Hello everyone,
Today I'd like to introduce you into oncology, specifically, sarcomas.

Sarcomas are a heterogenous group of cancers stemming from mesenchymal tissues, and can be classified into soft-tissue and bone sarcomas. These broad tumor categories are further divided based on distinct morphology and genetic changes into more than 100 subtypes as defined by the World Health Organization.

Alexis Boyer was a French surgeon. He was the first who coined the term 'osteosarcoma'.

William Hey included among his Practical Observations on Surgery a chapter entitled "Fungus Haematodes," which contained a description of 10 patients with tumors. Some of them were cancers of the breast, but several were undoubtedly sarcomas of bone or soft tissue. Also he gave his name to Hey's amputation (a tarso-metatarsal amputation), Hey's internal derangement (dislocation of the semilunar cartilages of the knee joint), Hey's ligament (the semilunar lateral margin (falciform margin) of the fossa ovalis), and Hey's saw, used in skull surgery. His colleague John Abernethy attempted to form a classification of tumors according to the appearance of the tissue. He listed eight types of sarcomas: 1) common vascular or organized, 2) adipose, 3) pancreatic, 4) cystic, 5)mammary,6) tuberculated, 7) pulpy or medullary,and 8) carcinomatous . In this classification, as in that of Hey, the categories did not separate cancers from what we now call sarcomas.

In 1818, Astley Cooper separated the bone tumors, both benign and malignant, into two types: intramedullary and extramedullary. It was Rudolf Virchow who separated the sarcomas from the cancers and defined them as a variety of tumors that evolved from non-epithelial and non-hematogenous tissues. Virchow distinguished six major types of sarcomas: 1) fibrosarcoma, 2) myxosarcoma, 3) gliosarcoma, 4) melanosarcoma, 5) chondrosarcoma, and 6) osteosarcoma.

The first great clinical-pathological correlation of a large number of sarcomas of bone was carried out by Samuel Weissel Gross, the son of the famous Philadelphia surgeon Samuel D. Gross. In a long article published in the American Journal of Medical Sciences in 1879, entitled "Sarcoma of the long bones: Based on a study of 165 cases," Gross discussed their histology, general pathology, symptomatology, diagnosis, prognosis, and treatment. He classified bone sarcomas as peripheral, periosteal, or periosseous, and central, endosteal, intraosseous, or myelogenic. He noted the tendency of these tumors to spread hematogenously to the lung and the low incidence of local lymphatic involvement. He advised amputating well above the lesion because of the high incidence of local recurrence. He observed that "nodules of sarcomatous tissue may exist in the medullary canal at some distance from the original growth," ie, "skip areas." It was his opinion that the histological appearance of the tumor could be correlated with the clinical course and prognosis. All in all, Gross's work has a very modern ring and was not surpassed of its type until well after the turn of the century.

The treatment of sarcomas, of bone or soft tissue, had always been surgical, involving wide local excision or amputation. The operative procedures, usually too little and too late, rarely were curative. The introduction of anesthesia and antiseptic and aseptic technique did little to change this. One experienced surgeon, in the course of his practice, encountered a case that raised other possibilities. During surgery on a round cell tumor, he accidentally infected the wound and noticed

that it decreased. Coley said that the pts was alive for 7 years after this operation. Dr. Coley became the founder of immunotherapy and for many years advocated the use of a mixture of toxins derived from streptococci causing erysipelas and from Bacillus prodigiosus for the treatment of inoperable sar- comas of both bone and soft tissue. Coley was a Clinical Professor of Surgery at the Cornell University Medical School and played an important role in founding the Memorial Hospital for the Treatment of Cancer and Allied Diseases. “Coley’s toxins” were used widely with mixed results. In 1872 Moritz Kaposi first described angiosarcoma.

The discovery of X-rays by Wilhelm Conrad Roentgen in 1895 was followed rapidly by their introduction into medical practice as a diagnostic aid. Ernest A. Codman began clinical work with X-rays in 1896 and for the next five years devoted most of his time to the new methodology.

James Ewing or as the New York Times called him ‘Cancer Man Ewing’ is an iconic figure in sarcoma diagnostic and treatment areas. In 1920, Dr. Ewing identified the eponymous malignant bone tumor he at first thought was an “endothelioma of bone,” believing it arose from the blood vessels of bone tissue. He later described Ewing’s sarcoma as an endothelial myeloma, distinctly separate from lymphoma or neuroblastoma.

There are more than 100 subtypes of both bone and soft tissue sarcomas. Among adult cancer sarcomas make up less than 1% and among childhood cancer near 20%. About 13-16 000 new cases per year are diagnosed in the USA and about 5-6 000 deaths. Around 30% of all sarcoma cases are misdiagnosed. STS diagnoses predominate over bone sarcoma diagnoses with a 4:1 incidence ratio, and there is a male preponderance for the incidence, with a ratio of approximately 1.4:1, male-to-female ratio.

The current WHO classification recognizes over 100 soft tissue and bone tumor types, over 70 of which are sarcomas,1 illustrating a nosologic complexity that reflects biological complexity and leads to substantial challenges in diagnosis and clinical management. Sarcoma diagnosis is based on morphology, immunohistochemistry, and clinicopathological correlation. In addition, molecular studies in the clinical setting provide refinements to morphologic sarcoma classification, and contribute diagnostic information (frequently), prognostic stratification (rarely) and predictive information concerning specific therapies (only occasionally, but most excitingly).

As in most tumors, particularly in rare tumors, the etiology of soft-tissue sarcomas is still largely unknown. There is, however, historical evidence of the association between sarcomas and various genetic syndromes as well as with radiotherapy; moreover, there is data indicating a possible role of environmental factors predisposing sarcoma development. Recognized predisposing genetic diseases associated with soft-tissue sarcomas are Li-Fraumeni syndrome (rhabdomyosarcoma), retinoblastoma (different histotypes, with leiomyosarcoma as the most frequent), and neurofibromatosis (malignant peripheral nerve sheath tumors).

Viral infection associated with immunodepression was shown to predispose to sarcomagenesis in HIV patients not only for Kaposi’s sarcoma, but also for leiomyosarcoma after infection by Epstein–Barr virus.

Additionally, exposure to some chemicals has been claimed as a predisposing factor for sarcoma onset, even if data reported are not univocal. Particularly, dioxins from waste incinerators have been reported as a possible predisposing factor, as well as phenoxy herbicides and other pesticides used in agriculture, but a meta-analysis of the literature could neither confirm nor rule out a possible role of these substances in sarcomagenesis.

For localized and early-stage lesions, curative resection can be done with good long-term survival, but recurrences are common. The risk of recurrence even persists after 10 to 15 years, and patients need indefinite follow up.

The majority of recurrences occur within the first 5 years.

For those with advanced disease, a cure is not possible, and the median survival is 12 to 18 months, depending on the subtype.

Management of soft-tissue sarcoma outside of specialist sarcoma referral centers results in significantly worse clinical outcomes. Adverse outcomes include increased morbidity from subsequent, potentially more complex surgeries and increased mortality. Unplanned sarcoma excision refers to removal of a mass without the knowledge of its malignant nature and without the application of sarcoma-appropriate oncologic margins. Evaluation prior to a planned oncological excision involves complete anatomic MRI of the affected part, CT of the chest, and tissue biopsy.

Surgery remains the primary treatment modality for sarcomas. Decisions about the optimal surgical procedure for the primary tumor are based on the tumor location, tumor size, involvement of adjacent anatomical structures, patient preference, and response to neoadjuvant therapies. Such decisions are often made with the consultation of a multidisciplinary team . The primary aim of curative surgery is to excise the whole tumor with tumor-negative margins.

The majority of sarcomas show a poor response to chemotherapy (10% to 50% response). The response also depends on histological subtype, grade, and patient. Chemotherapy is deemed an essential part of standard treatment for Ewing's sarcoma and osteosarcoma, but routine use in STS remains largely unproven. Standard treatment often comprises preoperative neoadjuvant systemic combination therapy, involving chemotherapy, surgical excision, and postoperative adjuvant chemotherapy.

Radiotherapy has a well-established role in the treatment regimen of both localized and metastatic sarcomas. Radiation treatment can lead to a late occurrence of STSs; 3 to 5% of STSs can be considered radiation-induced. Other historical exposures to radiation have been linked to the occurrence of sarcoma, such as workers dealing with radium in watch factories in the 1920’s.

Tyrosine kinase inhibitors were recently introduced for the treatment of advanced STSs not responding to more traditional medical treatment, with interesting results, as well as immunotherapy treatments such as immune checkpoint inhibitors (ICIs), vaccination against tumor-related antigens or dead cells, and engineered T cells. A recent, accurate summary of ongoing experiences in all these fields can be found in.

Due to the heterogeneity and complexity of STSs and their response to treatment, a multidisciplinary approach to any single case is mandatory to define a tailored therapeutic plan with a case-specific evaluation, in order to decide which treatments must be applied and in which order.