The most common primary malignant tumors of bone after osteosarcoma is chondrosarcoma (1;2). The highest incidence is in the fourth decade of life (2). In addition to bone sarcomas several benign bone neoplasms are known, from some of which little etiology and epidemiological information is available, because many of them are asymptomatic and therefore diagnosed only incidentally. Benign bone tumors are more frequent than bone sarcomas and may in case of cartilaginous tumors act as precursor of their malignant counterpart. The preoperative assessment of cartilaginous lesions is based upon careful radiological documentation, clinical presentation and histopathologic evaluation of a biopsy specimen (3;4). In general practice, the primary differential diagnosis will be made based upon radiology and clinico-demographic data (2). Usually plain radiographs provide substantial information. Within the diagnostic field of cartilaginous tumours additional progress has been made using (dynamic) MRI, especially for the distinction between benign and low-grade malignant cartilaginous lesions. Regarding the differential diagnosis of osteochondroma versus low-grade peripheral chondrosarcoma the thickness and staining characteristics on (dynamic) MR of the cartilaginous cap provide a rather reliable assessment of the likelihood of malignancy (5). For the distinction between enchondroma and central grade I chondrosarcoma, clinical symptoms and radiographic features are of help, but both lack specificity (Sanerkin, 1980 3587; Schiller, 1985 3588; Geirnaerdt, 1997 4214). Localisation in the axial skeleton and size greater than 5 cm have been shown to be a reliable predictor for malignancy (6). Previous studies demonstrate that conventional radiography is not reliable in this differential diagnosis, amongst others hampered by the absence of objective and reproducible criteria (6). Recent studies however using dynamic contrast enhanced MR-imaging show increased sensitivity (5;7;8). However, even by means of dynamic contrast enhanced MR-imaging evaluated by an experienced bone tumor radiologist, an absolute distinction between malignant and benign can not be made on radiological grounds alone (9;10). Therefore, when the radiological assessment of a benign versus a low-grade malignant central cartilaginous tumor remains in doubt, a biopsy has to be taken and assessed by an experienced pathologist, who evaluates the biopsy using all available radiological information and applying defined histopathologic criteria.

Cartilaginous bone tumors are characterized by production of a characteristic chondroid matrix. As such they comprise a heterogeneous group of lesions with diverse morphological features and clinical behavior. Cartilaginous tumors are classified based on their histological features and the location within the bone and can be clinically divided according to their
behavior into benign and malignant tumors (3;4;11). Within the malignant group, here only
central chondrosarcomas will be considered. The distinction between peripheral and
conventional chondrosarcomas based upon clinicoradiological as well as tumor genetic differences
has been a major finding contributing to the tumorigenesis of cartilaginous tumors (12). Based
upon the genetic and protein studies performed thus far a multi-step genetic model for
peripheral cartilaginous tumorigenesis was introduced (4).

Peripheral cartilaginous tumors, as the name implies, are located at the periphery of bone.
Most are benign tumors (osteochondroma and periosteal chondroma), but also malignant
tumors can occur (secondary peripheral chondrosarcoma and periosteal chondrosarcoma).

The majority (90%) of conventional chondrosarcoma however arise centrally in the medullar
cavity of bone, either as a primary lesion or secondary to a pre-existing benign enchondroma
(13). Approximately 75% of primary central chondrosarcoma arise in the pelvis, scapula and
upper part of the femur and humerus. Histologically central chondrosarcomas are similar to
secondary peripheral chondrosarcoma and are graded both into three grades of malignancy
using the same criteria (14). Enchondroma is the benign counterpart of central
chondrosarcoma (15). Most enchondromas occur in the medullar cavity of small tubular bones
of the hand and feet, but also the long tubular bones are regularly affected. Unlike
osteochondroma, chondrocytes in enchondroma do not display any longitudinal organization.
Chondrosarcoma of bone is distinguished from chondroma by its higher cellularity, nuclear
pleomorphism, its plump cells with large or double nuclei, while mitoses are infrequent. The
distinction between benign and low-grade tumors is however considered difficult both
radiological (6) and histological (16). Consequently, the diagnosis is usually based on a
combination of clinical, radiological and histologic findings. At the histologic level, the
distinction between enchondroma and low grade central chondrosarcoma is mainly based on a
variety of growth patterns, in which amongst others the presence of entrapment and the absence
of encasement favor malignancy {Schiller, 1985 3588 /id; Mirra, 1985 754 /id; Brien, 1997
4394}. Central chondrosarcomas are genetically characterized by peridiploidy with limited
LOH, frequently targeted at the 9p12-22 region, whereas numerical abnormalities involve
chromosome 22 (trisomy), which is not seen so far in peripheral chondrosarcomas (17).
Comparative Genomic Hybridization studies point to deletions of chromosome 9p as well
(18). Array CGH analysis points to RPS6 and CDK4 as candidate genes (19). P 16 is a
potential targeted gene, however mutations are not documented so far in chondrosarcomas.
P16 was shown to be methylated in a substantial number of cases (20;21). Centrał
chondrosarcomas and enchondromas have been found to occur in high association with the
development of breast cancer at early age, not associated with known breast cancer
syndromes such as BRCA1, BRCA2, Li-Fraumeni’s syndrome etc (22;23). This association in
occurrence of these two tumors has not led to the identification of a responsible gene so far.

Enchondromas occur both solitary or in the context of several rare developmental disorders
that are classified as enchondromatosis and include Ollier disease and Maffucci syndrome (24-
26). The malignant transformation of solitary enchondroma is rare (<1%), whereas in
enchondromatosis the risk of malignant transformation can be as high as 15-30%. As yet the
causative gene defect for this syndrome has not been undisputedly settled (27;28).

Osteochondroma is the most common benign bone tumor arising at the periphery of long
bones preformed by endochondral ossification (29;30). Osteochondroma (osteoartilaginous
exostosis as it was sometimes called in the past) is defined as a bony projection covered by a
cartilaginous cap on the external surface of bone (31). The stalk consists of medullar and
cortical bone and projects from the surface of bone. They may have either a broad base (sessile) or a narrow base (pedunculated). The medulla within the lesion is in direct connection with the medulla from the long bone it originates from. The lesion is covered by periost. The stratified zones of chondrocytes that are normally found in the growth plate can sometimes still be recognized in osteochondroma. Osteochondromas develop in the first decade of life and cease to grow at puberty when the skeleton matures. Most of the lesions occur in a solitary (non-hereditary) setting; however 15% of the patients have multiple lesions, usually in the context of the hereditary syndrome known as Multiple Osteochondromas. In a small percentage of osteochondromas, the cartilage cap transforms into malignancy: secondary peripheral chondrosarcoma. For solitary osteochondroma malignant transformation is estimated to occur in less than 1%, whereas for hereditary lesions the risk of malignant transformation is estimated at 0.5-3% (29). Secondary peripheral chondrosarcomas arise thus in the cartilage cap of osteochondromas. They constitute approximately 17% of all conventional chondrosarcomas (13).

Like all conventional chondrosarcomas, secondary peripheral chondrosarcomas are graded based upon several histological features (14). Histological grading is still the most important predictor of clinical behavior and prognosis for chondrosarcoma. Grade I chondrosarcomas rarely metastasize, but the risk increases to 10-33% and 70% for grade II and grade III lesions, respectively (14;32).

Secondary peripheral chondrosarcomas are usually low-grade tumors and in daily practice, it can be difficult to distinguish these lesions from osteochondroma both radiologically (7) and histologically. So far, the diagnosis is based on a combination of clinical, radiological and histological findings. Though secondary peripheral chondrosarcomas are usually low-grade, they can recur with a higher histological grade, suggesting progression in malignancy with time (14;32).

Multiple Osteochondromas (MO) is an autosomal dominant disorder, characterized by the presence of multiple osteochondromas of which the number can vary significantly between and within families (33;34). It is a heterogeneous disorder for which two causative genes have been identified, Exostosin-1 (EXT1) located at 8q24.11-q24.13 and Exostosin-2 (EXT2) located at 11p11-p12 (35-37). Most germ-line mutations are non-sense, frame shift or splice-site mutations and cause loss of EXT protein function (38;39). Loss of the remaining wild type allele of EXT1 has been demonstrated in osteochondroma (40), proving that EXT1 acts as a classical tumor suppressor gene in osteochondroma formation in Multiple Osteochondromas patients. In solitary osteochondromas somatic EXT1 mutations are extremely rare (41-43). However, loss of heterozygosity (LOH) and clonal rearrangement of 8q24 in non-hereditary osteochondroma are frequently found (40;44;45). No somatic EXT2 mutations have been reported in solitary osteochondroma and LOH at the EXT2 locus has been shown only once (45). In the endoplasmatic reticulum EXT1 forms a hetero-oligomeric protein complex with EXT2, which after formation transfers to the Golgi apparatus where it is involved in the heparan sulphate proteoglycan (HSPG) biosynthesis (46). All EXT family members are involved in the attachment and polymerization of heparan sulphate (HS) chains to HSPG core proteins (47). HSPGs are large macromolecules present at the membrane or residing in the extracellular matrix and are involved in several growth signaling pathways, anchorage of cells to the extracellular matrix and sequestering of growth factors (48). HSPGs are important for proper growth signaling in the growth plate. In both murine and chick growth plate, syndecan-2 and syndecan-3 were shown to be involved in signaling pathways in proliferating chondrocytes, like Indian Hedgehog (IHH)/parathyroid hormone-like hormone (PTHLH) signaling and fibroblast growth factor (FGF) signaling (49-52). Hecht and colleagues were able to demonstrate greatly diminished protein levels of EXT1 in cultured osteochondroma...
chondrocytes, which was often accompanied by loss of EXT2 protein expression (42). This study was followed by two publications in which they were able to identify complete loss of heparan sulphate in osteochondroma as well as diminished and abnormal distribution of perlecan (41;53). However, no second mutational event to inactivate the remaining wild type allele could be detected. It was therefore concluded that loss of one copy of either EXT1 or EXT2 disables the function of EXT1/2 complex sufficient to induce osteochondroma formation. This conflicts with Knudson’s two-hit model for the EXT1 gene demonstrated in osteochondromas from Multiple Osteochondromas patients (40). Array-CGH analysis using a chromosome 8q specific BAC-array and subsequent MLPA analysis demonstrated the occurrence of two distinct (simultaneous or consecutive) genomic deletions involving both alleles of EXT1 at chromosome 8 (54). Both events covered the EXT1 locus, resulting in (partial) homozygous deletion of the EXT1 gene. These results clearly demonstrate that in solitary osteochondroma there is biallelic inactivation of EXT1, which is one of the hallmarks of a classical tumor suppressor gene (54). IHH belongs to the hedgehog (HH) protein family, which contains morphogens that play a crucial role during embryonic and post-embryonic development. In osteochondroma, a different effect of possible disrupted HSPG synthesis due to loss of EXT1 gene function was observed. All chondrocytes in the cartilage cap of hereditary osteochondromas expressed IHH (55), in contrast to the expression restricted to the transition zone as normally seen in normal growth plate (56). Despite the presence of IHH in osteochondroma, it was previously demonstrated that PTHLH signaling downstream of IHH is absent (57), suggesting that the IHH/PTHLH feedback loop is disrupted in osteochondroma. Up regulation of PTHLH and BCL2 characterized malignant transformation towards secondary peripheral chondrosarcoma (57;58). However for central chondrosarcomas, up regulation of BCL2 was only seen in high-grade tumors (57;59).

Three groups investigated the protein expression of PTHLH in cartilaginous tumors (60-62), all showing that chondrosarcomas expressed PTHLH, which increased with increasing histological grade. Amling et al. demonstrated that only high-grade chondrosarcomas expressed BCL2 protein (60), which is in concordance with the results found in the central chondrosarcomas (57;59), but not with the results of peripheral chondrosarcoma (57). Recently, active HH signaling accompanied with increased proliferation, was demonstrated in both chondrosarcoma and the benign cartilaginous tumors enchondroma and chondroblastoma (63). In both enchondroma and chondroblastoma, but also in chondromyxoid fibroma, PTHLH signaling is known to be active (59;64;65). In the growth plate, both TGF-β and BMP signaling have been shown to interact with IHH/PTHLH signaling to regulate the onset of hypertrophic differentiation (56;66). TGF-β2 has been suggested to act as a mediator between IHH and PTHLH (67). In sum during the recent years rapidly the molecular mechanisms underlying the development of benign cartilaginous tumors and subsequent malignant transformation have been beginning to be unraveled. This might opens the identification of pathways for treatment of these tumors which till now are notorious for their resistance to conventional radiation and chemotherapy (4).

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Bullet Points

Cartilage tumors include enchondroma, osteochondroma, and chondrosarcoma which can be divided into forms central and peripheral forms based on clinical, radiographic, and genetic differences. Their evaluation depends a multidisciplinary approach including imaging studies.

Central chondrosarcomas arise in the pelvis, scapula and upper femur and humerus, sometimes in a pre-existing enchondroma. They are distinguished from enchondroma by higher cellularity, nuclear atypia, and binucleate forms and are characterized genetically by peridiploidy, limited LOH frequently of 9p12-22, and numerical abnormalities of chromosome 22. Deletions of 9p may correspond to RPS6 and CDK4 as likely candidate genes. Histologic grading is an important predictor of behavior.

Enchondroma may occur singly or multiply (enchondromatosis, Ollier disease, Mafucci syndrome). Malignant transformation is rare (<1%) in solitary enchondromas but high in syndromic forms (15-30%)

Osteochondromas arise at the periphery of long bones formed by endochondral ossification, and consist of a bony projection covered by a cartilage cap. The incidence of malignant transformation is low unless they occur multiply. Multiple osteochondromas is an autosomal dominant disorder for which 2 causative genes, exostosin 1 and exostosin 2, which encode proteins important for heparin sulphate proteoglycan biosynthesis have been identified.