Leiden University Medical Center

Improving the understanding of primary bone cancer

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LUMC

Bone tumours

Bone tumours are rare

Difficult for pathologists: considerable morphological overlap

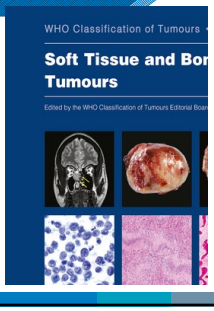
Subtypes differ in clinical behaviour and treatment

In bone tumours: role of immunohistochemistry and molecular analysis is limited

Diagnosis of bone tumours: multidisciplinary

Diagnosis of bone tumours: multidisciplinary

Classification of bone tumours



WHO classification 2020

Three groups:
1. Soft tissue tumours
2. Undifferentiated Small Round Cell sarcomas of bone and soft tissue

Four biological categories:

- benign
- intermediate locally aggressive
- intermediate rarely metastasizing
- malignant

Evaluation by an expert pathologist is crucial

Research Article

Histopathological Diagnostic Disc Soft Tissue Tumours Referred to a

Sarcoma: concordance between initi centralized expert review in a popula within three European regions

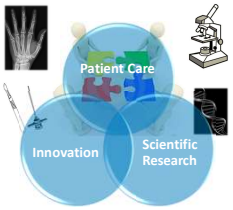
349 cases; 73% concordance
16% minor discrepancy
11% major discrepancy (5% benign / malignant) leading to management change

1463 patients, systematic review, 56% full concordance
35% partial concordance (different grade or subtype)
8% complete discordance (different diagnosis)

Sarcoma 2009 Ann Oncol 2012

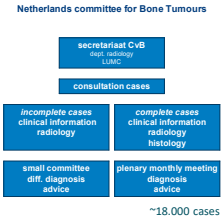
Centres of Expertise

- Topreferral care
- NFU: centre of expertise
- EU: european reference network



Netherlands Bone tumor committee

Netherlands Committee on Bone Tumours (since 1953)
www.beentumoren.nl



~18.000 cases

Classification of Bone Tumours (WHO 2020)

Benign	n=20
Intermediate	n=8
Malignant	n=26
Total	n=54

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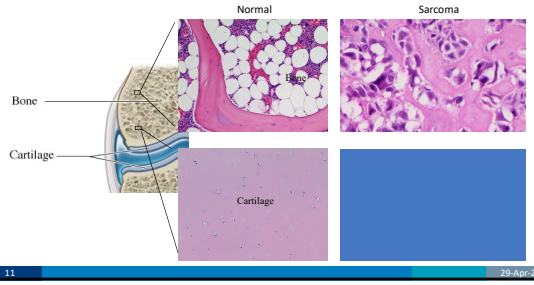
Classification is based on resemblance to normal



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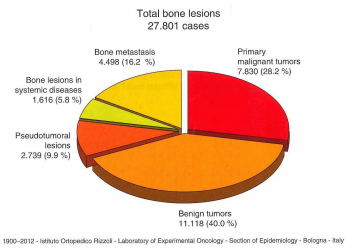
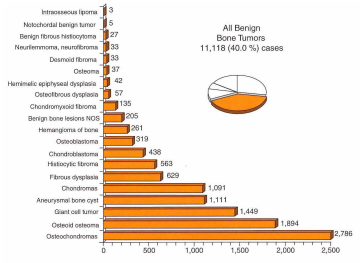
Total bone lesions

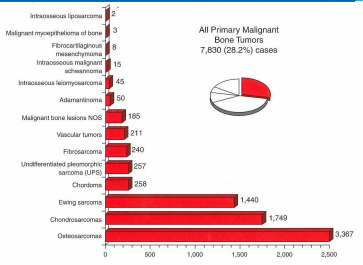


1900–2012 - Istituto Ortopedico Rizzoli - Laboratory of Experimental Oncology - Section of Epidemiology - Bologna - Italy

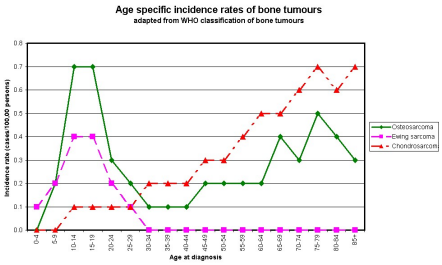
Benign bone tumors



Malignant bone tumors



Age specific incidence of bone sarcomas



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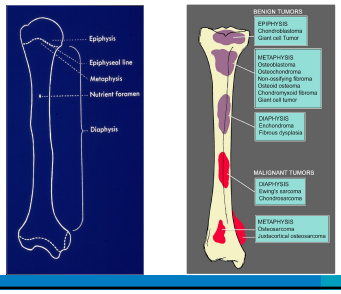
Sarcomas can occur in syndromes

Syndrome	Gene	inheritance	bone tumours encountered
Enchondromatosis (Ollier disease, Maffucci syndrome)	*IDH1,IDH2*	Somatic mosaicism	Enchondromas, secondary central chondrosarcoma
Li Fraumeni syndrome	*TP53*	AD	osteosarcoma
Cherubism	*SH3BP2*	AD	Spindled giant cell containing tumours of the jaw
McCune Albright syndrome and Mazabraud syndrome	*GNAS1*	Somatic mosaicism	Fibrous dysplasia
Multiple osteochondromas	*EXT1, EXT2*	AD	Osteochondroma, secondary peripheral chondrosarcoma
Retinoblastoma syndrome	*RB1*	AD	Osteosarcoma
Rothmund-Thomson syndrome	*RECQL4*	AR	Osteosarcoma
Werner syndrome	*WRN*	AR	Osteosarcoma
Diaphyseal medullary stenosis with undifferentiated pleomorphic sarcoma	*MTAP*	AD	Undifferentiated pleomorphic sarcoma
Infantile myofibromatosis	*PDGFRB, NOTCH3*	AD	myofibromas

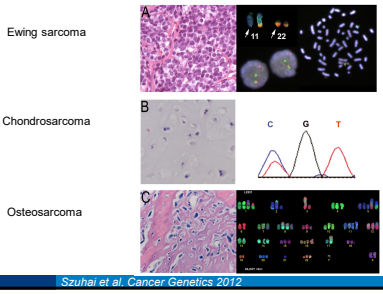
Location in the bone is important



Grading of bone sarcomas

Grade I	Low-grade intramedullary osteosarcoma
	Parosteal osteosarcoma
	Osteofibrous dysplasia-like adamantinoma
	Clear cell chondrosarcoma
Grade II	Periosteal osteosarcoma
	Classic adamantinoma
	Chordoma
Grade III	Osteosarcoma (conventional, teleangiectatic, small cell, secondary, high-grade surface)
	Undifferentiated high-grade pleomorphic sarcoma
	Ewing sarcoma
	Dedifferentiated chondrosarcoma
	Mesenchymal chondrosarcoma
	Dedifferentiated chordoma
	Malignancy in giant cell tumour of bone
	Angiosarcoma
Variable	Conventional Chondrosarcoma (Grade 1-3 according to Evans)
	Leiomyosarcoma of bone (Grade 1-3 according to FNCLCC)

sarcomagenesis



Ewing sarcoma	Specific translocation
Chondrosarcoma	Specific mutation; multistep model
Osteosarcoma	Complex karyotype

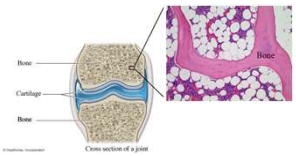
Szuhai et al. Cancer Genetics 2012

Osteogenic tumors

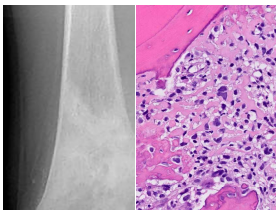
Benign
- Osteoma
- Osteoid osteoma

Intermediate, locally aggressive
- Osteoblastoma

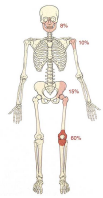
Malignant
- Low-grade central osteosarcoma
- Osteosarcoma
  - conventional osteosarcoma
    - chondroblastic osteosarcoma
    - fibroblastic osteosarcoma
    - osteoblastic osteosarcoma
  - teleangiectatic osteosarcoma
  - small cell osteosarcoma
- Parosteal osteosarcoma
- Periosteal osteosarcoma
- High-grade surface osteosarcoma
- Secondary osteosarcoma



osteosarcoma



- Most common primary malignant bone tumor
- Peak incidence <20 years, 2nd peak >40
- Resection, pre- and postoperative chemotherapy
- Survival 50-60%



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Cartilage tumors

Benign
- Subungual exostosis
- Bizarre parosteal osteochondromatous proliferation
- Periosteal chondroma
- Enchondroma
- Osteochondroma
- Chondroblastoma
- Chondromyxoid fibroma
- Osteochondromyxoma

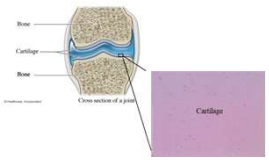
} >60% of the benign bone tumors

Intermediate, locally aggressive
- Synovial chondromatosis
- Atypical cartilaginous tumour

Malignant
- Chondrosarcoma grade 1
- Chondrosarcoma grade 2
- Chondrosarcoma grade 3

} 10-20% of the malignant bone tumors

- Periosteal chondrosarcoma
- Clear cell chondrosarcoma
- Mesenchymal chondrosarcoma
- Dedifferentiated chondrosarcoma

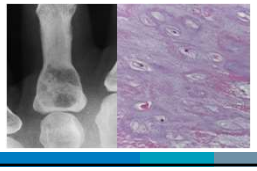


22 *WHO blue book 2020*

Benign cartilage tumours

Osteochondroma
- Bone surface
- Cartilage cap
- Stalk continuous with underlying bone

Enchondroma
- In marrow of bone
- Hands and feet



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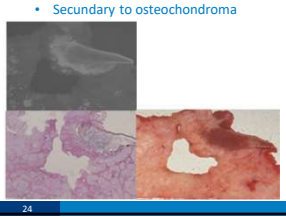
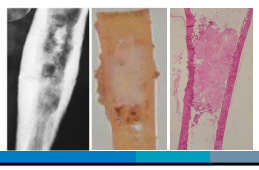
Malignant cartilage tumours

Peripheral chondrosarcoma (~15%)
- Bone surface
- Secundary to osteochondroma



Central chondrosarcoma (75%)
- In marrow
- Primary or secondary to enchondroma



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Cartilaginous tumours: a spectrum

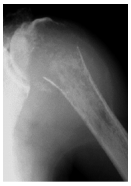
	Enchondroma	ACT/ Grade 1	Grade 2	Grade 3
	Benign	Intermediate, Locally aggressive or malignant	Malignant	Malignant
5 survival rate	100%	87-99%	74-99%	31-77%
10 survival rate	100%	88-95%	58-86%	26-55%
Metastasize in	0%	0%	10-30%	32-71%
Treatment	none	curettage + adj or wait and see or resection	en bloc resection	

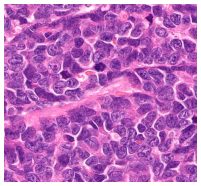
Evans 1977. WHO 2013. Duchman et al 2014. Nota et al Sarcoma 2015

WHO classification of undifferentiated s sarcomas of bone and soft tissue

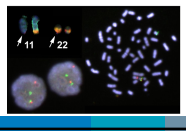
9364/3	Ewing sarcoma
9366/3*	Round cell sarcoma with *EWSR1*–non-ETS fusions
9367/3*	*CIC*-rearranged sarcoma

Ewing sarcoma

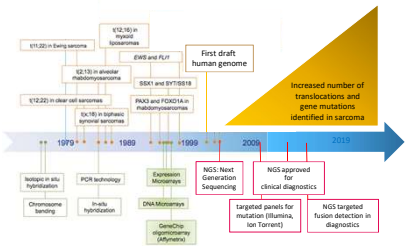




White young people
Bone and soft tissue
Resection, chemotherapy, radiation
5 years survival about 60-65%
Characteristic translocation



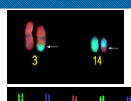
Molecular alterations in sarcoma

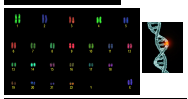


Sarcomagenesis

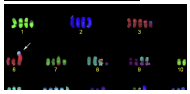
>170 different bone and soft tissue tumours

Simple karyotype
- Translocations
- Mutations
- Specific amplifications / gains



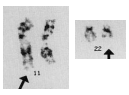


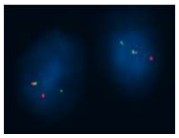
Complex karyotype
- Chromothripsis
- Multistep progression model



Development of translocation detection in pathology

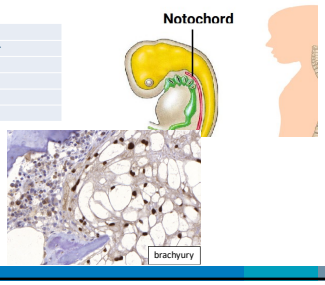
Traditional pathology → **Pathology 2021**
1 test for fusions in multiple genes



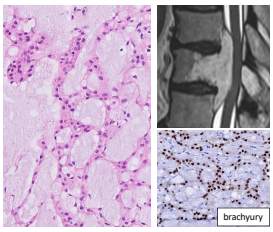


Notochordal tumors

Benign
Benign notochordal cell tumour
Malignant
Conventional chordoma
Dedifferentiated chordoma
Poorly differentiated chordoma



chordoma



- Location:
  - skull base
  - mobile spine
  - sacrum and coccyx
- All ages, 5th-7th decade most common
- Present with pain
- Surgical resection
- Overall median survival 7 years

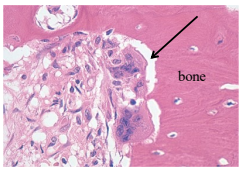
29-Apr-21

Osteoclastic giant cell rich tumors

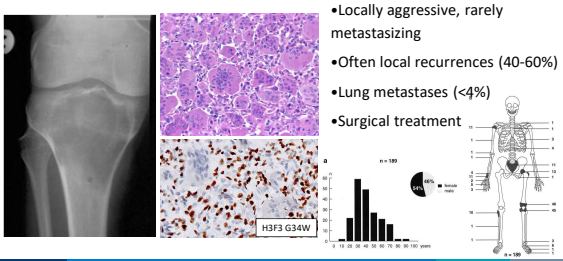
Benign
Aneurysmal bone cyst
Non ossifying fibroma

Intermediate (locally aggressive, rarely metastasizing)
Giant cell tumor of bone

Malignant
Malignancy in giant cell tumor of bone



Giant cell tumor of bone



- Locally aggressive, rarely metastasizing
- Often local recurrences (40-60%)
- Lung metastases (<4%)
- Surgical treatment

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Improving the understanding of primary bone cancers: Bovee lab