

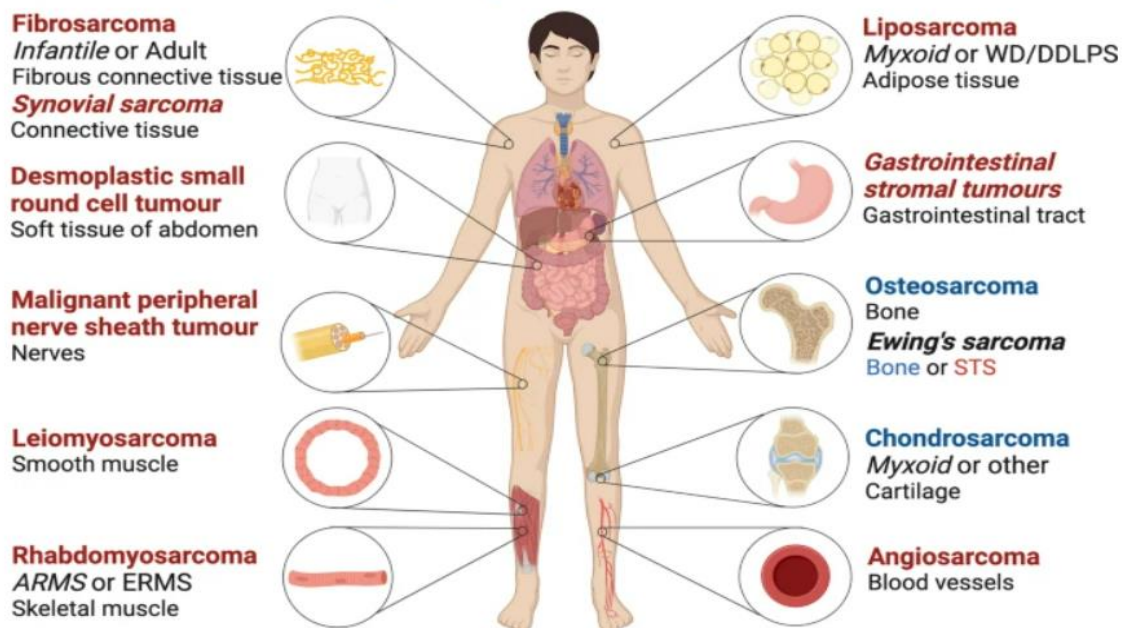
Sarcomas

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Sarcomas are a heterogeneous group of rare malignancies arising from mesenchymal tissues such as bone, cartilage, muscle, and other connective tissues.¹ They are much rarer than carcinoma and tend to grow locally and invade adjacent tissues.⁷ Sarcomas pose significant challenges in terms of diagnosis, classification, and treatment due to their diverse histology and variable clinical behaviour. Heterogeneity is highlighted by the identification of over 100 different sarcoma subtypes which vary in pathology, clinical presentation, molecular characteristics, and response to therapy. In recent years, progress in understanding the genetic and molecular alterations underlying sarcomas, has led to improved diagnostic techniques and therapeutic strategies.^{1,2} 80% of sarcomas are classed as soft tissue sarcomas (STS), 15% as bone sarcomas, and 5% as gastro-intestinal stromal tumours (GISTs).^{3,4} Bone sarcomas are more common among children while soft tissue sarcomas are more common in adults.⁹ About 220 people are diagnosed annually in Ireland with some type of sarcoma.⁸

The most common type of sarcoma is soft tissue sarcoma. Four out of five sarcomas are found in soft tissues. STS are a group of more than 60 different neoplasms that can originate from any location throughout the human body and can span a range of clinical presentations, from aggressive metastatic angiosarcomas to benign lipomas.⁷ More than half of soft tissue sarcomas are found in the leg. Globally, the incidence of STS is around 3–4 per 100,000 annually which accounts for 1% of all adult solid malignant tumours and more than 20% of paediatric cancers.⁵

SOFT TISSUE (STS) AND BONE SARCOMAS



Types of soft tissue sarcomas (STS)

Liposarcoma is the most common soft tissue sarcoma. They are most common in adults between 30 and 60 years of age and are slightly more common in men. These tumours usually develop in the deep fatty tissue and are most often found in the upper leg, behind the knee, the groin, the buttock area or behind the organs in the abdominal cavity. There are different types of liposarcoma, which include: **well differentiated liposarcoma** usually a large tumour in the deep tissues of the abdominal cavity, mediastinum, and groin region; **dedifferentiated liposarcoma** found in similar areas to differentiated liposarcoma but the tumour is of higher grade; **pleomorphic liposarcoma** (high grade) most commonly found on the lower limbs and feet; and **myxoid liposarcoma** most commonly seen in the deep soft tissue of limbs, especially behind the knee. Well differentiated liposarcoma and dedifferentiated liposarcoma are associated with a particular gene alteration involving chromosome 12. Myxoid liposarcoma is associated with an alteration of the DDIT3 gene. There is currently no known recurrent gene alteration associated with pleomorphic liposarcoma.⁸

Myxofibrosarcomas are sarcomas in fibrous tissue such as muscles, nerves, and blood vessels. They are usually found in the arms or legs or on the trunk of the body but can occur in any fibrous tissue. They can occur around scars, muscles, nerves, tendons, and around the lining of the bone. There is currently no known recurrent specific gene alteration associated with myxofibrosarcoma.⁸

Dermatofibrosarcoma protuberans (DFSP) is a sarcoma of superficial soft tissues, usually involving the skin. It is most common in people aged between 20 and 50, although a small percentage can occur in children. Most commonly it affects the head and neck area, trunk and upper arms and legs. DFSP is characteristically associated with a particular gene alteration involving the COL1A1 gene.⁸

Synovial sarcoma usually occurs in young adults and is mainly found in the arms or legs next to a joint. They are usually found around the joint capsule but rarely spread into the joint itself. The most common site is next to the knee. They are also commonly found near the foot, ankle, and hand. Unlike other soft tissue sarcomas, synovial sarcomas are frequently painful. Nearly all synovial sarcomas are associated with an alteration in the SS18 gene. This can help to confirm a diagnosis of synovial sarcoma.⁸

Epithelioid sarcoma is divided into classical and proximal types. Classical epithelioid sarcomas are usually found in the hand or foot of young adults. Proximal type epithelioid sarcoma is usually found on the trunk and upper arm and leg areas. They appear like small lumps, which sometimes co-join. The cancer spreads to the lymph nodes in about 1-5 cases.⁸

Perivascular epithelioid cell tumours (PEcoma) are a rare type of soft tissue tumour, which may be found in the lung, intra-abdominal cavity, or female genital tract. Most of these tumours are benign, but some show malignant pathological features and behave more aggressively.⁸

Rhabdomyosarcoma (striated muscle tumour): About half of all soft tissue sarcomas found in children are rhabdomyosarcoma. There are many different types, including embryonal, alveolar, botryoid and pleomorphic.⁸

Leiomyosarcomas are another type of muscle tumour which usually occur in the leg, bowel, or uterus. Symptoms of bowel or uterine leiomyosarcomas are bleeding and pain.⁸

Gastro-Intestinal Stromal Tumours (GIST) develops in tissue around the stomach and intestines and are relatively common. They are usually treated with surgery alone, but some people require drug treatment before or after removal.⁸

Myxomas occur in men and women around the age of 50, and are most often found in the arms and legs. Tumours can be small lumps or very large tumours. They are benign and do not spread to other parts of the body; however, they can spread to tissue close to the tumour.⁸

Solitary Fibrous Tumour (SFT) is a soft tissue tumour that can affect any site in the body including the pleura, and soft tissues of the limbs, trunk and within the abdominal cavity. Most SFTs are benign, but some display more aggressive pathological features and have the potential to spread to other parts of the body. SFTs are associated with a particular gene alteration termed a 'NAB2-STAT6 gene fusion', detected in the vast majority of SFTs.⁸

Mesenchymomas can be distributed throughout the body and about 3 in 4 are malignant. The tumours are invasive, especially when they are in the skeletal muscle. Treatment is wide excision surgery, sometimes combined with radiation and or chemotherapy.⁸

Vascular Sarcomas: Epithelioid Haemangioendotheliomas are very rare tumours of the blood vessels, which can be cancerous. They are found in men and women but rarely in children. They may be found in the skin, liver, or bone. Angiosarcomas are rare. About a third of cases occur on the skin and a quarter are found in the soft tissue or organs such as breast, liver, heart, and lungs.⁸

Kaposi Sarcoma is a vascular tumour that has different clinical subtypes. The classical type arises within the skin, especially over the lower legs in adults. A second type can affect children or adults and may involve lymph nodes. A third type affect patients with retroviral infection and may involve skin, lungs, the digestive tract, and the mouth. All variants of Kaposi sarcoma are associated with Human Herpes Virus-8 (HHV8).⁸

Malignant peripheral nerve sheath tumours are usually found in young to middle-aged adults and are more common in males. They occur in nerves which are not in the brain or spinal cord. These tumours spread to the surrounding soft tissue forming a lumpy tumour. This type of cancer can spread through the bloodstream. They can be painful and tender and may occur in patients who have neurofibromatosis.⁸

Alveolar soft part sarcoma is a very rare tumour that occurs in adolescents and young adults. It is usually a slow-growing tumour found in the arms and legs. It is associated with an alteration in the TFE3 gene.⁸

Desmoid tumours are slow-growing soft tissue sarcomas and tend to spread to nearby tissues but not to other parts of the body. Desmoid tumours may occur sporadically (sporadic desmoid) or may occur in association with an underlying genetic condition known as familial adenomatous polyposis (FAP) syndrome (hereditary desmoid). Patients with this syndrome may also be at risk for tumours in the lower digestive tract.⁸

Types of Bone Sarcoma

There are several different types of bone sarcoma, and like soft tissue sarcomas, most are named after the cells in which they grow.

Ewing's sarcoma is several types of sarcomas known as the Ewing's family of tumours. In Ireland, there are about 20 cases diagnosed each year, usually in children and young adults under the age of 30. It can be found in any bone but is most common in the bones of the lower body such as the pelvis, tibia, fibula, and femur. The vast majority of Ewing's sarcoma are associated with an alteration in the EWSR1 gene, which is helpful in confirming the diagnosis on core biopsy.⁸

BCOR associated sarcoma is like Ewing's sarcoma but the gene alteration with this type of tumour affects the BCOR gene.⁸

Chondrosarcoma develops from cartilage producing cells. Less than one-third of bone sarcomas are chondrosarcomas, and it is usually found in older people. Unlike other bone cancers, chondrosarcoma is more often found in the spine and pelvis than in the arms or legs.⁸

Osteosarcoma mainly occurs in adolescents and young adults. It usually affects the humerus of the upper arm and the femur and tibia of the leg. In children and adolescents, 80% of these tumours arise from the bones around the knee. It is slightly more common in males than females. Although osteosarcoma is a common malignant bone tumour, it is still rare with fewer than 30 new cases annually in Ireland.⁸

Parosteal osteosarcoma is a slow growing low-grade tumour that grows on the surface of the bone. It typically occurs in adults between the ages of 20 and 40 and it is mainly found on the upper leg, behind the knee. ⁸

Periosteal osteosarcoma is an uncommon tumour that grows on the surface of the bone, usually the lower leg. It is a fast-growing high-grade tumour and occurs in younger people. ⁸

Multifocal sclerosing osteosarcoma is an extremely rare form of osteosarcoma, that tends to occur in children under 10. ⁸

Osteosarcoma of the jaw and skull are rare and typically occur in people between the ages of 20 and 40. The bones most often affected are the mandible and the maxilla. ⁸

Osteosarcoma in Paget's disease usually occurs in people over the age of 60. About 1 in 100 patients with Paget's disease develop primary bone sarcoma. The tumours usually start in the pelvis, femur, or humerus. ⁸

Radiation-induced osteosarcoma is a rare form of osteosarcoma which occurs in people who have undergone radiation treatment for other cancers. These tumours appear about 10 years after radiation therapy. Post-irradiation osteosarcomas are mainly found in the spine, pelvis, hips, and shoulders. ⁸

Extra-osseous sarcomas develop away from the bone and are usually found in the muscle or skin. There are three types: giant cell tumours, osteosarcomas, and Ewing's sarcoma. ⁸

Risk Factors

Most sarcomas do not have a known cause, although there are several factors that could increase a person's risk. Patients who have received radiation therapy for previous cancers may have a higher risk. People with a family history of inherited disorders, such as Von Recklinghausen's disease (neurofibromatosis), Gardner syndrome, Werner syndrome, tuberous sclerosis, naevoid basal cell carcinoma syndrome, Li-Fraumeni syndrome or retinoblastoma, have a higher risk of developing a sarcoma. Exposure to vinyl chloride monomer a chemical substance used to make some types of plastics, dioxin or arsenic may increase the risk of sarcoma. However, most sarcomas are not known to be associated with specific environmental hazards. Having lymphedema, or swelling, in the arms or legs for a long time could also increase the risk of developing a sarcoma. ⁹

Symptoms

Neoplasms that are small, superficial, and mobile are highly suggestive of a soft tissue sarcoma. STS present as a lump usually more than 4-5cms in diameter, deep in the body tissues, underneath the skin. They are not painful to touch, but pain may occur as the lump gets bigger. Several conditions can mimic soft tissue sarcoma including hypertrophic scars, haematoma, benign lipoma, cysts, abscesses, and melanoma. Symptoms of bone sarcomas,

include a hard growing lump and pain around a bone, a limited range of motion in a joint, or a bone that breaks from no apparent cause.^{8,9}

Diagnosis/ Evaluation

Diagnosis is based on symptoms, medical history, clinical examination, and tests including x-ray, blood tests, MRI, CT scan, Ultrasound scan, PET Scan, biopsy, core needle biopsy and surgical biopsy. Indications for preoperative imaging and biopsy consider the extent of the mass on physical examination and the anticipated neurovascular involvement. The likelihood of nodal involvement or distant metastases must be considered as well as the relative resectability and potential postoperative functional deficits. MRI is generally considered the most informative for trunk and extremity STS. Chest CT with contrast is considered in cases with high metastatic potential, as the lungs are often involved. The use of PET/CT in the workup of sarcomas has not yet become the standard of care. If a biopsy is recommended, then the choice is a core-needle biopsy, and if this is nondiagnostic, then an incisional biopsy may need to take place.⁷

Staging

Staging of soft tissue sarcomas utilises the TNM system as well as tumour grading.¹¹

Primary Tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor 5 cm or less in greatest dimension
T1a	Superficial tumor
T1b	Deep tumor
T2	Tumor more than 5 cm in greatest dimension
T2a	Superficial tumor
T2b	Deep tumor
Note: Superficial tumor is located exclusively above the superficial fascia without invasion of the fascia; deep tumor is located either exclusively beneath the superficial fascia, superficial to the fascia with invasion of or through the fascia, or both superficial yet beneath the fascia.	

Regional Lymph Nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1*	Regional lymph node metastasis
*Presence of positive nodes (N1) in M0 tumors is considered Stage III	

Distant Metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis

Anatomic Stage / Prognostic Groups

GROUP	T	N	M	Grade
IA	T1a	N0	M0	G1,GX
	T1b	N0	M0	G1,GX
IB	T2a	N0	M0	G1,GX
	T2b	N0	M0	G1,GX
	T1a	N0	M0	G1,GX
	T1b	N0	M0	G1,GX
IIA	T1a	N0	M0	G2,G3
	T1b	N0	M0	G2,G3
IIB	T2a	N0	M0	G2
	T2b	N0	M0	G2
III	T2a, T2b	N0	M0	G3
	Any T	N1	M0	Any G
IV	Any T	Any N	M1	Any G

Treatment

Sarcoma is treated with a combination of chemotherapy, radiation, and surgery. Treatment plans and recovery depend on a variety of factors, including the type of sarcoma, the tumour location, grade and size, patients age and whether the cancer is new or recurrent.^{8,9} Surgical resection is a mainstay of sarcoma treatment. Patients that are operative candidates are encouraged to undergo resection.⁷

Treatment for liposarcoma is surgical resection with wide margins. Local recurrence is common. For liposarcomas of the extremities, the goal of care is limb-sparing resection with a gross negative margin. For retroperitoneal liposarcomas, the goal is complete resection. Typically, well-differentiated liposarcomas have a low risk of distant metastases, whereas de-differentiated extremity liposarcoma generally benefits from neoadjuvant radiation therapy.⁷

The modern surgical approach to sarcoma resections consists of a wide en-bloc resection with the goal of at least a 1cm margin of uninvolved tissue in all directions. A 2cm margin may be considered for tumours with infiltrative borders. However, this may not be possible due to the extent of the disease or proximity to neurovascular structures. However, if the tumour is close to or displacing neurovascular structures, they do not need to be resected if the adventitia and/or perineurium are removed. While bone is rarely involved, it may need to be resected if involved to obtain adequate margins. A planned positive margin followed by adjuvant therapy may be needed.⁷

For locally recurrent tumours, surgery may still be an option with either a wide excision or amputation. The decision to operate and type of operation is based on location, size, proximity to vital structures, and ability to preserve limb function. Tumours that are large and unresectable or present in the patient not considered a surgical candidate may be observed if there are no symptoms. In symptomatic individuals, palliative surgery may be used.⁷

Surgery alone in the case of high-grade sarcomas has a recurrence rate of 33% at five years, and adjuvant radiotherapy is typically recommended. Radiotherapy can be incorporated into any phase of treatment for STS of the trunk and extremities i.e., pre-operatively, post-operatively, intraoperatively, and concurrently with chemotherapy. Indications for radiotherapy include high-grade, Stage II+, inoperable disease, recurrent disease, or positive margins. The two most used techniques are External Beam Radiotherapy and Brachytherapy. External beam radiotherapy is the most common means of treating sarcomas and requires the patient to undergo a CT simulation. Pre-operative radiotherapy is the preferred method because of several advantages. It allows for lower doses of radiation, easier target delineation, ease of set-up, smaller radiation field size, and better functional outcomes with similar rates of local control. However, adjuvant therapy may be needed in the case of positive margins or a high-grade tumour where pre-operative treatment was not planned. Postoperative radiotherapy is more challenging from a planning perspective due to the

surgical manipulation of the tissue. Pre-operative and postoperative imaging are required and should be incorporated into treatment planning.⁷

Brachytherapy delivers radiation precisely to the target tissue with high conformity sparing the nearby normal tissues and eliminating the possibility of normal tissue toxicities. Brachytherapy is typically utilised post-operatively as either monotherapy combined with external beam radiotherapy as a boost, as well as for recurrent disease. It may be delivered at a high dose rate (HDR), low dose rate (LDR), or pulsed dose rate (PDR).^{7, 10}

Chemotherapy uses anti-cancer drugs such as doxorubicin and ifosfamide to destroy cancer cells. It is most frequently used if the sarcoma has spread to other parts of the body and is also used for sarcomas such as osteosarcoma, Ewing's sarcoma, and rhabdomyosarcoma. Chemotherapy can also be given before or after radiotherapy and surgery or in adjunct with radiotherapy, to make the radiotherapy work better.⁸

Prognosis

Despite the heterogeneity of sarcomas, the most important prognostic factors are histologic grade and tumour size. Histologic grade predicts distant metastasis and survival, while primary tumour size predicts local recurrence and distant metastasis. In general, for localised and early-stage lesions, curative resection can be done with good long-term survival, but recurrences are common. For those with advanced disease, a cure is not possible, and the median survival is 12 to 18 months, depending on the subtype. The risk of recurrence persists even after 10 to 15 years, and patients need indefinite follow-up. Most recurrences occur within the first five years. Most sarcomas show a poor response (10% to 50%) to chemotherapy. The response also depends on histological subtype, grade, and patient.⁷

Future Directions and Challenges

Novel therapeutic modalities, such as antibody-drug conjugates, bispecific T-cell engagers (BiTEs), and chimeric antigen receptor (CAR) T-cell therapy, hold potential in the treatment of sarcomas. These innovative approaches are being investigated in preclinical and early-phase clinical trials. Despite much progress, several challenges remain in the field of sarcoma research and management, including the need for larger clinical trials, identification of biomarkers for treatment response, and optimisation of multimodal treatment strategies. Collaboration among researchers, clinicians, and patient advocacy groups is paramount in addressing these challenges and improving outcomes for sarcoma patients.^{1,6}

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