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Chondrosarcoma in the XXI century

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Chondrosarcoma (CHS) is a rare oncopathology, is the third most common primary bone tumor after multiple myeloma and osteosarcoma. It accounts for about 25 % of the total number of bone sarcomas. CHS mainly affects adults and occurs more often in people older than 40 years, in children and adolescents it is less than 5 % of all cases of primary CHS. The most common CHS sites can be any bone containing cartilage, but most often this tumor is found in pelvis, femur and shoulder bones, and ribs. CHS are divided: by origin (primary and secondary), anatomical site (central — inside the bone marrow canal, peripheral — inside the existing osteochondroma, periosteal — on the bone surface), histological degrees GI-GII-GIII. The WHO classification (2020) includes central normal, secondary peripheral, periosteal, dedifferentiated, mesenchymal and clear-cell CHS. More than 90 % of conventional CHS are tumors of low and medium malignancy degree, with a low potential for metastasis. CHS is caused by mutations in genes that control bone growth and development. The main risk factors are the patient's age, previous radiation, genetic factors and predisposition to oncological diseases. Diagnosis of CHS is based on a complex algorithm, which involves collecting the patient's complaints, anamnesis, clarifying clinical symptoms, imaging (X-ray, CT, MRI), histopathological picture. The biopsy conclusion is the most important in establishing the final diagnosis. However, there are several tumors whose histological picture is similar to CHS: enchondroma, chondroblastoma, osteosarcoma, giant cell tumor of bone, dedifferentiated liposarcoma, synovial sarcoma. The CHS treatment protocol is determined based on the results of anamnestic data, imaging, histopathological results, CHS classification, and its final tumor subtype. The «gold standard» remains surgical removal of the tumor. Radiation and chemotherapy don't play a significant role in the treatment of CHS, but require further study. Targeted and immunotherapy have a certain potential, even with a high degree of CHS resistance to traditional chemotherapy.

Хондросаркома (ХС) — рідкісна онкопатологія, третя за поширеністю серед первинних пухлин кісток після множинної мієломи й остеосаркоми та становить близько 25 % від загальної кількості сарком кісток. ХС уражає здебільшого дорослих і частіше виникає в людей старших за 40 років, у дітей і підлітків становить менш ніж 5 % усіх випадків первинної ХС. Патологія локалізується в кістках, які містить хрящ, але найчастіше її виявляють у кістках таза, стегновій і плечовій, ребрах. ХС розп оділяють: за походженням (первинні та вторинні), локалізацією (центральна — усередині кістковомозковаого каналу, периферична — усередині існуючої остеохондроми, періостальна — на поверхні кістки), гістологічними ступенями GI–GII–GIII. Класифікація ВООЗ (2020) розподіляє ХС на центральну звичайну, вторинну периферичну, періостальну, дедиференційовану, мезенхімальну та світлоклітинну. Понад 90 % звичайних ХС є пухлинами низького та середнього ступенів злоякісності, з низьким потенціалом метастазування. Ця патологія виникає внаслідок мутацій у генах, які контролюють зростання та розвиток кісток. Основні чинники ризику — генетичні, вік пацієнта, попереднє опромінення, схильність до онкологічних захворювань. Діагностика ХС базується на комплексному алгоритмі, який передбачає збір скарг пацієнта, анамнезу, з'ясування клінічних симптомів, результатів рентгенографії, комп'ютерної та магнітно-резонансної томографії і гістологічного аналізу після біопсії. Патологоанатомічний висновок є найвагомішим у встановленні остаточного діагнозу. Проте існує кілька пухлин, гістологічна картина яких подібна до ХС: енхондрома, хондробластома, остеогенна саркома, гігантоклітинна пухлина кістки, дедиференційна ліпосаркома, синовіальна саркома. Протокол лікування ХС визначають на підставі результатів анамнестичних даних, променевої візуалізації, гістопатологічної картини, класифікації. «Золотим стандартом» залишається хірургічне видалення новоутворення. Променева та хіміотерапіія не відіграють суттєвої ролі в лікуванні ХС, але потребують подальшого вивчення. Певний потенціал мають таргетна й імунотерапія. Ключові слова. Хондросаркома, класифікація, діагностика, лікування.

Key words. Chondrosarcoma, classification, diagnosis, treatment

Introduction

Chondrosarcoma (CS) is a rather rare abnormality, which is a heterogeneous group of malignant bone tumors characterized by the formation of neoplastic hyaline cartilage tissue [1]. It was separated into an independent form by Phemister in 1930. It is the third most common among large primary malignant bone tumors after multiple myeloma and osteosarcoma, making up 20–25 % of the total number of all tumors of the musculoskeletal system and is characterized by the initial development from cartilage cells [2–4]. It has been proven that CS accounts for about 3.6 % of the annual incidence of all primary malignant tumors and 20–30 % of primary malignant bone tumors in the United States [5]. On a global scale, the total incidence of CS is estimated at approximately 0.1–0.5 cases per 100,000 population per year [3]. CS usually affects adults, and the incidence increases with the age of patients, and it is more often found in people over 40 years of age. The peak incidence falls on the fifth-seventh decade of life. Patients with secondary CS are mostly younger than those with primary CS, with an average age of 34 years [6]. The incidence of CS varies greatly depending on the specific subtype and primary location of the neoplasm. For example, juxtacortical CS (a rare subtype) accounts for less than 1 % of all CSs, and mesenchymal CS accounts for 3–10 %. It should be noted that the incidence of CS in the gender ratio (male: female) is approximately 1.5:1.

Regarding children and adolescents, CS is a very rare neoplasm in the age group of less than 18 years, and the incidence rate of CS differs significantly from adults. In particular, Finnish scientists demonstrated an overall incidence of 3.6 children or adolescents per 1 million for osteosarcoma, 1.2 for Ewing's sarcoma, and only 0.3 for CS [7]. And according to the Japanese National Registry of Bone and Soft Tissue Tumors, 521 young patients (under 15 years) with primary diagnosed malignant bone neoplasms were identified between 2006 and 2013. Among them, only 8 (1.5 %) people had CS [8].

Any bone containing cartilage can be the most common anatomical site of CS origin, but it is most often found in the proximal part of the femur and humerus, the distal part of the femur, pelvic bones, and ribs. The femur is one of the most frequent locations in the lower extremity for common CS and accounts for approximately 20–35 % of cases, while the upper extremity is affected in 10–20 % of cases (proximal humerus) [9, 10]. Damage to long bones usually involves the metaphysis (49 % of cases) [11]. Common CS also often affects flat bones, such as the bones of the pelvis, scapula. CS of pelvic bones is observed in about 10–15 % of the total number of CS [12], in particular, in the ilium — up to 70 % versus 30 % in the femur [13]. Distant metastases develop in approximately 26 % of patients with CS, and most often in the lungs [14, 15].

CSs that arise de novo are called primary, and those that develop on the basis of existing benign cartilage tumors (enchondroma or osteochondroma) are called secondary. CSs are a heterogeneous group of tumors that can be classified according to their anatomical location as central (arising in the medullary canal) or peripheral (in the cartilaginous «lid» of the exostosis). Secondary CS, which develops on the bone surface as a result of malignant transformation within the cartilage of a previously existing osteochondroma, is also called peripheral. The risk of CS in single osteochondroma is known to be less than 1 %. However, with multiple osteochondromatosis, the risk increases to 5 %, mostly after the maturity of the bone skeleton [16]. Patients with Ollier disease and Mafucci syndrome may have up to a 40 % risk of developing CS. In addition to the usual primary SCs that show hyaline cartilage differentiation, there are other types of tumors such as dedifferentiated, mesenchymal, or clear cell subtypes with distinct genetic and clinicopathological characteristics [17].

As mentioned above, CSs are distinguished by their origin (primary and secondary), localization (central — inside the intramedullary cavity, peripheral — inside the cartilage cover of a pre-existing osteochondroma, periosteal — juxtacortical, on the surface of the bone) [3, 4, 18]. Further classification of CSs is based on histological subtypes of the tumor, including normal (grades I–III), clear cell, mesenchymal, and dedifferentiated CS [19, 20]. Finally, the 2020 World Health Organization classification divides CS into subtypes: central common, secondary peripheral, periosteal, dedifferentiated, mesenchymal, and clear cell CS [21]. Characteristic features of visualization of numerous categories of CS can contribute to their accurate diagnosis and classification. Radiography helps to identify chondroid tumors of the enchondroma type with their characteristic features. Computed tomography (CT) and magnetic resonance imaging (MRI) can usually reveal features of the visual picture of malignancy to differentiate between chondrosarcoma and enchondroma [22].

The average survival rate of patients with CS is higher than that of patients with osteosarcoma and Ewing's sarcoma: 5 years in 72–75 %, 10 years in 69 % [21, 23–25]. Wide ablastic resection of the tumor has become the «gold standard» of CS treatment, which

has hardly changed during the last decades. However, no difference in overall survival of patients who underwent wide excision or intra-focal curettage was found for G-I CD [22, 26, 27]. For more aggressive subtypes of CS (G-II, G-III), surgical resection is associated with a longer period of life of patients compared to marginal or intrafocal [24, 28, 29]. This may be due to the fact that mostly CSs are resistant to both chemo- and radiotherapy due to the presence of extracellular matrix, a low percentage of dividing abnormal cells, and poor vascularization [26, 30–32].

The results of treatment of patients with CS depend on the degree of tumor differentiation, stage and limits of surgical intervention, and a high degree of malignancy of CS indicates a decrease in patient survival [33–35]. Despite advances and numerous attempts to improve treatment techniques, survival rates have remained largely unchanged over the past decades. The studies conducted were within a single institution or used the SEER (Surveillance, Epidemiology and End Results) database, and mainly analyzed median survival and changes in patient status associated with poor prognosis. To date, there is a fairly large study of CS, which analyzed 2,890 CS cases from the SEER database [36], but it examined cases from 50 years ago, from 1973 to 2003. No work has examined CS rates within the National Cancer Data Base (NCDB), created by the American College of Surgeons and the American Cancer Society, which includes more than 30 million patient demographics and accounts for more than 70 % of new cancer diagnoses in of the United States [37, 38]. With the emergence of new surgical and general oncology treatments, the current study seeks to use the latest data from the authoritative NCDB database to update the scientific literature on CS, recognize recent trends in CS incidence, evaluate demographics, changes in therapy tactics associated with improved diagnostic outcomes and treatment of patients with CS.

Etiology

The exact etiology of CS is currently not well understood, research in this direction is constantly ongoing. The causes of CS, like most malignant tumors, are not completely understood. However, it has been established that the disease is usually caused by mutations in the genes that control bone growth and development.

Several identified CS risk factors are as follows:

– age — CS is more often observed in the elderly, with the peak incidence in patients at the age of 50–70;

– previous radiation — ionizing radiation used during the treatment of cancer or other diseases can increase the risk of developing CS;

– genetic factors and genetic predisposition to oncological diseases — some family syndromes (for example: multiple hereditary exostoses and Ollier's disease, Mafucci syndrome) are associated with an increased risk of developing CS. Mutations in the IDH1 and IDH2 genes have also been found in some cases of CS;

– Paget's disease — characterized by abnormal bone remodeling and growth, may increase the risk of developing CS;

– bone infarcts — areas of dead bone tissue caused by impaired blood supply, associated with an increased risk of CS;

– chondroma of soft tissues is a benign tumor that can sometimes transform into CS;

– history of skeletal bone injuries;

– toxic substances — included in the composition of such materials as asbestos and carbon, with prolonged toxic effects on the human body can cause aberrations at the cellular level and lead to the development of CS;

– Li-Fraumeni syndrome — occurs due to mutations in the TP53 gene, which is responsible for the synthesis of the so-called «tumor protein» P53. The latter is a suppressor of tumor growth and without its proper functioning, cells can divide uncontrollably and turn into sarcoma. All individuals with Li-Fraumeni syndrome have a 90 % chance of developing one or more types of cancer [39].

In the preventive aspect, screening of patients with benign bone-cartilage lesions plays a certain role. The increased risk of malignant transformation by osteochondroma, chondroma and enchondroma has been proven. The risk of secondary malignancy in single osteochondroma is usually lower than in patients with multiple osteochondromatosis. An annual MRI examination is recommended for such patients, especially in the presence of relevant clinical symptoms. A thorough radiographic examination should be performed when any pain and/or swelling first appear or progress over time [40–43].

Overall, the etiology of CS is complex and likely involves a combination of genetic and environmental factors that influence the development and differentiation of cartilage and bone tissues. Further research is needed to better understand the causes of this disease and to develop more effective prevention and treatment strategies.

Types of chondrosarcoma

CS is considered a slow-growing and low-aggressive tumor, but there are also quite aggressive subtypes. Several types of CSs are divided based on localization and histological and molecular features. Each type of CS has its own characteristic pathohistomorphological features, which usually determine the choice

of treatment tactics and the prognosis of the disease. The main types of CS include:

1. Common or central CS is the most common type, occurs in the bone marrow cavity of long bones and accounts for approximately 85 % of cases. It consists of well-differentiated cartilage cells and hyaline cartilage matrix. Central CS occurs in the pelvis, femur, or humerus.

2. Dedifferentiated CS is a rare and aggressive subtype, containing a well-differentiated tumor of cartilage, or enchondroma, or CS of low degree of malignancy, with a sharp transition to a focus with non-cartilaginous sarcoma of high degree of malignancy. More aggressive than usual, it accounts for about 10 % of all cases of CS and has a higher risk of metastases. The average age of patients is from 50 to 60 years. Men and women are affected equally. The most common sites of damage are the femur and pelvis. Most lesions occur centrally in the medullary cavity of the bone, although there are reports of dedifferentiation in the case of juxtacortical type of CS or from an existing osteochondroma.

3. Mesenchymal CS is a rare subtype (less than 2–13 % of all primary CSs), consists of small undifferentiated small round or spindle-shaped cells with areas of hyaline cartilage, characterized by the production of both cartilage matrix and fibrous or myxoid stroma. It occurs in the bone, in the soft tissues of the head, neck or trunk at any age, with a peak incidence in the second or third decade of life. The craniofascial area is most often affected (15~30 %), in particular the lower and upper jaws. Other common localizations are femur and shoulder bones, ribs, spine, pelvis. About 7 % of bone lesions are multicentric. About 1/3 of the lesions are mainly extraskeletal areas, of which the meninges (cranial > spinal) are more often affected. It is more aggressive than conventional CS in terms of course, and also has a higher risk of metastasis [44].

4. Clear cell CS is a rare subtype (about 1–2 %) of all low-grade CSs, characterized by the presence of specific «clear» cells (clear cytoplasm) in tumor tissues. It affects men more often than women (2.6:1) and has a predominant localization in the epiphyses of long bones (proximal femur and humeral head in 2/3 of cases), but most bones, including the spine, ribs, pelvis, and hands and feet may be involved. The age range is wide, with peak incidence from 30 to 40 years. Clinically, clear cell CS appears one to two decades later than chondroblastoma. It mostly has a good prognosis [45, 46].

5. Juxtacortical (periosteal) CS occurs in the periosteum or soft tissues adjacent to the bone, is localized on the surface of the femur or humerus, in the metaphyseal zone. It is characterized by the production of hyaline cartilage matrix and can be mistaken for a benign tumor, for example, osteochondroma. The peak incidence is from 30 to 40 years. The tumor mostly has a low degree of malignancy and a good prognosis [47, 48].

6. Secondary CS is a rare subtype that occurs in previously benign cartilaginous tumors, such as enchondromas or osteochondromas, which can be both central and peripheral (more often). It usually develops in older people and has a better prognosis than other types of CS. Malignant transformation into peripheral CS is observed in 1 % of cases with solitary osteochondroma, in 3–5 % with osteochondromatosis (hereditary multiple exostoses) [49, 50]. Central secondary CS develops as a malignant transformation of enchondroma (extremely rare) or enchondromatosis, such as Ollier disease or Maffucci syndrome. Patients with Ollier disease and Maffucci syndrome have a 25–30 % risk of developing CS. Ollier's disease is a non-hereditary developmental anomaly characterized by numerous enchondromas in the epiphyses, metaphyses and diaphyses of skeletal bones.

The size, number, location and evolution of enchondromas are quite diverse. Clinically, the disease is characterized by asymmetric, unilateral damage to the lower extremities, but often bilateral damage to the hands and feet. Any part of the skeleton formed by endochondral ossification can be affected. Maffucci syndrome is a condition in which enchondromatosis is combined with soft tissue hemangiomas [51, 52].

About 80 % of primary CSs are common. Secondary abnormalities account for less than 10 % [9, 53]. Some authors report that they develop from 0.4 to 2.2 % of patients with solitary osteochondroma or enchondroma [54], in 27.3 % with hereditary multiple exostoses [55], 30–50 % with Ollier's disease, up to 100 % with Maffucci syndrome [56, 57]. Enchondromas are considered as precursors of secondary central CS, osteochondromas as peripheral ones. There are genetic differences between primary and secondary CSs, causing variations in clinical presentation and behavior [11]. Secondary tumors usually have a low degree of malignancy. Changes in clinical symptoms in patients with known previous pathology indicate the development of CS. The most frequent site of damage for secondary CS is the pelvis, followed by the proximal part of the femur, the scapula, and the proximal part of the humerus [58].

Myxoid CS is another so-called «subspecies» of CS, characterized by noticeable myxoid changes of ordinary highly differentiated CS. However, extraskeletal

myxoid CS is a disease different from bone CS: these soft tissue sarcomas most often occur in the lower extremities [59, 60]. The term «chondrosarcoma», which is used to describe extraskeletal myxoid CS, is incorrect, since well-formed hyaline cartilage is determined only in a minority of cases of this disorder [61, 62]. The 2020 WHO classification distinguishes extraskeletal myxoid CS as a «tumor of uncertain differentiation» [63]. Myxoid CS of bone is also not designated as a unique independent neoplasm, and that is why these tumors should rather be considered as myxoid variants of ordinary CS [21].

According to the degree of differentiation, CS tumors are divided into high- and low-differentiated, as well as intermediate level of differentiation. The most aggressive subtype is highly differentiated CS, characterized by the highest risk of metastases and local recurrences. Fortunately, this is an uncommon subtype of CS, accounting for approximately 5–10 % of all cases. This abnormality is characterized by a high degree of cellular atypia, mitotic activity, and invasion of adjacent tissues. It is usually removed surgically, followed by radiation and chemotherapy. The goal of surgery is to remove the entire tumor within healthy tissue and reduce the risk of recurrence. However, highly differentiated CS is often resistant to chemotherapy and therefore has a poor prognosis.

Poorly differentiated CS is the most common subtype of CS, accounting for approximately 70–80 % of all cases. It usually grows slowly and has a low risk of metastases. However, it can be locally aggressive and often requires surgical intervention to remove the tumor to prevent its spread.

Intermediate class CS does not occur as often as poorly differentiated one, but is characterized by a higher risk of developing metastases and local recurrences. In most cases, it is removed surgically, followed by radiation therapy, because chemotherapy is almost ineffective.

A very important distribution of CS is their gradation according to the degree of malignancy according to histological assessment. Biological behavior of CS is evaluated from 1 to 3 based on the size of cell nuclei, staining pattern (hyperchromasia), mitotic activity and cell density [64]. Grade CS1 is a low-grade tumor that contains chondrocytes with small, dense nuclei, but cells with enlarged nuclei (> 8 μm) and a few multinucleated cells (most often binucleated) may be present. The stroma is mainly chondroid, with rare or absent myxoid areas [31]. The CS2 grade includes CSs of moderate degree of malignancy, which contain less cartilaginous matrix and a larger number of cells compared to CS1 tumors. Chondrocyte nuclei are enlarged, vesicular or hyperchromatic, there are binucleate and multinucleate cells [3]. CS3 (CS3), a high degree of malignancy, is characterized by greater cellularity compared to CS1 and CS2 tumors, nuclear pleomorphism with minor areas or absence of cartilaginous matrix. Nuclei are usually vesicular, often spindle-shaped and may be 5–10 times larger than normal. Non-mineralized tissue in CS has high water content, histologically varying from mature hyaline cartilage to a more myxoid stroma [3]. The periphery of CS is characterized by invasion of chondroid tissue into trabecular bone. After determining this morphological feature, the degree of cellularity is used to determine the degree of malignancy of CS. Invasion of the endosteal surface reflects the beginning of extraosseous spread of the tumor, as the first step to high-grade CS [65]. Most CSs are common, about 60 % of them are classified as CS1 or CS2 [66].

Classification

It is a very important and mandatory stage in the diagnostic and treatment process, required for accurate diagnosis, choosing the appropriate treatment with an emphasis on surgical intervention, and finding out the prognosis of the course of a malignant neoplasm. CSs can be classified on the basis of several factors, including localization, histological characteristics and the degree of differentiation, aggressiveness of the tumor.

Classification based on localization: for example, CS of the pelvic bones, CS of the femur or humerus with the definition of the site (diaphysis, metaphysis, epiphysis), etc.

Histological classification of CS is based on the distribution of tumors according to histological characteristics (the presence of hyaline cartilage matrix, fibrous or myxoid stroma, or clear cell cytoplasm). Also, CS is classified on the basis of the histological degree of differentiation into 3 classes — GI, GII, GIII. Low-differentiated CSs contain cells that resemble normal chondrocytes by phenotype, while highly differentiated ones contain significantly more atypical cells and may resemble other types of bone sarcomas. Histological grading is an important prognostic factor for the course of CS, playing a significant role in the choice of treatment tactics. At the same time, it has been proven that highly differentiated tumors have a much worse prognosis.

Class I (low-differentiated CS) is the most common type, accounting for approximately 70 % of cases. Class I CSCs have low cellularity, slow growth, low risk of metastasis, and are mostly successfully treated surgically.

Class II (intermediate degree of CS differentiation) has greater cellularity and more nuclear atypia than grade I tumors. They are more aggressive, have

a higher risk of metastases. Treatment usually involves surgical removal of the tumor and may also include radiation therapy.

Class III (highly differentiated CS) is the most aggressive type, with high cellularity, frank nuclear atypia, and high mitotic activity. They have a high risk of metastases and are usually treated comprehensively.

Surgical classification

For onco-orthopedics and specialists who implement the surgical stage of treatment of CS, the most important is the surgical classification of bone tumors according to Enneking, which is based on the anatomical location of the tumor, the histological degree of its malignancy, the presence or absence of metastases. With the help of this classification, it is possible to clearly clarify the options for surgical treatment of CS depending on the stage of the tumor. In the Enneking system, malignant bone tumors (CS, etc.) are divided into three categories:

Stage I: poorly differentiated tumors that are limited to the bone and do not spread to other parts of the body, divided into two subcategories:

– IA — the tumor is intracompartmental, that is, it is limited to the cortical layer of one bone and does not violate the periosteal zone;

– IB — the tumor is extraosseous, violates the periosteum and can be in contact with the adjacent soft tissues.

Stage II: highly differentiated tumors limited to bone, not spreading to other parts of the body, divided into two subcategories:

– IIA — intracompartmental, that is, limited to the cortical layer of one bone and do not violate the periosteal zone;

– IIB — the tumor is extraosseous, violates the periosteum and may be in contact with the adjacent soft tissues.

Stage III includes tumors that have metastasized to other organs and systems of the body (lungs, liver, brain, etc.), have two subcategories:

– IIIA — metastases are single, limited to the lungs and can be removed surgically;

– IIIB — metastases of significant size, inoperable, or there are too many of them.

The international classification of bone tumor stages is based on determining the degree of malignancy, size and presence of metastases (Table) [21].

Symptoms and clinical characteristics of chondrosarcoma

Presentation of CS depends on its level of malignancy, clinical symptoms are mostly non-specific. For example, G1 CS can develop gradually over several years. At first, the patient feels discomfort at the site of the neoplasm, followed by the development of pains, weak at first, but intensifying over time. Painful sensations disappear after rest, later on patients usually start to take painkillers. At night, the pain intensifies, over time the tumor increases in size, it can be seen visually or palpated. Hyperemia of the skin over the location of the CS, a slight increase in temperature, an increase in the intensity of the pattern of blood vessels, and pain during movement are possible. The patient may note a decrease in motor activity and coordination.

In CS GII–GIII degrees of malignancy, the disease progresses quite acutely, and already 2–3 months after the development of a tumor, the patient turns to specialists. He is bothered by severe pain in the location of the neoplasm, painkillers do not help. The pain increases every day and does not leave the patient even during the day. The patient complains of weakness and weight loss. This type of CS most often affects young people and is characterized by frequent relapses. Symptoms of the disease largely depend on the location of the tumor. If the pelvic bones are affected, the pain may radiate to the buttock and lower limbs. Possible symptoms may include difficulty urinating, swelling of the lower limbs, paresis and muscle atrophy.

General clinical symptoms of CS may vary depending on the location and size of the tumor. Common symptoms include:

– pain that is often described as dull and getting worse over time. Can be localized at the site of the tumor or radiate to other areas;

– swelling or formation at the site of the tumor. It can be hard or soft and accompanied by increased local sensitivity or hyperthermia;

– limited mobility if the tumor is located near a joint or bone. This can cause stiffness, weakness, or difficulty moving the affected limb or joint;

– deterioration of bone quality and increased risk of pathological fractures, especially in the bones of the lower limbs. The latter can be observed even at the time of initial treatment (up to 27 %);

– neurological symptoms due to tumor compression of adjacent nerves — such as numbness, tingling or weakness in the affected area;

– fatigue or weakness, especially if the tumor has spread to other parts of the body.

It is important to note that some CSs do not cause any symptoms in the early stages and may be accidentally detected during imaging studies. In the case of advanced stages of CS with the presence of distant metastasis, the clinical manifestations of the abnormality correspond to the symptoms of the affected organ.

Table

International TNM classification of primary malignant tumors, 6th edition according to [21]

Stage	Tumor (T)	Limph Node (N)	Metastases (M)	Grade (G)
IA	T1	N0	M0	G1 or G2
IB	T2	N0	M0	G1 or G2
IIA	T1	N0	M0	G3 or G4
IIB	T2	N0	M0	G3 or G4
III	T3	N0	M0	Any G
IV	Any T	N0	M1	Any G

Notes. Tumor (T): TX — primary tumor cannot be assessed, T0 — no evidence of primary tumor, T1 — tumor 8 cm or less in greatest dimension, T2 — tumor greater than 8 cm in greatest dimension, T3 — tumor ruptures in primary bone, skip metastases. Lymph node (N): NX — regional lymph nodes cannot be evaluated, N0 — no regional lymph node metastasis, N1 — regional lymph node metastasis. Distant metastases (M): MX —presence of distant metastases cannot be assessed, M0 — no distant metastases, M1 — other distant metastases, M1a — lung metastases, M1b — other distant metastases. Grade of malignancy (G): G1 — highly differentiated, G2 — moderately differentiated, G3 — poorly differentiated, G4 — undifferentiated.

Most often, metastases affect nearby lymph nodes, then the lungs, liver, and can even reach the brain.

Diagnosis

Diagnosis of CS involves a combination of data from the patient's presentation, history, clinical symptoms, radiological imaging studies; biopsy with histological analysis.

Radiographic research methods — X-ray, CT and MRI, positron emission CT (PET-CT) — make it possible to determine the location, size, and degree of a tumor, to assess damage to adjacent tissues and organs, as well as the presence of metastatic spread of the tumor. Histological analysis of microspecimens after biopsy is necessary to confirm the diagnosis of CS, determine its subtype and degree of malignancy. In addition to these diagnostic tests, clinical, biochemical and immunological studies of the patient's biological fluids are carried out, as well as, as indicated, molecular analysis to detect specific genetic mutations or other molecular markers that can significantly affect the choice of treatment tactics. It is important to note that CS can be difficult to diagnose, especially in the early stages or in cases where the tumor is small and located in a hard-to-reach anatomical area. A multidisciplinary group of experts in bone and soft tissue tumors should be involved in the diagnosis and treatment of the disorder.

X-ray, CT and MRI are considered to be the standard radiological diagnosis of bone tumors. Since X-rays usually do not distinguish between CS and other types of bone tumors, a CT scan or MRI is used to analyze the tumor in more detail. These research methods can also be used for guided biopsy in the most difficult diagnostic cases. It should be noted separately that PET-CT, in addition to cases of primary diagnosis of CS, can also be used to monitor the response of the tumor to treatment in time course and to detect any early relapse.

Radiographic images of common CS reveal a mixed lytic and sclerotic pattern with characteristic small calcifications, often called «popcorn» or «rings». In long bones, primary CS most often involves the metaphysis (49 %), followed by the diaphysis (36 %). Sclerotic areas are mineralization of the chondroid matrix, which is observed in 60–78 % of cases. The presence of typical calcifications is a radiological feature of cartilaginous neoplasms, but often does not allow distinguishing benign, borderline or malignant types. The size of the lesions (< 5 cm); the absence of a breakthrough through the cortical bone layer, an infiltrative pattern, and a lytic component indicate a benign or borderline tumor. The location of the focus in the axial skeleton and its size of more than 5 cm is a reliable predictor of CS of low degree of malignancy [65]. Radiographic features, including cortical destruction, soft tissue enlargement, and characteristic changes, the so-called «moth-eaten pattern», are usually associated with malignancy. It is often observed for CS with a high degree of malignancy.

Endosteal ridge is a sign of aggressiveness of intramedullary cartilaginous lesions, but it is not a complete diagnosis of malignant process. Sensitive radiographic features that distinguish enchondroma from CS include deep endosteal crestal (≥ 2/3 of the normal thickness of the cortical layer) and longitudinal endosteal (≥ 2/3 the length of the abnormal focus) lesion [3, 66]. CS often grows slowly and the periosteal layer reacts to keep the tumor in the medullary cavity. This leads to preservation of the edge of chondrosarcoma, which is manifested by remodeling of the cortex, its thickening and periosteal reaction [20]. Thus, enchondromas and intramedullary poorly differentiated CS (borderline tumors) of long bones often have similar X-ray features. These lesions should be diagnosed by histological examination after complete resection of the lesion, whether by total tumor excision or intrafocal curettage.

MRI is the best way to diagnose a cartilage tumor specifically for assessing the degree of bone marrow damage and the presence of changes in soft tissues. T1-images after injection of gadolinium contrast show pronounced «septal» or «ring-arc» enhancement is typical of enchondromas and poorly differentiated CS, corresponding to fibrous bands between fused carti-

lage lobules on histological analysis. Heterogeneous or homogeneous amplification of highly differentiated forms of CS correlates with cellular areas under microscopic examination [67]. In addition, contrast-enhanced MR imaging can help differentiate between enchondromas and CS [68].

Secondary peripheral CS have characteristic radiological signs of malignant transformation and include the growth of a previously unchanged osteochondroma in a mature skeleton, an irregular or unclear surface of the lesion, focal areas of osteolysis in its bone component; erosion or destruction of the adjacent bone, a significant increase in the volume of soft tissues containing scattered or irregular calcifications [69]. The thickness of the cartilaginous membrane of the tumor in such cases can be estimated quite accurately with the help of CT and MRI [70]. On MRI scans, CS is characterized by low signal on T1WI and markedly high signal on T2WI, showing peripheral and septal enhancement with a partial growth pattern. Mineralization of the matrix manifests itself in the form of point or curvilinear foci with a low signal level [70, 71]. Some authors emphasize precisely the qualitative assessment of the cartilaginous membrane of the tumor. The unevenness of its surface may indicate the invasive nature of tumor growth [58].

Secondary central CS is characterized by an extended endosteal comb lesion, remodeling of the cortical layer, its destruction and periosteal reaction on radiography, especially in comparison with previous images of the main enchondroma [72, 73]. On CT scans, characteristic features of a malignant neoplasm are lytic areas, endosteal festoon on 2/3 of the cortex and more, or spread to soft tissues [72]. Criteria for malignant transformation of enchondroma on MRI images: destruction of the cortical layer, spontaneous pathological fracture, periosteal reaction, peritumor edema and soft tissue neoplasms [72]. However, the conversion of a solitary enchondroma to CS remains controversial, mainly because of the need for radiographic evidence of an enchondroma to demonstrate its transformation to CS over several decades of follow-up. However, the signs of ordinary CS (endosteal festoon, thickening of the affected bone, cortical thickening and amorphous calcification) in combination with the features of typical benign enchondromas (clear ring-shaped calcifications) justify the diagnosis of secondary central CS [9].

Radiologically, periosteal CS has the appearance of a soft tissue component of round or oval shape on the surface of the bone, which raises the periosteum above the tumor in the form of a fibrous pseudocapsule. The cortical layer of the bone remains almost unchanged, may be thickened or thinned, but complete destruction of the cortex is not often observed. Codman's triangle can be seen at the place where the periosteum is raised. Typical mineralization of the chondroid matrix is usually present, and metaplastic ossification is often determined to varying degrees [3, 20]. The medullary canal is mostly not involved, although its expansion is sometimes detected on MRI [74, 75]. Periosteal chondroma and periosteal osteosarcoma are the most difficult tumors to differentiate from periosteal CS. The size of the tumor is the only distinguishing feature between the first (average size 2.5 cm) and the second CS (4 cm) [74, 76, 77]. Periosteal osteosarcomas and CS contain cartilage, but osteoid formation is not detected in CS during histological examination [75, 76].

In the clear-cell form of CS, X-rays show mainly a lytic epiphyseal lesion with clear sclerotic edges, which simulate a benign lesion. In cases of clear-cell CS, mineralization of the matrix is observed in approximately 30 % of cases [46, 78]. Moderate bony expansion may be evident, but soft tissue thickening occurs in less than 10 % of cases [22, 51]. Because of the epiphyseal location, clear-cell CS is difficult to distinguish from chondroblastoma [22]. On MRI, clear-cell CS is heterogeneous due to areas of hemorrhage or cystic changes. Peritumor edema is uncommon and always mild, unlike chondroblastoma [46].

Radiological pattern of mesenchymal CS is aggressive bone destruction with a «moth-eaten» pattern and a vaguely expressed periosteal reaction [77, 79]. The tumor is often very large, with significant extraosseous components [3]. CT scans show mineralization of the chondroid, which may make the lesion appear overly calcified, but more commonly, calcification with a «fine point» [80]. On MRI images, mesenchymal CS has a different pattern of contrast enhancement than normal CS; diffuse and typical chondroid septal and peripheral enhancements are often absent. In some zones, in contrast to other CS, serpentine vessels with a low signal are observed. An aggressive bone lesion with thin mineralization of the cartilage matrix, an intermediate signal on T2WI (lower than in ordinary CS) and sharp enhancement than in other types of CS are defined [3].

Dedifferentiated CS has a wide range of radiological signs, but their characteristic features are polymorphism of the tumor, including aggressive bone destruction with extraosseous spread into soft tissues, associated with the main damage to the cartilage [54]. On the basis of radiological manifestations, this type of tumor can be classified into three types: 1 — radiological signs are the same as in central CS, with the addition

of a suspected area with dedifferentiation; 2 — the tumor resembles a normal benign enchondroma, but with destructive changes and/or a large soft tissue component; 3 — significant destructive lesions of bone tissue without signs of a cartilaginous component [81]. CT and MRI can reveal two areas with different internal characteristics [3]. This bimorphic pattern is valuable for targeting high-grade malignancy during CT- or MRI-guided puncture biopsy [82].

Interesting and useful for practical use is the Birmingham protocol for imaging CS, created for tumors of cartilage tissue that were localized in the proximal part of the humerus and in the area around the knee joint. The categories of this protocol are: (A) — cartilage lesion less than 4 cm, focal/generalized endosteal lesion — 10 % or less, or 36° of lesion circumference on axial image with largest area of destruction; (B) — destruction of cartilage over 4 cm; (C) — cartilage lesions of any size with aggressive features (bone growth and/or cortical thickening, periostitis, cortical destruction and soft tissue neoplasms) [83].

Genetic testing may also play a role in the diagnosis of CS, although it is not used as a stand-alone test. There are several genetic abnormalities associated with CS. The most famous of them are mutations in the isocitrate dehydrogenase (IDH) genes, in particular IDH1 and IDH2. These mutations are found in the majority of CS, mainly in central or secondary malignant variants. To test for IDH mutations, a sample of tumor tissue is analyzed using molecular techniques such as DNA sequestration. This helps identify specific mutations in the IDH genes, which can help confirm the diagnosis of CS as well as provide important prognostic information. It is worth noting that IDH mutations are not present in all cases of CS, and their detection alone is not sufficient for a definitive diagnosis. Other genetic and molecular alterations can also be found in CS and current research is aimed at identifying additional markers useful for diagnosis, prognosis and targeted therapy [84].

Differential diagnosis

More than 90 % of conventional CS are tumors of low and intermediate grade of malignancy and should be distinguished from enchondromas. The most likely diagnostic procedure in this situation is a biopsy. It is very important to take biopsy material from the cortical and medullary parts of the bones in the affected area. Some studies show that the presence of a myxoid matrix of 20 % or more strongly suggests CS. Significant myxoid change is an ominous sign of cartilage involvement, and in such cases, other histological features suggestive of CS should be sought. If areas with a clear neoplastic osteoid are found in the specimens, the lesion should be considered an osteosarcoma with chondroblastic differentiation [85, 86].

The differential diagnosis between enchondroma and CS is crucial, since CS requires surgical treatment and close follow-up with X-rays, CT, MRI, while most enchondromas do not require either treatment or follow-up [87]. Enchondroma can be distinguished from CS by the following signs: cortical destruction, extraosseous increase in soft tissue, periosteal reaction, size 5 cm or more, endosteal festoon (more than 2/3 of the thickness of the cortical layer) [88, 89]. In the absence of specific diagnostic criteria for the histopathological differentiation between these two diseases, the final diagnosis is established on the basis of consensus between radiological, pathological and clinical findings [66]. Some MRI features have been identified that help differentiate CS from enchondroma: the presence of a predominantly intermediate signal matrix on T1WI, a multilobular pattern of enhancement on enhanced T1WI, cortical destruction, reaction of adjacent soft tissues, lesions of the epiphyseal or flat bone [90, 91.]

It is sometimes difficult to distinguish CS from other types of bone tumors, such as osteosarcoma or Ewing's sarcoma. To establish a final diagnosis, additional testing may be required—immunohistochemistry or genetic analysis. There are several tumors that can be similar to CS histologically:

– chondroblastoma is a benign tumor that develops in cartilage cells and may histologically resemble low-grade CS. However, chondroblastoma occurs in younger patients and has a more favorable prognosis;

– osteosarcoma is a malignant tumor that develops from bone cells and may contain areas of cartilage formation that are characteristic of CS. But it usually has a more aggressive clinical course and early metastasis;

– giant cell tumor of the bone is mostly benign, may also contain cartilage tissue and is histologically similar to CS of a low degree of malignancy. However, giant cell tumor occurs in younger patients and has different patterns of growth and behavior;

– dedifferentiated liposarcoma is a malignant tumor in which the inclusion of cartilaginous cells is sometimes detected on histological specimens, so it can be mistaken for dedifferentiated CS. However, dedifferentiated liposarcoma usually occurs in soft tissues and has completely different distribution characteristics;

– synovial sarcoma is an aggressive malignant tumor that sometimes has a similar pathomorphological pattern to mesenchymal CS. But its clinical course is completely different, occurring purely in soft tissues and has progressive growth, distant metastases in a short period of time.

It is important to distinguish CS from other tumors, as the treatment and prognosis of the disease can differ significantly. This requires careful analysis of presentation, identification of specific histological features, use of diagnostic imaging methods, as well as additional diagnostic tests, such as genetic and molecular analyses.

Biopsy

To confirm the diagnosis, establish the type of CS and determine its histological degree of malignancy, it is necessary to perform a biopsy of the pathological focus. This surgical manipulation stands alone in the entire complex of diagnosis, because it is practically the most important part of the diagnostic protocol, and in case of suspected tumor malignancy, it is a mandatory procedure. There are several different types of biopsies that can be used to diagnose CS:

– «Needle biopsy»: to obtain a small sample of tissue from the tumor, mostly for its soft tissue components. It can be performed even under local anesthesia and, if necessary, additionally use ultrasound or CT navigation for the most accurate targeting of the pathological focus;

– «Core biopsy» with a special bone needle: it involves the use of the latter with a larger diameter and strength, which allows obtaining a larger amount of material with different sections of the tumor with bone tissue. CT and MRI control is a desirable accompaniment for performing this diagnostic procedure;

– «Open biopsy» is performed through a small incision in the skin in the area where the tumor is located, which allows removal of a small sample of tissue under visual control. It is performed under general anesthesia and is used for neoplasms that are significant in size or in complex anatomical areas;

– «Excision biopsy» (resection), when the diagnosis and treatment plan involves the removal of the entire tumor along with a reserve of healthy tissue. It is performed for small or easily accessible tumors, when the histological diagnosis does not involve preoperative specific treatment.

The type of biopsy method chosen depends on several factors, including each specific clinical situation, the size and location of the tumor, general somatic health of the patient, and the preference of the surgeon.

Performing this important diagnostic manipulation requires strict adherence to the basic principles of biopsy of tumors of the musculoskeletal system, namely:

– minimal contamination of healthy tissues;

– a biopsy under the control of imaging methods (X-ray, CT, MRI or ultrasound) is clearly a better alternative to an open biopsy;

– open biopsy should be used only in exceptional situations, when mini-invasive manipulations are impossible. It is performed only with the help of longitudinal cuts, clearly marked with a marker the day before;

– in cases of damage to the spinal cord, laminectomy is performed to decompress the spinal cord;

– the material should be taken from representative areas of the tumor in sufficient volume;

– the amount of research material should be sufficient, with additional written information about tumor localization, patient age and radiological images;

- all samples of pathological tissues should be sent for microbiological examination for the purpose of differential diagnosis with any inflammatory process;

- interpretation of histological specimens should be performed in collaboration with an experienced pathologist with a clinician and a radiologist in reference laboratories specializing in skeletal sarcomas. The pathologist who analyzes the material must have sufficient experience in the field of diagnosing bone tumors and have the appropriate material and technical base;

– in case of discrepancy between the clinical and radiological diagnosis and the morphological conclusion, an additional examination of the histological material or even a repeated biopsy is necessary;

– it is mandatory to recommend the storage of fresh frozen tissues and tumor samples, since the molecular analysis of the abnormality can be performed later;

– the degree of malignancy must be indicated in the histological report;

– a histological diagnosis made outside the reference centers requires confirmation.

Diagnostic algorithm for CS is often associated with giving the answer to the following question: biopsy or further dynamic monitoring of the neoplasm? The widespread use of MRI, which is now available in most medical facilities, has led to an increase in the incidental identification of cartilage lesions in long bones. Most of these lesions are not amenable to biopsy and usually do not require histological confirmation of the diagnosis [83]. This may result in overly aggressive treatment of an enchondroma diagnosed radiographically as CS. Or, on the contrary, insufficient treatment, if CS is radiographically diagnosed as an enchondroma and the patient is mistakenly discharged without follow-up [92]. However, there is no general consensus on the treatment of these lesions. Some centers recommend curettage, others — observation using radiographic imaging methods [93, 94]. Some suggest protocols for radiological observation instead of biopsy, especially for lesions without signs of local aggressiveness (cortical destruction and increase in

the volume of soft tissues), which makes it possible to reduce morbidity and reduce diagnostic costs [92–95]. In recent years, active monitoring of neoplasms has been recommended to avoid unnecessary operations [95, 96].

Pathomorphology

After obtaining the appropriate biopsy material, pathomorphological verification of the neoplasm is carried out. Histologically, CS is characterized by the presence of atypical malignant cartilage cells in the hyaline cartilage matrix, with varying degrees of pleomorphism and mitotic activity depending on the degree of tumor differentiation. The hyaline matrix is a dense, fibrous material that gives the tumor its characteristic appearance. The cells are large, round or oval, with a centrally located nucleus and transparent cytoplasm. Nuclei are hyperchromatic and show pleomorphism, that is, they change in size, shape, and staining features. Mitotic figures may be found, but are mostly rare. The histological degree of differentiation is the most important factor for determining the prognosis and tactics of treatment of CS.

Based on the histological picture, CS is divided into three classes, degrees of differentiation of tumor cells: I (low level) — well classified and resemble normal cartilage; II (intermediate class) — moderately differentiated and have signs of certain atypia; III (high grade) — poorly classified and showing obvious signs of malignant atypia.

The given histological grading is based on the size of the nucleus, hyperchromasia, cellularity and mitoses. Nuclear size is assessed regardless of whether these cells are small and darkly stained, medium-sized with visible intranuclear detail, or large and pleomorphic. The background is considered chondroid if the presence of lacunae is observed; myxoid — if the cells are separated by a basophilic intercellular substance without clear lacunae.

Grade 1 (low) lesions are small cells with hyperchromatic round nuclei the size of a mature lymphocyte. There are no mitotic figures or nuclear atypia; the cells retain a lacunar pattern. There is no myxoid background, but there may be some degenerative changes. Binucleate cells are rare. High cell density, the presence of a significant number of nuclei of moderate or larger size, and mitotic figures are not signs of low-grade CS. If they are present, this indicates a high degree of differentiation of CS [97]. Tumors of the 2nd degree (intermediate) are more significant cellular lesions, characterized by cells with an increased size of the nucleus; mitotic activity is almost not detected. The lacunar pattern is also preserved, there are no myxoid changes. When a myxoid stroma appears, it indicates that the tumor may become aggressive or frankly malignant. Grade 3 (high) tumors are characterized by 2 or more mitoses per ten fields of view in most cellular zones. Here, there is usually a myxoid background associated with spindle-shaped or pleomorphic cells, and the lacunar pattern is mostly lost. Foci of necrosis are mostly visible. A myxoid change may be associated with the malignancy of a cartilage tumor or be a sign of a degenerative process. The characteristic features of these changes associated with the malignancy of the process are the appearance of a histological picture without a lacunar pattern with atypical spindle-shaped or stellate cells located in the myxoid stroma [3, 97].

Some characteristic pathomorphohistological features of the main types of CS are presented. Periosteal abnormality is histologically similar to traditional CS, consisting of hard nodules of hyaline cartilage with a variable amount of myxoid stroma without osteoid. Nuclear anaplasia is usually not detected. Tumor nodules can penetrate into the surrounding soft tissues, but not into the cancellous bone. Almost all periosteal CS correspond to tumors of the 1st or 2nd degree of activity [98, 99].

The main structural features of secondary CS are the loss of cartilage architecture, fibrous bands between cartilage lobes, increased nuclear atypia, mitosis or myxoid changes, indicating malignant transformation of the neoplasm.

Dedifferentiated CS is a separate variant of cartilaginous tumors, containing either well-differentiated chondroid cells or characteristic signs of CS of low degree of malignancy, with a sharp transition to a focus with non-cartilaginous sarcoma of high degree of malignancy. There are at least three hypotheses that explain the origin of the dedifferentiated type of CS: 1 — the non-cartilaginous component of a tumor of a high degree of malignancy arises in a long-existing cartilaginous tumor of a low degree of malignancy (for a recurrent tumor); 2 — the non-cartilaginous component occurs simultaneously with CS with the ability to differentiate; 3 — non-cartilaginous sarcoma is a malignant transformation of adjacent inflamed but normal tissue [100].

Histologically pathognomonic for mesenchymal CS is a bimorphic pattern with areas of undifferentiated small or spindle-shaped cells and islands of hyaline cartilage. The number of chondrocytes is highly variable. The transition from cellular areas to areas with hyaline cartilage is usually abrupt, but may be gradual.

Undifferentiated cells with oval nuclei often tend to be arranged in a vague alveolar pattern or solid sheets, reminiscent of Ewing's sarcoma. In most cases,

a hemangiopericytomatous vascular pattern is observed. Osteoclastic giant cells can be seen adjacent to cartilage islands [44].

Clear-cell CS consists of clear cells that have round, large, centrally located nuclei with clear cytoplasm and distinct cytoplasmic membranes. The clear cell components of this type of CS are accompanied by «ordinary» foci of CS in less than 50 % of cases. Areas of osteogenesis, osteoclast-like giant cells, and areas resembling an aneurysmal bone cyst or giant cell tumor may be detected. Mitotic figures hardly occur [101]. Clear-cell CS should be differentiated from other bone tumors that may have focal or diffuse clear cell changes, such as osteosarcomas, chondroblastomas, chordomas, adamantines, and Ewing's sarcoma, metastatic clear cell carcinoma of the kidney [102].

At the current level of laboratory diagnosis, immunohistochemical studies play a certain role in the diagnosis and classification of CS. Immunohistochemistry involves the use of antibodies that bind to specific proteins in the tumor tissue, which can help identify the type of cells and determine how aggressive the tumor is. Here are some of the markers that are usually used in immunohistochemical studies and help in the diagnosis of CS:

– protein S100 — a marker of chondrocytes;

– type II collagen - a marker of hyaline cartilage;

– Ki-67 — a marker of cell proliferation (the degree of malignancy of CS);

– P53 – a tumor suppressor gene that is often mutated in CS (it is used to detect tumors with a higher risk of progression);

– CD99 – positive in Ewing's sarcoma (used for differentiation from mesenchymal CS).

In general, immunohistochemical studies can be a useful tool in the diagnosis and classification of CS, especially in cases where the histological features are ambiguous or the tumor is atypical. However, immunohistochemistry should be used in conjunction with other diagnostic tests, such as radiographic imaging of the tumor and molecular analysis, to help establish a more accurate diagnosis.

Treatment

Treatment of CS, for the most part, involves surgical removal followed by radiation or chemotherapy in some cases. The prognosis of complex treatment of CS varies depending on the localization and degree of gradation of the neoplasm, the patient's age and the presence of comorbidities. In recent years, certain advances have been made in understanding the molecular mechanisms that underlie the development of CS, which may lead to the creation of more targeted and effective treatment methods. In addition, research into the use of immunotherapy and other new approaches to the treatment of CS is ongoing.

The most common surgical interventions in the case of CS are divided into intrafocal (removal of the tumor by curettage), marginal (removal of the tumor within the limits of adjacent healthy tissues while preserving adjacent anatomical structures), total (along with wide excision of healthy tissue, including areas of bone involved in the pathological process and joint) resection; in some cases — amputations or even exarticulation of the limb. The main goal of surgical treatment of CS is its ablative removal within healthy tissues to minimize the risk of local recurrence. The choice of the method of surgical intervention depends on a number of factors: size and localization of CS, age and general condition of the patient, classification features of CS. A multidisciplinary team of specialists (onco-orthopedics, plastic, general and vascular surgeons, medical and radiation oncologists, pathomorphologists, radiologists, anesthesiologists) develops a personalized operation plan for each patient with CS.

Radiation therapy is used together with surgery to prevent or reduce the risk of local recurrence; as the primary main treatment of CS in cases where the intervention is technically impossible or the patient has contraindications to it; as the primary treatment of CS with a low degree of differentiation, within one bone segment; as an adjuvant treatment after surgery (for CS of intermediate and high grades of differentiation, poorly differentiated CS that violated the integrity of the periosteum or is located near the joint). One of the indications for radiation therapy is palliative treatment to relieve pain and other symptoms associated with inoperable CS. It stands to mention that chondrogenic tumors are considered radioresistant because radiation-induced cytotoxicity requires active cell division. Instead, chondrogenic tumors are characterized by slow growth and a relatively low rate of cell division. However, radiation therapy potentially improves local control after partial resection of conventional, dedifferentiated, or mesenchymal SC. Final radiation may also be prescribed for palliative purposes [103].

Chemotherapy is usually ineffective in treating CS, but in some cases it can be used to shrink the tumor before surgery or to treat metastatic disease. Of course, a chondroid tumor is resistant to chemotherapy because it usually grows slowly and the abnormal cells do not divide quickly. However, a systematic review of 31 studies showed that adjuvant chemotherapy combined with surgical resection significantly improved the recurrence-free survival of patients in dedifferentiated CS compared with surgery without chemotherapy [104]. But in a non-randomized clinical cohort,

anthracycline-based combination chemotherapy showed rather low efficacy against mesenchymal CS [105]. Thus, chemotherapy is not an effective method of treating CS, but it can be used depending on the type of CS in a complex of therapeutic measures to improve the overall results of treatment.

Immunotherapy is a type of cancer treatment that involves stimulating the patient's immune system to recognize and attack cancer cells. Currently, it is a progressive and promising method of treatment for some types of cancer, but there is no approved immunotherapy protocol for CS. It is known that chondrocytes are not targeted by the body's immune system, which greatly complicates the development of immunotherapy methods for CS. However, studies have been published that demonstrate some potential of immunotherapy for the treatment of CS. One approach is focused on specific molecular markers on the surface of CS cells; the other is on stimulating the immune system to have a destructive effect on pathological CS cells. Although immunotherapies for CS are in the early stages of development, they hold promise for future improvements in CS treatment. Long-term clinical trials are currently underway to evaluate the safety and efficacy of immunotherapy for CS.

Survival and prognosis

Compared to other types of bone and soft tissue sarcomas, the survival prognosis for CS is relatively good: 1-year overall survival is approximately 90 %, 5-year survival is 80 %, and 10-year survival is 70 %. However, the indicator decreases with increasing degree of malignancy of the tumor. CSs with a high degree of malignancy have a worse prognosis — the 5-year survival rate is approximately 50 % [15, 25, 27]. As a result of conducting significant population studies, it was established that for tumors of a low degree of malignancy, the 5-year survival rate is approximately 80–90 %, intermediate class — 60–80 %, high degree of malignancy — 20–40 %, with a frequency of local recurrences and distant metastases 14–20 % [53, 54, 106].

The overall prognosis and survival time are also affected by tumor location. In particular, CS located in the extremities have a better prognosis than those arising in the axial skeleton (spine, pelvic bones, ribs) due to a higher risk of local and distant recurrences and metastasis.

Although some histological and clinical parameters, such as tumor necrosis, mitotic rate, type of surgery and tumor location, directly affect the prognosis of the disease, the most important predictor of local recurrence and/or metastasis is the histological grade of the tumor. 5-year survival for patients with 1 histological grade of CS malignancy was shown to be 89 %, for the combined group with 2 and 3 grade — 57 %. Only high malignancy grades 2 and 3 were significantly associated with the probability of metastasis [54, 106].

The presence of metastases already at the time of diagnosis is an additional poor prognostic factor for the long-term survival of patients, which is reflected in a sharp decrease in the relative 5-year survival rate from 75.2 to 28.4 %. This marked decrease in survival indicates a more aggressive phenotype or an active spread of the disease against the background of metastasis, which may affect the course of CS as a whole [25, 27].

The prognosis for patients with periosteal type of CS is more favorable than in intramedullary type, with an overall 5-year metastasis-free survival rate of approximately 83 %. Also, 5-year metastasis-free survival is lower for patients with a grade 2 tumor (50 %) than with a grade 1 tumor (94 %). Metastases are exceptional and occur very late. Sarcoma dedifferentiation is a relatively rare aberration, but it has been shown to be associated with a poor prognosis [107, 108].

Secondary CS, as a type of malignant transformation of osteochondroma, is usually treated surgically. Because most of these lesions are poorly differentiated, the overall prognosis is good with long-term survival in 70–90 % of patients. The frequency of local recurrences varies depending on the adequacy and quality of the performed tumor resection from 0–15 % in cases with wide «en bloc» resection to 57–78 % in cases with marginal or intrafocal resection [107, 109]. Malignant transformation of enchondromatosis is greater in the case of Maffucci syndrome than in Ollier's disease, accordingly, the prognosis is much worse.

Since the dedifferentiated component significantly affects and almost determines the prognosis of the course of dedifferentiated CS, its detection is essential. Despite comprehensive, aggressive treatment of this type of CS, the overall survival rate is less than 10 % at five years. Even when local control with appropriate surgery is achieved, distant metastasis remains the greatest clinical problem, developing in 90 % of patients [110].

The survival prognosis for mesenchymal CS is poor in advance. However, in the case of adequate treatment, the clinical course of the disease can be prolonged. Since local recurrences or metastases sometimes occur even more than 20 years after the start of treatment, long-term follow-up and continuous monitoring of the patient is important. According to statistics, in the observation group from the Mayo Clinic (USA),

the 5-year survival rate was 54.6 %, and the 10-year survival rate was 27.3 %. The most common site of metastasis in this abnormality is the lungs [44].

Clear-cell CD has a low degree of malignancy and is usually successfully treated by radical resection of the tumor en bloc. But in about 25 % of patients, local relapses or metastases to other organs and systems occur in the period up to five years after the operation. Mortality associated with this type of CS is uncommon, especially when the neoplasm is ablastic and simultaneously completely removed [110].

Surgery is the mainstay of treatment for CS, and therefore radical surgical removal of the tumor «en bloc» is associated with a better prognosis. But the development of postoperative complications, such as infection or problems with wound healing, can significantly affect the final result of treatment. Radiotherapy and chemotherapy are used in addition to surgery, especially for tumors with a high degree of malignancy or recurrences, which in the complex can improve the effectiveness of treatment.

It is important to note that the survival rate of patients with sarcomas is a statistical average and does not predict the outcome of an individual patient. The prognosis for CS is best determined by a multidisciplinary team of specialists who can develop a personalized treatment plan based on the data for each specific patient. With timely diagnosis and appropriate treatment, many patients with CS can achieve long-term survival and maintain a good quality of life.

In general, survival after treatment of CS depends on many factors, and each case should be evaluated individually by a team of experts in bone and soft tissue tumors.

Conclusions

CS is the third most common primary bone tumor after multiple myeloma and osteosarcoma, accounting for about 25 % of all bone sarcomas.

The overall incidence of CS is estimated at approximately 0.1–0.5 primary cases per 100,000 population per year. CS mostly affects adults, with peak incidence from 50 to 70 years of age. CS in children and adolescents is a rare abnormality, accounting for less than 5% of all cases of CS, but the principles of treatment are similar to the principles of therapy in adults. CSs are localized in any bones that contain cartilage, but most often occur in the bones of the pelvis, femur and shoulder, ribs.

Although most SCs have a low metastatic potential, some are quite aggressive, with a poor prognosis. Diagnosis of CS is based on a complex algorithm of step-by-step measures, which makes it possible to establish a final diagnosis and classify CS according to its type, histological degree of gradation of malignancy and activity, localization, surgical approaches to treatment, etc. The treatment protocol for CS is determined on the basis of the results of history indicators, X-ray imaging, histopathological picture based on the results of a biopsy with further classification of CS and the final determination of its type.

Most studies and scientific publications indicate relatively high 5- and 10-year survival rates for patients with CS compared to other sarcomas, but during the last two to three decades, minimal progress has been made in improving the effectiveness of the treatment of this disorder. Given this trend, the absence of a reliable improvement in survival rates in the case of CS confirms the continued reliance on traditional treatment algorithms. Thus, the effectiveness of existing treatment protocols for CS has reached a certain plateau today, with no improvement in the survival rate of patients with CS over the past 30 years.

Surgical removal of the neoplasm remains the «gold standard» of treatment, given the limited response of CS to radiation and chemotherapy. In the presence of distant metastases for CS, surgery also remains the most recognized method of treatment, but well-founded studies have proven the possible benefit of radiation and chemotherapy for metastatic CS. However, further research in this direction is necessary.

The achievements of recent years in the treatment of CS allow us to optimistically evaluate the progress in this direction of onco-orthopedics. In particular, potential targets for targeted therapy of CS have been identified, even with a high degree of its resistance to conventional chemotherapy. Immunotherapy is also seen as promising. The combined use of immune checkpoint inhibitors and radiation therapy has been shown to be effective in the treatment of the metastatic form of dedifferentiated CS. Advances in molecular testing have made it possible to more accurately diagnose and classify CS. For example, some CSs have mutations in the IDH1 or IDH2 genes, which can be affected by specific inhibitors. The use of advanced surgical techniques (computer navigation and 3D printing) led to an increase in the accuracy and safety of surgical resection of CS, and the latest radiation therapy techniques (intensity modulation and proton therapy) increased the accuracy and efficiency of this type of CS treatment.

Overall, the new knowledge gained opens up additional opportunities for the treatment of CS, and ongoing research should be focused on further improving the prognosis for patient survival. Modern scientific developments are necessary for a better understanding

of the causes of CS and the creation of more effective methods of early diagnosis and treatment of this complex oncopathology.

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