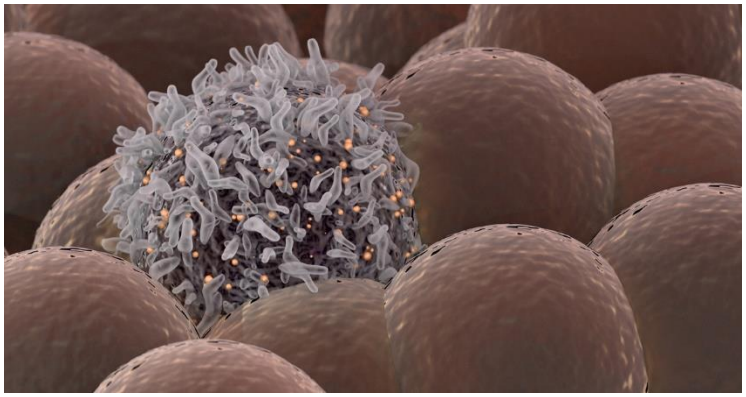
Cancer Association of South Africa (CANSA)

Research • Educate • Support

Fact Sheet on Sarcoma Cancer

Introduction

Cancer happens when cells start to divide uncontrollably and spread to other tissues. This creates masses called tumours.



[Picture Credit: Sarcoma vs Carcinoma}

Most cases of cancer involve either a carcinoma or a sarcoma. There are four other main types of cancer:

- Lymphomas – these affect cells in the lymph nodes
- Myelomas – these affect plasma cells in the bone marrow
- Melanomas – these affect melanocytes which produce pigments
- Leukaemias – these affect bone marrow cells and are responsible for various blood cancers

Sarcomas start in connective tissues, which are the supporting tissues of the body. Connective tissues include the bones, cartilage, tendons and fibrous tissue that support organs.

Sarcomas are much less common than carcinomas. They are usually grouped into 2 main types:

- bone sarcomas (osteosarcoma)
- soft tissue sarcomas

Altogether, these make up less than 1 in every 100 cancers (1%) diagnosed every year.

Elsamna, S.T., Amer, K., Elkattawy, O. & Beebe, K.S. 2020.
Background and objectives: Epithelioid sarcoma (ES) is an aggressive malignancy scarcely reported on due to its rarity. This study is a review of its traits and features of prognosis and survival by analyzing both the literature and a national cancer database.
Methods: Data were acquired from both the Survival, Epidemiology, and End Results database and literature. 1, 5, and 10-year Disease Specific Survival rates and hazard ratios (HR) were determined. Data

were split into pre-2000 (<2000) and post-2000 (>2000) groups. Overall survival, recurrence, and metastasis rates were obtained.
Results: Ninety hundred and ninety eight and 992 cases of ES were identified from the database and literature, respectively. Age, anatomical site, grade, TNM staging, treatment modality and year of diagnosis were demonstrated to be independent predictors of survival. Overall 5- and 10-year survival were 60.4% and 50.2%, respectively. Overall recurrence and metastasis rates were 63.4% and 40.3%. Using cases diagnosed prior to 2000 as reference, those diagnosed after 2000 had a worse prognosis (HR: 1.55).
Conclusions: We report using the largest cohort of ES to date. Despite ES's often dismal prognosis, there are factors associated with better outcomes. A worsening survival over the years warrants further investigation into this sarcoma.

Bourcier, K., Le Cesne, A., Tselikas, L., Adam, J., Mir, Ol., Honore, C. & de Baere, T. 2019.
"Sarcoma is rare and heterogenous with various subtypes having a different prognostic. Desmoid is a tumour with a local aggressiveness; GIST with KIT mutation responds massively to target treatment as IMATINIB, whereas soft tissue sarcoma and leiomyosarcoma are very aggressive with poor response to systemic therapies. Interventional radiology plays an important role in the diagnosis of sarcomas with image-guided percutaneous core needle biopsy being the most commonly used biopsy technique in the diagnosis of sarcomas. Biopsy access routes discussed with the surgeon, and skin access is tattooed. Surgery is a mainstay of sarcoma treatment; the resection can be large. Indeed, resection objective is R0 because quality of surgical margins impacts local control and survival. Radiotherapy is possible in neoadjuvant or in adjuvant treatment to improve local control rate. Recently radiotherapy enhancer injected percutaneously in soft tissue sarcoma has proven benefit in increasing the rate of R0 complete surgical resection. Several studies showed better local control rate linked with post-operative radiotherapy. In patients affected by oligometastatic disease, complete surgical resection of all metastatic sites is in fact considered the primary treatment because complete remission is critical for cure. The decision making to use local therapies is complex, depends upon diverse presentations and histologies, and should always be taken in a multidisciplinary discussion. Today, percutaneous image-guided treatments with ablation technologies (radiofrequency ablation, cryotherapy, microwaves ablation) provide high rate of durable local control for small-sized malignant deposit in many organs including lung, liver and bones. Sarcoma must be managed by multimodality treatment in expert reference centres. Such management has a considerable impact on the prognosis."

Differences Between Carcinoma and Sarcoma
The following table provides the main differences between carcinoma and sarcoma:

	Carcinoma	**Sarcoma**
Where it Originates	Epithelium	Connective Tissue
Age Group	Older persons – usually over 50	Younger persons – mostly under 50
Vascularity	Less vascular	More vascular
Rate of Growth	Less rapid	More rapid
Means of spread	Early by lymphatics	Early by blood
Prognosis	Less worse	More worse
Microscopic	Cells arranged in groups	Cells arrange individually
Behaviour	Always malignant	Always malignant
Occurrence	More common	Less common

In situ phase	Yes	No
Occurrence in body	Lungs Liver Stomach Colon Rectum	Bone & Cartilage Muscle Fat Nerves Fibrous Tissue

Incidence of Sarcoma in South Africa
The National Cancer Registry (2016) does not provide any information on sarcoma.

Sarcoma Subtypes
The following is an indication of the most well-known subtypes of sarcoma:

- **ALVEOLAR SOFT-PART SARCOMA**
  This extremely rare sarcoma typically arises in the thigh or buttock of patients in their 20s. Men are much more commonly affected than women. This form of sarcoma is relatively resistant to standard chemotherapy. Despite its early spread, people with this diagnosis can live for 10-20 years or more after diagnosis, in some cases.

- **ANGIOSARCOMAS AND OTHER SARCOMAS OF BLOOD VESSELS**
  This uncommon group of sarcomas appear to arise from the lining of blood vessels (endothelial cells) or their precursors.

- **ATYPICAL FIBROXANTHOMA**
  An unusual and relatively less aggressive form of sarcoma that shows features of both fibroblasts and cells that retain fat (xanthomas). The primary treatment is surgical. Radiation is occasionally used to try and prevent tumour recurrence, and chemotherapy is largely ineffective for this diagnosis. These tumours metastasize (spread) very, very rarely.

- **BONE AND CARTILAGE SARCOMAS OF SOFT TISSUE**
  Some sarcomas that arise in soft tissue mimic those that typically arise in cartilage or bone.

- **CLEAR CELL SARCOMA**
  This unusual hybrid tumour appears to be biologically related to alveolar soft-part sarcoma. It is one of the rare tumours with features of both sarcoma and melanoma, including the ability to travel to lymph nodes (typical of melanoma) and to lung (more common for sarcomas). Surgery and radiation of the primary tumour site provide the best chance for cure.

- **DERMATOFIBROSARCOMA PROTUBERANS**
  This tumour typically arises in the skin and must be excised by an appropriate expert, as less extensive resections often end in failure.

- **DESMOPLASTIC SMALL ROUND-CELL TUMOUR (DSRCT)**

It typically arises in young men between 15 and 35. The tumour can travel not only elsewhere in the abdominal or pelvic cavity where it starts, but it can also spread to liver, lung, or the space between the lungs (mediastinum).

- **EPITHELIOID SARCOMA**
  Typically affects the extremities (arms and legs) and tends to travel early to other sites of the body, affecting younger people more commonly than older people. Unlike other sarcomas, epithelioid sarcoma can travel to lymph nodes and cause side effects in lymph nodes and other body components.

- **EWING SARCOMA/PRIMITIVE NEUROECTODERMAL TUMOUR (PNET)**
  Typically occurs in children or young adults, although cases in people up to age 80 or more are occasionally seen. Ewing sarcomas more commonly affect bone in children and soft tissue in adults, and can be seen in any site of the body. They commonly recur in the lungs and bones.

- **(EXTRASKELETAL) MYXOID CHONDROSARCOMA**
  An unusual form of chondrosarcoma that shows a wide variety of features under the microscope and typically arises in people from 20 to 40 years of age. It grows relatively slowly but has a high risk of recurrence elsewhere in the body, such as the lung. It is largely insensitive to standard chemotherapy drugs.

- **EXTRASKELETAL OSTEOSARCOMA**
  This sarcoma (also called extraskeletal osteogenic sarcoma) arises in soft tissue but looks just like its counterpart in bone. Typically arises in older adults, not in children. It does not respond very well to the chemotherapy drugs used in osteogenic sarcoma of bone and is more commonly treated like other soft-tissue sarcomas.

- **EXTRARENAL RHABDOID TUMOUR**
  A very aggressive form of sarcoma that nearly always arises in childhood. It affects the kidneys and other structures in the abdomen and has a high risk of early spread to liver, lung, and other sites.

- **FIBROSARCOMA**
  Arises from fibroblasts or their precursors and forms a group of tumours that are difficult to diagnose correctly, given their relative scarcity. These tumours most frequently affect the extremity and trunk, and can metastasise to the lungs, like other sarcomas.

- **GASTROINTESTINAL STROMAL TUMOUR (GIST)**
  GIST is one of the most common types of sarcoma. It appears to arise from the interstitial cells of Cajal (or its precursors), which are the pacemaker cells of the intestines. The common places that GIST recur are in the abdominal cavity or in the liver.

- **GIANT CELL TUMOURS (GCT) OF TENDON SHEATH**
  Arises most commonly near the knee joint, but they can also affect large and small joints alike. They are initially removable with surgery, but some have a high risk of recurrence.

- **LEIOMYOSARCOMA**

This is a tumour of smooth muscle (or its precursors), and can arise anywhere in the body. This is one of the most common types of sarcoma. Common initial sites for this tumour are the uterus, small intestine or stomach, or the wall of a blood vessel in the abdomen, extremity, or skin.

- **LIPOSARCOMA**
  A sarcoma that arises from fat cells or their precursors. There are three families of liposarcoma: well-differentiated and/or dedifferentiated (~50%), myxoid and/or round cell (~ 40%), and pleomorphic (10%). Each has its own specific biology and risk of recurrence or spread.

  - **MYXOID AND/OR ROUND-CELL LIPOSARCOMA**
    The second-most-common family of liposarcomas. This type of sarcoma is considered relatively chemotherapy-sensitive.

  - **PLEOMORPHIC LIPOSARCOMA**
    This is the least common form of liposarcoma, and it also tends to affect an extremity. It is often more aggressive than other liposarcomas and can spread to other sites of the body such as lung and soft tissue.

  - **WELL-DIFFERENTIATED AND/OR DEDIFFERENTIATED LIPOSARCOMA**
    This sarcoma typically arises in the abdominal cavity or in an extremity. It appears as a large painless mass. Primary therapy is surgical, although the recurrence risk in the abdomen is very high, at least 70-80% over 10 years. The less aggressive form of this tumour is termed "well-differentiated". The more aggressive version of this sarcoma is called "dedifferentiated", but is often less aggressive than other so-called "high-grade" sarcomas.

- **MALIGNANT PERIPHERAL NERVE SHEATH TUMOURS (MPNST)**
  Sarcomas that arise from the insulating cells that surround nerve endings.

- **MESENCHYMAL CHONDROSARCOMA**
  Another unusual version of chondrosarcoma more common in the soft tissues rather than in the cartilage. Primary therapy is typically surgery and radiation, and some doctors advocate the use of chemotherapy in primary treatment of this tumour, given its distant kinship with Ewing sarcoma. When such tumours are treated successfully with chemotherapy, they often leave behind a less aggressive version of the tumour, which should be surgically removed to obtain the best overall outcome for patients with this very rare diagnosis.

- **RHABDOMYOSARCOMA**
  This rare sarcoma typically affects children. At most, 20% of rhabdomyosarcomas occur in adults. Rhabdomyosarcomas are themselves a separate family of sarcomas, with several recognized subtypes, including Embryonal, Botryoid, Alveolar, and Pleomorphic. Treatment for these sarcomas nearly always involves surgery, radiation, and chemotherapy. Cure rates are better for children than for adults, for unclear reasons. This is one form of sarcoma that can travel to lymph nodes, though it can also travel to lungs and other sites.

- **SOLITARY FIBROUS TUMOUR**
  This sarcoma is an uncommon tumour that is found in the chest cavity, the orbits (which contain the eye), the covering of the brain (dura mater) or the pelvis. There are less aggressive and more aggressive versions of this tumour, which can easily grow to a size of 15-50cm or more in size.

- **SYNOVIAL SARCOMA**
  Synovial Sarcoma is usually seen in patients between the ages of 15 and 35, and often affects the leg, foot, and hand, although other unusual sites such as the chest cavity are seen. It is often a chemotherapy-sensitive form of sarcoma. Therapy for a primary leg tumour often involves surgery, radiation, and sometimes chemotherapy. The lungs are the most common site of recurrence for synovial sarcomas. This is the subtype of sarcoma about which there is the most interest in using immunotherapy for treatment.

- **UNDIFFERENTIATED PLEOMORPHIC SARCOMA (UPS)**
  UPS used to be called MFH (malignant fibrous histiocytoma) by pathologists. It tends to affect people over 50 years of age in the leg, trunk, or arm. The most common place for MFH to recur is in the lungs.

Shahin, O.A. & Ravandi, F. 2020.
Purpose of review: Myeloid sarcoma; also known as granulocytic sarcoma and chloroma, often occurs concomitantly with AML, and rarely without bone marrow involvement. In this article, we review the recent literature on myeloid sarcoma, focusing on treatment approach for this rare disease, and addressing the prognostic and therapeutic role of molecular and cytogenetic aberrations.
Recent findings: Molecular testing and cytogenetics are important adjunct to conventional diagnostic methods. The significance of cytogenetic and molecular abnormalities in myeloid sarcoma is not completely established, but testing for targetable mutations on myeloid sarcoma cells is feasible, imperative, and may guide treatment decisions. Outcomes in myeloid sarcoma largely depend on the background of its development. Almost all patients with myeloid sarcoma eventually develop AML typically in a short period after its diagnosis; therefore, remission induction treatment using AML type chemotherapy has been the standard of care. Postremission therapy is controversial; allogenic SCT, radiotherapy or consolidation chemotherapy should be considered according to patient risk.
Summary: Further research is required to understand the nature of myeloid sarcoma, and inclusion of patients with this condition in clinical trials should be considered to better identify the best diagnostic, prognostic, and therapeutic approach in managing this rare disease.

Sarcoma Diagnosis
Diagnosis of sarcoma is often challenging.

Pei, J., Zhao, X., Patchefsky, A.S., Flieder, D.B., Talarchek, J.N., Testa, J.R. & Wei, S. 2019.
"Accurate diagnoses of sarcoma are sometimes challenging on conventional histomorphology and immunophenotype. Many specific genetic aberrations including chromosomal translocations have been identified in various sarcomas, which can be detected by fluorescence in situ hybridization and polymerase chain reaction analysis. Next-generation sequencing-based RNA sequencing can screen multiple sarcoma-specific chromosome translocations/fusion genes in 1 test, which is especially useful for sarcoma without obvious differentiation. In this report, we utilized RNA sequencing on formalin-fixed paraffin-embedded (FFPE) specimens to investigate the possibility of diagnosing sarcomas by identifying disease-specific fusion genes. Targeted RNA sequencing was performed on 6 sarcoma cases. The expected genetic alterations (clear cell sarcoma/EWSR1-ATF1, Ewing sarcoma/EWSR1-FLI1, myxoid liposarcoma/DDIT3-FUS) in four cases were detected and confirmed by secondary tests. Interestingly, three SS18 fusion genes (SS18-SSX2B, SS18-SSX2, and SS18-SSX4) were identified in a synovial sarcoma case. A rare fusion gene (EWSR1-PATZ1) was identified in a morphologically challenging case; which enabled us to establish the diagnosis of low grade glioneural

tumor. In conclusion, RNA sequencing on FFPE specimen is a reliable method in establishing the diagnosis of sarcoma in daily practice."

Sarcoma Treatment Modalities

Because of their rarity and the frequent need for multimodality treatment, evaluation and management of soft tissue sarcomas (STS) should ideally be carried out in a centre with expertise in the treatment of sarcomas, including surgical oncology, orthopaedic surgery, plastic surgery, adult or paediatric medical oncology, and radiation oncology. The multidisciplinary team approach to care of STS optimizes treatment planning, minimizes duplication of diagnostic studies, and reduces the time to implementation of the definitive therapeutic protocol.

Petitprez, F., de Reyniès, A., Keung, E.Z., Chen, T.W., Sun, C.M., Calderaro, J., Jeng, Y.M., Hsiao, L.P., Lacroix, L., Bougoüin, A., Moreira, M., Lacroix, G., Natario, I., Adam, J., Lucchesi, C., Laizet, Y.H., Toulmonde, M., Burgess, M.A., Bolejack, V., Reinke, D., Wani, K.M., Wang, W.L., Lazar, A.J., Roland, C.L., Wargo, J.A., Italiano, A., Sautès-Fridman, C., Tawbi, H.A. & Fridman, W.H. 2020.

"Soft-tissue sarcomas represent a heterogeneous group of cancer, with more than 50 histological subtypes[1,2]. The clinical presentation of patients with different subtypes is often atypical, and responses to therapies such as immune checkpoint blockade vary widely[3,4]. To explain this clinical variability, here we study gene expression profiles in 608 tumours across subtypes of soft-tissue sarcoma. We establish an immune-based classification on the basis of the composition of the tumour microenvironment and identify five distinct phenotypes: immune-low (A and B), immune-high (D and E), and highly vascularized (C) groups. In situ analysis of an independent validation cohort shows that class E was characterized by the presence of tertiary lymphoid structures that contain T cells and follicular dendritic cells and are particularly rich in B cells. B cells are the strongest prognostic factor even in the context of high or low $CD8^+$ T cells and cytotoxic contents. The class-E group demonstrated improved survival and a high response rate to PD1 blockade with pembrolizumab in a phase 2 clinical trial. Together, this work confirms the immune subtypes in patients with soft-tissue sarcoma, and unravels the potential of B-cell-rich tertiary lymphoid structures to guide clinical decision-making and treatments, which could have broader applications in other diseases."

Iwata, S., Katoh, Y. & Kawai, A. 2020.

"Challenges in the treatment of sarcoma as a rare cancer include(1)inexperience of sarcoma physicians due to the small number of patients,(2)insufficient information due to the lack of evidence,(3)lack of opportunities to provide information to non-specialists and to educate young physicians,(4)low adherence to standard treatments presented in clinical practice guidelines,(5)insufficient number of researchers engaged in basic research on rare cancers and their research funds, and(6) low number of clinical trials for the development of orphan drugs. This paper describes the current status and future prospects for the centralization and networking of sarcoma treatment, problems in pathological diagnosis, clinical evidence creation, information provision and human resource development, and information dissemination and consultation support to sarcoma patients."

Jakob, J. & Hohenberger, P. 2019.

"Soft-tissue sarcomas are rare malignant tumors. Surgery remains the most important treatment modality. Neoadjuvant and/or adjuvant chemo- and radiotherapy may be administered to improve the local and systemic outcome. Advances in oncological and reconstructive surgery, combined with the use of multimodal therapies, have made mutilating surgery rare events in extremity sarcomas. In retroperitoneal sarcomas, local recurrences are life-threatening events and multivisceral resection has become the standard

surgical procedure. The subjects of this review are diagnostics, multimodal therapy, and resection strategy from a surgical point of view."

Sandler, G., Yokoi, A. & Hayes-Jordan, A. 2019.
Purpose of review: Nonrhabdomyosarcoma soft tissue sarcoma (NRSTS) is a rare subgroup of malignancy in childhood that is composed of a variety of soft tissue and bony tumors. Prognosis for resectable localized disease is usually good and improved with systemic treatment. However, survival from locally advanced and metastatic disease remains poor. There have been numerous preclinical and clinical studies to define histopathology, biology, and genetic alteration of sarcomas. The purpose of this review is to clarify the progress in the management of NRSTS.
Recent findings: Genomic analysis, including the use of next-generation sequencing, has revealed fusion transcripts or specific genetic alterations which provide diagnostic biomarkers and potential targets for novel therapies.
Summary: Most cases are sporadic, but some are associated with genetic predispositions. Most present as a painless mass and diagnosis is frequently delayed because of a low index of suspicion. There is a wide array of histopathological subtypes. Investigations usually involve core, incisional or excisional biopsy for tissue diagnosis, and cross-sectional and nuclear imaging for staging. Management of pediatric sarcoma is largely dependent on the patient's histopathological diagnosis, age, disease stage, and co-morbidities but usually involves a combination of systemic and local therapies. Preclinical studies and phase I/II trials of newer targeted therapies are ongoing.

Medical Disclaimer

This Fact Sheet is intended to provide general information only and, as such, should not be considered as a substitute for advice, medically or otherwise, covering any specific situation. Users should seek appropriate advice before taking or refraining from taking any action in reliance on any information contained in this Fact Sheet. So far as permissible by law, the Cancer Association of South Africa (CANSA) does not accept any liability to any person (or his/her dependants/estate/heirs) relating to the use of any information contained in this Fact Sheet.

Whilst the Cancer Association of South Africa (CANSA) has taken every precaution in compiling this Fact Sheet, neither it, nor any contributor(s) to this Fact Sheet can be held responsible for any action (or the lack thereof) taken by any person or organisation wherever they shall be based, as a result, direct or otherwise, of information contained in, or accessed through, this Fact Sheet.

Sources and References Consulted and/or Utilised

Bourcier, K., Le Cesne, A., Tselikas, L., Adam, J., Mir, Ol., Honore, C. & de Baere, T. 2019. Basic knowledge in soft tissue sarcoma. *Cardiovasc Intervent Radiol*. 2019 Sep;42(9):1255-1261. doi: 10.1007/s00270-019-02259-w. Epub 2019 Jun 24.

CureSarcoma
https://www.curesarcoma.org/patient-resources/sarcoma-subtypes/

Elsamna, S.T., Amer, K., Elkattawy, O. & Beebe, K.S. 2020. Epitheloid sarcoma: half a century later. *Acta Oncol*. 2020 Jan;59(1):48-54.

Iwata, S., Katoh, Y. & Kawai, A. 2020. Sarcoma. *Gan To Kagaku Ryoho*. 2020 Jul;47(7):1016-1019.

Jakob, J. & Hohenberger, P. 2019. Principles of sarcoma surgery. *Pathologe*. 2019 Jul;40(4):431-435. doi: 10.1007/s00292-019-0631-2.

Pei, J., Zhao, X., Patchefsky, A.S., Flieder, D.B., Talarchek, J.N., Testa, J.R. & Wei, S. 2019. Clinical application of RNA sequencing in sarcoma diagnosis: an institutional experience. *Medicine (Baltimore).* 2019 Jun;98(25):e16031. doi: 10.1097/MD.0000000000016031.

Petitprez, F., de Reyniès, A., Keung, E.Z., Chen, T.W., Sun, C.M., Calderaro, J., Jeng, Y.M., Hsiao, L.P., Lacroix, L., Bougoüin, A., Moreira, M., Lacroix, G., Natario, I., Adam, J., Lucchesi, C., Laizet, Y.H., Toulmonde, M., Burgess, M.A., Bolejack, V., Reinke, D., Wani, K.M., Wang, W.L., Lazar, A.J., Roland, C.L., Wargo, J.A., Italiano, A., Sautès-Fridman, C., Tawbi, H.A. & Fridman, W.H. 2020. B cells are associated with survival and immunotherapy response in sarcoma. *Nature*. 2020 Jan;577(7791):556-560.

Sandler, G., Yokoi, A. & Hayes-Jordan, A. 2019. An update in the management of pediatric sacoma. *Curr Opin Pediatr*. 2019 Jun;31(3):368-377. doi: 10.1097/MOP.0000000000000767.

Sarcoma
https://www.cancercenter.com/community/blog/2017/11/whats-the-difference-carcinoma-and-sarcoma
https://health.clevelandclinic.org/whats-the-difference-between-a-sarcoma-and-carcinoma/
https://www.healthline.com/health/carcinoma-vs-sarcoma
https://www.cancerresearchuk.org/what-is-cancer/how-cancer-starts/types-of-cancer
https://www.uptodate.com/contents/overview-of-multimodality-treatment-for-primary-soft-tissue-sarcoma-of-the-extremities-and-chest-wall

Sarcoma Alliance
https://sarcomaalliance.org/resources/sarcoma-subtypes/

Sarcoma vs Carcinoma
https://www.cancercenter.com/community/blog/2017/11/whats-the-difference-carcinoma-and-sarcoma
https://pediaa.com/difference-between-cancer-and-sarcoma/
https://www.slideshare.net/Himesharo/spread-of-tumours
https://quizlet.com/206153065/hemeonc-week-3-flash-cards/
https://doctorlib.info/anatomy/staging-atlas-oncoanatomy/50.html
https://health.clevelandclinic.org/whats-the-difference-between-a-sarcoma-and-carcinoma/

Shahin, O.A. & Ravandi, F. 2020. Myeloid sarcoma. *Curr Opin Hematol*. 2020 Mar;27(2):88-94.