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Diagnostics and treatment of enchondromas

Diagnostična obravnava in zdravljenje enhondromov

Rok Vojković,[1] David Martinčič,[1,2] Blaž Mavčič[1,2]

Abstract

Enchondromas are benign intramedullary tumours of mature hyaline cartilage, accounting for 10–25% among all benign bone tumours.They are present in almost 3% of magnetic resonance examinations of knees and shoulders as an asymptomatic random finding. This paper presents epidemiology, clinical picture, imaging diagnostics, differential diagnostics, biopsy indications, histopathology, clinical monitoring, and treatment of enchondromas. Randomly discovered asymptomatic intramedullary solitary enchondromas in long bones mainly do not require treatment, as the risk of subsequent malignant alteration is less than 1%. Enchondromas in small bones of hands and feet are treated by excochleation biopsy due to a high risk of pathological fracture. Cartilaginous tumours exhibiting growth, local pain, or aggressive radiological characteristics require treatment at a tertiary facility with a possible biopsy and decision on observation/discharge/resection. The most complex clinical challenge is distinguishing common enchondromas from rare atypical cartilage tumors and even rarer chondrosarcomas, whereby the BACTIP guidelines can be very useful.

Izvleček

Enhondromi so benigni intramedularni tumorji iz zrelega hialinega hrustanca, ki obsegajo 10–25 % vseh benignih kostnih tumorjev. Kot naključna najdba brez simptomov so prisotni pri 2–3 % magnetnoresonančnih preiskavah kolen in ramen. Članek predstavi enhondrome z vidika epidemiologije, klinične slike, slikovne diagnostike, diferencialne diagnostike, indikacij za biopsijo, histopatologije, kliničnega spremljanja in zdravljenja. Naključno odkritih intramedularnih solitarnih enhondromov dolgih kosti brez izraženih simptomov v večini primerov ni treba zdraviti, tveganje za kasnejšo maligno alteracijo pa je manjše od 1 %. Enhondrome v malih kosteh rok in nog se zdravi z ekskohleacijsko biopsijo zaradi možnosti patološkega zloma. Hrustančne spremembe, ki rastejo, povzročajo bolečine ali imajo po slikovnih preiskavah t.i. agresivne značilnosti, zahtevajo obravnavo v terciarni ustanovi in odločitev glede indikacij za biopsijo, opazovanje, izpraznitev ali izrez. Najtežji klinični izziv je razločevanje pogostih enhondromov od redkih atipičnih hrustančnih tumorjev in še redkejših hondrosarkomov, pri čemer pa so nam v oporo smernice BACTIP.

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1 Introduction

Enchondromas are benign tumours of the mature hyaline cartilage, most commonly located in the long and short tubular bones. The term enchondroma denotes cartilage tumours that grow within the bone; outside the bone, they are known as chondromas (1). The vast majority of enchondromas are asymptomatic and do not require treatment; however, with imaging studies, they can be difficult to differentiate from other locally aggressive or malignant cartilage tumours (2). Cartilage tumours are classified into three groups according to their aggressiveness: enchondroma, atypical cartilaginous tumour (previously known as grade I chondrosarcoma) and high-grade chondrosarcoma (grade II, III and dedifferentiated chondrosarcoma) (2). Although the incidence of benign and malignant mesenchymal tumours has remained unchanged for decades (3), the number of incidentally detected cartilage lesions has increased dramatically in Slovenia and worldwide due to the wider availability of magnetic resonance imaging (MRI). For this reason, in recent years, there has been a tendency to establish guidelines for the uniform treatment of enchondromas (4-6). The purpose of this article is to present enchondromas: their epidemiology, clinical presentation, imaging studies, differential diagnostics, biopsy indications, histopathology, clinical monitoring and treatment. The main focus is on distinguishing between common benign lesions and rare aggressive or malignant tumours. The conclusion of the article presents clinical guidelines for the treatment of enchondromas (4-5), adopted by the Orthopaedic Society of the Slovenian Medical Association for Slovenian orthopaedic surgeons at its annual assembly on 29 November 2019 (7).

2 Epidemiology and clinical presentation

Enchondromas account for 10–25% of all benign bone tumours detected, and are the second most common, behind osteochondromas. The incidence of incidentally detected proximal upper arm enchondromas on MRI of the shoulder is 2.1% (8), and 2.8% on MRI of the knee (9). When converted to the Slovenian population, this would mean that approximately 42,000 Slovenians have a cartilage tumour of the proximal humerus and 56,000 of the femur or tibia. The vast majority of these enchondromas are asymptomatic and will never be detected. Exceptions to this rule are enchondromas of the hands and feet, which can cause pathological fractures and, in most cases, can be easily diagnosed by X-ray or MRI (10).

The aetiology of enchondromas is unknown. They most commonly occur between the second and sixth decade with a peak in the fourth and fifth decade; they are slightly more common in women (1). The majority are located in small tubular bones of the hands; among the long tubular bones, they are found in the proximal humerus, proximal and distal femur and tibia. Enchondromas in the spine and flat bones (ribs, scapula, sternum and skull roof) are very rare; in the bony pelvis, almost all cartilage tumours are malignant (11). Enchondromas occur as part of Ollier disease (multiple enchondromatosis) or Maffucci syndrome (in addition to multiple enchondromas, spindle-cell haemangiomas and lymphangiomas are also present); in these cases, they are associated with an increased risk of malignant transformation (12).

Local pain at the enchondroma site (pain at rest, nocturnal pain) requires appropriate imaging studies, as pain may be a sign of an active or even malignant tumour affecting the periosteum with expansive growth. The appearance of pain in a known enchondroma may reflect its malignant transformation, but not necessarily; benign enchondromas can also be painful, while in middle-aged patients, it is often difficult to distinguish between tumour pain and degenerative symptoms of nearby joints (e.g. shoulder compression syndrome or initial knee osteoarthritis). On clinical examination, pain is elicited by local pressure on the bone. In addition to local examination, a comprehensive physical examination is particularly important for patients with suspected enchondromatosis or Maffucci syndrome (2).

3 Imaging studies

On plain radiographs, enchondromas of hands and feet have thin, sharply defined margins and lobulated structure, frequently with endosteal scalloping and bone expansion, sometimes even with a pathologic fracture (Figure 1). Unlike at other sites, enchondromas on the hands and feet do not normally have calcifications. Individual rare bone lesions with sharp sclerotic margins in the short tubular bones of the hands and feet are managed as enchondromas, unless additional investigations reveal aggressive characteristics. In differential diagnosis, they can be enchondromas, but other benign lesions

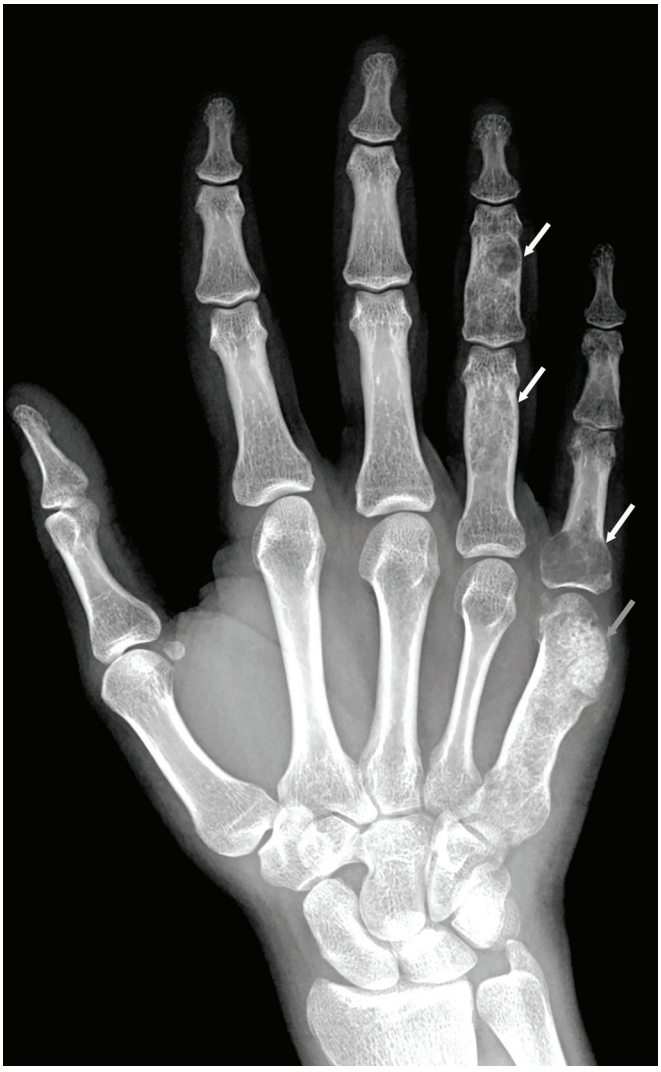

Figure 1: Radiographic image of a hand with multiple enchondromas of metacarpals and phalanxes.
White arrows indicate unoperated enchondromas, grey arrow indicates enchondroma after curettage and filling with bone substitute – calcium triphosphate granules.

cannot be excluded. In the long tubular bones (humerus, femur, tibia), enchondromas are commonly located in the medullary cavity or they are in an eccentric position with an osteolytic structure with calcifications; they do not exhibit aggressive characteristics (bone destruction and outward growth, periosteal reaction and a soft tissue growth) (13). Computed tomography (CT) allows better assessment of endosteal cortical surfaces in intramedullary cartilage tumours of long tubular bones. On MRI, the tumour margins are well-circumscribed with low signal intensity on T1 sequences with high signal intensity on T2 sequences. The lobulated tumour margins are characteristic, and low signal intensity is observed in calcified areas (1).

The Enneking staging system for benign bone tumours consists of three categories according to the tumour's level of activity: latent tumours (G1), active, growing tumours (G2) and aggressive, rapidly growing tumours with extension through the cortex (G3) (14). The majority of asymptomatic enchondromas are latent (G1) and are incidental findings in adolescence or adulthood. These tumours are characterized by slow, self-limiting growth without cortical bone weakening; they normally do not grow again after puberty (Figure 2). The faster growth of grade 2 benign tumours can result in more frequent pain, but the cortex remains intact, although bone expansion can occur. Due to the rapid dynamics of growth, pain is normally present in the short medical history in grade 3 tumours. There is endosteal scalloping and discontinuation of the cortex; the clinical examination may reveal a palpable soft tissue mass (Figure 3). Distinguishing enchondromas from atypical cartilaginous tumours and chondrosarcomas based on radiological examinations is very difficult and not always reliable (2). Therefore, observation of cartilage tumour dimensions on serial radiographs or MRI images is one of the key methods for detecting active or malignant cartilage tumours (4-5).

MRI does not clearly distinguish benign enchondromas from atypical cartilaginous tumours; sometimes, it may even be difficult to distinguish them from high-grade chondrosarcomas. Enchondromas show benign or intermediate malignant changes in T1 sequences with a relatively homogeneous decrease in signal, while fluid-sensitive sequences and fluid-sensitive sequences with fat suppression show an increase in tumour signal due to the higher water content in the chondrogenic tumour matrix. In contrast-enhanced sequences, enchondromas normally have a characteristic lobulated structure with homogenous contrast uptake centrally and peripherally; contrast uptake is normally even more pronounced peripherally. Due to more extensive tumour cell dedifferentiation, malignant chondrosarcomas no longer exhibit an ordered lobulated structure and have more areas of necrosis, increased connective tissue and reduced tumour matrix. Thus, the lesion has an inhomogeneous appearance, particularly in sequences with high signal intensity of contrast enhancement (15). Aggressive or malignant CT or radiographic characteristics are endosteal scalloping and bone expansion, cortical thinning or thickening and cortical infiltration (1). Peripheral bone marrow oedema around the tumour, subperiosteal oedema or soft tissue mass on MRI suggest low-grade chondrosarcoma. Features suspicious of a malignant tumour are also significantly greater tumour size on MRI

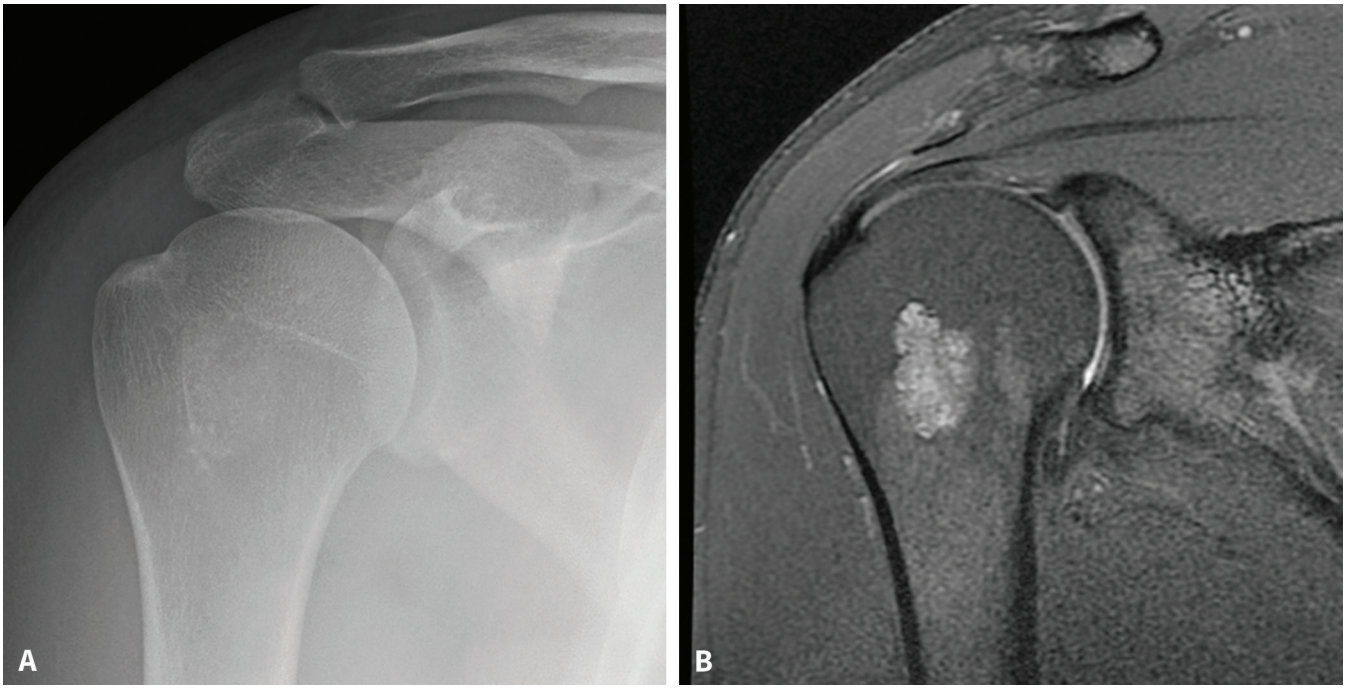

Figure 2: Radiographic (A) and MRI (B) images of an incidental enchondroma of right shoulder.
The lesion is located in the metaphyseal medullary cavity, is not in contact with the cortex and does not cause endosteal scalloping; it has a typical lobulated structure without oedema or other aggressive radiological features.

than on radiograph, epiphyseal location or tumour extension along the epiphysis; benign cartilage tumours are located in the metaphyses (13). Bone scintigraphy has lost its significance for multiple enchondromas detection due to whole-body MRI. Additionally, scintigraphy cannot distinguish between benign enchondromas, atypical cartilaginous tumours and chondrosarcomas, so it is no longer suitable as a routine diagnostic method in enchondroma management. On the other hand, bone scintigraphy and positron emission tomography (PET) frequently show enchondromas as incidental findings; even though they are benign, they can significantly accumulate radionuclides (2).

4 Differential diagnosis and indications for biopsy

According to the World Health Organization (WHO) classification of bone tumours (16), when a benign-looking cartilage tumour is detected, other chondrogenic tumours in addition to enchondroma are considered in the differential diagnosis, depending on their tissue of origin and tumour matrix: periosteal chondroma, osteochondroma (cartilaginous exostosis), chondromyxoid fibroma, atypical cartilaginous tumour (previously known as grade I chondrosarcoma), chondroblastoma and high-grade chondrosarcoma. Chondromyxoid fibroma and atypical cartilaginous tumours are considered locally aggressive, and chondroblastoma and atypical cartilaginous tumours can rarely metastasize (<2%).

A biopsy of the suspected enchondroma should be performed if malignancy cannot be ruled out, or if the clinical presentation and imaging studies suggest a locally aggressive benign cartilage tumour. An inconclusive radiological report or physician's doubts should not be the only reason for an unnecessary biopsy; in uncertain cases, a referral to a specialized tertiary institution for bone tumours must be made (in Slovenia, this is the Division of Tumour Surgery at the Department of Orthopaedic Surgery at the University Medical Center Ljubljana).

As a rule, the biopsy should be performed at the tertiary institution that would perform definitive surgery in case the tumour proves aggressive or malignant. During a biopsy, avoidance of anatomical structures (blood vessels, nerves, certain muscle groups) and a choice of proper approach in an area where there is a possibility of a subsequent surgical tumour resection are crucial. The anatomical approach should take into account the possibility that, for oncological reasons, the entire biopsy canal would need to be resected with a safety margin and histological examination performed during definitive surgery. Both the biopsy approach and the possible exit point of the drainage tube should be carefully chosen so

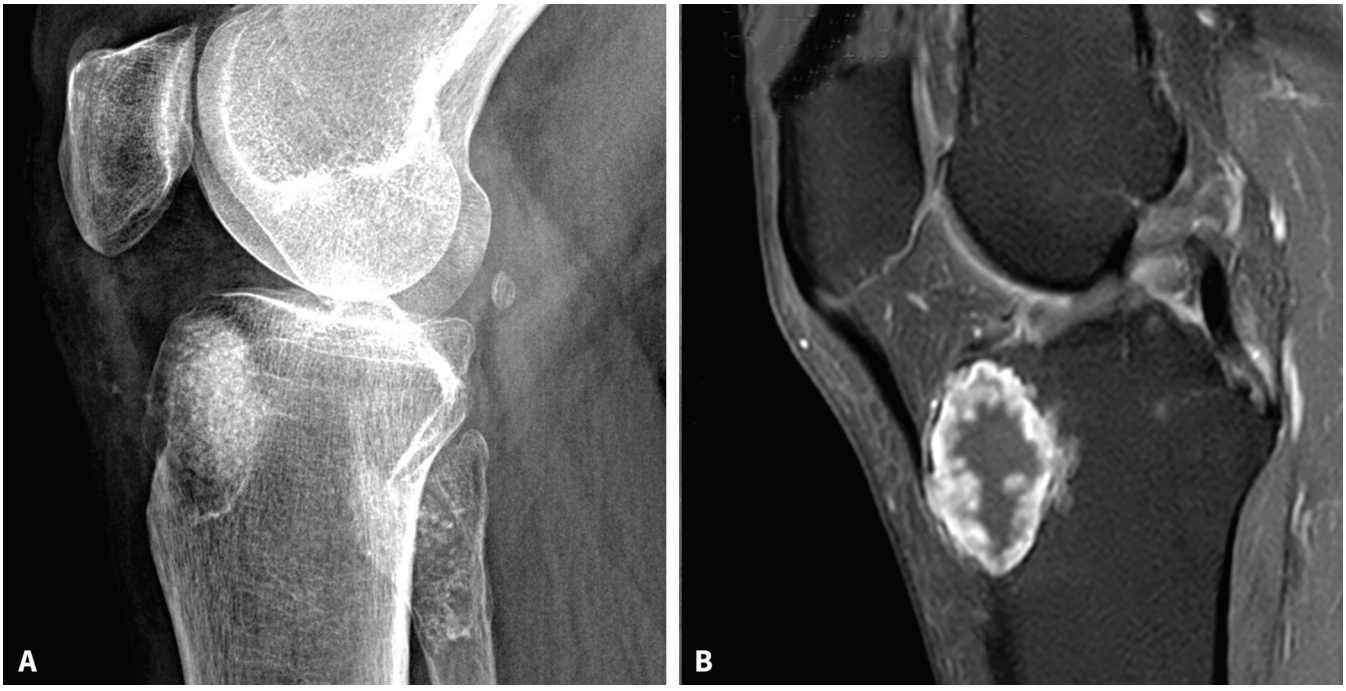

Figure 3: Radiographic (A) and MRI (B) images of a painful atypical cartilaginous tumour in the proximal tibia; on the right lower side of the radiographic image, there is also an asymptomatic enchondroma of the proximal tibia.
The atypical cartilaginous tumour exhibits aggressive features: bone expansion, endosteal scalloping, focal cortical destruction and spread into soft tissues. It is not clearly demarcated from the cancellous bone.

as not to contaminate the surrounding uncontaminated compartments (2). Proper surgical technique requires care to minimize contamination tumour seeding of the biopsy canal (preferably wide-bore needle biopsy of the soft tissue tumour component or core biopsy with a drill for intramedullary lesions) and precise imaging guiding (radiographic, CT or ultrasound-guided) to ensure that a sufficiently large sample is taken from the tumour area with the most aggressive features. Each biopsy is associated with a risk of sampling error or unrepresentative samples being taken (17), as benign, well-differentiated and malignant (undifferentiated) segments can be found in a cartilage tumour. Curettage with subsequent histological examination, in which the entire tumour cavity is removed, is used for small cartilage tumours of the hands and feet.

In certain cases, even histological examination cannot reliably distinguish between enchondroma, atypical cartilaginous tumour and chondrosarcoma. Therefore, a comparison between the histopathological presentation and MRI, where we look for signs of cortical permeation, is crucial (17). In uncertain cases, they should be overseen by a multidisciplinary medical council, taking into consideration all available clinical, radiological and histopathological data (for the Republic of Slovenia, it is the Radiological-Pathological-Orthopaedic Council at the Department of Orthopaedic Surgery at the University Medical Center Ljubljana); if necessary, histological samples should be sent to a reference centre abroad for consultation (17,18).

5 Histopathology

Surgical treatment of enchondromas in most cases involves intralesional curettage, so tumours are removed in small fragments, which often makes it impossible to microscopically assess the relationship of the tumour to the surrounding bone and thus some important parameters for separating enchondromas from other cartilage tumours (infiltrative growth, cortical erosion). A typical enchondroma has the appearance of grey-blue hyaline cartilage. Microscopic features of enchondromas are: paucicellular appearance; absence of cytological atypia (chondrocyte nuclei are small, round, dark, without nucleoli); lobular growth; frequent calcifications and absence of infiltrative growth between trabeculae (1). The microscopic characteristics of enchondromas differ according to their anatomical location, so the tumour site, together with radiological findings and clinical features, must be taken into account when interpreting the microscopic image; in enchondromas of hands and feet and multiple enchondromatosis enchondromas, the

histopathological presentation is frequently the same as in atypical cartilaginous tumours (1,19).

Atypical cartilaginous tumours are microscopically slightly more densely cellular than enchondromas, calcifications are less extensive or absent and mild cellular atypia (larger clear nuclei with nucleoli) are present. The most important and reliable histopathological criteria for distinguishing between atypical cartilaginous tumours and enchondromas are the presence of a myxoid tumour matrix, infiltrative growth and endosteal scalloping (usura). The latter two features are rarely seen in biopsy specimens of cartilaginous tumours. It should be noted that there is a morphological spectrum from the classical microscopic presentation of the enchondroma without atypical features to differently expressed atypical changes that speak in favour of an atypical cartilaginous tumour. Therefore, a correlation between histopathological picture and MRI picture is crucial for distinguishing between enchondroma and atypical cartilage tumour.

In addition to the changes seen in atypical cartilaginous tumours, the microscopic characteristics of chondrosarcomas (grades II and III) are increased cell density, significant cellular atypia and the presence of mitoses. These characteristics are normally so severe that in large bones, chondrosarcomas can be easily distinguished from enchondromas and atypical cartilaginous tumours (20). In the small bones of hands and feet, enchondromas can be densely cellular (similar to atypical cartilaginous tumours or even grade II chondrosarcomas); imaging studies show significant endosteal scalloping and bulging into surrounding soft tissues, so it can be very difficult to distinguish between enchondroma and chondrosarcoma in small bones. Microscopically, the diagnosis of chondrosarcoma of small bones can be confirmed if infiltration into soft tissues is found; finding mitoses in tumour cells also strongly suggests chondrosarcoma.

Enchondromas of the bony pelvis, spine, ribs and sternum are very rare, so all cartilage tumours at these locations need to be managed as aggressive and potentially malignant (1,20).

6 Clinical monitoring and treatment

Incidental asymptomatic intramedullary solitary enchondromas of long bones do not normally require treatment if they do not grow and cause endosteal scalloping. The principles of treatment of cartilage tumours needs to be explained to patients in detail, as many of them express a desire for biopsy or complete removal of the tumour just for fear of subsequent malignant transformation. Unfortunately, patients are occasionally unnecessarily unnerved by an ambiguous radiological report in which, despite the absence of any aggressive imaging features, an unlikely differential diagnostic option is mentioned: low-grade chondrosarcoma (2). As it is not always possible to reliably determine the tumour's nature radiologically, there may be a need for additional investigations or multidisciplinary management, which is stressful for patients. In this regard, it is important to note that the possibility of transformation from solitary enchondroma to malignant disease is less than 1% (21).

In case an enchondroma presents with local pain, appropriate treatment consists of thorough curettage after a biopsy and bone grafting or filling the bone defect with cement. Enchondromas of small bones of the hands and feet are normally actively treated with curettage due to the possibility of pathologic fracture (1). All patients with multiple enchondromas (Ollier disease, Maffucci syndrome) should receive life-long monitoring due to increased risk of malignant transformation, which is estimated at 15–30% (12).

One of Britain's leading sarcoma centres, The Royal Orthopaedic Hospital in Birmingham, recently developed the Birmingham Atypical Cartilage Tumour Imaging Protocol (BACTIP) to monitor solitary cartilage tumours of the proximal humerus and knee (4), which, in a retrospective evaluation of 387 cases over a 10-year data collection period, proved to be excellent (5). The use of BACTIP clinical guidelines for Slovenian orthopaedic surgeons was adopted by the Orthopaedic Society of the Slovenian Medical Association at its annual assembly on 29 November 2019 (7). The BACTIP protocol is based on radiological assessment of cartilage tumour length and endosteal scalloping, as shown schematically in Figure 4. Tumour length corresponds to the maximum measured tumour size on MRI, and a threshold of four centimetres determines whether the tumour is classified into Category I (tumours < 4 cm) or Category II (tumours ≥ 4 cm). Endosteal scalloping can be absent (A), focal (B) or generalised (C). Based on these two parameters, tumours are classified into the first six categories (IA, IB, IC, IIA, IIB, IIC). Category III includes tumours with aggressive radiological features (bone expansion or cortical thickening, cortical destruction, periosteal reaction or spread into soft tissues), regardless of size.

Category IA intramedullary tumours do not require follow-ups, while category IB tumours with focal endosteal scalloping are recommended for a follow-up MRI after three years. If the control MRI doesn't show changes, monitoring is concluded; if the tumour length increases by > 1 cm, the extent of endosteal scalloping increases or aggressive characteristics develop, a referral

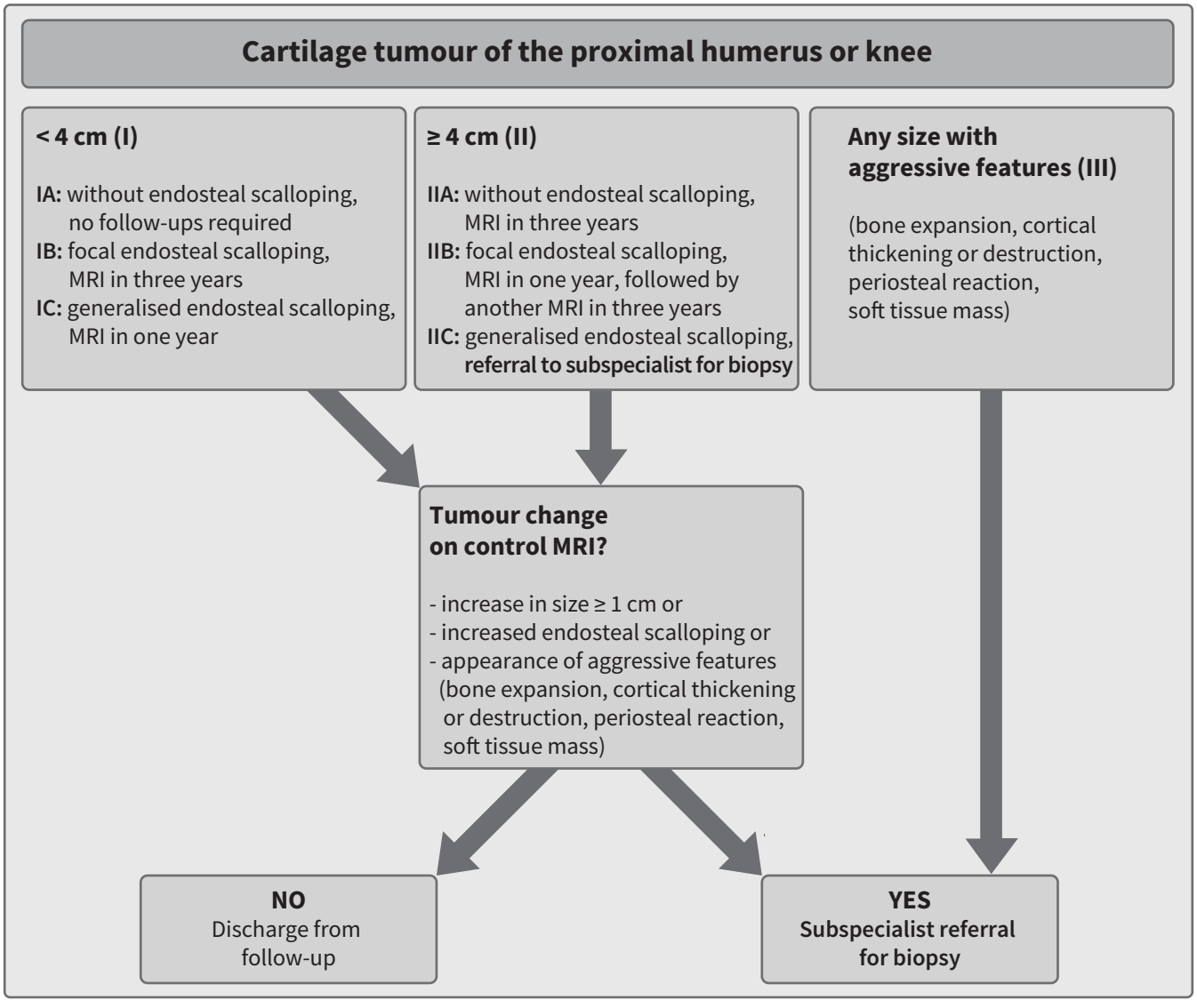

Figure 4: Schematic representation of the BACTIP for the monitoring of solitary cartilage tumours of the proximal humerus and knee with magnetic resonance imaging (MRI) with contrast. Summarized and adapted from (4,5).

to a subspecialist for bone tumours is recommended. Generalised endosteal scalloping (IC) also warrants immediate subspecialist referral.

Category II tumours without endosteal scalloping (IIA) are recommended to undergo a control MRI after three years; if there is no change, the patient is discharged from follow-up. For tumours with focal endosteal scalloping (IIB), a control MRI after one year is recommended, followed by another MRI after three years; if radiological changes are found, a specialist referral is recommended. Cartilage tumours with a size of ≥ 4 cm (IIC) or aggressive features (III) and generalised endosteal scalloping warrant an immediate subspecialist referral for assessment of biopsy indications.

7 Conclusion

Enchondroma is a common, mostly asymptomatic benign neoplasm of the mature hyaline cartilage, which does not require treatment. However, they are sometimes difficult to distinguish from other benign aggressive or malignant cartilage tumours. The combination of the relative frequency of enchondromas in the general population and the current routine use of MRI in diagnosing common orthopaedic diseases (e.g. meniscus and rotator cuff injuries) results in a large number of incidentally found enchondromas of the knee and shoulder, requiring further clinical management. The UK-developed BACTIP guidelines (4-5), also adopted for use

in Slovenia by the Orthopaedic Society of the Slovenian Medical Association (7), represents the basis for clinical treatment of patients with incidentally detected cartilage tumours in Slovenia. This protocol allows a safe distinction between common benign enchondromas and rare cartilage tumours requiring surgical treatment based on assessment of cartilage tumour size, endosteal scalloping and the presence or absence of other aggressive radiological features (bone expansion or cortical thickening, cortical destruction, periosteal reaction or spread to soft tissues).

Conflict of interest

None declared.

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