ABSTRACT

Background: In 2020, the World Health Organization (WHO) published the 5th version of the soft tissue and bone tumor classification. Based on this novel classification system, we reviewed the current knowledge on all tumor entities with spinal manifestations, their biologic behavior, and most importantly the appropriate treatment options as well as surgical approaches.

Methods: All tumor entities were extracted from the WHO Soft‑Tissue and Bone Tumor Classification (5th Edition). PubMed and Google Scholar were searched for the published cases of spinal tumor manifestations for each entity, and the following characteristics were extracted: Growth pattern, ability to metastasize, peak age, incidence, treatment, type of surgical resection indicated, recurrence rate, risk factors, 5-year survival rate, key molecular or genetic alterations, and possible associated tumor syndromes. Surgical treatment strategies as well as nonsurgical treatment recommendations are presented based on the biologic behavior of each lesion.

Results: Out of 163 primary tumor entities of bone and soft tissue, 92 lesions have been reported along the spinal axis. Of these 92 entities, 54 have the potential to metastasize. The peak age ranges from conatal lesions to 72 years. For each tumor entity, we present recommended surgical treatment strategies based on the ability to locally destruct tissue, to grow, recur after resection, undergo malignant transformation as well as survival rates. In addition, potential systemic treatment recommendations for each tumor entity are outlined.

Conclusion: Based on the 5th Edition of the WHO bone and soft tumor classification, we identified 92 out of 163 tumor entities, which potentially can have spinal manifestations. Exact preoperative tissue diagnosis and interdisciplinary case discussions are crucial. Surgical resection is indicated in a significant subset of patients and has to be tailored to the specific biologic behavior of the targeted tumor entity based on the considerations outlined in detail in this article.

Keywords: Chordoma, primary spinal tumors, sarcoma

INTRODUCTION

The core principles guiding surgical treatment for primary bone and soft-tissue tumors have been introduced by Enneking et al. more than 40 years ago and comprise three different types of surgical tumor resection: Intralesional, marginal en bloc, and wide en bloc resection.[1] It has been suggested that tumor location (intracompartmental versus extracompartmental) and histologic grade should be used
to determine the mode of resection. Since the introduction of Enneking’s system additional research regarding primary bone and soft-tissue tumors, new nonsurgical treatment modalities such as stereotactic radiosurgery or targeted molecular therapies and novel radiographic techniques together have significantly improved demarcating tumor extent and curbing tumor invasion.

This article is based on the 5th Edition of the World Health Organization (WHO) tumor classification of bone and soft-tissue tumors, published in 2020. We compiled the most recent knowledge of all tumor entities, which have been described to occur along the spinal axis and surrounding soft tissues. This comprehensive overview summarizes clinical knowledge as well as imaging findings of all primary, extradural spinal tumors described in the literature.

We describe our treatment algorithms, which is individualized for each tumor entity and loosely based on Enneking’s classification system, and modified by contemporary imaging protocols.

METHODS

The 5th Edition of the WHO soft tissue and bone tumors classification, published in 2020 was reviewed and individual tumor entities extracted into a spreadsheet. Medical databases (PubMed and Google Scholar) were searched for publications reporting occurrences of each entity listed in the WHO classification along the spinal axis (spinal bones or paraspinal soft tissues). If an entity has been reported to occur along the spinal axis, a case report with exemplary imaging findings was obtained. For each tumor entity, the following data were extracted from the WHO classification or other key references: Relevant differential diagnoses, growth pattern (infiltrative/destructive), potential for malignant transformation, potential to metastasize, peak age, incidence, recommended type of surgical resection (A, B, C), recurrence rate, treatment, risk factors, 5-year overall survival rate, key molecular or genetic alterations, and possible associated tumor syndromes. All primary bone and soft tissue tumor entities listed in the 5th Edition of the WHO tumor classification were listed in a spreadsheet and a note was made on entities reported to occur along the spinal axis. In a second spreadsheet, exemplary imaging findings of each entity have been listed or say: “Exemplary imaging findings of each entity are listed in a second spreadsheet.” Moreover, finally, in a third spreadsheet, the above-mentioned key characteristics for each entity have been listed.

RESULTS

A comprehensive list of all primary bone and soft-tissue tumors, as listed in the most recent WHO classification is given in Appendix 1 and comprises a total of 163 entities. Of note, the following tumors can arise in either bone or soft tissue: Hemangioma, epithelioid hemangioma, epithelioid hemangioendothelioma, angiosarcoma, desmoplastic fibroma, fibrosarcoma, chondroma, and osteosarcoma.

Tumor entities are classified by the cell of tumor origin [Appendix 1]. For soft-tissue neoplasms, the following cells of origin are as follows: Adipocytic, fibroblastic and myofibroblastic, fibrohistiocytic, vascular, pericytic (perivascular), smooth muscle, skeletal muscle, gastrointestinal stromal, chondro-osseous, and peripheral nerve sheath. Two further categories exist for all soft-tissue tumors that do not fall into the above mentioned: Tumors of uncertain differentiation and undifferentiated small round cell sarcomas. In the case of bone tumors, the following subclassification based on the cell population of origin exists: Chondrogenic, osteogenic, fibrogenic, vascular, osteoclastic giant cell-rich, or notochordal. Two further subcategories are listed in the WHO classification: Other mesenchymal bone tumors and hematopoietic neoplasms of the bone.

The results of our literature search are outlined in Appendixes 2 and 3 and show that 92 out of 163 entities were reported to occur either in spinal bones or paraspinal soft tissue. We categorized 92 entities with imaging [Appendix 2] and clinical/molecular findings [Appendix 3], as well as recommended surgical and nonsurgical treatment options.

Appendix 3 shows a comprehensive characterization of each tumor by: Growth pattern (infiltrative/locally destructive or not), ability to metastasize, ability to undergo malignant transformation, mean age at diagnosis, incidence, suggested mode of resection (intralesional resection A, marginal en bloc resection B, wide, or compartmental en bloc excision C), recurrence rate, treatment strategy, tumor risk factors, 5-year overall survival (OS) rate, genetic/molecular tumor characteristics, possible associated tumor syndromes, and corresponding cross-sectional imaging findings are presented in Appendix 2.

As shown in Appendix 3, the incidence rates for primary extradural spinal bone or soft-tissue tumors range from 2% (hemangioma) to a low of only two published cases for spinal nodular fasciitis. The survival rates of malignant lesions range from 94% for 5 year OS for ossifying fibromyxoid tumor to 7% for dedifferentiated osteosarcoma. A total of 54 entities...
DISCUSSION

The most recent edition of the WHO classification of bone and soft-tissue tumors lists a total of 163 tumor entities, out of which 92 have been previously reported in the literature to potentially occur in the spine. Surgical resection is the integral part of treatment for most of these lesions and follows the overriding principles outlined by Enneking et al. in 1980,[1] as shown in Figure 1. Type B and C resections are more complex than type A resections with higher rates of complications; however, type B/C resections are associated with superior oncologic outcome as compared to type A resections for malignant lesions.[3] It must be noted that given to the unique anatomy of the spine, when compared to long bones, in many cases, a type B resection might be indicated. While type B resections may not be technically feasible, spine surgeons may opt for type C resections with a wider excision. Figure 2 provides an overview of important growth characteristics of malignant bone and soft-tissue tumors. As indicated, the growth pattern of sarcomas is infiltrative. Even with a rim of reactive tissue, the pseudocapsule may act only as a weak barrier to prevent tumor spread. While the pseudocapsule has been shown to restrict tumor permeation after radio- or chemotherapy it is not a true barrier for tumor spread.[4] Cortical bone as well as major fascial planes, such as pleura or peritoneum are considered bone fide barriers. It is known from radiologic studies that infiltrating tumor nests, known as skip lesions, outside the primary tumor can be depicted on magnetic resonance imaging (MRI) in up to 16.5% of patients.[5] As shown in Figure 2, once the cortical bone of the vertebra is breached, the tumor cells can freely spread until they reach the next level of solid barrier [routes A-D in Figure 2]. As has been shown in previous correlating studies between preoperative imaging and intraoperative histologic analysis, the mean discrepancy between tumor margin on preoperative MRI and intraoperative histology for osteosarcomas is 5 mm.[6,7] Since short-tau inversion recovery and postcontrast T1 imaging overestimates the tumor extend by 1.68 cm, tumor outline is best depicted on noncontrast-enhanced T1 images.[6] Therefore, in our own experience if a malignant tumor is confined to one compartment, we perform either a type B resection with a margin of 5 mm on top of the tumor outline in the preoperative noncontrast T1 images, or we perform a type C resection, which will remove the whole tumor bearing compartment. If a malignant tumor extends into more than one compartment (e.g., cortical bone erosion in the case of vertebral osteosarcomas), we prefer to discuss either neo-adjuvant treatment to "downsize" the tumor (the more compartments the tumor extends into, the less likely a true wide en bloc resection can be achieved) or surgery to encompass an en bloc resection of the primary tumor bearing compartment plus the extension into a neighboring compartment with a safety margin of at least 5 mm.

How to incorporate these principles into surgical practice depends on the index level. In the case of C1 and C2, oncologic resections type B and C in most cases require a transmandibular approach [Figure 3]. When compared to the rest of the cervical spine negative margins are less likely to be obtained due to the anatomical complexity of the region.[9] For the rest of the mobile spine the WBB system has been proposed to choose the appropriate approach or combination of approach to perform a type B or C resection [Figure 4].[10] The choice of approach for oncologic resections of the sacrum is mainly determined by

![Figure 1: Overview of the three different surgical types of resection in the treatment of spinal tumors](image-url)
the anatomic level of the lesion as well as the presence of visceral tumor infiltration. Figure 5 outlines our institutional algorithm to such lesions. Only lesions located below the inferior margin of the sacroiliac joint (SIJ) without visceral invasion are resected using a posterior-only approach. All other lesions are resected using an anterior/posterior approach. Reconstruction of the pelvic ring is necessary if more than 50% of the SIJs are resected. In instances where the tumor extends by more than 3 cm beyond the SIJ, we consider them as primarily inoperable (due to the large tumor volume and complexity of reconstruction).

Reconstruction of large resection cavities in many cases requires the involvement of plastic surgery and is beyond the scope of this article.

*En bloc* resections are technically demanding and have been shown to have higher complication rates when compared to type A resections, particularly when more than 1 level is being resected (Spiessberger A, PubMed ID pending), even though lesion etiology seems to have less impact on complication rates.

Given the profile of potential complications in the case of type B and C resections, rigorous preoperative planning is of paramount importance. Neurologic deficits are particularly devastating to patients and should be avoided at all costs. Other than direct mechanical injury, ischemic spinal cord injury has been reported to occur on rare occasions.\(^{[11,12]}\) Even though spinal cord blood supply is highly collateralized, postoperative infarcts can be a complication due to segmental vessel ligation.\(^{[11,13]}\) Spinal cord blood supply is established through the anterior spinal artery, a branching vessel of the vertebral arteries, as well as from posterior spinal arteries through branching vessels of either vertebral or posterior inferior cerebellar arteries. Collateral flow is provided through variable radiculomedullary vessels, typically 2-3 cervical (bilaterally equal), 2-3 thoracic (left more than right), and 0-1 lumbar (left more than right).\(^{[12]}\) Three major radiculomedullary vessels are described: The artery of cervical enlargement (usually a branching vessel from the ascending cervical artery at C6), the artery “von Haller” (usually the T5 segmental vessel) as well as the artery of Adamkiewicz (usually the T10 segmental vessel).\(^{[14]}\) Watershed areas, susceptible to ischemic infarction in cases of hypotension or hypoxia have been suggested in the mid thoracic spine as well as the posterior aspect of the conus medullaris.\(^{[15]}\) Type B and C resections require segmental artery ligation; however, recent studies have suggested that up to three adjacent segmental vessel can be sacrificed safely.\(^{[16,17]}\) We believe, that caution should be taken when ligating one of the three major radiculomedullary vessels, as described above. Preoperative high-resolution CT angiography can help localize the level of these three vessels. Intraoperative temporary nerve root/segmental vessel clamping with cautious observation of motor evoked potential/somatosensory evoked potential is important as well. In addition, intraoperative and postoperative hypotension should be avoided at all costs when a major radiculomedullary vessel has been sacrificed. It is also worth noting that the choice of vasopressor might make a difference as well. Animal studies comparing norepinephrine and phenylephrine in their properties to increase spinal cord perfusion in the setting of hypotension have shown, that norepinephrine provides better restoration of blood flow and oxygenation.\(^{[18]}\) One should also recognize that radiculomedullary vessel ligation may not only render the patient more susceptible to ischemic cord injury, but also
surgical trauma to segmental vessels or vertebral arteries can lead to embolic cord infarcts caused by vessel dissections.\cite{19}

In the case of cervical type B and C resections, preoperative endovascular sacrifice of one vertebral artery in case high degree tumor encasement (>180°) can be safely performed following careful study of a CT angiogram of both cervical vessels and posterior circulation. Side dominance, potential stenoses, size or absence of the posterior communicating arteries (in the case of fetal posterior cerebral artery variants) must be determined. Moreover, temporary endovascular balloon occlusion can be considered to determine the safety of vessel occlusion.

**CONCLUSION**

Based on the 5th Edition of the WHO bone and soft tumor classification, we identified 92 out of 163 tumor entities, which potentially can have spinal manifestations. Exact preoperative tissue diagnosis and interdisciplinary case discussions are crucial. Surgical planning has to be tailored to the specific biologic behavior of the targeted tumor entity based on the considerations outlined in detail in this article.

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**Conflicts of interest**

There are no conflicts of interest.

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APPENDIXES

Appendix 1: List of bone and soft tissue tumors

| Soft tissue tumours                                                                                                                                   | Appendix 1: Contd...                                                               |
|------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|
| Adipocytic tumours                                                                                                                                  | Superficial CD34-positive fibroblastic tumour                                        |
| Angiolipoma                                                                                                                                         | So-called fibrohistiocytic tumours                                                 |
| Atypical lipomatous tumour/well-differentiated liposarcoma                                                                                    | Deep fibrous histiocytoma                                                          |
| Atypical spindle cell/pleomorphic lipomatous tumour                                                                                               | Giant cell tumour of soft tissue                                                   |
| Chondroid lipoma                                                                                                                                   | Plexiform fibrohistiocytic tumour                                                  |
| Hibernoma                                                                                                                                          | Tenosynovial giant cell tumour                                                     |
| Lipoblastoma and lipoblastomatosis                                                                                                                  | Vascular tumours                                                                   |
| Lipoma                                                                                                                                             | Angiosarcoma                                                                        |
| Lipomatosis                                                                                                                                      | Haemangiendothelioma, composite                                                    |
| Lipomatosis of nerve                                                                                                                                | Haemangiendothelioma, epithelioid                                                  |
| Liposarcoma, dedifferentiated                                                                                                                     | Haemangiendothelioma, pseudomyogenic                                              |
| Liposarcoma, myxoid                                                                                                                                | Haemangiendothelioma, retiform                                                     |
| Liposarcoma, myxoid pleomorphic                                                                                                                   | Haemangioma                                                                         |
| Liposarcoma, pleomorphic                                                                                                                           | Haemangioma, anastomosing                                                          |
| Myolipoma of soft tissue                                                                                                                          | Haemangioma, epithelioid                                                           |
| Spindle cell lipoma and pleomorphic lipoma                                                                                                          | Intramuscular angioma                                                              |
| Fibroblastic and myofibroblastic tumours                                                                                                             | Kaposi sarcoma                                                                     |
| Acral fibromyxoma                                                                                                                                  | Lymphangioma and lymphangiomatosis                                                 |
| Angiobroma of soft tissue                                                                                                                         | Papillary intralymphatic angioendothelioma                                           |
| Angiomyofibroblastoma                                                                                                                               | Synovial haemangioma                                                               |
| Calcifying aponeurotic fibroma                                                                                                                    | Tufted angioma and kaposiform haemangiendothelioma                                 |
| Cellular angiofibroma                                                                                                                              | Venous haemangioma, venous                                                         |
| Dermatofibrosarcoma protuberans                                                                                                                    | Pericytic (perivascular) tumours                                                   |
| Desmoid fibromatosis                                                                                                                               | Angioleiomyoma                                                                      |
| Desmoplastic fibroblastoma                                                                                                                        | Glomus tumour                                                                       |
| Elastofibroma                                                                                                                                     | Myopericytoma, including myofibroma                                               |
| EWSR1-SMAD3-positive fibroblastic tumour (emerging)                                                                                               | Smooth muscle tumours                                                               |
| Fibroma of tendon sheath                                                                                                                          | EBV-associated smooth muscle tumour                                                |
| Fibromatosis colli                                                                                                                                  | Inflammatory leiomyosarcoma                                                        |
| Fibrosarcoma, adult                                                                                                                                | Leiomyoma                                                                           |
| Fibrosarcoma, infantile                                                                                                                             | Leiomyosarcoma                                                                      |
| Fibrous hamartoma of infancy                                                                                                                      | Skeletal muscle tumours                                                            |
| Gardner fibroma                                                                                                                                   | Ectomesenchymoma                                                                    |
| Giant cell fibroblastoma                                                                                                                           | Rhabdomyoma                                                                         |
| Inclusion body fibromatosis                                                                                                                        | Rhabdomyosarcoma, alveolar                                                        |
| Inflammatory myofibroblastic tumour                                                                                                                 | Rhabdomyosarcoma, embryonal                                                       |
| Ischaemic fasciitis                                                                                                                                | Rhabdomyosarcoma, pleomorphic                                                     |
| Juvenile hyaline fibromatosis                                                                                                                     | Rhabdomyosarcoma, spindle cell                                                     |
| Lipoblastoma                                                                                                                                     | Gastrointestinal stromal tumour                                                    |
| Low-grade fibromyxoid sarcoma                                                                                                                     | Gastrointestinal stromal tumour                                                    |
| Low-grade myofibroblastic sarcoma                                                                                                                  | Chondro-osseous tumours                                                            |
| Myofibroblastoma                                                                                                                                  | Soft tissue chondroma                                                               |
| Myoositis ossificans and fibro-osseous pseudotumour of digits                                                                                     | Extraskeletal osteosarcoma                                                          |
| Myofibrosarcoma                                                                                                                                  | Peripheral nerve sheath tumours                                                    |
| Myxoinflammatory fibroblastic sarcoma                                                                                                               | Benign triton tumour/neuromuscular choristoma                                       |
| Nodular fasciitis                                                                                                                                  | Dermal nerve sheath myxoma                                                         |
| Nuchal-type fibroma                                                                                                                                | Ectopic meningioma and meningothezial hamartoma                                    |
| Palmar fibromatosis and plantar fibromatosis                                                                                                      | Granular cell tumour                                                               |
| Proliferative fasciitis and proliferative myositis                                                                                               | Hybrid nerve sheath tumour                                                         |
| Sclerosing epitheloid fibrosarcoma                                                                                                                  | Malignant melanotic nerve sheath tumour                                            |
| Solitary fibrous tumour                                                                                                                            | Malignant peripheral nerve sheath tumour                                           |
|                                                                                                                                                    | Neurofibroma                                                                         |
### Appendix 1: Contd...

| Perineurioma | Osteosarcoma, high-grade surface |
| Schwannoma | Osteosarcoma, low-grade central |
| Solitary circumscribed neurona | Osteosarcoma, parosteal |
| Tumours of uncertain differentiation | Osteosarcoma, periosteal |
| Alveolar soft part sarcoma | Osteosarcoma, secondary |
| Angiomatoid fibrous histiocytoma | Fibrogenic tumours (see soft tissue tumors) |
| Atypical fibroxanthoma | Vascular tumours of bone (seesoft tissue tumors) |
| Clear cell sarcoma of soft tissue | Osteoclastic giant cell-rich tumours |
| Deep (aggressive) angiomyxoma | Aneurysmal bone cyst |
| Desmoplastic small round cell tumour | Giant cell tumour of bone |
| Epithelioid sarcoma | Nonossifying fibroma |
| Extrarenal rhabdoid tumour | Notochordal tumours |
| Extraskeletal myxoid chondrosarcoma | Benign notochordal cell tumour |
| Haemosiderotic fibrolipomatous tumour | Conventional chordoma |
| Intimal sarcoma | Dedifferentiated chordoma |
| Intramuscular myxoma | Poorly differentiated chordoma |
| Juxta-articular myxoma | Other mesenchymal tumors of bone (see soft-tissue tumors) |
| Myoepithelioma, myoepithelial carcinoma, and mixed tumour | Haematopoietic neoplasms of bone |
| NTRK-rearranged spindle cell neoplasm (emerging) | Erdheim-chester disease |
| Ossifying fibromyxoid tumour | Langerhans cell histiocytosis |
| PEComa | Plasmyctoma of bone |
| Phosphaturic mesenchymal tumour | Primary non-Hodgkin lymphoma of bone |
| Pleomorphic hyalinizing angiectatic tumour of soft parts | Rosai-Dorfman disease |
| Synovial sarcoma | **EBV** - Ebstein Barr virus |
| Undifferentiated sarcoma | |
| Undifferentiated small round cell sarcomas of bone and soft tissue | |
| CIC-rearranged sarcoma | Osteosarcoma, high-grade surface |
| Ewing sarcoma | Osteosarcoma, low-grade central |
| Round cell sarcoma with EWSR1-non-ETS fusions | Osteosarcoma, parosteal |
| Sarcoma with BCOR genetic alterations | Osteosarcoma, periosteal |

### Bone tumours

Chondrogenic tumours

- **Bizarre parosteal osteochondromatous proliferation**
- Central atypical cartilaginous tumour/chondrosarcoma, Grade 1
- Chondroblastoma
- Chondromyxoid fibroma
- Chondrosarcoma, central Grades 2 and 3
- Chondrosarcoma, clear cell
- Chondrosarcoma, dedifferentiated
- Chondrosarcoma, mesenchymal
- Chondrosarcoma, periosteal
- Chondrosarcoma, secondary peripheral Grades 2 and 3
- Enchondroma
- Osteochondroma
- Osteochondromyxoma
- Periosteal chondroma
- Secondary peripheral atypical cartilaginous tumour/chondrosarcoma, Grade 1
- Subungual exostosis
- Synovial chondromatosis

Osteogenic tumours

- Osteoblastoma
- Osteoid osteoma
- Osteoma
- Osteosarcoma

Contd...
### Appendix 2: Radiographic overview of primary spinal neoplasms

#### Adipocytic Tumors

| Tumor Entity | Patient Age/Sex | Imaging Details |
|--------------|-----------------|-----------------|
| Angioproliferative tumor | 69m, axial T1W+ L2 | Kang H et al. |
| Angioprolificative tumor | 67m, axial T1W+ L3 | Maniago P et al. |
| Lipoma | 54m, axial CT L3 | Hooshnavine K et al. |
| Liposarcoma | 79m, axial T2W T5-7 | Rovlias A et al. |
| Liposarcoma, myxoid | 75m, axial T2W T5 | |

#### Fibroblastic / Myofibroblastic Tumors

| Tumor Entity | Patient Age/Sex | Imaging Details |
|--------------|-----------------|-----------------|
| Desmoid-type fibromatosis | 31m, axial CT L5/4 | Kwon Y et al. |
| Desmoplastic fibroblastic sarcoma | 85m, axial T1W+ L3 | Zhang Y et al. |
| Eosinophilic fibroma | 1m, axial T1W+ L2 | Wang S et al. |
| Fibrosarcoma, adult | 33m, axial T2W C3 | Simone C et al. |
| Fibrosarcoma, infantile | 0.25m, axial T2W T12 | Weng S et al. |
| Inflammatory myofibroblastic tumor | 5m, axial T2W L4/S | Weng S et al. |
| Lipofibromatosis | 1.5m, axial T2W T7 | Sibiya V et al. |

#### Fibrohistiocytic Tumors

| Tumor Entity | Patient Age/Sex | Imaging Details |
|--------------|-----------------|-----------------|
| Benign fibrous histiocytoma | 23m, axial CT T7 | Liu S et al. |
### smooth muscle tumors

| Tumor Entity | Patient Age/sex; Imaging | Source |
|--------------|--------------------------|--------|
| EBV associated smooth muscle tumor | 24m; axial T1W T2    | Ehresman JS et al. |
| Leiomyoma | 44f; axial T2W C5/6 | lwakura K et al. |
| Leiomyosarcoma | 47f; axial T2W T11 | Lo TH et al. |

### pericytic tumors

| Tumor Entity | Patient Age/sex; Imaging | Source |
|--------------|--------------------------|--------|
| Myopericytoma | 50f; axial T2W T8    | Agiwal N et al. |

### skeletal muscle tumors

| Tumor Entity | Patient Age/sex; Imaging | Source |
|--------------|--------------------------|--------|
| Ectomesenchymoma | 61m; axial T2W L5    | Kimura S et al. |
| Rhabdomyosarcoma, alveolar | 20f; axial T2W T3/4 | Sotene B et al. |
| Rhabdomyosarcoma, embryonal | 5m; sag T1W+ C5-T3  | Kumboldt Z et al. |
| Rhabdomyosarcoma, pleomorphic | 59m; sag T2W T9/10 | Spaleholz M et al. |
| Rhabdomyosarcoma, spindle cell | 70f; axial CT L5 | Tagami M et al. |

Contd...
## Appendix 2: Contd...

### Vascular Tumors

| Tumor Entity | Patient Age/sex; Imaging | Source |
|--------------|--------------------------|--------|
| Angiosarcoma | 38m; axial T2W T11       | Gao X et al. |
| Hemangiendothelioma, composite | 41m; sag T2W T4       | Thomas AC et al. |
| Hemangiendothelioma, epithelial | 78m; axial CT L4  | Lee C et al. |
| Hemangiendothelioma, kaposiform | 50m; axial CT C3 | Makis W et al. |
| Hemangiendothelioma, reiform | 45m; axial T1W T5 | Vadillo LM et al. |
| Hemangioendothelioma | 0.5 m; axial T1W T5 | Ghermandi R et al. |

### Peripheral Nerve Sheath Tumors

| Tumor Entity | Patient Age/sex; Imaging | Source |
|--------------|--------------------------|--------|
| Ectopic meningioma | 46m; sag T1W+ sacral | Lo I et al. |
| Hybrid nerve sheath tumor | 47m; sag T2W lumbar | Masselli M et al. |
| Malignant peripheral nerve sheath tumor | 30y; sag T2W L5 | Keitel SA et al. |
| Neurofibromatosis | 54f; axial T1W T3 | De Wandeler T et al. |

### Uncertain Differentiation

| Tumor Entity | Patient Age/sex; Imaging | Source |
|--------------|--------------------------|--------|
| Clear cell sarcoma | 48f; sag T1W+ sacral | Tse K et al. |
| Desmoplastic small round cell tumor | 51m; sag T2W T11 | Loo G et al. |
| Neurofibrosarcoma | 54m; sag T2W T5 | Mak W et al. |
| Extramedullary histiocytosis tumor | 87m; sag T1W+ sacral | Cheung WY et al. |
| Myoepithelioma | 54m; axial T2W 111 | Tse K et al. |

### Undifferentiated Small Round Cell Tumors

| Tumor Entity | Patient Age/sex; Imaging | Source |
|--------------|--------------------------|--------|
| Neuroblastoma | 32m; axial T1W+ L1 | Elshafi M et al. |
| Ewing sarcoma | 58m; axial T2W 111 | Iacoangeli M et al. |
| Synovial sarcoma | 39m; sag T2W T11 | Kim W et al. |
| Liposarcoma | 54m; sag T2W T5 | Yang et al. |

**Contd...**
### Appendix 2: Contd...

#### chondrogenic tumors

| Tumor Entity        | Patient Age/Sex | Imaging          | Source                      |
|---------------------|-----------------|------------------|-----------------------------|
| Chondroblastoma     | 21f, axial CT L3 |                  | Shakir TM et al.            |
| Chondroblastoma     | 21m, axial CT L5 |                  | Gutierrez-Gonzalez R et al. |
| Chondroblastoma, clear cell | 61m, axial T1W T4 |                  | Padole A et al.             |
| Chondroblastoma, mesenchymal | 31m, axial CT L4 |                  | Fukuda A et al.             |
| Chondrosarcoma      | 61m, axial CT L1 |                  | Strike SA et al.            |
| Chondrosarcoma, dedifferentiated | 81m, axial CT C2 |                  | Kataki Y et al.             |
| Chondrosarcoma      | 41f, axial CT T3 |                  | Guo J et al.                |

| Chondroblastoma     | 21f, axial CT C3 |                  | Veilandi R et al.            |
| Chondroblastoma     | 21f, axial T1W T9 |                  | Yu W et al.                 |
| Chondroblastoma     | 29m, axial CT L2 |                  | Abreuza A et al.            |
| Chondrosarcoma      | 46m, axial CT C2 |                  | Strike SA et al.            |
| Chondrosarcoma      | 31m, sag T2W T10 |                  | Greyede RS et al.           |

#### osteogenic tumors

| Tumor Entity        | Patient Age/Sex | Imaging          | Source                      |
|---------------------|-----------------|------------------|-----------------------------|
| Osteoblastoma       | 20f, axial CT T12|                  | Bhargava P et al.           |
| Osteosarcoma, chondroblastic | 21m, axial T2W L5 |                  | Sapkas G et al.             |
| Osteosarcoma, fibroblastic | 81m, sag T2W T12 |                  | Forlizzi J et al.           |
| Osteosarcoma, osteoblastic | 32f, axial CT T3 |                  | Scudday TS et al.           |
| Osteosarcoma, teleangiectatic | 18f, axial T2W T11 |              | Katoni P et al.             |

| Osteosarcoma, low grade central | 42f, sag T1W L5 |                  | Asdi ARB et al.             |
| Osteosarcoma, secondary | 72m, axial CT T12 |                  | Softa CM et al.             |

#### osteoclastic giant cell-rich tumors

| Tumor Entity        | Patient Age/Sex | Imaging          | Source                      |
|---------------------|-----------------|------------------|-----------------------------|
| Aneurysmal bone cyst | 15m, axial T2W T1 |                  | Kish J et al.               |
| Giant cell tumor    | 21f, axial CT T6 |                  | Wang K et al.               |
| Malignant giant cell tumor | 22m, axial T2W T16 |              | Yuge Y et al.               |

| Aneurysmal bone cyst | 15m, axial T2W T1 |                  | Kish J et al.               |
| Giant cell tumor    | 21f, axial CT T6 |                  | Wang K et al.               |
| Malignant giant cell tumor | 22m, axial T2W T16 |              | Yuge Y et al.               |

Contd...
### Appendix 2: Contd...

#### notochordal tumors

| Tumor Entity | Patient Age/sex; Imaging | Source |
|--------------|--------------------------|--------|
| Benign notochordal tumor | 22m; sag T2W S1 | Tateda S et al. 85 |
| Chordoma, conventional | 64m; axial T2W T6 | Liu S et al. 86 |
| Chordoma, dedifferentiated | 41f; axial T2W S2 | Kim SC et al. 87 |
| Chordoma, poorly differentiated | 58m; cor T2W S1 | Rekhi B et al. 88 |

#### haematopoietic neoplasms of bone

| Tumor Entity | Patient Age/sex; Imaging | Source |
|--------------|--------------------------|--------|
| Non-Hodgkin lymphoma of the bone | 23m; sag T2W C7 | Smith ZA et al. 89 |
| Plasmacytoma | 64f; sag CT T5 | Röpke EF et al. 90 |
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## Appendix 3: Characteristics of primary spinal neoplasms

### Adipocytic Tumors

| Tumor Type                      | Important differential diagnosis | Infiltrating/malignant transformation/local destruction/metastasis | Peak age | Incidence | Type of surgical resection | Recurrence rate | Recurrence treatment | Risk factors | 5y OS | Protein/gene | Possible associated Tumor syndromes |
|---------------------------------|---------------------------------|---------------------------------------------------------------|----------|-----------|-----------------------------|-----------------|------------------------|-------------|-------|--------------|-----------------------------------|
| Angiolipoma                     | -                               | possible/no/no                                                | 2nd-3rd decade | ~1% of spinal tumors | A                  | <5%                | resection               | -           | NA    | PRKD2       |                                    |
| Atypical lipomatous tumour/ well-differentiated liposarcoma | -                               | possible/no/no advanced/yes in 2nd-3rd decade | 4th-5th decade | 50% of liposarcomas     | B                  | 11%                 | resection; RT or Sx + RT** | -           | 92%   | MDM2 and/or CDK4 amplification | Li Fraumeni Syndrome |
| Hibernoma                       | atypical lipomas, well-differentiated liposarcoma | no/no/no                                                       | 38       | 1% of adipocytic tumors | A                  | <5%                 | resection if symptomatic | -           | NA    | Chromosome 11q13 deletion | MEN 1 |
| Lipoblastoma, lipoma, hibernoma, liposarcoma | no/no/no                             |                                                                  | 4        | ?               | B                  | 13-46%*             | resection               | -           | NA    | PLAG1       |                                    |
| Lipoma                          | no/no/no                           |                                                                  | 36       | 14 cases        | A                  | <5%                 | resection if symptomatic | obesity | NA    | HMGA2       | PTEN hamartoma syndrome |
| Lipomatosis                     | no/no/no                           |                                                                  | 68       | 6% of patients with spinal stenosis | A                  | 5%*                 | resection if symptomatic | steroid, alcohol | NA    | -           |                                    |
| Liposarcoma, myxoid             | yes/no                           | childhood, 4th-5th decade                                      | 20%      | 20% of liposarcomas | C                  | 12-25%              | resection; RT*, CH*     | -           | 89%   | FUS-DDIT3 or rarely EWSR1-DDIT3 | - |
| Liposarcoma, pleomorphic         | yes/no                           | 7th decade                                       | <5% of liposarcomas | 5% of liposarcomas     | C                  | 45%                 | resection; CH          | -           | 57%   | -           |                                    |
| Myolipoma                       | no/no/no                           | adulthood                                        | ?        | ?                | A                  | resection if symptomatic | resection | - | NA    | HMGA2       |                                    |
| Spindle cell lipoma             | Liposarcoma                       | possible/no/no                                                | 45-60    | ?                | A                  | <5%                 | resection               | -           | NA    | Chromosome 13 and/or 16 deletion | - |

### Fibroblastic and Myofibroblastic Tumours

| Tumor Type                      | Important differential diagnosis | Infiltrating/malignant transformation/metastasis | Peak age | Incidence | Type of surgical resection | Recurrence rate | Recurrence treatment | Risk factors | 5y OS | Protein/gene | Possible associated Tumor syndromes |
|---------------------------------|---------------------------------|-------------------------------------------------|----------|-----------|-----------------------------|-----------------|------------------------|-------------|-------|--------------|-----------------------------------|
| Desmoid-type fibromatosis       | -                               | yes/no/no                                       | 37-39    | 0.4/100000 | B or C***                  | 33%             | resection vs close observation; CH alone in FAP associated cases | trauma, pregnancy | 52%*** | CTNMB1 or APC mutations | FAP |
| Desmoplastic fibroblastoma      | -                               | yes/no/no                                       | 6th decade | ?         | A                  | <5%             | resection               | -           | NA    | t (2;11)(q31;q12) |                                    |
| Elastofibroma                   | -                               | no/no/no                                        | 7th-8th decade | 2%        | A                  | <5%             | resection if symptomatic | -           | NA    | gains of 6q25-q25 and Xq12-q22 | - |
| Fibrosarcoma, adult             | yes/yes/yes                      | 50                                              | <1% of STS | C         | 20%                | resection + CH vs neoadjuvant CH + resection* | foreign body, previous irradiation | 55% | STRN3-NTRK3 fusion | - |

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Contd...
### Appendix 3: Contd...

| Diagnosis                        | Incidence% | Type of surgery | Treatment | Risk Factors | Protein/Gene | Possible Associated Tumor Syndromes |
|----------------------------------|------------|-----------------|-----------|-------------|--------------|-------------------------------------|
| Fibrosarcoma, infantile          | -          |                 |           |             | ETV6-NTRK3 fusion |                                     |
| Inflammatory myofibroblast tumor  | -          |                 |           |             | ALK fusions (EGF, HBEGF, TGF-α) to EGFR (HER1) or EGR |                                     |
| Lipofibromatosis                 | -          |                 |           |             |             |                                     |
| Low grade fibromyxoid sarcoma    | -          |                 |           |             |             |                                     |
| Solitary fibrous tumor           | -          |                 |           |             |             |                                     |

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### Fibrohistiocytic Tumors

| Diagnosis                        | Incidence% | Type of surgery | Treatment | Risk Factors | Protein/Gene | Possible Associated Tumor Syndromes |
|----------------------------------|------------|-----------------|-----------|-------------|--------------|-------------------------------------|
| Deep benign fibrous histiocytoma | -          |                 |           |             | PRKCB or PRKCD rearrangements |                                     |

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### Smooth Muscle Tumors

| Diagnosis                        | Incidence% | Type of surgery | Treatment | Risk Factors | Protein/Gene | Possible Associated Tumor Syndromes |
|----------------------------------|------------|-----------------|-----------|-------------|--------------|-------------------------------------|
| EBV associated smooth muscle tumor | -          |                 |           |             |              |                                     |
| Leiomyoma                        | -          |                 |           |             |              |                                     |
| Leiomyosarcoma                    | -          |                 |           |             |              |                                     |

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### Pericytic Tumors

| Diagnosis                        | Incidence% | Type of surgery | Treatment | Risk Factors | Protein/Gene | Possible Associated Tumor Syndromes |
|----------------------------------|------------|-----------------|-----------|-------------|--------------|-------------------------------------|
| Myopericytoma                    | -          |                 |           |             |              |                                     |
### Skeletal Muscle Tumors

| Important differential diagnosis | Infiltrating/malignant transformation/metastasis | Peak age | Incidence | Type of surgical resection | Recurrence rate | Treatment | Risk factors | 5y OS | Protein/gene | Possible associated Tumor syndromes |
|----------------------------------|-----------------------------------------------|----------|-----------|---------------------------|----------------|-----------|-------------|-------|-------------|-------------------------------------|
| Ectomesenchymoma<sup>1,32</sup>  | - yes/NA/yes                                   | 0.6      | 50 cases  | C                         | 50%            | resection, CH/RT | -          | 83    | Hras mutations complex | -                        |
| Rhabdomyosarcoma, pleomorphic<sup>1,33,34</sup> | - yes/NA/yes                                   | 72       | 3.5% of STS (all rhabdoses) | C                         | 54%            | resection, CH/RT | -          | 26    | -                        | -                        |
| Rhabdomyosarcoma, alveolar<sup>1,35</sup> | - yes/NA/yes                                   | 10-24    | 25% of rhabdoses | C                         | 63%            | resection, CH/RT | -          | 27    | PAX3-FOXO1 or a PAX7-FOXO1 fusion gene complex | -                        |
| Rhabdomyosarcoma, embryonal<sup>1,36</sup> | - yes/NA/yes                                   | 2-20     | 0.45/100000 | C                         | 28%            | resection, CH/RT | -          | 58    | Castello syndrome, NF 1, Noonan syndrome, Li–Fraumeni syndrome | -                        |
| Rhabdomyosarcoma, spindle cell<sup>1,37</sup> | - yes/NA/yes                                   | 34       | 3-10% of rhabdoses | C                         | 33%            | resection, CH/RT | -          | 18    | VGLL2/NCOA2 or TFCP2/NCOA2 rearrangements | -                        |

### Vascular Tumors

| Important differential diagnosis | Infiltrating/malignant transformation/metastasis | Peak age | Incidence | Type of surgical resection | Recurrence rate | Treatment | Risk factors | 5y OS | Protein/gene | Possible associated Tumor syndromes |
|----------------------------------|-----------------------------------------------|----------|-----------|---------------------------|----------------|-----------|-------------|-------|-------------|-------------------------------------|
| Angiosarcoma<sup>1,38</sup>     | - yes/no/rarely                               | 7<sup>th</sup> decade | 2% of STS | C                         | 20%            | resection + RT/CH/TT | radiation, lymph-edema, forie<br> bodies, AV fistulas, hemangiom<br> as radiation, lymph-edema, | 30-40% | MYC gene amplifications | NF, Maffucci syndrome |
| Hemangioblastoma<sup>1,39</sup>  | - yes/no/rarely                               | 43       | 26 cases  | B                         | 50%            | resection         |                         | 62-83% | PTBP1-MAML2 and EPC1-PCH2 gene fusion | -                        |
| Hemangioblastoma<sup>1,40</sup>  | - yes/no/rarely                               | adulthood | 0.1/100000 | C                         | ?             | resection + CH/RT |                         | 59%   | WWTR1-CAMTA1 gene fusion | -                        |
| Hemangioblastoma<sup>1,41</sup>  | - yes/no/rarely                               | 1        | 0.9/100000 | B                         | <5%            | vincristine, steroid, sirolimus vs resection   |                         | -     | GNA14 mutations | -                        |
| Hemangioblastoma<sup>1,42</sup>  | - yes/no/rarely                               | 30       | ?         | A                         | 60%            | resection         |                         | -     | SERPINE1 to FOSB or ACTB-FOSB fusion | -                        |
| Hemangioblastoma, retiform<sup>1</sup> | - no/no/rarely                               | childhood | 40 cases  | B or C                    | 60%            | resection         | radiation, lymph-edema, lymph-angioma trauma | -     | -                        | -                        |
| Hemangioma, epitheloid<sup>1,43</sup> | - rarely/no/rarely                           | 4<sup>th</sup> decade | ?       | A or B                    | 33%            | resection         | -                        | -     | FOS or FOSB gene | -                        |
| Hemangioma<sup>1,44</sup>       | - no/no/no                                    | 51       | 2%        | A or B                    | 3-50%          | if symptomatic: Embo + resection { +/- kypho, +/- adjuvant RT} vs Rt alone, vs | -     | -                        | -                        |
| Kaposi sarcoma<sup>1,45,46</sup> | - yes/no/yes                                  | ?        | 400-600/100000 | -                         | -             | immunoreconstitution, CH resection | immunosuppression | 74%   | -                        | -                        |
| Lymphangioma<sup>1</sup>        | - no/no/no                                    | congenital | ? | A or B | 20% | resection | - | PIK3CA mutations | Tumor syndrome | - | - |
| Important differential diagnosis | Infiltrating/malignant transformation/metastasis | Peak age | Incidence | Type of surgical resection | Recurrence rate | Treatment | Risk factors | 5y OS | Protein/gene | Possible associated Tumor syndromes |
|----------------------------------|-------------------------------------------------|----------|-----------|---------------------------|----------------|-----------|-------------|-------|-------------|-----------------------------------|
| Ectopic meningioma\(^{147,48}\) - | occasionally/no/occasionally/6% | 2\(^{nd}\) + 5\(^{th}\) decade | 1% of meningiomas | A | 26% | resection if high grade, symptomatic or progressive transformation/metastasis | - | 92% (3y) | - | Cowden, Li-Fraumeni, Von Hippel-Lindau syndrome, NF1, NF2, schwannomatosis |
| Hybrid nerve sheath tumor\(^{1,49}\) - | no/no/no | 38 | ? | A | < 5% | resection if high grade, symptomatic or progressive transformation/metastasis | - | - | - | |
| Malignant peripheral nerve sheath tumor\(^{1,50,51}\) - | yes/NA/yes | 20-50 years | 2-5% of STS | C | 56% | Resection + CH/TT | benign nerve sheath tumor, radiation | 53% complex | NF1 |
| Neurofibroma\(^{52,53}\) rarely/in NF1/rarely/no | 45 | 0.3/1000000 | A or B | 17% | resection if symptomatic | - | - | - | inactivation NF1 gene |
| \(\) Uncertain Differentiation | | | | | | | | | | |
| Clear cell sarcoma\(^{1,55,56}\) - | yes/no/yes | 3-4\(^{th}\) decade | ? | C | 40% | resection + RT/CH | - | 60% | reciprocal translocation t(12;22)(q13;q12) |
| Desmoplastic small round cell tumor\(^{1,51,57}\) - | yes/no/yes | 19 | 0.1/1000000 | C | 89% | neo CH + resection + CH/RT vs TT | - | 15% | EWSR1-WTI gene fusion |
| Epithelioid sarcoma\(^{1,62}\) - | yes/no/yes | 39 | <1% STS | C | 25% | resection + RT/CH | trauma | 54% | loss of SMARCB1 expression |
| Extrareal rhabdoid tumor\(^{1,64,65}\) - | yes/no/yes | 13 | <1% of childhood STS | C | 22% | resection + RT/CH | - | 15% | SMARCB1 gene alterations |
| Extraskeletal myxoid chondrosarcoma\(^{1,66}\) - | yes/no/yes | 50 | <1% STS | C | 37% | resection + RT/TT | - | 82-90% | NRR4AS gene rearrangement |
| Intramuscular myxoma\(^{1}\) - | yes/no/no | 40-70 years | ? | A | <5% | resection | fibrous dysplasia | - | GNAS mutation |
| Myoepithelioma\(^{1,67}\) - | possible/no/possible | 40 years | ? | B | 20-50% | resection | - | 90% | EWSR1 gene rearrangements |
| NTRK-rearranged spindle cell neoplasm\(^{1,68,69}\) - | yes/no/yes | 1-2\(^{nd}\) decade | 1% of STS | C | 11-44% | resection + CH/TT | - | ? | NTRK-rearrangements |
| Ossifying fibromyxoid tumor\(^{1,70}\) - | yes/no/possible | 58 years | ? | B | 0-60% | resection | - | 94% | PHF1 gene fusion |
| Pecoma\(^{1,71}\) - | yes/no/yes | 45 | 234 cases | C | 0-70% | neo CH + resection + CH/RT vs TT | - | 45% | LOH TSC2 locus |
| Phosphaturic mesenchymal tumour\(^{1,72}\) - | no/yes/possible | 53 years | < 0.01% of all STS | B | 0-13% | resection | - | 100% | \(\alpha\)-Klotho upregulation |
| Synovial sarcoma\(^{1,73}\) - | yes/no/yes | 3-4\(^{th}\) decade | 0.08/1000000 | C | 42% | Resection + RT | radiotherapy | 75-83% | SS18-SSX1/2/4 fusion gene |

Contd...
### Undifferentiated Small Round Cell Tumors

| Chondrogenic Tumors | Important differential diagnosis | Infiltrating/malignant transformation/metastasis | Peak age | Incidence | Type of surgical resection | Recurrence rate | Treatment | Risk factors | 5y OS | Protein/gene | Possible associated Tumor syndroms |
|---------------------|---------------------------------|-----------------------------------------------|---------|-----------|---------------------------|----------------|----------|-------------|------|-------------|----------------------------------|
| Ewing Sarcoma<sup>16,17</sup> | yes/no/yes                      | 16                                            | 0.3/100000 | -                     | 50% chemotherapy             | -               | -        | -           | 39-69% | FET-ETS fusion genes | -                               |
| Chondroblastoma<sup>1</sup> | chondroblastoma-like osteosarcoma | no/no/benign lung mets                         | 2-3rd decade | <1% of bone tumors | A                          | 10-18%          | resection vs RFA     | -               | NA         | H3.3 alterations            | -                               |
| Chondromyxoid fibroma<sup>2,3</sup> | -                               | no/very rare/no                                | 2-3rd decade | ?                     | A or B                     | 15%             | resection           | -               | NA         | GRM1 gene recombination       | -                               |
| Chondrosarcoma, clear cell<sup>3</sup> | renal cell carcinoma, chondroblastoma, osteosarcoma | yes/rare/rare                                  | 3-4th decade | 2% of chondrosarcomas | C                          | 86%             | resection           | -               | 85%        | -                         | -                               |
| Chondrosarcoma, mesenchymal<sup>4,5</sup> | -                               | yes/no/yes                                     | 26       | 2-9% of chondrosarcomas | C                          | 55%             | resection + CH      | -               | 60%        | HEY1-NCOA2 rearrangement       | -                               |
| Chondrosarcoma, central grade II, III<sup>6</sup> | chondroblastic osteosarcoma | possible/yes/no                                | 3-6th decade | 0.18/100000 | C                          | 19-26%          | resection           | -               | 31-74%     | WNT/β-catenin signalling loss  | -                               |
| Chondrosarcoma, dedifferentiated<sup>7,8</sup> | -                               | yes/no/yes                                     | 59       | 11% of chondrosarcomas | C                          | 50%             | resection + CH      | -               | 7-24%      | IDH1 or IDH2 mutation          | -                               |
| Enchondroma<sup>9</sup> | secondary peripheral atypical cartilaginous tumour/chondrosarcoma | no/very rare/no/                              | 36       | 2%                     | A                          | <5%             | resection if symptomatic | -               | NA         | IDH1 or IDH2 mutations         | Chondromatosis Enchondromatosis |
| Osteochondroma<sup>10</sup> | secondary peripheral atypical cartilaginous tumour/chondrosarcoma | no/possible/no                                | 18       | 0.9/100000 | A                          | <5%             | resection radiation  | NA             | inactivation EXT1 or EXT2 gene | multiple osteochondromas syndrome Carney complex |
| Osteochondromyxoma<sup>11,12</sup> | -                               | possible/no/possible/no                        | 1        | ?                     | A or B                     | ?               | resection           | -               | NA         | PRKAR1A gene mutation          | -                               |
| Secondary peripheral atypical cartilaginous tumour/chondrosarcoma grade II<sup>13</sup> | -                               | yes/yes/yes/                                   | 49       | 0.66/100000 | A or B                     | 11%             | resection vs RFA    | -               | 87-99%     | IDH1 or IDH2 mutation          | Enchondromatosis                |
| Secondary peripheral atypical cartilaginous tumour/chondrosarcoma grade II, III<sup>14</sup> | periosteal osteosarcoma       | yes/no/rarely                                  | 3-4th decade | 5% of osteochondromas | B or C                     | 16%             | resection           | -               | 98%        | -                         | -                               |
| Synovial chondromatosis<sup>15</sup> | yes/possible/possible           | 3-5th decade                                  | 0.18/100000 | B                     | 20%             | resection           | -               | NA         | FN1-ACVR2A and ACVR2A-FN1 fusions | -                               |
### Osteogenic Tumors

|                       | Important differential diagnosis | Infiltrating/malignant transformation/metastasis | Peak age | Incidence | Type of surgical resection | Recurrence rate | Treatment | Risk factors | 5y OS | Protein/gene | Possible associated Tumor syndroms |
|-----------------------|----------------------------------|-----------------------------------------------|----------|-----------|----------------------------|-----------------|-----------|--------------|-------|--------------|----------------------------------|
| Osteoblastoma\(^1\)   | -                                | yes/rare/no                                  | 2-3\(^{rd}\) decade | 1% of bone tumors | B                           | 23%             | resection | -            | NA    | FOS rearrangements |                                    |
| Osteoid osteoma\(^1\)| -                                | no/no/no                                     | 24       | 10% of all bone tumors | A                           | <5%             | resection if symptomatic vs RFA (lesion might disappear) | -            | NA    | FOS rearrangements |                                    |
| Osteoma\(^1\)         | -                                | no/no/no                                      | 37       | 6.4%      | A                           | <5%             | resection if symptomatic | -            | NA    | LEMD3 gene | Gardner Syndrome, Osteopoikilosis |
| Osteosarcoma, (chondroblastic, fibroblastic, osteoblastic, telangiectactic)\(^1\) | -                                | yes/no/yes                                    | 10-14 years and 65 years | 0.46/100000 | C                           | 30-50%         | neoadjuvant CH + resection + RT/CH | -            | 68%  | Gans 6p, 8q | liFraumeni, Werner, Rothmund-Thomson, Bloom syndrome |
| Osteosarcoma, low grade central\(^1\) | fibrosarcoma                     | yes/rare/rare                                 | 3\(^{rd}\) decade | 1.2% of osteosarcomas | B                           | 7%             | resection | -            | 90%   | Amplification of 12q13-q15 |                                    |
| Osteosarcoma, secondary | -                                | yes/no/yes                                    | 6-7\(^{th}\) decade | 1-7% in Paget disease | C                           | ?               | neoadjuvant CH + resection + RT/CH | Paget disease, radiation, Caisson disease, Sickle cell disease, implants, chronic osteomyelitis | 10-32% | ?              | Rothmund-Thomson syndrome |

### Osteoclastic giant cell-rich Tumors

|                       | Important differential diagnosis | Infiltrating/malignant transformation/metastasis | Peak age | Incidence | Type of surgical resection | Recurrence rate | Treatment | Risk factors | 5y OS | Protein/gene | Possible associated Tumor syndroms |
|-----------------------|----------------------------------|-----------------------------------------------|----------|-----------|----------------------------|-----------------|-----------|--------------|-------|--------------|----------------------------------|
| Aneurysmal bone cyst\(^1\) | -                               | no/no/no                                      | 1-2\(^{nd}\) decade | 0.015/100000 | A or B                      | 20-70%         | resection vs denosumab vs embo vs RT | -            | NA    | USP6 rearrangements |                                    |
| Giant cell tumor\(^1\)  | yes/rare/rare                   | yes/rare/rare                                 | 31       | 0.15/100000 | B                           | 15-50%         | resection vs denosumab vs embo vs RT | Paget disease, radiation | 87%*** | H3.3 mutation | Gorlin-Goltz syndrome, Jaffe-Campanacci syndrome |
| Non-ossifying fibroma\(^2\) | no/no/no                        | 2\(^{nd}\) decade                             | ?        | A         | <5%                         | resection if symptomatic | Paget disease, radiation | -            | NA    | KRAS and FGFR1 mutations | Jaffe-Campanacci syndrome, NF1, KRAS |

Contd...
### Notochordal Tumors

| Important differential diagnosis | Infiltrating/malignant transformation/metastasis | Peak age | Incidence | Type of surgical resection | Recurrence rate | Treatment | Risk factors | 5y OS | Protein/gene | Possible associated Tumor syndroms |
|----------------------------------|-----------------------------------------------|----------|-----------|----------------------------|-----------------|-----------|-------------|-------|-------------|-----------------------------------|
| Benign notochordal tumor<sup>1,2</sup> | no/rarely/no | 58 | 1.7% | A | <5% | resection if symptomatic | - | NA | expression of brachyury | - |
| Chordoma, conventional, dedifferentiated, poorly differentiated<sup>3</sup> | yes/yes/yes | 6-8<sup>th</sup> decade | 0.08/100000 | C | 35% | resection + RT/TT | - | 68% | expression of brachyury | - |

### Haematopoietic Neoplasms of Bone

| Important differential diagnosis | Infiltrating/malignant transformation/metastasis | Peak age | Incidence | Type of surgical resection | Recurrence rate | Treatment | Risk factors | 5y OS | Protein/gene | Possible associated Tumor syndroms |
|----------------------------------|-----------------------------------------------|----------|-----------|----------------------------|-----------------|-----------|-------------|-------|-------------|-----------------------------------|
| Plasmacytoma WHO<sup>4</sup> | yes/yes/yes | 55-60 | 6.8/100000 | - | 22% | RT | - | 57% | - | - |
| Non-Hodgkin lymphoma of the bone<sup>5</sup> | yes/yes/yes | 50-60 | 7% of bone tumors | - | 10% | CH, RT | HIV | 75% | Immunglobulin rearrangements | - |

<sup>1</sup> In high risk/systemic/recurrence patients,  
<sup>2</sup> Depending on mutation status: CTNNB1 p.Ser45Phe,  
<sup>3</sup> 20 year survival rate in patients with FAP associated lesions,  
<sup>4</sup> Patients with malignant variant,  
<sup>5</sup> Mean survival time in aggressive variant (EIMS),  
<sup>6</sup> At 46 month,  
<sup>7</sup> Very rare malignant variant, among immunosupressed, can arise secondarily in previous enchondroma, on the surface of osteochondromas. CH: Chemotherapy; TT: Targeted therapy
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