SARCOMA connect®

POWERED BY COR2ED

THIS MODULE HAS BEEN DEVELOPED BY TWO INTERNATIONAL EXPERTS

SARCOMA connect
POWERED BY COR2ED

Prof. Florence Duffaud,

Aix-Marseille University (AMU) & La Timone University Hospital, Marseille, France

Dr. Silvia Stachiotti

Fondazione IRCCS Istituto Nazionale Dei Tumori, Milan, Italy

The programme is supported by an independent educational grant from Bayer.
The programme is therefore independent; the content is not influenced by the supporter and is under the sole responsibility of the experts.
The views expressed in this slide deck are the personal opinions of the experts. They do not necessarily represent the views of the experts' institutions.

BONE SARCOMA: INTRODUCTION

SARCOMA connect® POWERED BY COR2ED

The main common types of bone sarcoma (mesenchymal origin) are:

Osteosarcoma (paediatric and adolescent 56%, adult 28% of bone sarcomas):

- Osteosarcoma cells express osteoblastic markers such as alkaline phosphatase, osteocalcin or bone sialoprotein
- Show a strong capacity to form osteoid tissue and induce the mineralisation of extracellular matrix

Ewing sarcoma (paediatric and adolescent 34%, adult 8% of bone sarcomas):

- Characterised by the expression of a fusion protein between the *EWS* gene and a gene of the ETS family

Included in this micro learning

Conventional chondrosarcoma (paediatric and adolescent 6%, adult 40% of bone sarcomas):

- Chondrosarcoma cells (common features with chondrocytes) usually express chondrocyte markers such as type II collagen or aggrecan

Other bone sarcoma types (paediatric and adolescent 4%, adult 24% of bone sarcomas):

- High-grade spindle cell/pleomorphic sarcomas of bone that do not fulfil the histologic criteria for a diagnosis of osteosarcoma, Ewing sarcoma or chondrosarcoma
- Several additional ultra-rare sarcoma types can originate from the bone, among which in particular chordoma and giant cell tumour of the bone

Not included in this micro learning

Thanindratarn P, et al. J Bone Oncol. 2019;15:100221

BONE SARCOMA: OSTEOSARCOMA AND EWING SARCOMA

SARCOMA connect
POWERED BY COR2ED

- Conventional **osteosarcoma** and **Ewing sarcoma** are **rare malignant mesenchymal tumours** that can arise at any site and are characterised by **unique biological characteristics**
- Ewing sarcomas generally arise from the bone but rare cases can originate from soft tissue
- Osteosarcomas and Ewing sarcomas **occur mainly in paediatric and young adult patients** and account for around 15% of childhood/adolescent cancers

	Osteosarcoma	Ewing sarcoma
Ratio male/female	• 1.4	• 1.5
Frequency	• 0.2–0.3/100,000/year (general population) • 0.8–1.1/100,000/year at age 15–19 years	• 0.3/100,000/year
Peaks of incidence	• A main peak at age 18 years • A second peak at age 60 years, with poor prognosis	• Age 15 years
Localisation	• Metaphysis of long bones • Distal end of femur + proximal end tibia/fibula (60%)	• Diaphysis of long bones (40%) and soft tissues (15%) • Flat bones (60%)

Brown HK, et al. Calcif Tissue Int. 2018;102(2):174-195

OSTEOSARCOMA AND EWING SARCOMA: MAIN CHARACTERISTICS

SARCOMA connect® POWERED BY COR2ED

- Osteosarcoma and Ewing sarcoma are high-grade sarcomas characterised by a **high mortality rate**

	Osteosarcoma	Ewing sarcoma
Imaging features	• Presence of a mineralised osteoid matrix: results in typical radiographic appearances ("sunburst" pattern)	• Long, permeative lytic lesion in the meta-diaphysis and diaphysis of the bone • Presence of a large soft tissue mass (MRI)
Pathological and biological characteristics	• Conventional osteosarcoma • Periosteal osteosarcoma (cartilaginous) • Low-grade central osteosarcoma (long-term swelling with no pain) • Parosteal osteosarcoma (fibrogenic, *MDM2* amplification) • *NTRK* fusion (extremely rare event)	• EWSR1 fusion is the diagnostic marker, rearranged with a member of the ETS family, –*FLI1* in 85% of cases • *NTRK* fusion (extremely rare event)
Survival rate	• 30–70% after 5 years	• 66% at 5 years • 20% at 5 years for poor responders

MRI, magnetic resonance imaging

Brown HK, et al. Calcif Tissue Int. 2018;102(2):174-195; Liu X-W et al. Int J Clin Exp Med. 2015;8(1):37-44; Tabatabaei SH, et al. J Dent Shiraz UnivMed Sci. 2015;16(2):62-67; Hang J-F, et al. Arch Pathol Lab Med. 2014:138(5):694-699; Lam SW, et al. Histopathology. 2021:79(5):880-885; Errani C, et al. JBJS Rev 2020;8(3):e0077; Zöllner SK, et al. J Clin Med. 202110(8):1685

WHEN TO SUSPECT BONE SARCOMA? (1/2)

SARCOMA connect
POWERED BY COR2ED

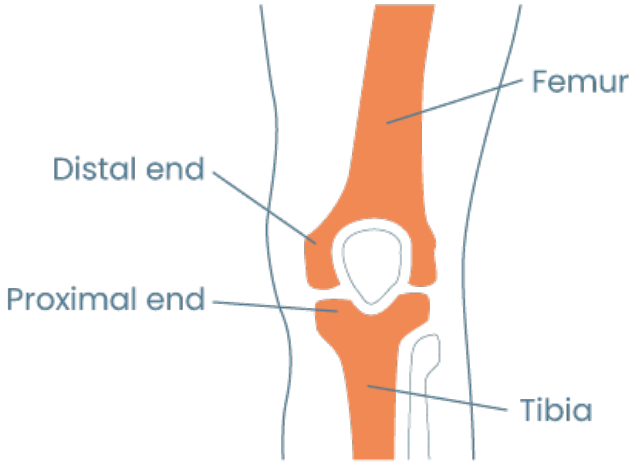
Diagnostic work-up:

- **Medical history**
- **Age and sex**
- **Duration, intensity, and timing of pain**
- **Physical examination**

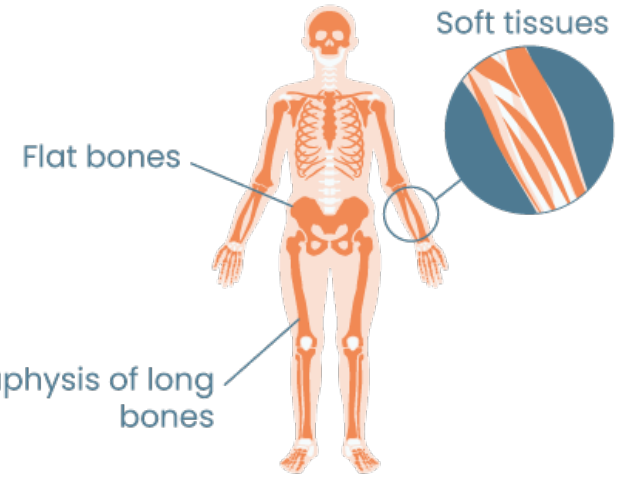
Most common signs and symptoms:

- **Bone pain and swelling**
  - Persistent and often progressive, non-mechanical bone pain, predominantly at night, and swelling at the site of the tumour in the bone
  - Most common sites in younger people: around the knee or in the upper arm
- **Limb pain and swelling: very common in children and teens**
- **Pathologic bone fractures**
- **Fever**
- **Weight loss**
- **Functional impairment**

Osteosarcoma



Ewing sarcoma



Source: https://www.mayoclinic.org/diseases-conditions/bone-cancer/symptoms-causes/syc-20350217, accessed 20 September 2021

WHEN TO SUSPECT BONE SARCOMA? (2/2)

SARCOMA connect
POWERED BY COR2ED

Differential diagnosis includes osteomyelitis, benign tumours, and bone metastases

- The variety and rarity of bone sarcoma may lead to difficulties in appropriate diagnosis
- Diagnosis can be strongly oriented by patient age

Prognostic laboratory values for osteosarcoma and Ewing sarcoma:

- **Lactate dehydrogenase** (LDH)
  - The glycolytic enzyme LDH is a biological marker for cytosol in various tissues
  - Serum levels are high in numerous pathological conditions
  - Serum LDH is also a prognostic factor for evaluating response to treatment in patients with osteosarcoma and Ewing sarcoma
- **Alkaline phosphatase** (ALP)
  - Elevated ALP in osteosarcoma due to increased osteoblastic activity
  - Higher levels are associated with heavy tumour burden and poor prognosis
  - Also used to monitor response to therapy
  - High levels after treatment may persist with residual disease or recurrence and in the presence of metastases

ALP, alkaline phosphatase; LDH, lactate dehydrogenase
Marais LC, et al. Bone Oncol. 2015;4(3):80-84

DOs & DON'Ts WHEN BONE SARCOMA IS SUSPECTED

SARCOMA connect
POWERED BY COR2ED

DO	• **DO REFER patients with suspected bone sarcoma to a sarcoma reference centre for diagnosis and treatment**
DON'T	• **DO NOT perform a biopsy as supervision by a multidisciplinary tumour board is critical** • **DO NOT initiate intervention/treatments such as surgery, chemotherapy, or radiotherapy**

BONE SARCOMA: GENERAL DIAGNOSTIC STRATEGY AT REFERRAL CENTRE (1/2)

- **All patients with a bone lesion that is likely to be a primary malignant tumour on radiology should be referred to a specialised sarcoma centre or network**
- **Imaging:**
  - X-ray: conventional radiograph in two planes is the first radiological investigation in case of pain swelling (bone sarcoma suspicion)
  - Magnetic resonance imaging (MRI): MRI scans the whole compartment with adjacent joints and is the best modality for local staging of extremity and pelvic tumours
  - Whole body computerised tomography (CT): imaging modality of choice for staging
  - Positron emission tomography (PET): shows spread to other bones and lungs and is increasingly used for staging Ewing sarcoma
  - Bone scintigraphy: shows spread to other bones

CT, computerised tomography; MRI, magnetic resonance imaging; PET, positron emission tomography
Source: https://www.mayoclinic.org/diseases-conditions/osteosarcoma/diagnosis-treatment/drc-20351053, accessed 20 September 2021

OSTEOSARCOMA AND EWING SARCOMA: GENERAL DIAGNOSTIC STRATEGY AT REFERRAL CENTRE (2/2)

SARCOMA connect® POWERED BY COR2ED

- Pathologic diagnosis of **osteosarcoma** is based on morphological findings
- Pathologic diagnosis of **Ewing sarcoma** is based on morphological findings, immunohistochemistry, and disease-specific genetic alterations

Biopsy:

- Core-needle biopsy:
  - Requires minimisation of contamination of surrounding tissue
  - Requires adequate multiple sampling of representative areas of tumours
- Open biopsy, if required

Pathological diagnosis

- Complemented by molecular assessment for Ewing sarcoma (*EWS–FLI1* fusion detection)

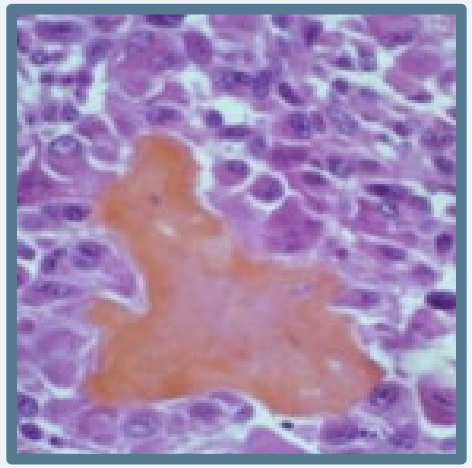
Tumour type must be diagnosed according to the most recent version of the World Health Organization (WHO) classification for tumours of soft tissue and bone (2020)

Brown HK, et al. Calcif Tissue Int. 2018;102(2):174-195; Ferguson JL et al. Am Fam Physician. 2018;98(4):205-213
Source: https://www.mayoclinic.org/diseases-conditions/osteosarcoma/diagnosis-treatment/drc-20351053, accessed 20 September 2021

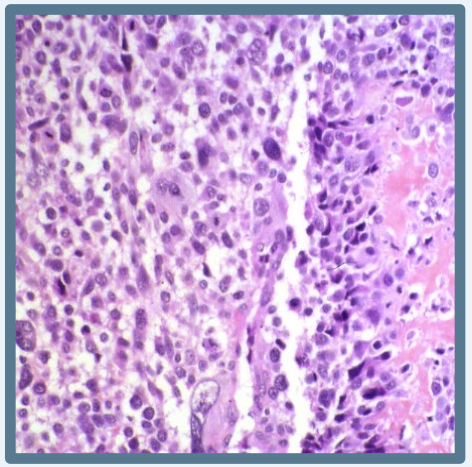
OSTEOSARCOMA AND EWING SARCOMA: HISTOPATHOLOGY

SARCOMA connect
POWERED BY COR2ED

Osteosarcoma



Bone tumour elaborating osseous matrix



Polyhedral cells forming +/- mature bone tissue and cartilage

Ewing sarcoma

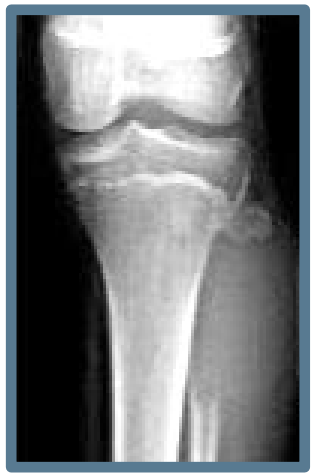
Small round blue-stained tumour cells

CD99-positive and FL1-positive tumour staining

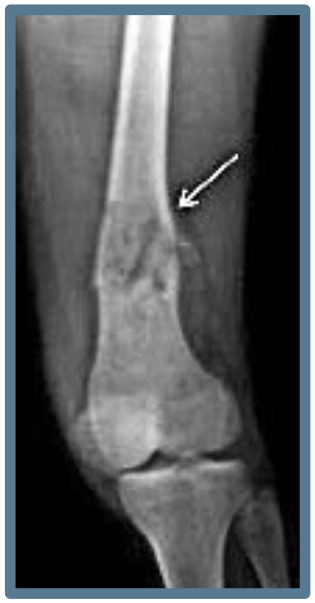
Images courtesy of Prof. F Duffaud

OSTEOSARCOMA: RADIOLOGY

X-ray

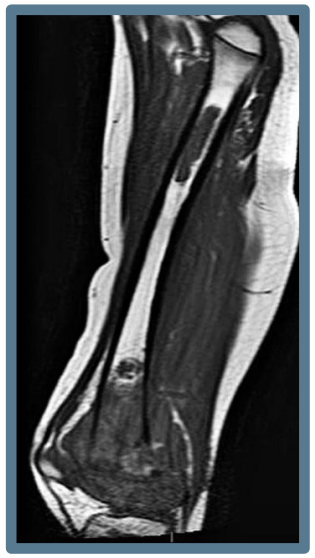


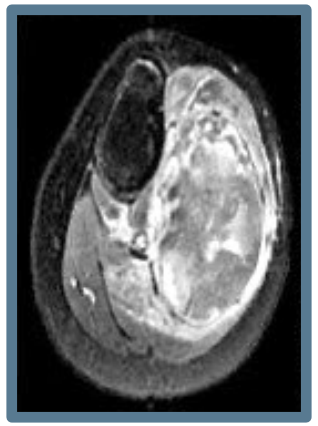
Upper extremity; fibula osteosarcoma

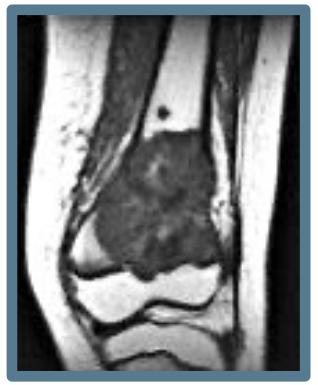


Lower extremity; femur osteosarcoma

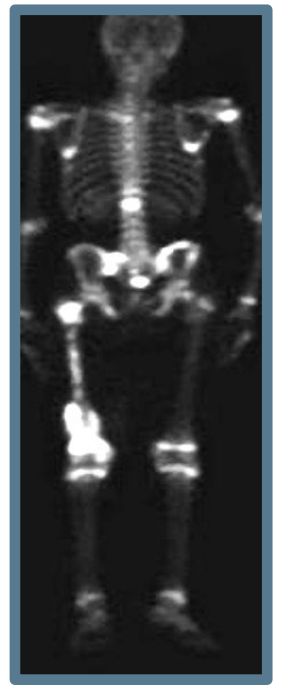
MRI







Bone scintigraphy



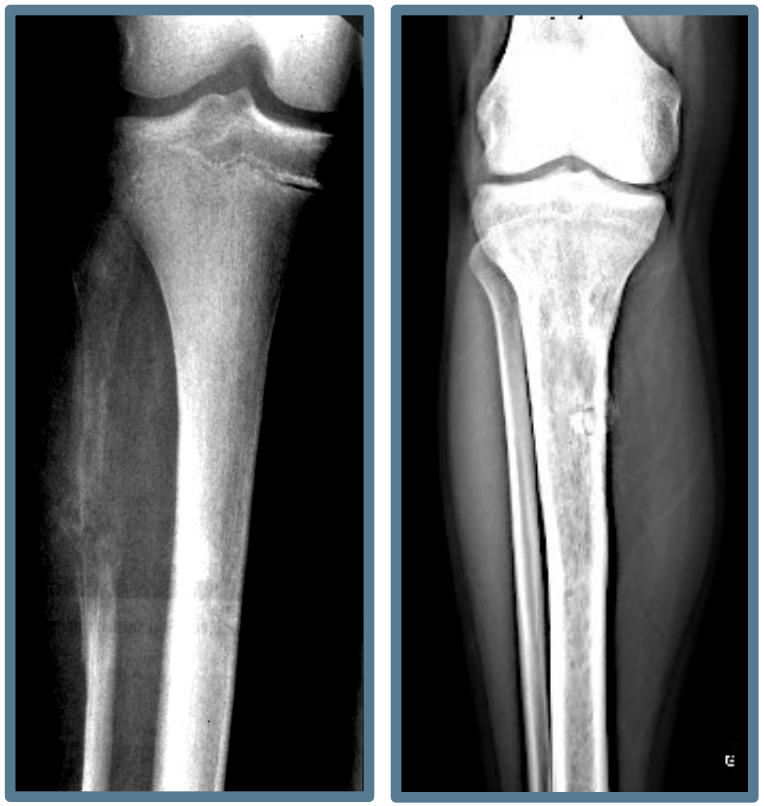
Lower extremity; femur osteosarcoma

MRI, magnetic resonance imaging
Images courtesy of Prof. F Duffaud

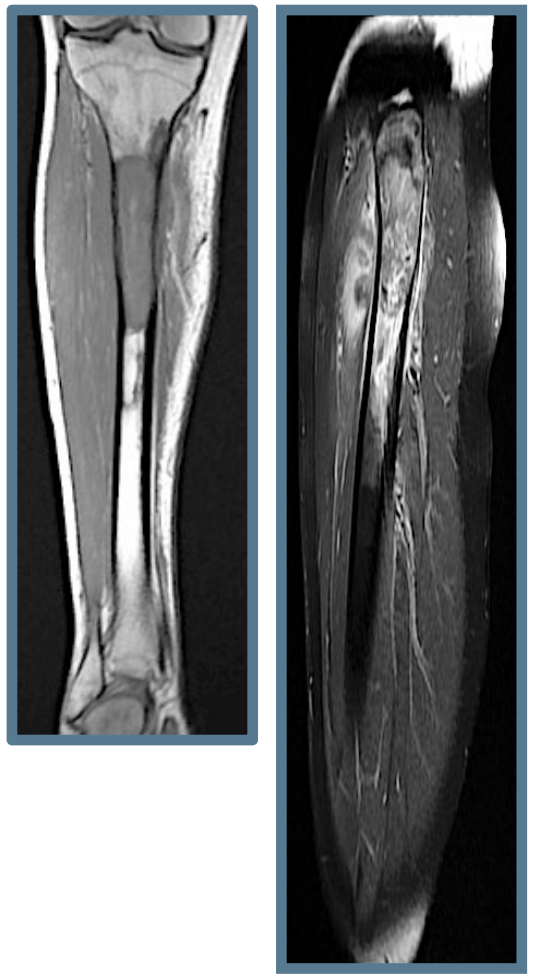
EWING SARCOMA: RADIOLOGY

SARCOMA connect
POWERED BY COR2ED

X-ray



MRI



MRI, magnetic resonance imaging
Images courtesy of Prof. F Duffaud

OSTEOSARCOMA AND EWING SARCOMA:
GENERAL TREATMENT PRINCIPLES

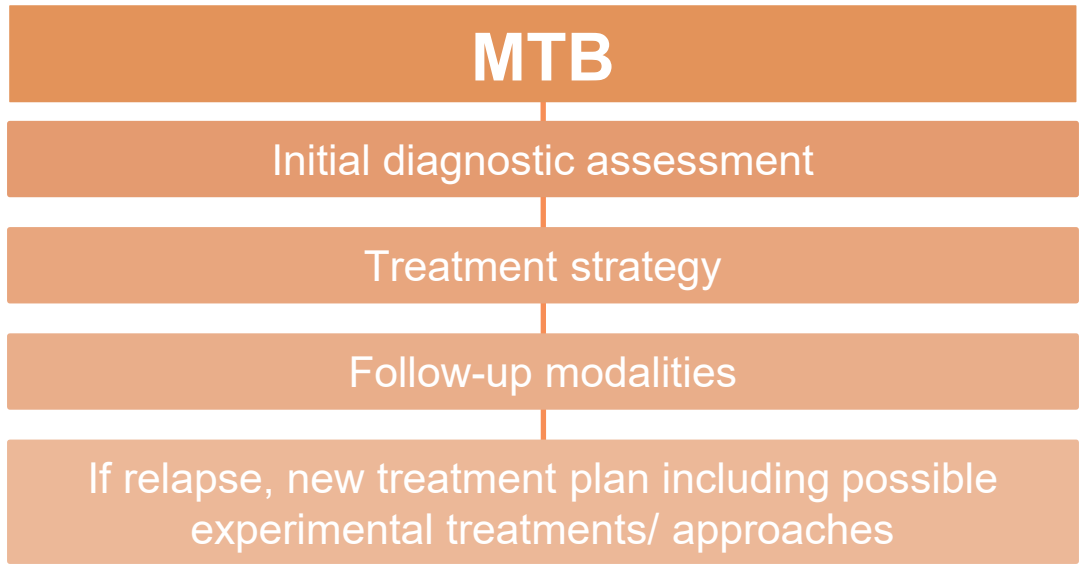
SARCOMA connect
POWERED BY COR2ED

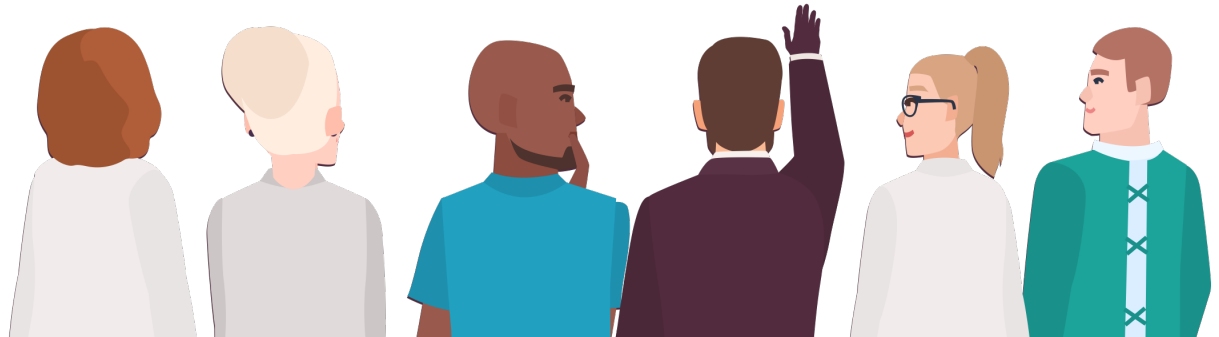
Multidisciplinary Tumour Board (MTB):

- Surgeon (orthopaedic surgical oncologist and/or general surgical oncologist)
- Radiation oncologist
- Medical and/or paediatric oncologist
- Radiologist
- Pathologist

Role:

- Supervise diagnostic assessment
- Define treatment strategy
- Define patient follow-up
- Direct patients to clinical trials where new therapies are under investigation





1. Pre- and/or post-operative chemotherapy
2. Optimal local treatment (surgery +/− radiation therapy)

MTB, multidisciplinary tumour board
Siegel GW, et al. J Multidiscip Healthc. 2015;8:109-115

CURRENT STANDARD OF CARE FOR OSTEOSARCOMA

- Neoadjuvant +/- adjuvant chemotherapy with a **multi-drug regimen** including doxorubicin, cisplatin, and high-dose methotrexate (HD-MTX) with leucovorin rescue, and ifosfamide for a total of 8–10 cycles and surgical resection +/- radiotherapy
  - MAP regimen (doxorubicin, cisplatin, and HD-MTX) most frequently used as front-line chemotherapy in children and young adults (age <40 years)
  - In patients age >40 years the use of HD-MTX is difficult and regimens combining doxorubicin, cisplatin, and ifosfamide are an alternative

→ Pre-operative chemotherapy facilitates local surgical treatment, allows assessment of tumour response, and reduces the risk of developing distant metastasis

- Surgery should be carried out by an **oncology surgical team** familiar with bone tumours and the wide range of surgical reconstructions
- **Radiotherapy may be considered in osteosarcoma** patients with unresectable primary tumours where surgery would be unacceptably morbid, as adjuvant treatment for tumours with high risk of local recurrence and limited option for further surgery, or after a marginal surgical resection

HD-MTX, high-dose methotrexate; MAP, doxorubicin, cisplatin, and HD-MTX

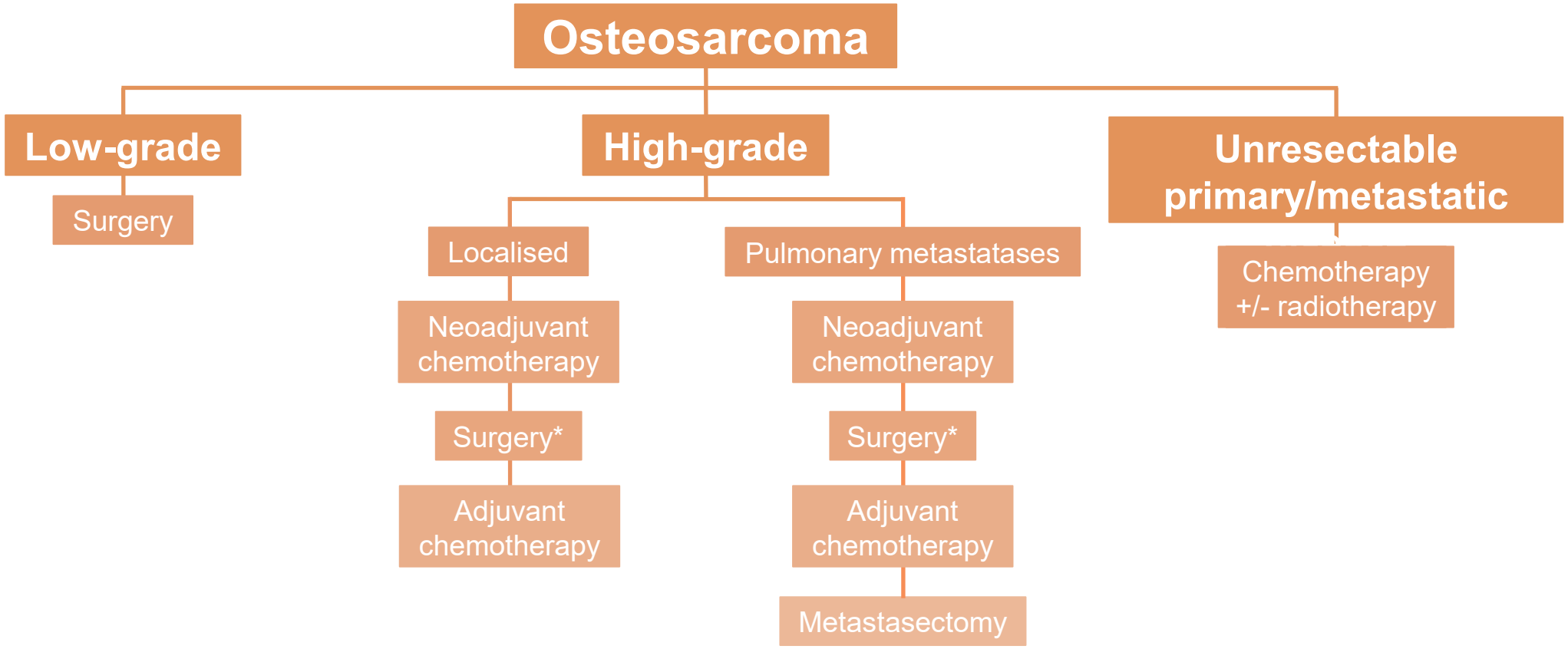
Strauss SJ, et al. Ann Oncol. 2021;32(12):1520-1536

HOW DO WE TREAT CONVENTIONAL OSTEOSARCOMA?

SARCOMA connect
POWERED BY COR2ED

Chemotherapy multi-drug approach:

- Doxorubicin
- Cisplatin
- Methotrexate
- Ifosfamide



*Radiotherapy can be used when adequate surgery is impossible and for high-risk locations (e.g. spine); however, osteosarcomas are usually considered as radioresistant. In general, there is no indication for radiotherapy, but there are anatomical locations in which the possibility of complete surgical resection is limited. In these cases, after a multidisciplinary discussion, radiotherapy may be an option

Strauss SJ, et al. Ann Oncol. 2021;32(12):1520-1536

CURRENT STANDARD OF CARE FOR EWING SARCOMA

- Current treatment strategy generally requires systemic chemotherapy in conjunction with surgery and/or radiotherapy for local tumour control
  - Up to 9 cycles of induction chemotherapy delivered after biopsy, followed by local therapy and consolidation chemotherapy
  - Overall treatment duration 10–12 months
  - Multi-agent regimen including vincristine, doxorubicin, cyclophosphamide/ifosfamide, and etoposide
- In selected cases, consider high-dose chemotherapy or whole-lung radiotherapy

Strauss SJ, et al. Ann Oncol. 2021;32(12):1520-1536

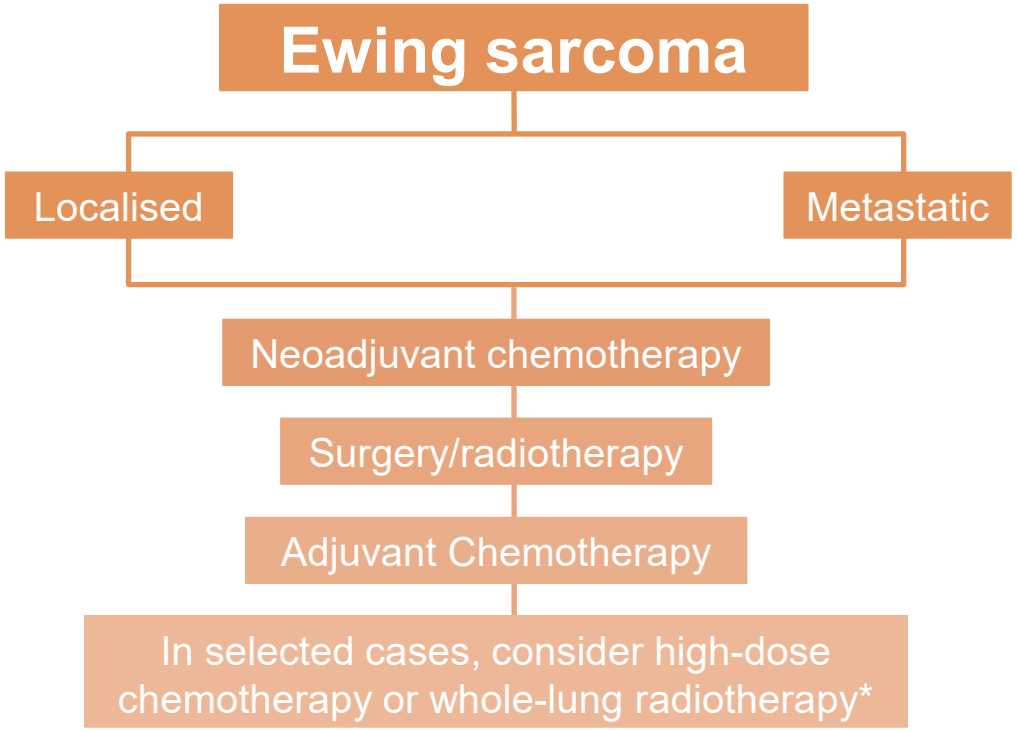
HOW DO WE TREAT EWING SARCOMA?

Chemotherapy includes:

- Vincristine
- Ifosfamide
- Doxorubicin
- Etoposide
- Cyclophosphamide

Radiotherapy:

- Definitive radiotherapy alone
  (**if complete surgical resection is not possible e.g. axial or spinal tumours**)
- Post-operative adjuvant radiotherapy
  (45–60 Gy) in case of inadequate surgical margins
- Post-operative radiotherapy discussed when histological response in the surgical specimen is poor (> 10% of viable tumour cells)



*High-dose chemotherapy not well established but to be considered in case of poor response or high volume if localised

Strauss SJ, et al. Ann Oncol. 2021;32(12):1520-1536

OSTEOSARCOMA: NOVEL STRATEGIES WITH THERAPEUTIC POTENTIAL

SARCOMA connect® POWERED BY COR2ED

Targeted therapy with small-molecule inhibitors and immunotherapies

Strategic approach	Example agents under investigation
Tyrosine Kinase Inhibition	• Cabozantinib • Regorafenib • Sorafenib +/- everolimus
Immune Checkpoint Inhibition	• Camrelizumab combined with pembrolizumab • Regorafenib combined with nivolumab • Regorafenib combined with avelumab • Mifamurtide
mTOR Inhibition	• Rapamycin • Ridaforolimus • Sirolimus • Temsirolimus
HER2-targeting	• Trastuzumab

Details of current clinical studies can be accessed here:
https://clinicaltrials.gov/
https://www.clinicaltrialsregister.eu/

HER2, human epidermal growth factor receptor 2; mTOR, mammalian target of rapamycin

Kansara M, et al. Nat Rev Cancer. 2014;14(11):722-735

EWING SARCOMA: NOVEL STRATEGIES WITH THERAPEUTIC POTENTIAL

SARCOMA connect® POWERED BY COR2ED

Targeted therapy with small-molecule inhibitors, immunotherapies, and combination therapy

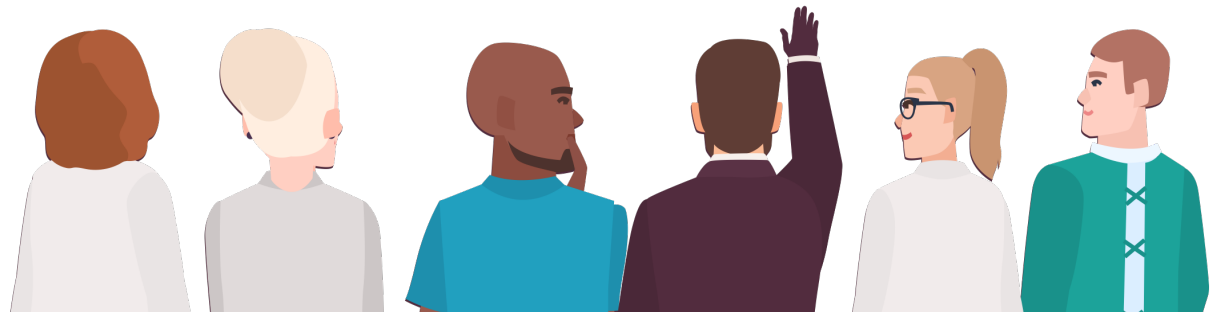
Strategic approach	Example agents under investigation
RNA Helicase A Activity Inhibition	• TK216 +/- vincristine
PARP1 Inhibition	• Olaparib combined with temozolomide
Anti-IGF-1R Immunotherapy	• Ganitumab with combination chemotherapy*
Therapeutic Vaccination	• FANG immunotherapy in combination with irinotecan and temozolomide

Details of current clinical studies can be accessed here:
https://clinicaltrials.gov/
https://www.clinicaltrialsregister.eu/

*Trial completed.
Casey DL, et al. Front Oncol. 2019;9:537

SUMMARY

- Patients suspected with bone sarcoma **MUST** be referred to a sarcoma reference centre or to an institution belonging to a specialised sarcoma network
- Diagnosis, staging, and risk assessment of bone sarcoma **SHOULD** be conducted at the sarcoma reference centre
- Biopsy and pathological diagnosis **SHOULD** be under the supervision of a **multidisciplinary tumour board**
- **Multidisciplinary tumour board** should include specialists such as a radiologist, pathologist, surgeon, radiation oncologist, and medical and/or paediatric oncologist
- Treatment strategy in case of primary, localised conventional osteosarcoma and Ewing sarcoma is based on the combination of **neoadjuvant chemotherapy, surgery** (**+/- radiotherapy**), and **adjuvant chemotherapy**



SARCOMA connect®

POWERED BY COR2ED

SARCOMA CONNECT
Bodenackerstrasse 17
4103 Bottmingen
SWITZERLAND

Dr. Froukje Sosef MD

+31 6 2324 3636

froukje.sosef@cor2ed.com

Dr. Antoine Lacombe Pharm D, MBA

+41 79 529 42 79

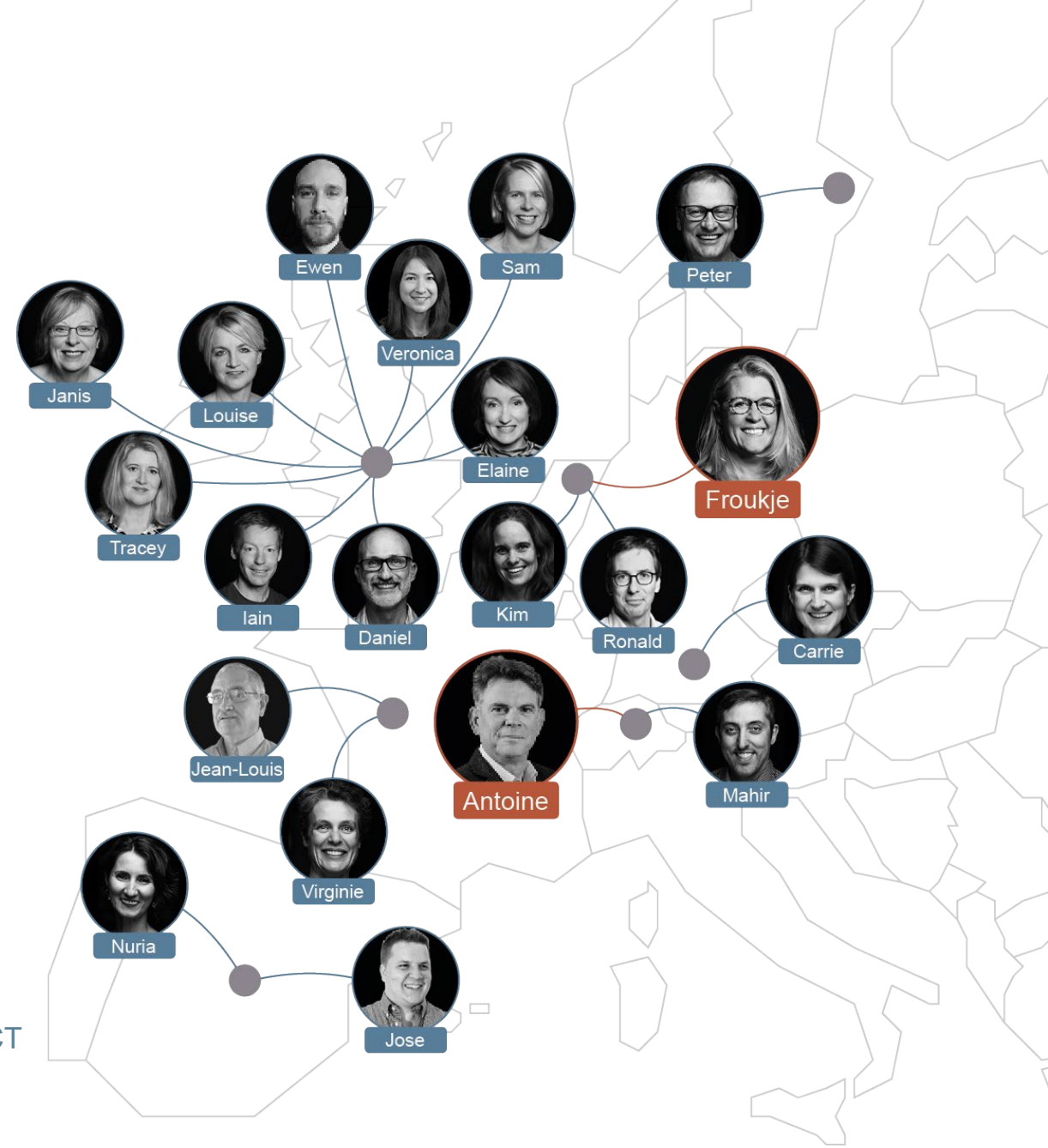
antoine.lacombe@cor2ed.com

Connect on
LinkedIn @SARCOMA CONNECT

Watch on
Vimeo @SARCOMA CONNECT

Visit us at
https://sarcomaconnect.cor2ed.com/

Follow us on
Twitter @sarcomaconnect



Heading to the heart of Independent Medical Education Since 2012