

Insights into Enchondroma, Enchondromatosis and the risk of secondary Chondrosarcoma. Review of the literature with an emphasis on the clinical behaviour, radiology, malignant transformation and the follow up

Minireview

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The Enchondroma is a common, benign, cartilage forming tumour. They usually occur as a single, asymptomatic lesion. Occasionally patients present with multiple enchondromas which is generally defined as enchondromatosis. This entity encompasses several different subtypes including Ollier disease and Maffucci syndrome (enchondromatosis associated with soft tissue haemangiomas) as the most commons. Some of them have a complicated clinical course when malignant transformation occurs. This malignant progression is a well known fact especially in enchondromatosis, but up to now there is still a lack of recommendations concerning the follow up. The aim of this article is to review the clinical and imaging features of patients with solitary enchondroma and enchondromatosis focusing on the development of secondary chondrosarcoma and the follow up.

Key words: enchondroma, enchondromatosis, Maffucci syndrome, Morbus Ollier, secondary chondrosarcoma, follow up

Enchondromas are common, benign, and usually asymptomatic hyaline cartilage forming tumors mostly located in the meta- and diaphysis, seldom in the epiphysis of the short and long tubular bones of the limbs (Figure 1) [1, 2, 3]. They usually occur as a single lesion (solitary enchondroma) and are most often found incidentally when radiographic studies are performed for other reasons [3]. In a Mayo Clinic study (en)chondromas constituted 15.6% of benign bone tumors and 4.7% of all tumors, however this do not reflect the true incidence since most of enchondromas are asymptomatic [4].

Occasionally patients present with multiple enchondromas. This is generally defined as enchondromatosis [5]. Its prevalence is estimated to be one in 100.000 [6]. The disorder manifests in early childhood without any significant gender bias [5].

Enchondromatosis encompasses several different subtypes of which Ollier disease (enchondromatosis) (Figure 2) and Maffucci syndrome (enchondromatosis associated with soft tissue haemangiomas) (Figure 3) are most common [7, 8]. Other subtypes such as metachondromatosis, genochondromatosis, spondyloenchondrodysplasia, dyspondyloenchondromatosis and cheirospondyloenchondromatosis are rare [5, 7]. Most subtypes are non-hereditary, while some are autosomal dominant or recessive [5]. Clinically, the bone deformities as well as malignant progression of enchondromas may require (multiple) surgical interventions [9-13].

The true rate of malignant transformation in solitary enchondroma is not known as most of the enchondromas are asymptomatic and go undetected. Not considering the selec-

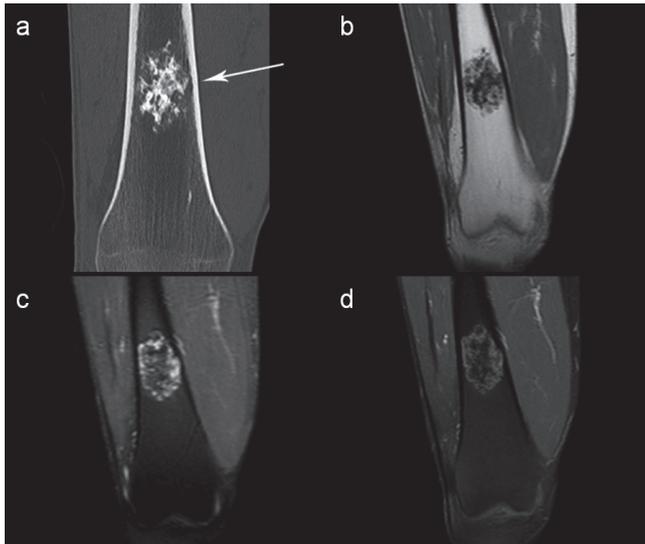


Figure 1 (a-d). 62-year-old man with incidental enchondroma in distal femoral diaphysis, initially seen on routine MRI of the right knee. **a:** Computed tomography of the right femur shows punctuate chondroid calcifications located centrally within the distal femoral diaphysis. There is minimal endosteal scalloping of the surrounding cortex (arrow). **b:** Coronal T1-weighted (TR/TE, 765/11) MR image shows circumscribed area of marrow replacement with low-intermediate signal intensity (SI). Coronal TIRM (C, TR/TE, 4,780/29) MR image demonstrates a lobulated endosteal lesion with high SI. Some intralesional areas of low SI located within the lesion are the chondroid matrix. No perilesional bone marrow edema is seen. **d:** Fat-suppressed, gadolinium-enhanced T1-weighted (TR/TE, 622/11) image shows a mild peripheral and septal “ring-and-arc” pattern of contrast enhancement of the lesion.

tion bias, the risk of developing a secondary chondrosarcoma in solitary enchondroma described to be up to 4% [10]. It is estimated that primary Chondrosarcoma is approximately two times more common than CS arising from a solitary enchondroma [14].

Of all patients diagnosed with Ollier disease, malignant transformation is believed to occur in 10–20% [14] and a recent study recorded the development of one or more chondrosarcomas in 40% of patients with Ollier diseases and Maffucci syndrome, respectively [15].

Most of the patients with malignant transformation complained of pain as the leading symptom, but there were also patients without any pain [16–18]. Furthermore, some of the patients with an enchondroma are also suffering from pain, which by itself by no means eliminates the benign enchondroma from consideration [16].

This knowledge of malignant progression of the enchondroma(tosis) motivates the desire for a definition of a follow up treatment. Until now, one does not exist.

For that a systematic review of the literature was conducted for selected articles published from January 1980 to December 2011. Searching was performed using a full-text electronic journal database (Pubmed). The terms ‘enchondroma’, ‘enchondromatosis’, ‘Maffucci syndrome’, ‘chondrosarcoma’ and

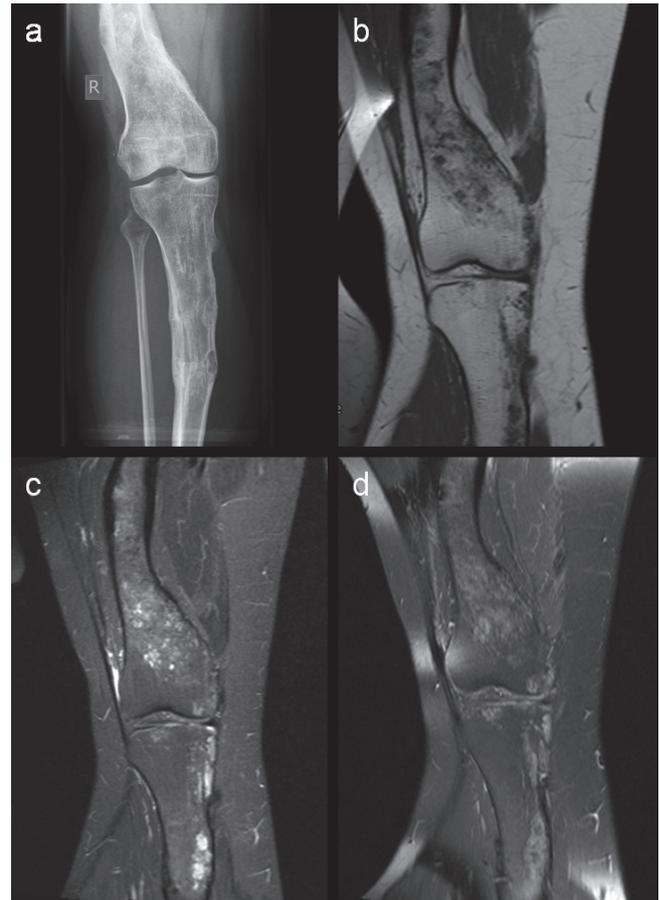


Figure 2 (a-d): 33-year-old woman suffering from Ollier disease. **a:** Plain film radiography shows a deformation of the right femur and tibia. Multiple enchondromas are localized in the right leg. There is an endosteal scalloping with thinning of the cortex, particularly in the tibial diaphysis. MRI demonstrates multiple enchondromas with low SI on coronal T1-weighted image (B, TR/TE, 700/17) and high SI on coronal TIRM images (C, TR/TE, 5,210/55). On fat-suppressed, gadolinium-enhanced T1-weighted images (D, TR/TE, 541/17) a mild contrast enhancement of the lesions can be seen. NB: Biopsies taken from the distal Femur as well as the proximal tibia showed no signs of malignancy.

‘secondary chondrosarcoma’ were MeSH (Medical Subheading) terms and the search sets were restricted to humans.

The characteristics of patients with secondary chondrosarcoma were evaluated including (a) age at onset of secondary malignancy, (b) interval between diagnosis of benign enchondroma (including enchondromatosis) and time point of malignant progression, (c) localisation of the secondary chondrosarcoma and (d) clinical symptoms. Furthermore typical radiographical characteristics of enchondroma and secondary chondrosarcoma are described.

Following these literature data a proposal for follow up of patients with solitary enchondroma and enchondromatosis of the axial skeleton and the long bones are made.

Clinical presentation. In our literature review the age of patients with secondary chondrosarcoma (sCS) arising from

a pre-existing enchondroma ranged from 31 years to 80 years. The age of patients with a sCS with an underlying enchondromatosis/Maffucci syndrome ranged from 10 to 69 years (Table 1). Summarizing, the average age of patients with an underlying enchondromatosis was about 10 – 15 years younger than these with a primary chondrosarcoma (with an average age about 52 years [1, 2, 3].

The risk of development of secondary chondrosarcoma in solitary enchondroma was up to 4.2% (Table 1). Malignant transformation in enchondromatosis is estimated to occur in 25-30% of the patients [2, 20], in a recent study up to 40% [15]. In our reported literature it was between 20% and 45.8% in pre-existing enchondromatosis, and ranged between 52% and 57.1% in patients with a Maffucci syndrome (Table 1).

Overall, the time between the initial diagnosis of a pre-existing (benign) enchondroma (including an enchondroma in enchondromatosis) and the diagnosis of malignancy was between 6 months and up to 30 years (Table 1), in a study by Schwartz et al. the interval was even up to 54 years [23]. However, these data were badly reported in most studies compared to stating the age of patients at transformation.

In most cases of malignant transformation to secondary chondrosarcoma the patient suffered from pain [4, 10, 14, 19-22, 24, 26-28]. It has been reported that in patients with low grade chondrosarcoma 43% - 60% have night pain or rest pain, 21% have vague regional pain, and 19% had lesions that were detected incidentally [27, 28]. People with higher grade tumors (grade II or III chondrosarcoma) have pain up to 80% of the time [28]. In another publication it was stated out that 97% of the patients with a secondary chondrosarcoma have pain [21]. Interestingly, as for the other chondrosarcomas, the delay between the first clinical signs and the diagnosis was often long, two to four years depending on the studies [22]. In some cases the malignant transformation became evident only during radiographic follow up (Table 1) [20, 22]

A palpable mass was detected in a very few cases. This is ascribed to the fact that the transformation occurs in a primarily intramedullary located lesion [27-30]. Rarely, people will discover they have a chondrosarcoma when they develop a fracture through the tumor [21, 27-30]. However, some of the patients with an enchondroma are also suffering from pain [30]. Therefore, pain in and of itself by no means eliminates the totally benign enchondroma from consideration. And, secondary chondrosarcomas could be radiological discoveries without any clinical symptoms [16].

Malignant transformation in solitary enchondroma and enchondromatosis (Ollier disease, Maffucci syndrome) preferentially affects the long bones of the lower limb, particularly the femur; other frequently involved sites are the pelvis, the humerus, scapula, ribs and the tibia (Table 1). Plurifocal malignant transformation is not unusual and is always reported for patients with Ollier disease or Maffucci syndrome [23, 31]. Further on, patients suffering enchondromatosis seems to be at a higher risk for primary brain tumors [32].

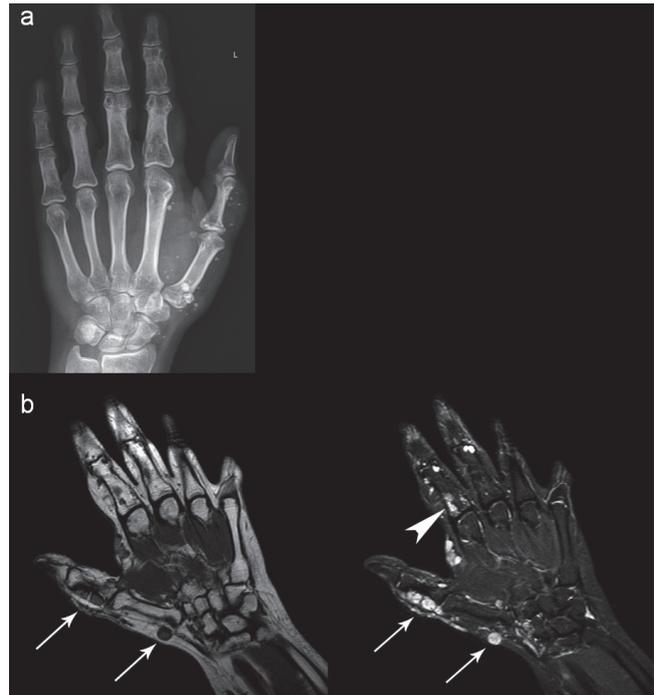


Figure 3 (a-c): 35-year-old woman suffering from Maffucci syndrome, diagnosed at the age of 3 years. **a:** Radiography shows enchondromas and multiple soft tissue phleboliths of the left hand. **b, c:** MRI demonstrates multiple soft-tissue masses representing hemangiomas that have low SI on T1-weighted (B, TR/TE, 653/24) and high SI on STIR (C, TR/TE, 4,660/45) images (arrow). Enchondromas with high SI on STIR-images are localized in the phalanges of the left hand (arrowhead).

Genetics. The exact cause of enchondromatosis is unknown. Most cases of enchondromatosis are sporadic, but families with multiple affected members have been reported, possibly suggesting autosomal dominant inheritance [5, 33]. Alternatively, a random spontaneous mutation is hypothesized. This might occur in early development, in mesoderm, therefore generating a mosaicism [2, 33].

It is speculated that a heterozygous PTHR1 mutation is likely to contribute to Ollier disease in a small subset of patients [34]. Enchondromas are usually in close proximity to, or in continuity with, growth-plate cartilage. Consequently, they may result from abnormal regulation of proliferation and terminal differentiation of chondrocytes in the adjoining growth plate [34]. In normal growth plates, differentiation of proliferative chondrocytes to post-mitotic hypertrophic chondrocytes is regulated in part by a tightly coupled signalling relay involving parathyroid hormone related protein (PTHrP) and Indian hedgehog (IHH) [34]. PTHrP delays the hypertrophic differentiation of proliferating chondrocytes, whereas IHH promotes chondrocyte proliferation [34]. Hopyan et al. identified a mutant PTH/PTHrP type I receptor (PTHR1) in human enchondromatosis that signals abnormally in vitro and causes enchondroma-like lesions in transgenic mice [35].

Table 1. Series on secondary chondrosarcoma (in alphabetical order)

Author	(Pre-existing) Lesion (No.)	Secondary chondrosarcoma / Pre-existing lesion (No.)	Age at the diagnosis of secondary chondrosarcoma Sex distribution	Cinical presentation – Symptoms of malignant transformation	Time of diagnosed malignancy after primary diagnosis – follow up	Localisation of sCS
Altay et al. [10]	143 SE 1 ME 1 MS [Total study group: 627 cartilage tumors, 331 SO and 92 MO were excluded]	6 sCS in pre-existing SE (4,2%) 2 sCS in 1 patient with pre-existing ME 3 sCS in 1 patient with pre-existing Maffucci syndrom	sCS (pre-existing SE): 31 – 80 years (median 49.8 years) sCS (pre-existing ME): 24 years sCS (pre-existing MS): 27 years	Pain	SE: 4 – 14 (median 7,7 years) ME: 10 years MS: 14 years	Enchondroma-group, (sCS affected the hand are excluded): Femur proximal (4), femur distal (4), Os ilium (3), humerus proximal (3), scapula (2), tibia (1)
Brien EW et al. [14]	Total study group: 1200 cartilage tumors [845 benign, 356 malignant; 39% of entire set of 3067 primary bone tumors (BT) studied 20 ME	104 sCS in pre-existing SE (86 sCS in pre-existing SE → sCS2 and 18 sCS in pre-existing SE → sCS2 → dCS) 4 sCS in pre-existing ME (20%)	sCS2: 52 years (average age) dCS: 70 years (average age) sCS (pre-existing ME): 27 years (average age) dCS (pre-existing ME): 45 years (average age) — No data on sex distribution	Most patients present with 6 months or more of steadily increasing pain, often worse at night NB: Pain must be differentiated from joint or soft tissue injury!	No sufficient data available	Femur > pelvis > humerus > ribs > tibia > scapula > hand
Coley BL, Higinbotham NL [19]	52 sCS [21 sCS in pre-existing SO and 4 in pre-existing MO]	23 in pre-existing SE 4 in pre-existing ME	Average age of all patients: 38.9 years 27 sCS (pre-existing enchondroma): 41 years (mean age) All cartilage lesions: 31 males and 21 females	Pain (in most of patients)	18 months - 30 years (in all of the patients) 8 cases exceeded 10 years	Femur (19), ilium (12), tibia (6), Humerus (4) and others (scapula, hand, sternum, ribs, fibula)
Liu J et al. [20]	55 ME (M. Ollier)	16 with malignant bone neoplasms (29,1%): 12 CS, 2 dCS, one chordoma, and one osteosarcoma	sCS: Average age 40.5 years (range 13 – 69 years) Approximately 33% of the patients were in the fifth decade of life — 6 males, 10 females	3 patients complained of pain only, 8 noted pain and mass, one has abnormalities of vision, and 4 had pronounced bony deformities and pain	No sufficient data available	Distal femur (4), shaft of the femur (1), proximal femur (3), proximal tibia (3), pelvis (2), proximal Humerus (1), proximal ulna (1), foot (1)
Mirra JM [21]	51 central cartilaginous tumors 9 primary and secondary CS1	11 sCS of 21 patients (with CS) with pre-existing SE and ME	Enchondroma → sCS1: 16 – 67 years (average 43 years) Enchondroma → sCS2: 50-64 years (average 58 years)	97% of patients with malignancy presented with pain, 24% with conventional and clearcell CS presented with a mass. 83% of those with fibro- or osteosarcomatous transformation had a mass.		-

Table 1. (continued)

Author	(Pre-existing) Lesion (No.)	Secondary chondrosarcoma / Pre-existing lesion (No.)	Age at the diagnosis of secondary chondrosarcoma Sex distribution	Cinical presentation – Symptoms of malignant transformation	Time of diagnosed malignancy after primary diagnosis – follow up	Localisation of sCS
	12 primary and secondary CS II / III		<p>Patients with SE transforming to CS further transforming to a fibro- or osteosarcoma were on the average 23 years older than those with enchondroma (62 versus 39 years).</p> <p>Patients with ME were 14 years younger (average, 36 years) when they presented with CS compared with the rest of the chondrosarcoma group (average 50 years).</p> <p>—</p> <p>No data on sex distribution</p>	No patients with pure, solitary enchondroma had a mass; 44% of these patients did present with pain.		-
Schaison et al. [22]	29 sCS in 25 patients with multiple cartilage disease	12 sCS (arising in ME, and one arising in Maffucci-syndrome) (12% secondary CS of all cartilaginous tumors)	sCS: 19 to 53 years (mean age 36.4 years)	7 cases with increased tumor volume or development of a tumor and pain in 11 patients	No sufficient data available	Preference for the long bones of the lower limb (57%), particularly the distal femur (32%). Involvement of the limb extremities is more exceptional (13.5%) in Ollier disease and Maffucci syndrome.
Schwartz et al. [23]	44 (37 ME, 7 MS)	4 sCS (arising in 37 ME) (10,81%) 4 Patients (MS) with 5 sCS (one patient with 2 sCS) (57%)	sCS (pre-existing ME): 16 – 54 years (median 32 years)	No sufficient data available	11 - 53 years (median 28 years)	Femur > tibia > others N: Four of the seven patients who had Maffucci syndrome had at least two malignant tumors each
Sun et al. [24]	9 Maffucci syndrome	5 sCS (55%) (1 patient with a secondary CS on the hand)	sCS (pre-existing MS): 13 – 55 years (median 54) — 2 males and 3sfemales	Pain in all patients	6 months – 5 years	Femur, tibia, fibula, [cuboid, phalanx]

Table 1. (continued)

Author	(Pre-existing) Lesion (No.)	Secondary chondrosarcoma / Pre-existing lesion (No.)	Age at the diagnosis of secondary chondrosarcoma Sex distribution	Cinical presentation – Symptoms of malignant transformation	Time of diagnosed malignancy after primary diagnosis – follow up	Localisation of sCS
Unni KK [4]	78 Chondromatosis (54 with benign multiple chondromas and 24 with secondary sarcomas)	24 secondary sarcomas (30.8%) with 10 pre-existing ME, 5 pre-existing MS and 6 pre-existing multiple chondromas. Two patients with 2 sCS (19 CS, 3 dCS, 1 chondroid sarcoma, 1 osteosarcoma)	(All of the) sCS: 52% in the third and fourth decade of life Approximately 57% were males	Pain as significant symptom. In the pelvic girdle or spinal column referred pain may precede local pain.	Patients with sCS are somewhat younger than patients with primary chondrosarcoma	Pelvis > proximal femur > ribs > humerus > scapula.
Unni KK, Dahlin DC [25]	36 ME	10 with malignant bone neoplasms (8 CS, 1 chondroid chordoma, 1 dCS) (27,7%) In 419 primary or sCS of bone none of the lesions had arisen from a clearly recognizable pre-existing enchondroma	No sufficient data available	No sufficient data available	No sufficient data available	Femur (3), tibia (3), humerus, [metatarsal (1)], skull (1)
Vazquez-Gracia et al. [26]	15 Ollier disease	5 sCS in 4 patients (23.5%)	median 45 years	Pain and growth in most cases	No sufficient data available	Distal femur > pelvis > fibula
Verdegaal et al. [15]	144 Ollier disease 17 Maffucci syndrome Ollier disease: mean age was 13 years (range, 0–59 years; data from 105 of 141 patients with Ollier disease). Maffucci syndrome: mean age was 12 years (range 1–65 years; data completed for 11 of 17 patients)	66 patients (41%) developed one or more sCS Ollier disease n=57 (45,8%) Maffucci syndrome n=9 (52,9%) Of 66 patients, 48 developed one CS, 18 developed two to four CS. Of these 18 patients, 33% had synchronous and 56% had metachronous CS (unknown n=2).	Mean age at first surgery for chondrosarcoma: sCS (pre-existing ME): 33 (range 10–59 years) sCS (pre-existing MS): 30 (range 14–51 years)	No sufficient data available	No sufficient data available	Femur (18), tibia (10), Humerus (10), flat bones (8 scapula, 11 pelvis) [Of the small tubular bones, the metacarpals and metatarsals were less often involved than the phalanges of the hands and feet (n=9 and n=14, respectively)]

E = Enchondroma, SE = Solitary Enchondroma, ME = Multiple Enchondromas / Enchondromatosis, MO = multiple Osteochondroma, MS = Maffucci Syndrome, CS = Chondrosarcoma, sCS = secondary Chondrosarcoma, dCS = dedifferentiated Chondrosarcoma

Another study group could not confirm this finding of an activating mutation in the parathyroid hormone receptor type 1 (PTH1R) gene. Rozeman et al. investigated PTH1R in enchondromas and chondrosarcomas from 31 enchondromatosis patients from three different European countries, thereby excluding a population bias [36]. PTH1R protein expression was studied using immunohistochemistry, revealing normal expression. The presence of the described PTH1R mutation was analyzed, in tumors from 26 patients [36]. In addition, 11 patients were screened for other mutations in the PTH1R gene by sequence analysis. They could neither confirm the previously found mutation nor find any other mutations in the PTH1R gene. Thus, PTH1R mutations may contribute to the disease in a small subset of Ollier patients but is probably not causative for the disease [36].

Recently, mutations in the gene encoding isocitrate dehydrogenase 1 (IDH1) and IDH2 were detected in solitary cartilaginous tumors as well as in patients with multiple enchondromas [15, 37]. These mutations might represent early postzygotic genetic events and account for the initiation of the disease process [15, 37]. Furthermore, rearrangements of chromosome 6 and the long arm of chromosome 12 (particularly q13q15) seem to be recurrent in chondromas, also including soft tissue chondromas [38]. Array comparative genomic hybridization data showed highly variable genetic abnormalities including gain and loss of several chromosomes [39].

For further chondrosarcoma development, a multistep genetic model is presumed. Complex karyotypes are found especially in high-grade chondrosarcoma, and 96% of them contains alterations at some level in the pRb pathway [40, 41].

Imaging. Conventional radiographs in two planes should always be the first imaging method used. MRI and CT should be used when diagnosis is difficult because they offer ability to visualize more clearly calcification, periosteal bone formation, cortical destruction or soft tissue involvement [23, 42-47].

Standard x-rays were suspicious for an aggressive tumor when extended endosteal scalloping, cortical remodelling (expansion of normal bone contour), cortical destruction, pathologic fracture and/or periosteal reaction were evident [1, 21, 29, 42]. On computed tomography, characteristic features of malignancy were lytic areas, especially when pronounced in comparison with previously made radiographs, cortical lesions with a scalloping greater than 2/3 of the cortex or extension to soft tissue [29, 42-48].

Magnetic resonance (MR) of an enchondroma demonstrates a lobulated lesion with intermediate signal intensity on T1-weighted images and predominantly high signal intensity on T2-weighted sequences.

The malignant progression of an enchondroma was in most cases evident if one of the following criteria was present (in MRI): cortical destruction, moth-eaten or permeative osteolysis, spontaneous pathologic fracture, periosteal reac-

Table 2. Clinical and radiographic (risk) factors of secondary chondrosarcoma in enchondroma(tosis)

Clinical [14, 15, 18, 20-24, 27, 28, 43, 48]	<ul style="list-style-type: none"> - Pain - Increasing tumor size - Palpable mass - Localisation: femur, proximal humerus, scapula, (tibia) - Localisation: pelvis (primary chondrosarcoma?) - Age in the mid 30s
Radiographic [29, 42-47, 49-59]	<ul style="list-style-type: none"> - Cortical destruction - Moth-eaten or permeative osteolysis - Spontaneous pathologic fracture - Periosteal reaction - Oedema surrounding the tumor - predominantly intermediate signal on T1-weighted images (in discussion) - multilocular appearance on contrast-enhanced T1-weighted images (in discussion) - Soft tissue mass - Endosteal scalloping > 2/3 of the cortex (with limitation in the metaphyseal region where the cortex is thin, especially in the proximal fibula) - Extent of endosteal scalloping superior to two-thirds of the lesion length - Cortical thickening and enlargement of the medullary cavity - Increased uptake in scintigraphy (more than that of the anterior iliac crest) - Lesion size > 5-6 cm (risk factor)
Pre-existing Lesion - Risk of malignant transformation [10, 15, 24]	<ul style="list-style-type: none"> - Enchondroma: risk of malignant transformation up to 4%, on average about 2% - Enchondromatosis / Ollier disease: risk of malignant transformation up to 46% - Maffucci syndrome: risk of malignant transformation up to 55%
Genetics [8, 15, 34-37, 40, 41]	<ul style="list-style-type: none"> - Mutation in parathyroid hormone receptor 1 (PTH1R)? - Rearrangements of chromosome 6 and chromosome 12 - PTPN11 mutations - Alterations at some level in the pRb pathway - Other highly variable genetic alterations

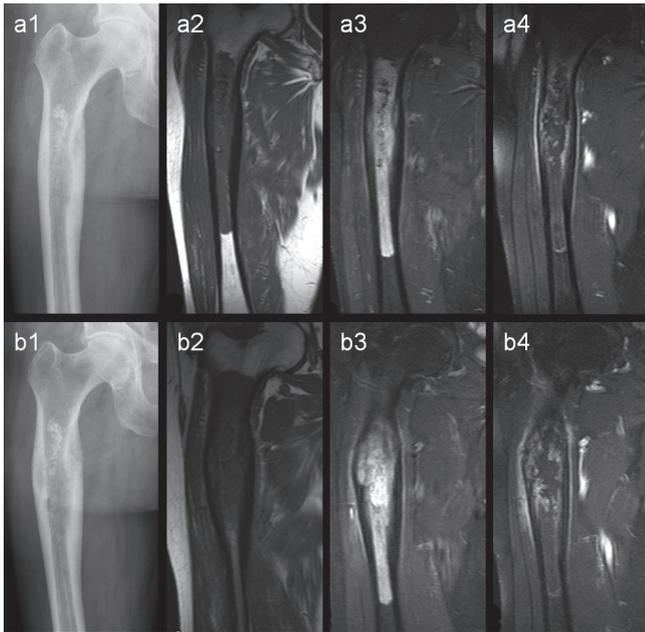


Figure 4 (a1-a4 and b1-b4): Secondary chondrosarcoma in 77-year-old woman with right leg pain. **a:** Initial plain film radiography (a1) shows evidence of enchondroma (DD chondrosarcoma) with calcifications of the chondroid matrix in the proximal femoral diaphysis. MRI demonstrates an enchondroma with characteristic SI on T1-weighted and on STIR images (a2, a3). Contrast-enhanced T1-weighted image (a4) shows a “ring-and-arc” pattern of contrast enhancement. There is no perilesional soft-tissue mass. An incisional biopsy of the tumor confirmed the diagnosis of an enchondroma. **b:** Six months after the initial examination, the lesion showed expansion of the proximal femoral bone and a soft tissue extension, suggesting sarcomatous transformation. Another incisional biopsy was performed and the histological specimens showed an intermediate grade (grade II) chondrosarcoma.

tion, edema surrounding the tumor on MR images, and soft tissue mass [2, 29, 42-47, 49]. Note that the use of scalloping in the diagnosis is limited when examining the metaphyseal region because the cortex is thin, especially in the proximal fibula [29].

In a recent study the predominantly intermediate signal on T1-weighted images [72% (13/18) in low-grade chondrosarcoma vs. 25% (4/16) in enchondroma], multilocular appearance on contrast-enhanced T1-weighted images [83% (15/18) vs. 44% (7/16)] was also discussed for differentiating low-grade chondrosarcoma from enchondroma [50].

The radiological aspects that were suspicious for a secondary chondrosarcoma are summarized in Table 2 (Figure 4 and 5).

In addition, lesion sizes of enchondroma and chondrosarcoma were often different. Malignant lesions had the expected larger average size. Although there is certainly overlap in size range, lesions larger than 5-6 cm in diameter are much more likely to represent chondrosarcoma [42].

If malignancy is diagnosed, general staging should be carried out to assess the extent to which the disease has spread

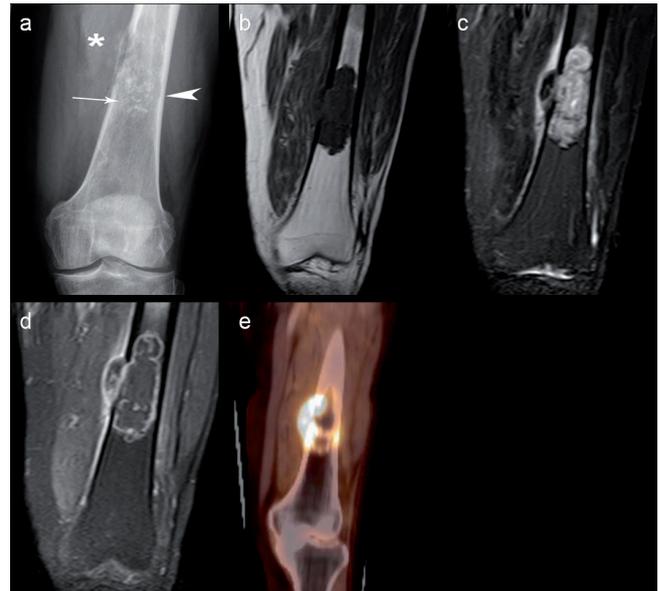


Figure 5. (a-e): 76-year-old man with persistent left leg pain. **a:** Radiograph demonstrates a dedifferentiated chondrosarcoma with bimorphic features in the left femoral diaphysis. There are calcifications within a part of the lesion (arrow), which is characteristic of a chondroid tumor. An area with endosteal scalloping (arrowhead), cortical thickening and calcifications is adjacent to a more aggressive-appearing area with cortical disruption and periosteal reaction (*). These findings indicate malignancy and the possibility of a biphasic tumor type. Coronal T1-weighted (B, TR/TE, 500/18), STIR (C, TR/TE, 2,800/60) and gadolinium-enhanced T1-weighted (D, TR/TE, 500/18) MR images demonstrate a periosteal reaction and a cortical breakthrough. Extension into the soft-tissue and a perilesional soft-tissue edema with contrast-enhancement is seen on MRI images. **e:** FDG PET-CT shows a circumscribed focus of intense uptake (Note: Histological examination showed a dedifferentiated chondrosarcoma consisting of two different components, an underlying benign enchondroma juxtaposed to a high-grade osteosarcoma)

including bone scintigraphy and chest radiographs and CT [42-48]; small nodules are not specific for malignancy Whole body MRI and PET are under evaluation for both staging and treatment response evaluation.

Nuclear medicine.

Bone scintigraphy. In the actual ESMO-guideline for diagnosis, treatment and follow-up of bone sarcomas, bone scintigraphy is recommended for initial staging of chondrosarcomas, as further skeletal lesions can be excluded by this examination [52]. It has been reported that radionuclide uptake is generally higher in chondrosarcoma than in enchondroma [42]. Compared to the tracer uptake in the anterior iliac crest, the uptake was, in difference to the majority of examined enchondromas, higher in 82 % of the examined chondrosarcomas. A correlation between intensity or pattern of uptake and histological grades was not found [53]. In chondrosarcoma it could be variable, but often in-

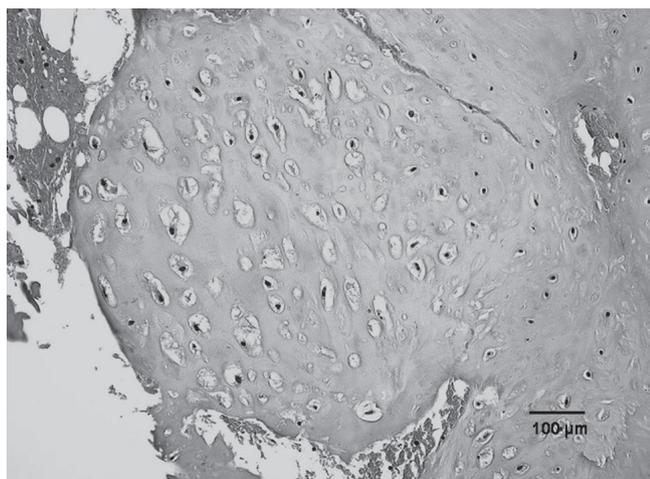


Figure 6. Enchondroma located in the humerus (female, 33y). Chondrocytes located within sharp-edged lacunar spaces (H&E, x100).

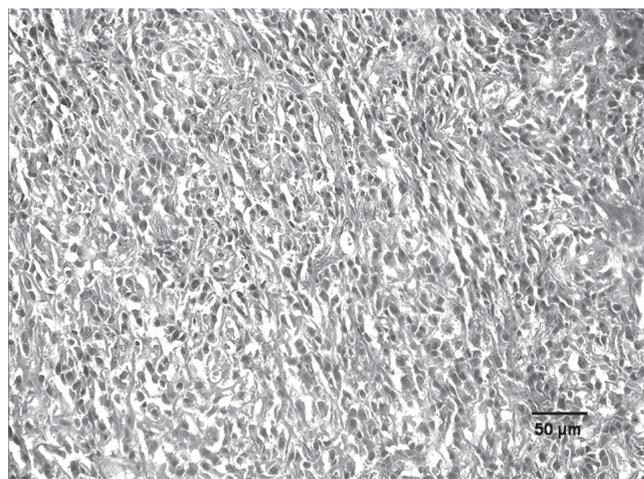


Figure 7. High-grade chondrosarcoma (male, 77y) arising in an enchondroma of the femur showing high cellularity of highly atypical tumor cells (H&E, x200)

tense [53-55]. Sometimes uptake in the centre of the lesion is lower than around its periphery (“doughnut” sign). However, a typical tumor pattern of distribution demonstrates areas of focal increased uptake throughout the tumor [53].

FDG-PET: In several publications increased uptake of the radiotracer was reported in chondrosarcomas, showing a positive correlation of the uptake intensity (measured as SUV) and tumor grade [56-61]. Significant differences between SUVmax levels in benign lesions/grade I chondrosarcomas and high-grade chondrosarcomas were found; such differences were not found between the SUVmax in benign cartilage tumors and grade I chondrosarcomas. With the use of 2.3 as the cut-off level for SUVmax, the positive predictive value of FDG-PET in this study was 0.82 in the diagnosis of grade II and grade III chondrosarcomas; the negative predictive value was 0.96 [58].

Based on these data, FDG-PET is a valuable tool to distinguish benign lesions and low grade (grade I) chondrosarcoma from intermediate (grade II) and high grade (grade III) chondrosarcoma. This can be of special interest for the prediction of a focus of dedifferentiation in patients with Ollier disease or Maffucci syndrome [61].

Beside the application of FDG-PET in the primary diagnosis and further characterisation of chondrosarcoma, it can be a useful tool for the diagnosis of metastatic disease and tumor recurrence in follow-up [59], especially in cases of limitations of CT and MRI due to metallic prosthesis. For biopsy planning, FDG-PET may be useful to localise the tumor site with the highest metabolic activity for selective sampling in cases of heterogeneous cartilage lesions [56]. This is of special interest as chondrosarcomas may have significantly different grades in different portions of the lesion.

Pathology. The diagnosis of secondary chondrosarcoma is confirmed by histological examination of biopsy samples. Like

conventional chondrosarcoma, secondary chondrosarcoma is not always easy to diagnose, and the histological features alone may not be sufficient to determine that a lesion has become malignant [3, 18]. However, a clearly benign enchondroma shows the typical pathological features (Figure 6).

Most secondary chondrosarcomas are low grade. The overlap in appearance between benign lesions and low-grade cartilage tumors has led to a high rate of inter- and intraobserver variability in diagnosis [62]. Therefore, information from the clinical history and imaging studies must be correlated with the pathologic data to render the correct diagnosis [3, 63].

On the pathology slides, sarcomatous transformation is usually identified by the presence of malignant chondroid tissue: Hypercellularity, binucleated cells, multiple cells in lacunae, atypical nuclei, and myxoid changes in the hyaline cartilage matrix (Figure 7) [3, 14]. An important feature consistent with malignancy is permeative infiltration of soft tissues and the presence of discrete nodules of cartilage in the soft tissues separated from the main tumor mass [18, 64]. Additional indicators of malignancy are the “chondrosarcoma permeation pattern” and infiltration of Haversian systems [14].

The grading of secondary chondrosarcomas is similar to that of primary chondrosarcomas and includes grade 1, low; grade 2, intermediate; and grade 3, high [65]. Most secondary chondrosarcomas are grade 1 or 2 lesions [48]. Only 1% of cases were reported to be grade 3 [18].

Biopsy

Usually it is advised to determine the local staging of the lesion before the biopsy. This biopsy of a suspected primary malignant bone tumor should be carried out at a medical centre, ideally by the surgeon who is to carry out the definitive tumor resection [66]. It should be planned so the entire

skin incision and biopsy track can be incorporated into the definitive surgical field [67]. In addition, the biopsy should provide sufficient tissue for gross pathological evaluation, histological analysis, immunohistochemistry and, if needed, cytogenetic testing.

Surgery

When histology confirms the diagnosis of a chondrosarcoma, there are basically two categories for surgical treatment of a secondary chondrosarcoma [68]. The first is (intralesional) curettage, adjunct chemical or thermal ablation, and cementation or bone grafting of the defect. The second is wide excision with structural graft or reconstruction [68].

Acceptable oncologic and functional results have been observed in patients with grade 1 chondrosarcoma treated with curettage and cryosurgery alone [64, 69]. However, local recurrence is not unusual if there is inadequate resection [68, 69]. Wide excision is performed in higher grade chondrosarcomas, and occasionally in grade 1 chondrosarcoma. Large lesions and chondrosarcomas in anatomic locations that do not allow adequate margins or complete excision (e.g. spine, craniofacial region, ribs and pelvis) have an obvious increased risk of local recurrence and metastatic disease [70, 71].

Additionally, there it is still a point of contention around the removal of a large enchondroma before the age of 32 since many chondrosarcomas can demonstrate a precursor enchondroma, and if the average age of a patient with primary or secondary CS was about 52 years, the initial "seeds" of malignancy probably developed around age 32 [14].

Follow up

The knowledge on the potential risk of undergoing malignancy requires a standardised follow up, since the risk of malignant transformation ranged up to 45.8% in patients with Ollier disease and 57% in patients with Maffucci syndrome, respectively (Table 1). And, increased risk of transformation of a solitary enchondroma in long and flat bones (scapula and pelvis) makes it necessary to follow up these patients too. But one should be aware of the fact that (solitary) enchondroma in the pelvis is very rare or may does not exist and lesion represents primarily a chondrosarcoma. Because of the different biology and clinical course of the tumors of the phalanx, these are not discussed in our paper.

In general, most of the studies propose clinical as well as radiological controls. The frequency of skeletal surveys must be weighed against the risk of cumulative radiation exposure. In a paper of Lin et al., the recommended follow up was to conduct surveys every one to two years with focal radiographs of symptomatic areas [18]. In a recent study the following was recommended in cases where two or more enchondromas are detected: staging should include a technetium scan and X-rays of each enchondroma to establish a baseline for future comparison [15]. Additionally, screening of enchondroma

of the long and/or flat bones should be done more carefully using plain x-rays when complaints of pain, swelling, or neurological disorders appear or increase [15].

This may be in contrast to the fact, that there are lesions undergoing malignant transformation without clinical symptoms. As mentioned, up to 19% of patients may not suffer from pain [27, 30]. And it should be noted that in most cases it is not possible to sufficiently interpret X-rays of anatomically difficult regions (pelvis, e.g.). Furthermore, signs of malignant transformation such as permeative osteolysis (in bone marrow), periosteal reaction (except periosteal/cortical bone remodelling) and oedema surrounding the tumor could be sufficiently detected only by MRI.

Recently, extended recommendations for the management of a solitary central cartilaginous tumor of long bones were published, depending on their clinical and radiographic appearance [29]. This classification is very practical, however, this proposed classification of cartilage tumors into aggressive, active, potentially active and quiescent lesions has not been shown to differentiate between enchondroma and chondrosarcoma in detail and has not been clinically validated yet.

Following the results of this review and summarising data from the literature, we would like to recommend our opinion on the initial diagnostic and follow up of patients:

Initial diagnostic. Choice of radiological modality depends on the lesions location. Plain radiographs are the standard. In anatomically difficult regions (pelvis and scapula, e.g.) CT scan could be considered. In addition, MRI is recommended as the method of choice to reduce inter-observer variability on evaluation of X-rays and because MRI affords the possibility of assessing the medullary spread of tumor (tumor size), visualisation of any reaction of the periost, assessment of the surrounding oedema and evaluation of the T1- and T2 signal intensity.

If two or more than two lesions are known, additionally a bone scintigraphy is recommended for screening for an underlying enchondromatosis. However, one should recognize the possibility of a whole body MRI, since this method has no radiation exposure and there is the possibility to describe the real size and characteristics of the lesion, if detected.

Enchondromas which at initial diagnosis raise clinical or radiological suspicion of a low-grade chondrosarcoma (Table 2) should be discussed in a multidisciplinary team in orthopaedic oncology centre and may require biopsy. The histology results inform subsequent steps.

Follow up of solitary enchondroma. In view of the fact that the vast majority of patients with chondrosarcoma suffer from pain, a pragmatic approach would be to rely on the occurrence of pain in the case of solitary enchondromas which are innocuous on imaging at the time of diagnosis [27-30].

In contrast, when tumor is located in the pelvis, proximal femur, humerus or scapula, and/or size > 5-6 cm an annual clinical examination and an annual/biennial (depending of risk factors) MRI of the affected area should be performed,

Table 3. Recommendation for initial management and follow up of enchondroma(tosis) of the axial skeleton and the long bones in asymptomatic patient

Enchondroma(tosis)	First step(s) / initial management	Recommendation for treatment / follow up
Clinical / radiological suspected malignancy (criteria seen on Table 2)	Completion of the diagnostic including plain radiographs, CT, MRI, biopsy. Scintigraphy on demand	Depending on the result of histology
Clinical / radiological unambiguously “enchondroma” with localisation in pelvis*, femur, scapula, humerus and/or size > 5-6 cm	Follow up	Annual clinical and annual/biennial radiological (MRI) examination
Clinical / radiological “enchondroma” with localisation in other sites than pelvis, femur, scapula or humerus and/or size < 5-6 cm	Follow up	Annual clinical. Consideration of bi-/triennial radiological examination (plain radiographs, in any doubt MRI)

*One should be aware of the fact that (solitary) enchondroma in the pelvis is very rare or may does not exist and lesion represents primarily a chondrosarcoma

concerning the higher risk of malignant transformation in these regions and the risk of undergoing “painless” transformation into chondrosarcoma (Table 3). Modest to large solitary enchondromas of long and flat bones probably require at least two decades of follow up if detected and treated after age 25 years [14], maybe they profit from a lifelong follow up.

Follow up of enchondromatosis. When tumor is located in the pelvis, femur, humerus or scapula, and/or size > 5-6 cm a yearly clinical examination and a MRI of the affected areas (may be in form of a whole body MRI) should be performed. For other locations a clinical survey should be conducted annually and radiographic control should be discussed every two to three years. In addition, if after reviewing X-rays malignancy is suspected or if a clinical symptom (pain) is evident, an MRI should be carried out (Table 3). Patients with enchondromatosis may also profit from a lifetime follow up.

Independently of previous described recommendations: In any case of pain, immediate clarification including clinical and radiological examination (plain radiographs, MRI and if needed CT) is advised.

Follow up of secondary chondrosarcoma. In the event of a secondary chondrosarcoma, follow-up of high-grade tumors should include both a physical examination of the tumor site and assessment of the function and possible complications of any reconstruction. Local imaging and chest X-ray/CT should be the norm. Recommended intervals for follow up after completion of chemotherapy are every six weeks to three months for the first two years; every 2–4 months for years 3–4; every 6 months for years 5–10 and thereafter every 6–12 months according to local practice [52].

Prognosis

The prognosis of patients with secondary chondrosarcoma is relatively good, and the tumors metastasize infrequently. The overall survival rate at five years is approximately 90% [10, 71]. However, several other studies report mortality rates of 11% to 16% with >5-year follow-up [16]. Metastasis may be more apt to occur in the rare high-grade secondary chondrosarcoma [10, 18, 52, 70-71].

Limitation of this study

The fact that the presented data were collected from a review of the literature in which data were presented mainly from referral centres for musculoskeletal oncology may have led to a selection bias and the true incidence of malignancy may be lower. Furthermore, the true incidence of malignant transformation is not known as most enchondromas are asymptomatic and go undetected. And the starting point of these cumulative incidence curve estimates was mostly the date of birth of the patient, and the patients follow up wasn't in most cases the date of death. Because of this construction, the probability estimates should not be interpreted as “life-long probabilities” since birth and all probabilities (or proportions) have only a descriptive meaning conditional on the disease having been diagnosed. The proposal for the follow up excluded the tumours of the hand and foot.

Conclusion

In enchondroma, much more in the enchondromatosis and Maffucci syndrome, the potential of a malignant progression into a secondary chondrosarcoma is a well known fact. And despite the fact that most of the cartilage tumors present with characteristic features on imaging, the differential diagnosis between a tumor being enchondroma and low grade chondrosarcoma remains difficult.

Chondrosarcoma patients (primary CS) have an average age of about 52 years. Patients with a secondary chondrosarcoma (SCS) arising from a solitary enchondroma are about 10 years older. Patients who develop a secondary chondrosarcoma having an enchondromatosis are on average 10 – 15 years younger. Main localisations include the pelvis, the scapula, the femur and the humerus. But one should be also aware of the chondrosarcoma of the rib and the tibia.

Clinically, the presence of non-mechanical pain or night pain in any age group is cause for concern and further immediate investigation is warranted. Indeed, pain is the typical symptom when a primarily benign lesion becomes malignant. In contrast benign enchondroma can also cause pain. There-

fore, pain does not eliminate the benign enchondroma from consideration. And, the absence of pain does not exclude a chondrosarcoma, which also makes a consistent radiological follow up necessary. Several imaging characteristics exist that suggest a secondary chondrosarcoma.

These radiographic risk factors, tumor characteristics, as well as clinical signs are summarised in Table 2. The recommendations for the follow up depend on these findings (Table 3). Especially patients with an enchondromatosis would benefit from lifelong follow up, additionally patients with solitary enchondroma of long bones and flat bones.

Early recognition of a secondary chondrosarcoma following consequently performed clinical and radiological examination and appropriate surgical treatment are necessary for successful outcomes. However, our recommendations must be measured against the long-term gold standard of patient outcomes.

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