellular tissue and in veins (inferior cava, saphenous, iliac, femoral and renal). The most frequent locations are uterine and retroperitoneum. Leiomyosarcomas of vascular origin are more common in large vessels such as the vena cava (50% of cases) and the pulmonary artery, according to data obtained from autopsies studies. Many of the leiomyosarcomas of the vena cava develop in the upper third or supra-hepatic region.

Leiomyosarcomas are mainly from adulthood and are more common in women. This may be due to smooth muscle growth and proliferation, which can be influenced by pregnancy and estrogenic stimulation, where increased gonadotrophin production is present.

The histopathological characteristics are variable, the most common image being the arrangement in fascicles, with fusiform, pleomorphic cell population, with foci of necrosis. Less frequently it may show myxoid areas and the presence of epithelioid cells.

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Differential diagnoses should be made with tumors derived from peripheral nerves. All these neoplasms have reactivity with immunostaining for S-100 and negativity for muscle actin. Clinical diagnosis is difficult in the initial stages. Symptoms are determined by the location, range of tumor growth, and degree of collateral blood flow or drainage of the affected segment. They are characterized by abdominal pain, presence of tumor on clinical examination and weight loss. Ultrasound, abdominal tomography, angiography, and magnetic resonance imaging are useful to define the characteristics of tumors, before deciding on surgery. Leiomyosarcomas that originate in the soft tissues of the mediastinum have a nonspecific clinical presentation, causing chest pain, cough, dyspnea, dysphagia, and superior vena cava syndrome. The most important predictive factor in leiomyosarcomas is the amount of mitosis (histological grade). Another prognostic factor is localization (retroperitoneal or vascular) and tumor size (>3 cm). These factors will determine the risk of local recurrence and metastasis. The recommended primary treatment is radical surgery, followed by chemotherapy and/or radiotherapy. Local recurrence is reported in 40% of cases, while metastases occur in 50%, located in the lungs, kidneys, chest wall, pleura, liver, and bones. In advanced disease, drugs that have demonstrated activity in addition to Doxorubicin, Cyclophosphamide and Ifosfamide, are Gemcitabine and Taxanes [4].

Rabdomiosarcomas

Rabdomyosarcomas are derived from the striated muscle of the body. They make up 15% of all sarcomas. Embryonic and alveolar varieties are usually seen in children. In the urogenital location they are called "Botryoid Sarcoma" and form large polypoid masses that are seen in young children, located in the bladder, oral and nasal region. It is the most common form of sarcomas in children. Occasionally they can be seen in adults. Regarding frequency, embryonic cases account for 49% of cases, alveolar cases for 32% and botryoid cases for 6%. The pleomorphic form can be seen in young people and adults. They preferentially affect the extremities. They are very anaplastic tumors, made up of small and large cells with bizarre-looking nuclei. By immunohistochemistry, the specific diagnosis of these lesions can be reached. In Rhabdomyosarcoma there are chromosomal alterations of a numerical and structural type. The cellular content of DNA (ploidy) may have prognostic significance. In the embryonic type hyper diploidy usually occurs and in the alveolar tetraploid. Regarding structural abnormalities, the alveolar presents a translocation of chromosomes 2 and 13, t(2; 13)(q35;q14), in which the PAX3 gene fuses within the 2q35 band with the FKHR gene in the 13q14 band. Mutations of the p53 gene have also been found, both in the alveolar and embryonic, in 50% of cases. In the embryonic subtype, point mutations of the proto-oncogenes NRAS and KRAS have been found, more frequently than in the alveolar. In the latter subtype, 10% amplification of the NMYC gene occurs. At present, a classification proposed in 1995 by a group of pathologists from the different international groups is followed. It is based on the meeting of the different histological types in prognostic groups.

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International Classification of Rhabdomyosarcomas (ICR)

I. Good prognosis

- Botryoid
- Of fusiform cells

II. Intermediate prognosis to Embryonic

III. Poor prognosis

- Alveolar
- Undifferentiated sarcoma the Pleomorphic.

The 5-year survival of the different subtypes varies from 95% of patients with botryoid rhabdomyosarcoma to 54% in those with alveolar type. The non-botryoid embryonics of the intermediate group are found in 67%. They are stratified as shown in Table 9.

Stage I: Localized	disease, completely resected (14%). Confined to the organ or muscle of origin. Infiltration out of the organ or muscle of origin; negative regional ganglia.
Stage II: Total	macroscopic resection with regional spread (20%) Macrocopically resected tumors with microscopic residual tumor regional disease, completely resected, with nodal metastases, infiltration by the tumor of an adjacent organ or both. Regional disease with affected nodes, macroscopically resected, but with microscopic residual tumor.
Stage III: Incomplete	resection or biopsy, with macroscopic residual disease-48%
Stage IV: Distant	metastasis (18%)

Table 9: Clinical Stages of Rhabdomyosarcoma According to the IRS Committee.

The mean age at the time of diagnosis is 7 years, but the incidence is maximum between 2 and 5 years. These tumors can develop anywhere in the body. The clinical signs they produce are those of a mass of different locations, with no history of associated trauma or the alteration of a certain organic function secondary to tumor growth. The percentage distribution of the different locations is:

- Genitourinary system: 24%
- Extremities: 19%
- Parameníngeos: 16%
- Head and neck: 10%
- Orbit: 9%
- Other: 22%

Depending on the location, the symptoms will manifest. Bladders present with hematuria or symptoms of urinary obstruction. Prostates present as a pelvic mass and by obstructive symptoms. Less frequent are those of vagina, typical of small girls and of Botryoid presentation, producing a serosanguinolent vaginal discharge. Paratesticulars occur in pre- and postpubertal males, manifesting as a unilateral painless or inguinal scrotal mass. Those of the extremities manifest as a soft tissue mass, which can be painful and reddened with increased sensitivity in the affected area. In 50% of cases, they are alveolar histology. Those located in the nasopharynx, nasal cavity, paranasal sinuses, middle otomastoid

region, pterygopalatine and infratemporal fossae, clinically cause nasal and auricular obstruction and can produce serousguinolent secretion and cranial nerve involvement.

They can spread directly to the central nervous system in almost 50% of cases. Those located on the scalp, face, buccal mucosa, oropharynx, larynx, and neck. They manifest as painless tumors. Those of Orbit, produce exophthalmos and eye pain and given their superficiality are usually diagnosed early before their dissemination at a distance.

Intrathoracic and retroperitoneal ones give few symptoms until they reach a large size. Those of thoracic location produce cough and respiratory distress.

Blood vessels

They originate in the cells that form the walls of blood and lymphatic vessels. They can be classified into:

- Angiosarcoma
- Malignant hemangioendothelioma
- Sarcoma de Kaposi
- Lymphangiosarcoma
- Malignant hemangiopericytoma

They are usually lesions of a high degree of aggressiveness. They make up 2% of all sarcomas.

Angiosarcoma

Angiosarcoma is a rare malignant vascular tumor (1 to 1.5% of all sarcomas). It predominantly affects males, and its highest incidence is from the age of 60. Although the initial histopathological criteria for the diagnosis of angiosarcoma were described by Stout in 1940, the distinction between benign and malignant lesions, as well as the definition of the primary site of the neoplasm can be difficult. In addition, similar histopathological findings can be found in bronchioloalveolar tumor, Kaposi's sarcoma, and other less differentiated vascular tumors

Any organ can be the primary origin of this tumor, being the most frequent places of involvement, the skin (33%) and deep soft tissues (24%). They are followed with lower incidence, breast (8%), liver (8%), bone (6%), spleen (4%), heart and large vessels (3%), orbit (3%), ENT area (4%) and others (7%).

The lung is one of the most preferred places for metastases, appearing in 60-80% of cutaneous and cardiac angiosarcomas and less frequently they spread in the liver and lymph nodes. In terms of etiology, hepatic angiosarcoma has been linked to exposure to vinyl chloride, arsenic-derived pesticides, and Thorotrast dioxide. Cases of bone and soft tissue angiosarcomas have also been reported after radiation and patients after radical mastectomy (with appearance of the tumor in the upper extremity with lymphedema). The relationship between the use of phenylethylehydrazine and the development of angiosarcoma has been published.

Clinically it stands out, in almost all cases, the presence of hemorrhage that can be episodic with free intervals, with self-limited hemorrhages. Another common symptomatology is weight loss and pain. Up to 20% of cases are asymptomatic and the tumor is only discovered at autopsy.

The treatment of choice is resection with adequate margins of the lesion. Prognosis in

metastatic angiosarcomas remains poor, with an average survival of a few months after diagnosis. Different therapeutic modalities such as surgery, radiotherapy, chemotherapy have been used, but none have been shown to be effective. The prognosis may be influenced by the degree of differentiation of the tumor, with well-differentiated neoplasms being a more indolent course.

Thalidomide has been used in these lesions as an antiangiogenic, in conjunction with radiotherapy.

Malignant hemangioendothelioma

The term hemangioendothelioma was coined by Mallory (1908) to describe all tumors that derive from the endothelium of blood vessels. In 1988, Enzinger and Weiss described hemangioendotheliomas as vascular tumors of intermediate malignancy, of uncertain evolution ("borderline tumor"), or of low grade. They are defined as a non-aggressive tumor that practically does not metastasize and is characterized by the presence of massive cell cords and endothelial vascular structures. Endothelial cells are usually prominent and globular but do not exhibit the malignant features of angiosarcoma. It is also known as hemangioendothelial sarcoma, low-grade angiosarcoma and lately, epitheloid hemangioendothelioma.

Hemangioendotheliomas are considered as neoplasms and not as vascular malformations, due to their independent growth capacity, their frequent nuclear atypia, their mitotic activity, and their capacity for local recurrence after inadequate resection. It may have a benign appearance, but it must be considered as a low-grade malignant lesion.

Macroscopically the lesion is characterized by a soft, red-dark hemorrhagic mass, which may be well circumscribed or have irregular margins. Tumor tissue may be crossed by some septa. Histologically, prominent endothelial cells are observed, with abundant weakly eosinophilic cytoplasm, which sometimes present intra-vascular papillary projections. These cells form small blood capillaries, which can alternate with areas of dilated cavernous capillaries with flattened endothelium. Mitoses are rare. An infiltrate of inflammatory cells (lymphocytes and plasma cells) is frequently observed. The stroma varies from fibrous to myxoid and may have a hyaline appearance, reminiscent of a matrix of hyaline cartilage.

The stromal cells between the neoformed vessels are fusiform and do not show the atypical features of angiosarcoma. Occasionally stages in transition can be found, between clearly differentiated types and highly anaplastic lesions, making it difficult to categorize some tumors. The gradation criteria of hemangioendotheliomas include the amount of mitosis, the degree of atypia, the presence of necrosis, and the morphological appearance of their vascular spaces.

Based on these criteria, four types of hemangioendotheliomas are recognized: epithelioid hemangioendothelioma, spindle cell-variant, Kaposiform hemangioendothelioma, and malignant papillary endovascular hemangioendothelioma, also known as Dabska tumor.

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Epitheloid

Your cells have an epithelial appearance are considered as border-line tumor or low-grade tumor.

Spindle cell

Spindle cell hemangioendothelioma shows features of cavernous hemangioma and Kaposi's sarcoma.

Of fusiform cells

Malignant papillary endovascular hemangioendothelioma

Most hemangioendotheliomas are in the liver, lungs, digestive system, head and neck, and bones. It occurs between 10 and 75 years of age, with a peak between 20 and 30 years and has a slight predilection for men.

It can be multifocal in 25% of cases (usually limited to a single limb, although it can be extended to other organs), and in these cases affects people 10 years younger than in solitary lesions. The most frequently affected bones are the dome of the skull, spine, and the bones of the limbs, especially the lower ones. They are located in the metaphysis or diaphysis and in adults can pass to the epiphysis. They cause pain, swelling and local lump, sometimes accompanied by joint effusion. The duration of symptoms is highly variable, from a few weeks to years. The presence of a pathological fracture and a mass of soft tissues is rare. The lesions are osteolytic, with a diffuse pattern and in other cases well delimited. The cortical may be expanded in the form of a soap bubble or partially destroyed, with occasional extension to the soft tissues. In general, there is no periosteal reaction. On some occasions have a trabeculated or honeycomb pattern was observed. Resonance shows a mixed signal pattern at T1 and moderate increase in signal strength at T2. The bone scan shows an increase in isotope uptake in the sarcoma area. It is difficult to differentiate from vascular lesions, both benign and malignant. As they are non-specific lesions, it is important to have good clinical information. The evolution of the tumor is unpredictable. The prognosis is better than that of poorly differentiated angiosarcoma. Hemangioendothelioma may recur locally after resection but rarely metastasizes, although new foci may appear after treatment of a solitary or multifocal lesion. In cases of low degree of malignancy evolves slowly or even very slowly and have a good prognosis in the case that they are treated surgically, with radiotherapy, or a combination of both.

In solitary lesions, broad resection is indicated. In the case of multiple lesions located in one or different bones of a limb, the most appropriate treatment is amputation. Radiation therapy may be associated with surgery. Radiation therapy alone has also been used in inoperable cases with good results. In cases of a hemangioendothelioma of low degree of malignancy, a marginal resection or intralesional excision can be performed on the vertebrae, completed the treatment with radiotherapy on the operative bed. In multicentric forms of low degree of malignancy, radiotherapy is used, which may be accompanied by endomedullary fixation.

Kaposi's sarcoma

Kaposi's sarcoma was described by Kaposi as a pigmented sarcomatous lesion of the skin

with no known local or systemic cause. They originate from the endothelial cells of the blood vessels of the skin. They present as café-au-lait lesions on the skin of the extremities, usually in men over 60 years of Mediterranean or Jewish origin. There are four clinical varieties of Kaposi's sarcoma (Table 10). It is a rare tumor and Reynols had reported a series with only 70 patients in 38 years. The lesions begin as reddish nodules on the lower extremities. They have an indolent course. They respond to radiant treatment. It has a mortality of 20% due to pulmonary or gastrointestinal involvement. Several of these patients develop lymphomas as a second tumor, being of generally fatal course. Liposomal Doxorubicin appears as one of the drugs with the highest response, but Doxorubicin, Vinblastine and Taxanes have also shown activity.

Hemangiosarcomas

Hemangiosarcomas can originate in deep tissues but also in the superficial vessels. Thus, of 366 Hemangiosarcomas, 33% were in the skin and 25% in the deep soft tissues.

They are very aggressive and in a holden post the survival at 5 years was 12%. Lymphangiosarcomas originate from the walls of lymphatic vessels. Woodward reported 23 cases of lymphangiosarcoma associated with chronic lymphedema. The most appropriate treatment for lymphangiosarcomas secondary to mastectomy requires amputation of the arm.

Guy	Population	Male:Female Ratio	Clinical features	Course
Classic	Jewish/Italian 50-80 years	1,5:1	Skin lesions on the lower extremities	Indolent survival 10-15 years
African	Young adults (25-40 years)	1,3:1	Nodular skin lesions on lower limbs	Indolent. Aggressive locally
	Children (2-13 years)	03:01	Generalized lymphadenopathies. Rare skin lesions.	Rapidly progressive. Survival 2-3 years
Kidney transplantation	Medically immunocompromised patients	2,3:1	Cutaneous or disseminated form	Indolent or progressive. Deadly in 30%
Epidemic	AIDS patients	20:01	Disseminated mucocutaneous lesions and visceral involvement.	Torpid. Survival at 2 years <20%

Table 10: Clinical manifestation of Kaposi's sarcoma.

Malignant hemangiopericitoma

It originates from the pericytes of the walls of blood vessels. They are very rare tumors, and it is difficult to make the differential diagnosis between the benign and malignant variety. It is characterized by the presence of vascular spaces lined with a single layer of endothelial cells and surrounded by zones of cell proliferation. It has a similar structure in

bones and soft tissues. The essentially vascular structure of this tumor is very well evidenced by staining the reticulin fibers. In some patients who have been diagnosed with hemangiopericytoma, they had mesenguinal chondrosarcomas or malignant fibrohistiocytomas. Its most frequent location is observed in vertebrae, ribs, ischium, and sacrum. Sometimes they can appear in other bony sites and in extraskeletal areas. They are more common in adults. Its manifestations may vary according to its location. The intensity of the pain can range from only mild pain to sharp and difficult to treat pain.

In soft parts it can behave like a deep and sensitive tumor. In its bone presentation it is an osteolytic tumor whose degree of malignancy is difficult to determine histologically. It can cause pathological fractures. The treatment is surgical and many times, by doing the histopathological analysis, its histological grade and its malignant characteristic can be determined.

It is recommended to resection widely and consider that due to its vascular origin it can cause significant bleeding during surgery. The therapeutic value of radiotherapy and chemotherapy for the treatment of this tumor is scarce, although the usefulness of irradiation in cases not accessible to surgical treatment has been pointed out. The average 5-year survival is 50%.

Peripheral nerves

Sarcomas originating from the peripheral nerves can be classified into:

- Schwanoma
- Malignant tumor of granulosa cells
- Neurinomas
- Estesioneuroblastomas
- Neuroblastoma
- Ganglioneuroblastoma
- Melanocytic malignant schwanoma
- Paraganglioma malign

Schwanoma

It is a peripheral nerve tumor, encapsulated, also known as Malignant Schwann, Neurogenic Sarcoma or Neurofibrosarcoma. It originates in Schwann cells and is frequently located on the flexor surface of the extremities, neck, mediastinum, retroperitoneum, posterior spinal muscles, and pontocerebellar angle. They are generally benign, and their malignant variety is rare.

Despite their name, these tumors almost never come from malignant degeneration from schwannomas, but arise as malignant tumors, or from a malignant transformation of a plexiform neurofibroma, often associated with Neurofibromatosis type I. They are usually located in extremities, and in many cases the nerve from which the tumor originated can be identified. Malignant Epithelioid Schwannoma is an extremely rare tumor. It accounts for 1 to 2% of peripheral nerve tumors with malignant transformation.

The histological study shows that the tumor is made up of solid nests. These nests of tumor cells, polygonal in shape, these tumors are composed of polygonal cells with acidophilic cytoplasm and epithelioid appearance, hence the term used of malignant Schwannoma epithelial, with large hyperchromatic nucleus, pleomorphic, presence of some nucleoli, dense nuclear chromatin and atypical mitosis, are separated by thin septums of connective tissue, with

lymphoplasmacytic inflammatory infiltrate, being the usual morphological aspect of these lesions that undergo malignant transformation. It presents as a monomorphic tumor, with abundant mitoses.

Studies carried out with immunohistochemistry techniques demonstrate reactivity for the S-100 protein, in half of the cases, vimentin positive in 70% and alpha actin negative.

The clinical evolution of this neoplasm is of a highly aggressive behavior, local recurrence and metastases are frequent, and can even appear after treatment with radiotherapy.

Malignant Granule Cell Tumor

Malignant Granule Cell Tumor (also called Triton Tumor) is a mixed tumor, with areas that suggest neural sheath differentiation and exhibits rhabdomyoblastic elements. Squamous, neuroendocrine, or glandular differentiation has sometimes been described. Despite the low mitotic activity, it may represent signs of vascular invasion.

The tumor is characterized by two types of cells, some fusiform and others with striations. Spindle cells could be framed by their phenotype within the type of myofibbroblasts. The other type of cells are rhabdomyoblasts with striations that express muscle markers. The stroma of the tumor is quite collagen and shows vessels, with the appearance of a tendon sheath tumor.

Differential diagnoses should be made with perineuroma and desmoplastic fibroblastoma (collagen fibroid).

Treatment is extensive resection of the lesion.

Esthesioneuroblastoma

Olfactory neuroblastoma or Esthesioneuroblastoma, is an embryonic tumor, uncommon, derived from neuroblasts of the nasal branches of the olfactory sensory system and is located in the neuroectodermal respiratory epithelium of the nasal cavity. The term derives from the Greek root aisthesis which means perception-sensation and it is thought that this neoplasm comes from the olfactory placoda. It makes up about 3% of all tumors of the nasal cavity and 6% of malignant tumors. The involvement of the cribriform lamina is typical and in its absence the diagnosis of this tumor should be doubted. From the clinical point of view, it presents a higher bimodal incidence, with a peak during adolescence and another during the third to fifth decades of life. Although cases have been described from 2 to 79 years of age, their presentation at the extremes of life is rare.

It prevails in males (ratio 1.5:1). Its origin has not been completely determined, being the neuroblasts of the deep layer of the olfactory epithelium of the nasal vault, its most accepted origin. The most common presentation is as a polypoid growth tumor in the nasal cavity. Other locations are the olfactory placoda, Jacobson's nasal vomero organ, and the sphenopalatine ganglion. Macroscopically it presents a pediculate or broad base in the vault of the nasal cavity and upper third of the septum, of hard or soft consistency and smooth surface. When it is of soft consistency, it is friable and bleeds easily, spontaneously and at the minimum contact. Microscopically, patterns of differentiation are found that fluctuate between paraganglioma and neuroblastoma.

Commonly, the cell may present a morphological spectus that fluctuates between the neuroblast to a mature neuron, with apparently benign morphology.

They are small, round, eosinophilic cells, with a tendency to organize themselves as nests or rosettes, separated by fibrovascular sheets or septa, with a thin fibrillar background, this characteristic being important to distinguish them from poorly differentiated carcinomas of the paranasal sinuses.

Epithelial differentiation and true olfactory rosettes are uncommon. Immunohistochemistry presents reactivity to markers of neural differentiation or neuroendocrine including: synaptophysin, neurofilament protein, beta tubulin III, chromogranin A, S-100 protein, and specific neural enolase.

It may exhibit immunoreactivity to cytokeratins and epithelial membrane antigen, which complicates its diagnosis. By electron microscopy you can see the presence of neurosecretory granules that contain low concentrations of catecholamines and dopamine and neuritic prolongations, which certifies the diagnosis.

The differential diagnosis is made with undifferentiated carcinomas of the paranasal sinuses, lymphomas, embryonic sarcomas, amelanotic melanomas and pituitary adenomas [5]. Hyams, classified esthesioneuroblastoma in degrees, based on histological aspects Table 11.

	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Arquitectura Lobar	Present	Present	+/-	+/-
Mythological Activity	Absent	Present	Celebrity	Marked
Pleomorfismo Nuclear	Absent	Moderate	Celebrity	Marked
Rosettes Necrosis	H-W +/- Away	H-W +/- Away	Flexner +/- Occasional	Common Absentees

Table 11: Histological grade of Esthesioneuroblastoma according to the Hyams classification. Grade 1+2: Low grade; Grade 3-4: High grade; H-W: pseudorosetas de Homer Wright; +/-: Present or absent.

Esthesioneuroblastoma is invasive and often causes regional invasion and distant metastasis. Some tumors may remain asymptomatic until transcranial growth through the cribriform lamina generates neurological symptoms. Clinically it is diagnosed in late stages and manifests itself with symptoms and nasal nonspecific signs such as obstruction, usually unilateral and epistaxis, less frequent are headache and rhinorrhea. It does not become apparent until it exhibits symptoms of orbital or intracranial involvement. Due to its invasive behavior, it tends to destroy the adjacent bone elements producing anosmia by compromising the cribose lamina of the ethmoid, sinusitis, by invading the maxillary, frontal and ethmoidal sinuses, respecting, characteristically, the

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sphenoid sinus. Invading the orbit causes proptosis and diplopia, and, less frequently, penetrating the anterior cranial fossa causes frontal signs and symptoms and endocranial hypertension. Exceptionally, it can invade the cavernous sinus causing paralysis of the neighboring cranial nerves. Lymphatic metastases to the cervical locoregional nodesmay occur in 20 to 40% of cases during the course of the disease, but less than 20% present with cervical metastases at the time of diagnosis. By hematogenous route it metastasizes to distant bones, lung, skin, peritoneum, heart, being often the first manifestation of recurrence and a sign of poor prognosis.

When a patient presents with a nasal cavity lesion diagnosed as Esthesioneuroblastoma, he should undergo a chest radiographic study, neck CT scan and bone scan to assess regional or distant metastases. Esthesioneuroblastoma does not present a characteristic imaging pattern because it is observed as a "glossy black" tumor of low attenuation on CT and hyperintense, in T2-weighted resonance sequences. Its diagnosis should invariably be suspected when observing a lesion of the upper third of the especially invasive nostril that causes changes in adjacent bone structures.

The resonance is ideal to assess the extent of the tumor in the cranial cavity and paranasal sinuses as well as the involvement of soft tissues.

Due to the neuroectodermal origin, Ramsay, et al. suggest the use of Octreotide labeled with Indio111 for the diagnosis and evaluation of probable metastases by bone scintigraphy. The same authors also propose the use of Bleomycin marked with Indio111 for therapeutic purposes in advanced stages not subject to surgery. Its relative rarity makes it impossible to carry out multicenter, prospective studies, so there is no agreement as to the optimal treatment or its prognosis. Current treatment guidelines are the result of retrospective and anecdotal analysis. It can be classified into stages Table 12.

Stage A	Tumor confined to the nasal cavity
Stage B	Tumor with extension to paranasal cavities
Stage C	Tumor involving the lamina cribose, orbit, or intracranial extension
Stage D	Presence of metastases in cervical lymph nodes or distant sites

Table 12: Stadiums: According to the Kadish classification of 1976, modified by Morita in 1993.

This classification has been questioned in multiple studies, but recent articles have shown that it is an important prognostic factor. Clinical staging of the tumor predicts evolution. The 5-year survival is 80% for patients with stages A or B of the disease and 40% for patients with classification C or D. To define the prognosis of the disease, Miyamoto, et al. state that 75% of patients in Stage A and B of Kadish presented 2 years free of the disease after treatment, while this evolution only occurred in 29% of patients in stage C.

There is no consensus as to the optimal treatment of esthesioneuroblastoma. In Kadish stage A, surgery is proposed by lateral

rhinotomy, associated with radiotherapy in cases of impossibility of resection with good safety margins; in stage B, directed radiotherapy is proposed at doses of 50 to 60 cGy followed by craniofacial resection, lateral rhinotomy+craniectomy by subfrontal approach extended; in stage C, chemotherapy based on Cyclophosphamide and Vincristine with or without Doxorubicin and Cisplatin is indicated, and/or radiotherapy with 65 or more cGy, followed by surgery. It has been proposed, with encouraging initial results, the combination of endoscopic surgery plus radiosurgery for esthesionuroblastomas that invade the anterior floor of the base of the skull without infiltrating the dura mater.

Neuroblastoma

Neuroblastoma is a common solid tumor in childhood. These tumors originate in neural crest cells in the sympathetic peripheral nervous system, which runs from the base of the neck to the caudal vertebra. Consequently, tumors can appear anywhere in this chain, although they are most often found near the adrenal gland and in the chest.

Each year, one in every 100,000 children in the United States develops neuroblastoma, which accounts for 7 to 10% of cancers in pediatric patients and 50% of all malignancies detected in infants. The most frequent is seen in children under 5 years of age. There are factors that influence its development:

- Boys are slightly more likely to develop neuroblastomas than girls.
- The presence of an oncogene called n-myc in tumor cells gives it a more aggressive behavior.

Neuroblastoma usually begins in the nerve tissue of the adrenal glands. It can also be in the chest, in nerve tissue near the spine in the neck, or in the spinal cord. It can be of congenital origin or appear after birth, and as the tumor begins to grow it can cause symptoms. In certain cases, neuroblastoma can be found before birth by ultrasound of the fetus.

The most common symptoms of neuroblastoma are due to the pressure exerted by the tumor, as it grows on neighboring tissues or because of its metastases. It causes tumor in the abdomen, neck, or chest, bone pain, weakness, or paralysis (loss of movement of a part of the body), fever, asthenia and weight loss, bleeding or petechiae, hypertension, severe diarrhea and liquid, sudden muscle movements, uncontrolled eye movement, edema of the legs, ankles, feet, or scrotum. Elevation of homovainilic acid (HMA) and vanillilmandelic acid (VMA) values in a urinalysis are typical of neuroblastoma. Certain factors affect prognosis (chance of recovery) and treatment options.

- Age of the child at the time of diagnosis
- Stage
- Location of the tumor
- Histology of the tumor

In neuroblastoma, the biology of the tumor has a prognostic effect, and the following details are analyzed:

- The patterns of tumor cells
- The difference between tumor cells and normal cells
- How fast they are growing

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- The number of chromosomes in tumor cells
- The number of copies of the N-myc gene

To classify neuroblastoma, the following stages are used in Table 13.

Stage I:	Tumor limited to the organ or structure of origin; has been completely removed, with or without residual microscopic disease; nodes not microscopically affected are identified.
Stage IIa:	A unilateral tumor with incomplete resection; microscopically unaffected nodes are identified
Stage IIb:	A unilateral tumor with complete or incomplete resection, with microscopically affected nodes on the
Stage III:	A tumor that extends by contiguity beyond the midline of the body, with or without regional node involvement; or unilateral tumor but with contralateral regional node involvement or midline tumor
Stage IV:	Tumor spread to bone, myelopoietic bone marrow, liver, distant nodes, and/or other organs (except those defined in the next stage).
Stage IVs:	Tumors definable as stages I or II with limited spread to liver, skin, and/or myelopoietic bone marrow.

Table 13: Neuroblastoma stage.

They can be divided into three risk groups.

Low risk

Survival between 80 and 100% of cases, (only with surgery) Stadiums I

Stages II (without amplification of the N-myc oncogene and 4S stages (also without N-myc amplification).

Intermediate risk

Survival of more than 80% of patients, with surgery, conventional chemotherapy, and local radiotherapy:

Stages III (without amplification of N-myc), without elevation of ferritin or neuro-specific enolase; with none or some neuroblasts in bone marrow and non-aggressive or favorable pathological tissue. Stages IV, less than 1 year of age, without amplification of N-myc, without elevation of ferritin or neuro-specific enolase, with none or few neuroblasts in bone marrow and favorable pathology.

High risk

Survival less than 10-15% with conventional chemotherapy surgery and local radiotherapy:

Stage IV in children 1 year of age or older. Any clinical stage or age with amplification of the N-myc oncogene. Treatment of these tumors is performed with surgery in low-risk cases and with chemo and radiation therapy in intermediate- and high-risk cases. With the exception of complete removal of the tumor, in all other cases treatment must be completed. Chemotherapy schemes include Adriamycin, Vincristine, Cyclophosphamide, Dacarbazine and Platinum.

Ganglioneuroblastoma

It is a tumor of the sympathetic nervous system. Tumors in this group include a

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frankly benign variety, such as ganglioneuroma, another of medium malignancy such as ganglioneuroblastoma, and a third, malignant, such as neuroblastoma. Many authors argue that the three tumors represent different stages of the same maturation process. It is an intermediate-grade tumor of malignancy, with components of ganglioneuroma and neuroblastoma in variable grade, consisting of a mixture of mature and immature nerve cells. It usually appears in boys between 2 and 10 years old. It is most often seen in the abdomen, followed by the mediastinum, neck and lower limbs.

Ganglioneuroblastomas tend to invade neighboring structures, causing symptoms as they occur and often requiring enlarged resections. Ganglioneuroblastoma is slow growing, may be partially encapsulated and attached to nerve trunks. Radiology or tomography shows the lesion and may present peripheral calcifications. Complete resection followed by irradiation and chemotherapy achieves 88% survival at 5 years. The rate of recurrence and distant metastasis is low. They are relatively sensitive to chemotherapy, a fact that allows the implementation of combined therapeutic strategies that can facilitate or complete surgical excision.

Malignant paraganglioma

Paragangliomas originate from the extraadrenal structures of the neural crest that form the scattered neuroendocrine system that extends from the base of the skull to the pelvic floor. Paragangliomas are located anywhere nodes of the autonomic system are located.

However, approximately 90% of these tumors appear in the adrenal glands and constitute Pheochromocytomas and the remaining 10% have an extraadrenal location. Extraadrenal paragangliomas most often originate in the abdomen (85%), others in the chest region (12%) and less frequently in the head and neck region (3%). The treatment of choice is extensive removal of the lesion Figure 4.

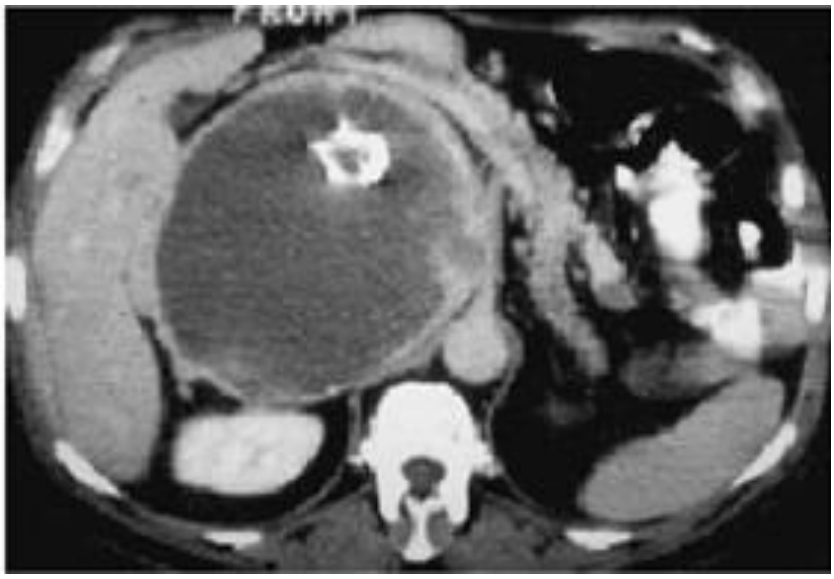

Figure 4: CT scan of the abdomen with bulky hypodense retroperitoneal tumor and with calcification inside (Paraganglioma).

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Synovial tissue

- Sarcomas derived from synovial tissue are:
- Biphasic tenosinovial sarcoma
- Sinoviosarcoma
- Biphasic: fibrous and epithelial
- Single phase: fibrous epithelial
- Clear cell sarcoma
- Cordoid sarcoma (Chordoma)

Sinoviosarcoma

It is a tumor that presents a biphasic cellular structure formed by indentations or acinous structures and lined with cells of epitheloid appearance with formation of mucoid material or without it. It makes up 5 to 10% of soft tissue tumors.

Etiologically as its histological structure is reminiscent of synovial membranes, its origin was postulated at the expense of synovial tissue. It is well established that any normal conjunctiva cell, subjected to the action of certain stimuli, can form malignant synovioblasts by metaplasia, which explains the not infrequent appearance of these tumors in distant sites and without any connection with the synovial membranes. Synoviosarcomas are classified from the histological point of view into:

Single-phase: filled with serous or mucoid liquids. It shows some papillary projections into the cavity, like synovial villi and calcifications or bone and cartilage formation may be found.

Biphasic: They are composed of epitheloid structures that form solid cords, clefts, or irregular spaces, surrounded by cylindrical, cuboid or polyhedral cells. They cause a glandular or adenoid picture, and the spaces are occupied by a homogeneous or pseudomucoid fluid.

Synoviosarcomas occur in the vicinity of joints, bursae, and tendons. They can also be in remote areas, such as the neck and abdomen, but the most frequent areas are in the knees, ankles and thighs. These tumors account for 5 to 10% of malignant soft tissue tumors. The treatment of choice is amputation or resection of the tumor. The oncology margin of safety must be respected. Resection is complemented by the association of radiotherapy and chemotherapy. Treatment with chemotherapy may occur preoperatively with which reductions in tumor mass have been observed. A study carried out by Eilber, treating 68 patients with Ifosfamide, had a 4-year survival of 88%, showing that it was possible to increase survival.

Clear cell sarcoma

Clear cell sarcoma of the tendons and aponeurosis was described by Enziger as a separate entity and originally published as synovial sarcoma of origin in the tendon sheath (Bennet). This rare tumor, which is more common in young adults (Dutra), is characterized by slow growing, usually painless swelling, most located in the heel, sole, and ankle region, particularly in close relationship with the Achilles tendon and plantar aponeurosis. Microscopically the tumor varies from firm to soft consistency, often nodular. Variable size. The histogenesis of clear cell sarcoma is still very controversial and it is possible that different tumors may appear with the typical appearance of a clear cell sarcoma. These tumors are of unknown origin but could form in the synovial cells that line the tendon sheaths. Until more is known

about these tumors (clear cell sarcoma, malignant giganto-cellular tumor of soft parts and malignant neuroepithelionoma of soft tissues), it is considered justified to classify it as a variant in the group of synovioms. The prognosis is poor since recurrences are frequent after local excision. However, according to Enziger, there were no important differences between those patients treated radically at an early stage and those treated after multiple recurrences [6].

Bones

- Osteosarcoma
- Sarcoma de Swing
- Multiple myeloma

They will be discussed in detail in another section.

Cartilage

Sarcomas derived from cartilaginous tissues are:

- Condrosarcomas
- Well differentiated
- Mixoides (sarcoma cordoide)
- Mesenquimáticos

Chondrosarcoma

It is a malignant tumor of cartilage-producing cells. This type of cancer is very rare among those under the age of 20 and is most common in people between the ages of 50 and 70. It affects both men and women.

It is the second malignant bone tumor in order of frequency, and accounts for 10-20% of all bone tumors. It can be primary or secondary resulting, for the most part, from the malignancy of pre-existing benign tumors. It often presents as a low-grade injury.

Secondary chondrosarcoma occurs in about 25% of cases.

Primary chondrosarcomas appear de novo and are not associated with a previous lesion, while secondary ones originate from benign pre-existing cartilage lesions, which may be enchondromas, osteocartilaginous exostosis, chondromyxoid fibroma, synovial chondromatosis, periostal chondromas, or chondroblastomas. Only patients with multiple hereditary osteocartilaginous exostosis or multiple enchondromas (Ollier's disease) have a recognized risk of developing secondary chondrosarcoma. Schwartz reported that the proportion of patients with Ollier disease who will develop a Chondrosarcoma is 25% before age 40.

Patients with Maffucci's disease (multiple enchondromas and hemangiomas) are at high risk of developing a malignant tumor (sarcoma or carcinoma) during their lifetime. Secondary chondrosarcomas have a better prognosis and rarely metastasize. An osseocartilaginous exostosis that increases in size in an adult should be respected, not because of its metastatic potential, but because of its local effect and small risk of developing chondrosarcoma. The resection should be complete, and the cartilaginous cover should be respected during the operation, as this may increase the local risk of recurrence. Histological interpretation is also difficult. The prognosis is variable and depends on the biological aggressiveness of the tumor.

The most important prognostic factors are:

The histological grade of the tumor

It is an important predictive factor in tumor behavior. The determination of the

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histological degree is subjective, so we have tried to find objective methods to be able to establish the prognosis with more reliability.

These methods are based on the investigation of DNA synthesis and content, flow cytometry, molecular markers (p53, MIB-1, src or ERB-1), cell proliferation, cytogenetics, histomorphometry and radiographic classifications.

Lee observed a significant relationship between DNA content, aneuploidy, and rates of metastasis and death secondary to the disease.

The location

Lesions located in the pelvis have a worse prognosis due to later diagnosis and more difficult resection.

The type of surgery (margins)

The incidence of metastasis, local recurrence, and death secondary to the tumor has been shown to be significantly higher in patients with marginal or incomplete tumor incision.

Treatment should be based on an early and accurate diagnosis, with an adequate biopsy, correctly planned and executed, with the precise determination of the location of the tumor and its complete resection with wide margins, with a cuff of normal tissue. Chemotherapy and radiation therapy are not very effective in these tumors.

They are located mainly in the pelvis, proximal femur and shoulder girdle, while osteosarcoma most often occurs around the knee. When chondrosarcoma occurs in the pelvis, it is often high-grade, a late diagnosis is made, and it has a poor prognosis.

Variants of chondrosarcoma

It is subdivided according to the amount of mitosis and the degree of cell differentiation into the groups:

Low grade (grading 1)

Graduation is based on the histological appearance of the tumor. The morphology closely resembles normal cartilage. They can cause local recurrence and do not metastasize. Their growth is slow, and they are associated with a survival of more than 90% at five years.

Intermediate grade (grade 2)

The morphology is different from normal cartilage and cells with atypical characteristics are seen. They behave more aggressively than low-grade ones. They have greater potential for recurrences and can exceptionally cause metastasis. The 5-year survival rate ranges from 55 to 70%

High grade (grade 3)

The morphology is totally different from normal cartilage. They have a high risk of recurrence and metastasis. The 5-year survival rate is 20 to 30%.

Clear cell

Slow growing often causes local recurrence and is seen in adults.

Mesenchymal

It is an aggressive variety, characterized by a biphasic histological pattern: small, compact cells in a cartilaginous matrix. They are seen in young and flat bones. They have high metastatic potential. The average survival at 10 years is 25%. Surgical treatment is combined with subsequent chemotherapy.

They are relatively radiosensitive and are used in the case of incomplete resections.

Borderline chondrosarcoma is a chondrosarcoma difficult to distinguish from benign lesions such as enchondroma and has a non-aggressive evolution.

Despite the obvious relationship between histological grade and prognosis, it is very difficult to predict clinical evolution.

Due to their location in the bone, they can be classified into central or peripheral.

The central ones originate in the bone marrow and the peripheral ones arise from the surface of the bone. Only secondary chondrosarcomas need to be subdivided into peripheral central. Primaries are almost always central. Most peripheral chondrosarcomas are secondary to osseocartilaginous exostosis, and secondary central chondrosarcomas almost always derive from an enchondroma. The treatment and prognosis of central secondary chondrosarcomas are identical to those of primary chondrosarcoma.

It can metastasize late and grow and infiltrate neighboring tissues locally to voluminous proportions. The tumor tends to destroy bone and spread into soft tissues. It can invade blood vessels and produce intravascular tumor emboli that sometimes reach the heart and pulmonary arteries.

Chordomas

They are rare neoplasms, originating in remains of the notochord, which persist in the adult spine They usually occur in bone structures of the axial skeleton or next to them. The main characteristic of malignancy of these tumors is their location and tendency to recurrence. Located in the vertebrae and intervertebral discs, they predominate in the sacrococcygeal region (48%) or the sphero-occipital region (39%). With rarity they can appear in the mobile spine, in ribs or other bones. Intracranial cases, mediastinal and other sites have been described.

They are slow growing, recurrent, and not very metastasizing, although the number of cases reported with metastases has increased in recent years.

Chordomas are lobed masses of encapsulated appearance, semi-translucent gray or yellowish-gray, gelatinous, sometimes they can be confused with cartilaginous tumors. Microscopically, in its classical form it offers a characteristic appearance consisting of lobes consisting of irregular nests and cords of rounded cells, of abundant cytoplasm and seal ring appearance, with vacuoles like soap bubbles (physaliphorous cells) and monomorphic rounded central nuclei, immersed in a large amount of extracellular substance of myxoid appearance. Mitotic activity is rare and pleomorphism, when present, is scarce and without great prognostic significance. Different authors reported the mixture of chordoid and chondroid elements, and called them Para chordomas and Chondroid Chordomas, which have been the subject of discussion. However, the differential diagnosis should be made with Chondrosarcomas, including the clear cell variety and extra skeletal Myxoid Chondrosarcoma.

Immunohistochemistry has a fundamental role in the diagnosis since these tumors have a mucinous matrix whose characteristics are present in other myxoid neoplasms. The matrix consisting of Glycosaminoglycans

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(GAG), and Proteoglycans (PG) can also be evaluated by biochemical and histochemical methods. It is considered that it may have value in the metastatic behavior of the tumor.

Various names are applied to the same neoplasm, as is the case with Paracord Oma which is considered synonymous with Cordaid Tumor, Cordaid Sarcoma and Peripheral Chordoma. This confusion appears to have been partly cleared up by identifying the immunophenotype of each tumor. The Chordomas, present positivity for epithelial markers 185-199-200 mainly Cytokeratin and EMA, both in the chordoidal areas and in the "chondroids", and the finding is so consistent that it is accepted as a differential diagnostic criterion. In addition, they usually present strong reactivity with Vimentin and weak with S-100. Parachordals or Cordoid Sarcomas, show immunophenotype like Chordomas according to most authors. The difference with the Chordomas is the location away from the axial skeleton. Chondrosarcomas, regardless of their location and morphology, do not present epithelial markers and are usually strongly reactive with Vimentin and S-100

Ultrastructural studies allow to group chordomatous neoplasms on the one hand (those that show epithelial markers usually present desmosomes or some type of intercellular junction) and chondromatouses on the other. Regarding Chondroid Chordoma, described by Heffelfinger, as a distinctive clinical-pathological entity, with preferential location at the base of the skull and has a worse prognosis. Several authors are of the opinion that it is a variant of Chordoma, which can occur at sites other than the base of the skull.

Although they are attributed a relatively benign behavior, given their slow growth that allows them to evolve over years, the long-term prognosis is poor conditioned by their tendency to recurrence and local aggressiveness, The Chordomas located at the base of the skull for their frequent recurrence, with high morbidity and mortality, added to the unrespectability by location they are the ones with the worst prognosis. Metastases have been described in the vertebra, lung, brain, skin, and other organs and are rarely the cause of death.

Some cases have a particularly aggressive behavior, in tumors with great cellular atypia, as well as in others of less aggressive appearance, so it is accepted that the histological grade does not serve as a prognostic marker

Treatment consists of extensive resection of the lesion with the greatest feasible margins [7].

Of indeterminate origin

It includes a group of sarcomas whose origin is not well clarified:

- Granulosa cell tumor
- Sarcoma alveolar
- Clear cell sarcoma
- Extra-skeletal Ewing sarcoma
- Sarcoma granulocítico
- Mesenquimoma

Granule cell tumor

The granule cell tumor was first described by Abrikosoff, who attributed its origin to a degenerative process of the striated muscle. It is a nodule of firm consistency, well delimited of variable size, usually unique, whitish of

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fleshy or encephalin appearance. In 10% of patients the lesions can be multiple.

It is more common in adulthood and in women.

The predominant location is the tongue and esophagus. The tracheobronchial presentation is another less frequent location of the granule cell tumor, within its intrathoracic manifestation. In general, it usually affects large-caliber bronchi, especially at the level of the bifurcations, being more frequent in the right bronchial tree. It can also appear on skin, subcutaneous cellular tissue, and viscera. There have been numerous theories proposed since then, but the most accepted seems to be the neurogenic, which proposes the neuroectodermal origin.

Histologically it is composed of large, elongated cells, with a small central nucleus, grouped in nests. The characteristic finding is the presence in the eosinophilic cytoplasm of POSITIVE PAS granules. Analyzed with an electron microscope, the cells seem to show similarity with degenerated Schwann cells, also related to the metabolic alteration of their lysosomes.

The epidermis lining the tumor is usually hyperplastic. It is now accepted that it is a tumor originating from Schwann cells, although the cause of the numerous lysosomal granules is unknown.

Sarcoma alveolar

Alveolar sarcoma is a rare and enigmatic neoplasm, whose histogenesis is controversial, has been a subject of discussion for clinicians and pathologists in recent years whose frequency has been estimated between 0.5% and 0.9% of all soft tissue sarcomas. Before it was not recognized as a separate entity but was diagnosed as a paraganglioma. It has received numerous names over time, including malignant myoblastoma, angioendothelioma and even liposarcoma. Christopherson, Foote and Stewart gave it the current name and described it as a neoplasm with unique clinical and pathological features, its histogenetic nature still uncertain.

The histopathological picture was completed by Masson, who described the characteristic intracytoplasmic crystals and Shipkey and colleagues studied their ultrastructural characteristics. Today, the histogenesis of alveolar soft tissue sarcoma remains controversial; however, most recent data suggest a muscular origin.

In large series, such as that of Lieberman, et al. up to 20% of patients present in the advanced stage of the disease, with hematogenous metastases, the most frequent being those of the lung, followed by bone and brain, although other unusual sites such as liver, tongue, skin, scalp, breast, heart, pancreas, adrenals, kidney, inguinal lymph nodes and gastrointestinal tract.

Macroscopically, they are lesions that vary from well to poorly circumscribed masses; the former, surrounded by a fibrous capsule of variable thickness and often incomplete. They are firm or soft tumors, of varied color (yellow, gray, brown), with necrosis and frequent hemorrhages. They can spread inside blood vessels and appear encapsulated, but almost always, histologically demonstrate infiltration. The cutting surface is divided into small lobes separated by septa of

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connective tissue that emerge from the capsule, giving it a honeycomb appearance.

Microscopically, they are made up of pseudo alveolar, glomerular, or organoid areas, consisting of tumor cells that vary in size, with one or two vesicular nuclei, finding up to five in some of them. The nucleus contains a prominent nucleolus. With hematoxylin eosin the cytoplasm is colored eosinophilic and finely granular. Mythotic figures are very rare. The cytoplasm of all alveolar sarcomas contains material resistant to PAS-positive diastase, creating crystalline structures of rhomboid or specular shape. In some studies, it has been documented that the presence of these crystals in fine needle aspiration material, associated with suspicion, facilitates the diagnosis. This tumor has been studied extensively by immunohistochemical methods, to establish histogenesis, without positive findings that are consistent, and sometimes with contradictory results. Therefore, some authors consider that the expression of these markers has no diagnostic value or importance in the immunotyping of the tumor.

The possibility of a neural origin was proposed by Karnauchow and Magner, who found histological and histochemical similarity with paragangliomas. Matthew subsequently found myelin and myelinated axons in one case, along with occasional traces of positivity for S-100 and NSE. These latest findings suggest neural differentiation, but glial fibrillar acid protein, neurofilaments, synaptophysin, methencephalins, and leu-enkephalins are negative. Christopherson, et al. in their original description, favored the muscle differentiation hypothesis, which was later supported in a study by Fisher and Reidbord, who found similarities between alveolar sarcoma crystals and benign rhabdomyoma crystals.

Markers of muscle differentiation such as myoglobin, desmin and smooth muscle actin have been used. MyoD1 is a specific myogenic regulation protein in normal skeletal muscle, expressed in the nuclei of rhabdomyosarcomas; reactivity in alveolar soft tissue sarcoma is usually cytoplasmic, not nuclear. There may be positivity for S-100 and specific neuronal enolase in up to 20% of cases, which have been evaluated by numerous researchers to confirm a possible neural differentiation. Epithelial membrane antigen, glial fibrillar acid protein and myogenin are negative. Neoplastic cells are arranged in nests with central lumen and loss of cell cohesiveness.

The cells have irregular contours, forming cytoplasmic projections. The most typical feature is given by crystalloid rods and electrodense granules located in the Golgi area. Apparently, the substance that makes up these crystalloids is actin. The granules have amorphous material with filaments of similar characteristics to rods.

Cytogenetic studies of alveolar sarcoma have identified a specific alteration der t(X;17) (p11.2;q25). This translocation results in the fusion of the transcription factor gene TFE3 (from Xp11) to ASPL (17q25). The ASPL/TFE3 fusion protein is in the nucleus and can function as an aberrant transcription factor. The presence of this fusion appears to be highly specific and sensitive to soft tissue alveolar sarcoma, but it can be found in renal adenocarcinoma of pediatric and young adult patients. Cytogenetically, some studies have shown two clonal abnormalities: trisomy 47, XX,+5 and 46, XX, 1p-,17q+.

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In addition, alterations of the trisomy 7 type and monosomies 8 and 18 have been found.

It must be differentiated from many neoplasms. Metastatic renal cell carcinoma is the most common differential diagnosis, but it lacks the rods typical of alveolar sarcoma. Other tumor lesions such as melanoma, granular cell tumor, paraganglioma, and alveolar rhabdomyosarcoma may show alveolar architecture leading to misdiagnoses.

It occurs in adolescents and young adults between fifteen and 35 years, but can appear at any age, although it is rare before the age of five and after the age of fifty.

Located mainly in the extremities, especially in the soft tissues of the thigh and buttocks, it has also been seen in the head and neck (orbit and tongue) female genital tract, stomach, breast, pituitary gland, sacral bone, lung, pancreas, mediastinum, and retroperitoneum.

Alveolar soft tissue sarcoma is a neoplasm, characterized by slow-growing, progressive masses. Metastases may appear after years of initial diagnosis; therefore, strict monitoring is important. They may also present as the first clinical manifestation of the disease.

The most important prognostic parameters are age at diagnosis (best when patients are in the first decade of life: 17% vs. 32% in people over thirty years of age); the size of the primary tumor and the presence of metastases, which defines an advanced tumor and in general of poor prognosis, being better if the metastases are unique and if they are multiple and unresectable [8].

Alveolar soft tissue sarcoma has some different clinical features from those of other adult soft tissue sarcomas; for example, local recurrence is less frequent, distant metastases are very frequent even without evidence of local recurrence of the primary tumor, metastatic disease may be the first manifestation of the disease, and metastases may be late (up to ten years after diagnosis). Cytological atypia and vascular invasion have prognostic value. The survival of these patients varies from the presence or absence of metastases when they appear. When diagnosed, the prognosis is very poor and varies between 5 and 45 months.

The role of proliferative markers and tumor suppression genes is not yet known. Apparently, Ki-67 may be a prognostic indicator for the development of metastases, but it is still under study.

The basis of treatment is initial surgical resection, which must be extensive and performed properly, being mandatory, to reduce the probability of local recurrence.

Adjuvant chemotherapy or radiation therapy has not resulted in an appreciable improvement in survival. The overall survival described by Lieberman et al. in the Memorial series was two years in 77%, five years in 60%, ten years in 38%, and twenty years in 15% of cases.

Clear cell sarcoma

Clear cell sarcoma of the tendons and aponeurosis was described by Enziger as a separate entity and was first published as synovial sarcoma of origin in the tendon sheath (Bennet). This rare tumor is more common in the young adult (Dutra) and is characterized by a slow growing, usually painless, tumor most located in the heel, plantar, ankle region, particularly in close

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relationship with the Achilles tendon and plantar aponeurosis.

The histogenesis of clear cell sarcoma is still highly controversial, and it is possible that different tumors of different origin may appear with the typical appearance of a clear cell sarcoma. They could form in the synovial cells that line tendon sheaths.

Macroscopically the tumor is of firm consistency and sometimes soft, nodular, of variable size.

Until more is known about these rare tumors (clear cell sarcoma, malignant giganto cell tumor of soft tissues and malignant neuroepithelionoma of soft tissues), it is considered justified to classify them as variants in the group of synovioms.

The prognosis is poor, recurrences are frequent after local excision. However, according to Enziger, there were no important differences between those patients treated radically at an early stage and those treated after multiple recurrences.

Granulocytic sarcoma

Granulocytic sarcoma is an unusual variant of myeloid neoplasms characterized by a tumor mass composed of myeloblasts or myeloblasts and neutrophil promyelocytes, formerly known as Chloroma, because of the green color of the freshly cut surface.

It is more common in children than in adults and is more commonly associated with bone structures. The tumor can occur simultaneously with a typical hematological and bone marrow or precede leukemia by many months and even, rarely, years.

In the literature, just over 400 cases of granulocytic sarcoma were reported, with more frequent appearance in children than in adults, usually associated with bone structures. However, the most frequently involved bones are flat bones such as skull, perinasal sinuses, sternum, ribs, vertebrae, and pelvis, it has not been reported so far in long bones.

Mesenchymomas

Mesenchymoma is a malignant tumor characterized by the presence of multiple types of differentiation and tissue structure, particularly those that are not usually found in the skeleton that sits in the bone. It was first published by Schajowicz, et al. As a distinct entity not included in any existing classification of bone tumors. The neoplasm showed a liposarcomatous predominance. However, there were also large areas in the central part of the tumor with all the macro and microscopic features of osteosarcoma, with no clearly defined boundaries between the two neoplastic types.

The designation of "malignant mesenchymoma", proposed by Stout, seemed more appropriate. Stout applied this term to those soft tissue tumors of mesenchymal origin that were composed of tumor cells differentiating into two or more unrelated malignant forms, retaining the multipotential capacity of the primitive mesenchyma. The malignant mesenchymoma has been accepted by Lichtenstein as a different entity and was included in his classification.

As most mesenchymal shunt tumors may have fibro sarcomatous areas, this form is not recognized as separate in the evaluation of tumors

The radiographic and macroscopic aspect forms a typical Codman spur; it extensively invades the parostal soft tissues, presenting a seemingly well-delimited lobular surface, with an evident yellow color in most of the tumor.

The treatment is surgery with wide margins (amputation or disarticulation), with the average survival being less than 2 years.

New Approaches for Soft Tissue Sarcomas

Modulating the immune response [9]

One treatment approach under investigation is utilizing immunotherapy to promote antitumor activity by the immune response. In a recent phase II clinical trial published in the AACR journal Clinical Cancer Research, researchers evaluated an investigational anti-PD-L1 immune checkpoint inhibitor, TQB2450, in combination with the anti-angiogenesis drug anlotinib in 30 patients whose metastatic soft tissue sarcomas did not respond to prior chemotherapy. Anlotinib is approved to treat sarcomas in China, where the trial was conducted.

Clinical responses were observed in approximately 37 percent of patients. The median progression-free survival was 7.85 months, and over 69 percent of patients were alive one year after starting treatment. Among the 12 patients with alveolar soft part sarcoma (ASPS), 75 percent had a clinical response, and all 12 patients had some level of disease control in response to the therapy. In contrast, only 11 percent of patients with other types of sarcomas had a clinical response. The researchers concluded that combining TWB2450 with anlotinib was effective against ASPS, suggesting that dual inhibition of immune checkpoint activity and angiogenesis may be a promising treatment strategy for this sarcoma.

Another clinical trial also demonstrated the potential of immune checkpoint inhibition to treat sarcoma. This trial, the results of which were published in Lancet Oncology and summarized in the AACR journal Cancer Discovery, evaluated the anti-PD-1 therapy pembrolizumab (Keytruda) in patients with Kaposi sarcoma, a cancer that typically develops in immunocompromised individuals. Reducing immunosuppression with other therapies has shown promise against this disease, but the impact of immunotherapy remains undefined.

The investigators observed that 71 percent of the 17 patients enrolled in the trial had a clinical response, with 10 partial and two complete responses. These results suggest that pembrolizumab could be effective for patients with Kaposi sarcoma, although studies in a larger group of patients are needed.

Another trial, published in Clinical Cancer Research, examined the immunomodulatory drug lenalidomide (Revlimid) in patients with Kaposi sarcoma who were positive for HIV. Lenalidomide activates various immune cells while suppressing the secretion of certain pro-inflammatory cytokines. Beyond these immunomodulatory functions, lenalidomide also blocks angiogenesis and induces cell death.

In the phase I/II trial, lenalidomide treatment led to clinical responses in 60 percent of evaluable patients. Immune analyses using patient samples demonstrated an increased number of T regulatory cells and a reduction in inflammatory cytokines, consistent with lenalidomide's known effects.

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The authors concluded that lenalidomide could be a viable treatment option for patients with Kaposi sarcoma. Several follow-up clinical trials of lenalidomide, alone or in combination with other therapies, have been initiated for patients with Kaposi sarcoma [10].

Targeting gene expression in ewing sarcoma

Ewing sarcoma is an aggressive cancer that primarily affects adolescents. In most cases, the disease is driven by a fusion of the EWS and FLI1 genes, EWS-FLI1, which results in extensive chromatin remodeling and widespread transcriptional dysregulation that promotes tumor formation and metastasis. EWS-FLI1 is, therefore, a potential therapeutic target.

Lurbinectedin (Zepzelca) selectively inhibits EWS-FLI$_1$ by relocating it to the nucleolus and has been shown to delay tumor growth in mouse models of Ewing sarcoma. A recent phase II clinical trial, the results of which were in Clinical Cancer Research, evaluated lurbinectedin in patients with relapsed Ewing sarcoma.

Approximately 57 percent of patients in the trial experienced some level of disease control, and 14 percent had a clinical response to lurbinectedin. The median duration of response was 4.2 months, and patients survived for a median of 12 months. Due to the antitumor activity observed in this trial, the authors of the study suggested that lurbinectedin could be effective in conjunction with other therapies.

In addition to inhibiting EWS-FLI$_1$ itself, targeting regulation of the fusion protein could be another therapeutic approach. A recent study from Clinical Cancer Research uncovered a new mechanism by which EWS-FLI1 activity is regulated. It was previously known that high levels of EWS-FLI1 activity promote proliferation, whereas low activity leads to mesenchymal features and metastatic proclivity. In addition, prior studies had shown that expression of the HOXD13 transcription factor in Ewing sarcoma promotes metastasis, but the underlying mechanism remained unclear.

In this study, researchers determined that HOXD13 was enriched at known EWS-FLI1 binding sites, where it impacted expression of EWS-FLI1-regulated genes, including activation of genes normally repressed by EWS-FLI$_1$. Activation of these genes led the cells to adopt a mesenchymal state that would typically be suppressed by the EWS-FLI1 fusion protein. The authors concluded that opposing functions of HOXD13 and EWS-FLI1 influence cell states and the metastatic potential of Ewing sarcoma. Understanding this intricate relationship could provide additional therapeutic opportunities.

Combining a tyrosine kinase inhibitor with chemotherapy for uterine sarcoma [11]

Cabozantinib is an inhibitor of multiple tyrosine kinases, including several expressed in sarcomas. As such, researchers are interested in examining its potential to treat patients with various sarcomas. Prior research suggested that cabozantinib could be an effective therapy for uterine sarcoma, both alone and in combination with other therapeutics. Temozolomide is a chemotherapeutic that kills cancer cells by damaging DNA. It has demonstrated antitumor activity against several sarcomas,

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including some activity against uterine sarcomas. In a recent study published in Clinical Cancer Research, researchers used preclinical models of uterine sarcoma to evaluate the impact of combining these two therapies.

They found that combining cabozantinib and temozolomide significantly decreased growth and viability and increased apoptosis in established cell lines and patient-derived sarcoma cells, compared with cells treated with each drug individually.

Furthermore, the combination led to a synergistic reduction in tumor size in a xenograft mouse model. Molecular analyses indicated that the combination led to a synergistic inhibition of AMPK phosphorylation, providing a potential mechanism of action. Based on these results, the authors concluded that cabozantinib in combination with temozolomide showed promise against uterine sarcoma and suggested that the combination be evaluated in a clinical trial.

Although sarcomas are relatively rare, they can be devastating for the patients who are diagnosed with them. Ongoing research will continue to uncover new treatment strategies to improve outcomes for those affected by these cancers.

Conclusion

Accounting for less than 1% of all newly diagnosed cancers each year, sarcomas are relatively rare. However, these cancers lead to death in approximately 35 percent of patients diagnosed with them.

Sarcomas can develop anywhere in the body in soft tissues such as muscle, fat, tendons, nerves, lymph nodes, or the tissue around joints. These contrast with carcinomas, a much more common form of cancer that develops in epithelial cells of various organs.

Sarcomas are frequently treated with surgery, which may be the only treatment required for early-stage, low-grade tumors. For more advanced sarcomas, however, additional therapies, such as chemotherapy, radiation, targeted therapy, or immunotherapy may be required.

Researchers continue to discover and evaluate novel strategies to treat various forms of sarcoma. Recent studies published in prestigious journals and elsewhere report promising results for a number of these approaches.

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