Pathology of primary malignant bone and cartilage tumours

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Received: 8 June 2006 / Accepted: 14 June 2006 / Published online: 30 August 2006
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Abstract Bone- and cartilage-forming tumours (osteosarcomas and chondrosarcomas) are rare malignant neoplasms. These tumours are clinically aggressive and often need extensive local and/or systemic treatment. Whereas no other treatment but surgery is currently available for chondrosarcomas, osteosarcomas show an approximately 50–80% response rate to adjuvant chemotherapy. Surgical removal of these tumours is currently mostly performed with limb salvage, but amputation may be required in some cases. In addition, the tumours have a risk of local recurrences adversely affecting the prognosis compared to the primary tumour. In this report we will mainly focus on two of the most prevalent malignant bone tumours, conventional osteosarcoma and conventional chondrosarcoma, and use these to illustrate the problems with the diagnosis of bone sarcomas in general.

Résumé Les tumeurs malignes d'origine osseuse ou cartilagineuse (ostéosarcomes et chondrosarcomes) sont rares. Elles sont cliniquement agressives et nécessitent souvent un traitement extensif, local ou général. Tandis qu'aucun autre traitement que la chirurgie est possible pour le chondrosarcome, l'ostéosarcome a un taux de réponse de 50 à 80% à la chimiothérapie adjuvante. L'ablation chirurgicale de ces tumeurs est le plus souvent menée avec conservation du membre mais une amputation est parfois nécessaire. De plus ces tumeurs ont un risque de récurrence, avec un moins bon pronostic que la tumeur initiale. Dans ce rapport, nous considérons essentiellement les deux tumeurs les plus fréquentes—ostéosarcome et chondrosarcome conventionnels—et les utilisons pour illustrer les problèmes de diagnostic des sarcomes osseux en général.

Malignant bone tumours are rare neoplasms with an incidence of around one to two new cases per 100,000 individuals per year. Clinical features of bone tumours are often non-specific or not recognised, and as a consequence they often are not detected in the early phases. Symptoms pointing to bone tumours are pain, swelling and a general discomfort. They can also be detected through spontaneous fractures, resulting from structural alterations of the tumour-bearing bone. The most common primary malignant bone tumours are osteosarcomas, followed by chondrosarcomas and Ewing's sarcomas. Both osteosarcomas and Ewing's sarcomas have the highest incidence in younger patients up to 20 years of age, whereas chondrosarcomas are more prevalent in the second to fourth decades of life (Table 1).

Whilst chemotherapy has improved the prognosis for osteosarcoma and Ewing's sarcoma, there are still no effective agents for other primary malignant bone tumours such as chondrosarcoma, chordoma and adamantinoma. Neoadjuvant chemotherapy is used both to decrease the size of the primary tumour and allow early treatment of micro-metastatic disease. The percentage of chemotherapy-induced necrosis determined after resection of the tumour is also used as a prognostic indicator. Tumours with more than 90% necrosis have a better prognosis.

This review focuses on the two by far most prevalent primary malignant bone tumours: conventional osteosarcoma and conventional chondrosarcoma, and will briefly mention their even more rare subtypes.

Osteosarcoma

Osteosarcomas are the most frequent malignant primary bone tumours. According to the 2002 WHO classification, several histological subtypes have been distinguished, of

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Table 1 Overview of incidence and age of presentation of the most common primary bone tumours

Tumour	ICD-O code	Incidence	Peak occurrence
<i>Benign bone tumours</i>			
Osteochondroma	9210/0	45%*	<20 years
Giant cell tumour	9250/1	20%*	20–45 years
Enchondroma	9220/0	10%*	10–50 years
Osteoid osteoma	9191/0	10%*	5–25 years
Aneurysmal bone cyst	-	7%*	0–20 years
Chondromyxoid fibroma	9241/0	2%*	10–30 years
Osteoblastoma	9200/0	1%*	10–35 years
Chondroblastoma	9230/0	1%*	10–20 years
<i>Bone sarcomas</i>			
Osteosarcoma	9180/3	21%**	10–20 and 50–70 years
Conventional	9180/3		
Telangiectatic	9183/3		
Small cell	9185/3		
Low grade	9187/3		
Chondrosarcoma	9220/3	20%	30–60 years
Conventional	9180/3		
Dedifferentiated	9183/3		
Mesenchymal	9185/3		
Clear cell	9187/3		
Ewing's sarcoma	9260/3	5%**	10–30 years
Malignant fibrous histiocytoma	8830/3	5%**	>30 years
Fibrosarcoma	8810/3	2%**	35–60 years
Adamantionoma	9261/3	Extremely rare**	10–40 years

*Incidence is percentage of all benign bone tumours

**Incidence is percentage of all malignant primary bone tumours

which conventional high-grade central or intramedullary osteosarcoma is the most common (75%). This highly malignant neoplasm is characterised by osteoid production and an intramedullary location, mostly at the metaphysis of long bones (Fig. 1a). Genetically they are characterised by gross cytogenetic changes, which are complex, containing both numerical and structural changes. Often these changes result in amplification, resulting in a hyperploid genotype [10].

The tumour occurs especially in children and adolescents, and there is a male prevalence (3:2). Osteosarcoma in patients over 40 years of age is mostly secondary since it occurs after exposure to radiation, chemical agents, viruses or arises in areas of pre-existing Paget's disease of bone [14]. It should therefore be considered as a disease different from osteosarcoma in young patients with regard to histogenesis, though its clinical course is comparable.

Often extended surgery is the standard local treatment for osteosarcoma. After the introduction of adjuvant chemotherapy in the 1970s, survival has improved from 10–20% to 50–80%. However, regardless of the regimen, chemotherapy has currently reached a plateau in terms of increasing survival, because of resistance to treatment in a subset of patients. A good correlation exists with the amount of chemotherapy-induced tumour cell death, which usually is graded according to Huvos criteria [22]. In larger studies it appeared that good responders have less than 10% remnant tumour, while in poor responders more than 10% of the tumour volume remains after chemotherapy.

The aetiology of high-grade central osteosarcoma in young patients is elusive. No benign or malignant precursor lesions are known; only a history of trauma may be associated. These tumours may have arisen from osteoblasts or cells driven towards the osteoblastic lineage, compliant with their capacity to produce osteoid, alkaline phosphatase, osteocalcin, osteonin and bone sialoprotein [21]. An alternative option for the origin of osteosarcomas is the mesenchymal stem cell, the precursor of osteoblasts.

Diagnosis

The diagnosis and treatment of osteosarcoma in general, and the differential diagnosis versus other, benign matrix-producing bone lesions is based on an intense interdisciplinary cooperation, involving orthopaedic surgeons, radiologists, oncologists and pathologists.

Imaging

Conventional radiography is used for the initial detection of the primary tumour. The radiographic appearance of conventional osteosarcoma is highly variable, but the location of this tumour at the metaphyseal centre is an important feature for the differential diagnosis. Most times the tumour appears as a mixed lytic/blastic lesion with cortical destruction.

Further imaging to detect extension of the tumour in adjacent joints and its possible relationship with soft tissue components is performed with MRI or dynamic enhanced MRI (DEMRI). In addition, DEMRI is able to monitor the effect of neoadjuvant chemotherapy prior to surgery [35]. Lung metastases or skip-lesions, non-contiguous metastases in the parent bone or across adjacent joints, can best be detected by CT, but identification of metastases can also be performed by isotope bone scanning [32]. Another application of this technology is the determination of multidrug resistance (MDR) of the tumour prior to treatment, since lipophilic radiopharmaceutical agents such as ^{99m}Tc-labelled MIBI and tetrofosmin are actively eradicated from

Fig. 1 Osteosarcoma. En bloc resection specimen of a high grade conventional osteosarcoma (**a**) and histological haematoxylin/eosin section (**b**)

tumour cells by the same MDR mechanism as used for cytostatic drugs [7].

Pathology

Conventional osteosarcomas have different cell shapes that are often spindle shaped and highly anaplastic with considerable pleomorphism including epithelioid, plasmacytoid, fusiform, ovoid, small round cells, clear cells, giant cells (both mono- and multi-nucleated) and spindle cells. Most cases contain a complex mixture of two or more of these cell types. Aspiration cytology alone is not sufficient to give a diagnosis with 100% certainty, even when combined with data from X-rays and histochemical detection of alkaline phosphatase. It can, however, be used to assess the mesenchymal nature and probably malignant nature of the tumour.

Histologically, osteosarcoma is characterised by the presence of osteoid-extracellular matrix, consisting mainly of collagen I with a dense pink amorphous appearance on haematoxylin/eosin staining (Fig. 1b). The matrix (present/absent and nature) of the tumour determines the histological subtype (Table 2). The histological subtype has been described as a factor predicting survival, with chondro-

blastic osteosarcoma having a better prognosis than fibroblastic osteosarcoma [20].

In general, diagnosis and prognosis may be assisted by immunohistochemical analysis; however, for osteosarcoma no specific markers are available. Alkaline phosphatase enzyme histochemistry can be used to establish the osteoblastic nature of this tumour. This, however, requires frozen samples, which are not always available. To date reliable immunohistochemical markers that can be used on paraffin are lacking.

With regard to possible resistance to treatment, makers have been investigated, such as HER2/neu and multidrug resistance (MDR) proteins such as P-glycoprotein, MDR1 and BCRP1. However, no conclusive markers were found useful due to the use of different methodology and interpretation (for instance with HER2/neu, for which nine studies have been performed, with different immunohistochemical scoring systems, shown to be positive in five and negative in four studies [1]), or small sample sizes of non-uniformly treated patients [27].

Differential diagnosis

The differential diagnosis of osteosarcoma is wide, due to the variety of forms. Radiological findings are indispensable for the diagnosis of osteosarcoma. However, a number of pitfalls exist as osteosarcomas might be confused with for instance aneurysmal bone cysts, conventional giant cell tumour and sclerosing osteomyelitis. Since the initial diagnosis is determined on small biopsy, some distinct osteosarcoma sub-forms could be misdiagnosed as chondrosarcoma, chondroblastoma, chondromyxoid fibroma, osteoblastoma or even Ewing's sarcoma (small cell variant).

Table 2 Subtypes of conventional osteosarcoma

Type	Frequency	Matrix and cell type
Osteoblastic	50%	Osteoid, bone
Chondroblastic	25%	Chondroid mixed with non-chondroid areas
Fibroblastic	25%	Minimal matrix present, mostly spindle-shaped tumour cells

Rare subtypes of osteosarcoma

Besides the conventional high-grade osteosarcoma, other subtypes are known: the telangiectatic (4%), the small cell (1.5%) and the low-grade central osteosarcoma (1–2% of all osteosarcoma). The presence of an osteosarcoma subtype other than the conventional might be an indication that the patient is affected with a cancer syndrome [18], and the family history of the index patient should therefore be carefully investigated.

The telangiectatic osteosarcoma is characterised by the occurrence of large spaces filled with blood with or without septa. Survival indications are similar to conventional high-grade osteosarcoma. Small cell osteosarcomas have a slightly worse prognosis compared to conventional osteosarcoma and are composed of small cells with variable degrees of osteoid production. Low-grade central osteosarcoma arises from the medulla of the bone and behaves more indolently than conventional osteosarcoma. However, recurrences of these tumours after inadequate resection can exhibit a higher histological grade associated with metastasis.

Treatment

Current treatment protocols for high-grade osteosarcoma consist of intensive neoadjuvant chemotherapy regimens followed by resection of the involved bone region and further courses of chemotherapy.

Surgery

Since the 1980s limb salvage surgery, combined with chemotherapy administration prior to surgery, has replaced amputation. This treatment is aimed at the majority of cases and can be performed without increasing the risk for recurrence and metastases. The chemotherapy is aimed at decreasing the tumour mass, suppressing metastases and eradicating micro-metastases. To further prevent metastatic spread, patients are also given chemotherapy after surgery, usually at high doses.

Chemotherapy

High-grade osteosarcoma is a systemic disease. At the time of diagnosis 20% of the patients already present with distant metastases, mostly to the lungs. The effect of neoadjuvant chemotherapy is that morbidity of the surgery has been reduced [26]. In addition, metastases develop later in the course of the disease. Treatment with a single agent is usually not very effective and because of that a protocol of at least two different cytostatic drugs is needed. Doxorubicin, cis-platinum and methotrexate are the current most

effective cytostatics in osteosarcoma. In terms of increasing chemotherapy regimens, a plateau has been reached where higher doses do not improve survival.

Factors that seem to have a negative impact on prognosis are site (axial locations fare worse), larger tumour size and, as the most clinically and consistently relevant, poor response to chemotherapy and the presence of metastatic disease [3]. Patients presenting with resectable pulmonary lesions have about a 30–50% chance of survival. Those with unresectable pulmonary metastases, lesions unresponsive to chemotherapy or multiple bone lesions have a poor prognosis. Histological response to chemotherapy, characterised by the degree of necrosis detected by histological examination of multiple sections in the tumour after treatment with a chemotherapy regimen is expressed by Huvos grading, ranging from little or no effect of chemotherapy on the tissue specimen (grade I) to no histological evidence of viable tumour (grade IV) [22]. This the best prognostic factor for the outcome of disease in patients without metastases at the initial diagnosis.

Late relapse (>5 years after the initial treatment) occurs in <5% of the patients. There is a trend for it to arise more commonly in chondroblastic subtypes and in patients with a primary in the tibia and fibula; it seems to be proportionately more common in patients with an initial good response to chemotherapy. These patients thus should be considered as at risk for late relapse, for which long-term follow-up for detection of relapse is warranted [19].

Targeted drugs

Recent developments involve drugs directed at specific molecules implicated in the pathogenesis of tumours [13]. For osteosarcoma such targeted drugs have not yet been identified, but some promising results have been obtained with in vitro studies on human osteosarcoma cell lines. Imatinib mesylate (Gleevec) is a small molecule inhibitor for c-kit and PDGFR and was shown to be able to induce apoptosis in osteosarcoma cells [28].

Another potential receptor tyrosine kinase in osteosarcoma is Ezrin, which was identified by microarray analysis of an osteosarcoma mouse model, was shown to be associated with the metastatic capacity of the tumour [24] and was expressed in 44% of high-grade osteosarcomas. Currently, no small molecule inhibitors are available for Ezrin.

Chondrosarcoma

Chondrosarcomas are the second most common malignant bone tumours, characterised by the production of cartilage [2]. As in osteosarcomas, different histological subtypes can be distinguished for chondrosarcomas, with

conventional chondrosarcoma as the most common (80–90%). Within conventional chondrosarcomas, based on the location, two types are described (Fig. 2a,b): central (originating from within the medullary cavity of the bone, possibly from the pre-malignant precursor “enchondroma”) and peripheral (originating from malignant transformation within the cartilage cap of a pre-malignant osteochondroma) [2, 5]. Both central and peripheral chondrosarcomas share the same histology, but do show genetic differences, with central chondrosarcomas being (near-)diploid and peripheral chondrosarcomas showing aneuploidy with progression toward polyploidisation in high-grade tumours [6].

For chondrosarcomas treatment is confined to surgery, because these tumours are refractory to chemotherapy and radiotherapy.

Diagnosis

The diagnosis of chondrosarcoma is, as with osteosarcoma, a multidisciplinary task, involving the radiologist, orthopaedic surgeon and pathologist.

Imaging

The primary differential diagnosis is made based upon radiology and clinico-demographic data. Usually radiographs combined with histology provide substantial information, but clinical information may aid in the determination of the correct diagnosis. Additional information can be obtained from (dynamic) MRI, especially to distinguish between benign and low-grade malignant cartilaginous lesions.

Fig. 2 Chondrosarcoma. En bloc resection specimen of a conventional central chondrosarcoma (**a**), en bloc resection specimen of a conventional secondary peripheral chondrosarcoma (**b**), macro slide of a conventional central chondrosarcoma, located in the scapula, showing a lobular architecture (**c**), and histological haematoxylin/eosin section of a conventional chondrosarcoma, demonstrating double nuclei and mitotic figure (**d**)

Pathology

Grading of both central and peripheral chondrosarcomas is based on histological features, i.e., the matrix composition, presence of nuclear atypia and mitotic rate (Table 3, Fig. 2d) [12]. Grading is one of the most important prognostic predictors. Grade I chondrosarcomas are not metastatic, whereas 10–33% of grade II and approximately 70% of grade III chondrosarcomas metastasise [2].

Differential diagnosis

The differential diagnosis of chondrosarcoma usually involves the low-grade chondrosarcomas versus pre-malignant lesions. In case 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 [15]. For the distinction, clinical symptoms and

radiographic features are of help, but both lack specificity [17, 34]. Previous studies demonstrate that the differential diagnosis of enchondroma vs. central grade I chondrosarcoma using conventional radiography is not reliable, but recent studies using dynamic contrast-enhanced MR imaging show increased sensitivity [15, 16]. However, an absolute distinction between malignant and benign cannot be made on radiological grounds alone [11, 17].

At the histological level, the distinction between enchondroma and low grade central chondrosarcoma is mainly based on a variety of growth patterns. The presence of entrapment (defined as the permeation of pre-existing lamellar host bone by tumour) and the absence of encasement (defined as new shells of lamellar bone at the periphery of cartilage nodules) favour malignancy, as does the presence of mucoid matrix in >20% of the tumour [29].

In case of doubt, the best procedure would be to have a biopsy taken and assessed by an experienced pathologist, who evaluates the biopsy using all available radiological information and applying defined histopathologic criteria.

Rare subtypes of chondrosarcoma

Apart from the conventional chondrosarcomas there are other more rare histological entities, i.e., dedifferentiated (10%), mesenchymal (3–10%) and clear cell chondrosarcomas (approximately 2% of all chondrosarcomas).

Dedifferentiated chondrosarcomas are especially aggressive, with a 5-year survival of less than 10%, due to distant metastasis. The tumour is histologically characterized by two components, with a well-differentiated cartilaginous tumour adjacent to a high-grade non-cartilaginous sarcoma. Genetic analysis of both components suggests that they originate from a monoclonal origin, followed by additional genetic alterations in the different compartments [4]. Mesenchymal chondrosarcomas have a generally poor long-term prognosis with 5- and 10-year survival rates of about 50 and 25%, respectively. The tumour presents as a bimorphic lesion consisting of low-grade cartilaginous cells and hypercellular small, uniform and undifferentiated cells that resemble Ewing's sarcoma cells. Clear cell chondrosarcomas have a generally good prognosis if provided with complete surgical eradication. They are histologically characterised by bland clear cells with areas of hyaline cartilage.

Treatment

Surgery

Surgery is currently the only treatment option for chondrosarcoma. These tumours are resistant to chemotherapy and radiotherapy. Limb-saving surgery is performed when

Table 3 Grading of conventional chondrosarcoma

Grade	Histological features	10-year survival
I	Marked preponderance of small densely staining nuclei Background varies from chondroid to myxoid Calcification and bone formation are frequent Multiple nuclei within one lacuna, sometimes infrequent Occasionally small number of larger, somewhat pleomorphic nuclei	80–90%
II	Proportion of nuclei is of moderate size Low mitotic rate (<2 mitoses/10 high-power fields) Increased cellularity, specifically toward periphery of tumour lobules Paler nuclei with visible intranuclear detail Background in more cellular areas tends to be more myxoid	65–80%
III	≥2 mitoses/10 high-power fields in most active areas Increased cellularity in periphery of tumour lobules Larger nuclei in areas with increased cellularity, compared to grade II chondrosarcoma Spindle-shaped cells in high cellular areas, no appreciable chondroid/myxoid matrix	30–40%

complete removal of the tumour is feasible, as recurrences of these tumours do occur, which may present as lesions with a higher tumour grade. This poses problems especially in regions where it is difficult to remove the entire tumour, such as in the pelvic region.

Radiation and chemotherapy

Although radiation and chemotherapy are normally not used, occasionally inoperable chondrosarcomas are treated with them [33]. However, there is no evidence of the efficacy of this treatment.

Targeted drugs

Molecular approaches are used to investigate conventional chondrosarcoma tumour development and progression aiming at the identification of possible targets for therapy. Examples of these are:

- (1) Inhibition of the reported active PTHLH pathway by PTHLH antibodies was performed on chondrosarcoma cell lines, inducing differentiation and apoptosis [30].
- (2) Activity of the oestrogen signalling was demonstrated in chondrosarcoma cell lines, and the presence of oestrogen receptors in the nuclei of primary tumours points to the possibility for interference with the sex steroids [9].
- (3) Blocking of the angiogenesis, combined with chemotherapy treatment, does show promising results in xenograft chondrosarcoma models [31].
- (4) A phase II trial of pemetrexed, a multitargeted antifolate, for advanced chondrosarcomas is currently in progress. Pemetrexed inhibits the *de novo* purine synthesis, which might be effective since approximately 50% of the high-grade chondrosarcomas show loss of the region containing the gene MTAP, which plays a role in the salvage pathway of adenine and in methionine synthesis [8].

Other targets investigated are kinases [25] and proteins involved in the degradation of the chondrosarcoma matrix [23].

However, in none of the cases have results been published on the effect of the treatment on the chondrosarcomas in patients. Therefore, expert diagnosis and early acknowledgement of these tumours are as yet the most effective therapy.

References

1. Anninga JK, Van de Vijver MJ, Cleton-Jansen AM, Kristel PMP, Taminiau AHM, Nooij M, Egeler RM, Hogendoorn PCW (2004) Overexpression of the Her-2 oncogene does not play a role in high-grade osteosarcomas. *Eur J Cancer* 40:963–970
2. Bertoni F, Bacchini P, Hogendoorn PCW (2002) Chondrosarcoma. In: Fletcher CDM, Unni KK, Mertens F (eds) World Health Organisation classification of tumours. Pathology and genetics of tumours of soft tissue and bone. IARC Press, Lyon, pp 247–251
3. Bielack SS, Kempf-Bielack B, Delling G, Exner GU, Flege S, Helmke K, Kotz R, Salzer-Kuntschik M, Werner M, Winkelmann W, Zoubek A, Jurgens H, Winkler K (2002) Prognostic factors in high-grade osteosarcoma of the extremities or trunk: an analysis of 1,702 patients treated on Neoadjuvant Cooperative Osteosarcoma Study Group Protocols. *J Clin Oncol* 20:776–790
4. Bovée JVMG, Cleton-Jansen AM, Rosenberg C, Taminiau AHM, Cornelisse CJ, Hogendoorn PCW (1999) Molecular genetic characterization of both components of a dedifferentiated chondrosarcoma, with implications for its histogenesis. *J Pathol* 189:454–462
5. Bovée JVMG, Cleton-Jansen AM, Taminiau AHM, Hogendoorn PCW (2005) Emerging pathways in the development of chondrosarcoma of bone and the implications for targeted treatment. *Lancet Oncol* 6:599–607
6. Bovée JVMG, Royen Mv, Bardoel AFJ, Rosenberg C, Cornelisse CJ, Cleton-Jansen AM, Hogendoorn PCW (2000) Near-haploidy and subsequent polyploidization characterize the progression of peripheral chondrosarcoma. *Am J Pathol* 157:1587–1595
7. Burak Z, Moretti JL, Ersoy O, Sanli U, Kantar M, Tamgac F, Basdemir G (2003) ^{99m}Tc-MIBI imaging as a predictor of therapy response in osteosarcoma compared with multidrug resistance-associated protein and P-glycoprotein expression. *J Nucl Med* 44:1394–1401
8. Chow WA, Bedell V, Gaytan P, Borden E, Goldblum J, Hicks D, Slovak ML (2006) Methylthioadenosine phosphorylase gene deletions are frequently detected by fluorescence in situ hybridization in conventional chondrosarcomas. *Cancer Genet Cytogenet* 166:95–100
9. Cleton-Jansen AM, van Beerendonk HM, Baelde HJ, Bovée JVMG, Karperien M, Hogendoorn PCW (2005) Estrogen signaling is active in cartilaginous tumors: implications for antiestrogen therapy as treatment option of metastasized or irresectable chondrosarcoma. *Clin Cancer Res* 11:8028–8035
10. Cleton-Jansen AM, Buerger H, Hogendoorn PCW (2005) Central high-grade osteosarcoma of bone: diagnostic and genetic considerations. *Curr Diagn Pathol* 11:390–399
11. Dietlein M, Féaux de Lacroix W, Neufang KFR, Steinbrich W, Schmidt J (1990) Zur Problematik der Dignitätsbeurteilung von Knorpeltumoren langer Rohrenknochen aus radiologischer und pathologischer Sicht. *Rontgen Blatt* 174:180
12. Evans HL, Ayala AG, Romsdahl MM (1977) Prognostic factors in chondrosarcoma of bone. A clinicopathologic analysis with emphasis on histologic grading. *Cancer* 40:818–831
13. Fabbro D, Ruetz S, Buchdunger E, Cowan-Jacob SW, Fendrich G, Liebetanz J, Mestan J, O'Reilly T, Traxler P, Chaudhuri B, Fretz H, Zimmermann J, Meyer T, Caravatti G, Furet P, Manley PW (2002) Protein kinases as targets for anticancer agents: from inhibitors to useful drugs. *Pharmacol Ther* 93:79–98
14. Fuchs B, Pritchard DJ (2002) Etiology of osteosarcoma. *Clin Orthop Relat Res* :40–52
15. Geirnaerdt MJ, Bloem JL, Eulerink F, Hogendoorn PCW, Taminiau AHM (1993) Cartilaginous tumors: correlation of gadolinium-enhanced MR imaging and histopathologic findings. *Radiology* 186:813–817
16. Geirnaerdt MJ, Hogendoorn PCW, Bloem JL, Taminiau AHM, Van der Woude HJ (2000) Cartilaginous tumors: fast contrast-enhanced MR imaging. *Radiology* 214:539–546

17. Geirnaerdt MJA, Hermans J, Bloem JL, Kroon HM, Pope TL, Taminiau AHM, Hogendoorn PCW (1997) Usefulness of radiography in differentiating enchondroma from central grade I chondrosarcoma. *A J R* 169:1097–1104z
18. Hauben EI, Arends J, Vandenbroucke JP, van Asperen CJ, Van Marck E, Hogendoorn PC (2003) Multiple primary malignancies in osteosarcoma patients. Incidence and predictive value of osteosarcoma subtype for cancer syndromes related with osteosarcoma. *Eur J Hum Genet* 11:611–618
19. Hauben EI, Bielack S, Grimer R, Jundt G, Reichardt P, Sydes M, Taminiau AH, Hogendoorn PC (2006) Clinico-histologic parameters of osteosarcoma patients with late relapse. *Eur J Cancer* 42:460–466
20. Hauben EI, Weeden S, Pringle J, Van Marck EA, Hogendoorn PC (2002) Does the histological subtype of high-grade central osteosarcoma influence the response to treatment with chemotherapy and does it affect overall survival? A study on 570 patients of two consecutive trials of the European Osteosarcoma Intergroup. *Eur J Cancer* 38:1218–1225
21. Hogendoorn PCW, Bovée JVMG, Karperien M, Cleton-Jansen AM (2003) Skeletogenesis: genetics. In: Cooper DN (ed) *Nature encyclopedia of the human genome*. Nature Publishing Group, London, pp 306–313
22. Huvos AG (1991) *Bone tumors. Diagnosis, treatment, and prognosis*, 2nd edn. W.B. Saunders Company, Philadelphia
23. Jiang X, Dutton CM, Qi W, Block JA, Brodt P, Durko M, Scully SP (2003) Inhibition of MMP-1 expression by antisense RNA decreases invasiveness of human chondrosarcoma. *J Orthop Res* 21:1063–1070
24. Khanna C, Wan X, Bose S, Cassaday R, Olomu O, Mendoza A, Yeung C, Gorlick R, Hewitt SM, Helman LJ (2004) The membrane-cytoskeleton linker ezrin is necessary for osteosarcoma metastasis. *Nat Med* 10:182–186
25. Lagonigro MS, Tamborini E, Negri T, Staurengo S, Dagrada GP, Miselli F, Gabanti E, Greco A, Casali PG, Carbone A, Pierotti MA, Pilotti S (2006) PDGFRalpha, PDGFRbeta and KIT expression/activation in conventional chondrosarcoma. *J Pathol* 208:615–623
26. Link MP, Gebhardt MC, Meyers PA (2002) Osteosarcoma. In: Pizzo PA, Poplack DG (eds) *Principles and practice of pediatric oncology*. Lippincott, Williams & Wilkins, Philadelphia, pp 1502–1589
27. Marina N, Gebhardt M, Teot L, Gorlick R (2004) Biology and therapeutic advances for pediatric osteosarcoma. *Oncologist* 9:422–441
28. McGary EC, Weber K, Mills L, Doucet M, Lewis V, Lev DC, Fidler IJ, Bar-Eli M (2002) Inhibition of platelet-derived growth factor-mediated proliferation of osteosarcoma cells by the novel tyrosine kinase inhibitor STI571. *Clin Cancer Res* 8:3584–3591
29. Mirra JM, Gold R, Downs J, Eckardt JJ (1985) A new histologic approach to the differentiation of enchondroma and chondrosarcoma of the bones. A clinicopathologic analysis of 51 cases. *Clin Orthop* :214–237
30. Miyaji T, Nakase T, Onuma E, Sato K, Myoui A, Tomita T, Joyama S, Ariga K, Hashimoto J, Ueda T, Yoshikawa H (2003) Monoclonal antibody to parathyroid hormone-related protein induces differentiation and apoptosis of chondrosarcoma cells. *Cancer Lett* 199:147–155
31. Morioka H, Weissbach L, Vogel T, Nielsen GP, Faircloth GT, Shao L, Hornicek FJ (2003) Antiangiogenesis treatment combined with chemotherapy produces chondrosarcoma necrosis. *Clin Cancer Res* 9:1211–1217
32. O'Flanagan SJ, Stack JP, McGee HMI, Dervan P, Hurson B (1991) Imaging of intramedullary tumour spread in osteosarcoma. A comparison of techniques. *J Bone Jt Surg [Br]* 73B:998–1001
33. Rizzo M, Ghert MA, Harrelson JM, Scully SP (2001) Chondrosarcoma of bone: analysis of 108 cases and evaluation for predictors of outcome. *Clin Orthop* 391:224–233
34. Schiller AL (1985) Diagnosis of borderline cartilage lesions of bone. *Semin Diagn Pathol* 2:42–62
35. Van der Woude HJ, Bloem JL, Hogendoorn PCW (1998) Preoperative evaluation and monitoring chemotherapy in patients with high-grade osteogenic and Ewing's sarcoma: review of current imaging modalities. *Skeletal Radiol* 27:57–71