

Premalignant Conditions of Bone

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ABSTRACT

Development of malignancy is a multifactorial process, and there are multitude of conditions of bone that may predispose patients to malignancy. Etiologies of malignancy include benign osseous conditions, genetic predisposition, and extrinsic conditions. New-onset pain or growth in a previously stable lesion is that should concern for malignant change and should prompt a diagnostic workup for malignancy.

Malignant conditions of bone can arise from numerous sources, and the exact etiology is not always known. Early identification of malignancy equates to earlier appropriate treatment and improved long-term patient outcomes.¹ Several conditions have been associated with a higher risk of malignant transformation. These conditions include benign osseous lesions with delayed malignant transformation, genetic predispositions to malignant degeneration, and extrinsic influences. This review discusses a multitude of diagnoses and factors that fall into these three categories.

Malignant transformation often results from abnormalities in either tumor suppressor genes or proto-oncogenes. Tumor suppressor genes are normal genes that regulate cellular processes, such as cell division, DNA repair, and apoptosis. When these genes are mutated, the normal regulation of these processes is lost and cells are able to proliferate and survive in an uncontrolled manner. Examples include *TP53* and *RB*.^{2,3} Inherited disorders, such as Li-Fraumeni and Retinoblastoma, associated with tumor suppressor genes often affect one of the two copies of the gene. The patient subsequently develops a mutation in the second copy of the gene, causing malignant transformation.⁴ Proto-oncogenes are normal genes that promote cellular growth and proliferation, which can become constitutively active due to gene mutation, examples being *RET* and *BCL-2*.^{5,6} Activation of proto-oncogenes results in unchecked growth and proliferation of cells, which can lead to papillary thyroid carcinoma,⁷ osteosarcoma,⁸ and lymphoma.⁹ Often tumor suppressor gene mutations are inherited, while proto-oncogene mutations are acquired.¹⁰ Table 1 presents all conditions included in this review and their associated protein mutations.

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None of the following authors or any immediate family member has received anything of value from or has stock or stock options held in a commercial company or institution related directly or indirectly to the subject of this article: Dr. Eckhoff, Wells, Dr. Padilla, Dr. Polfer, Castagno, Dr. Thabet, Dr. Elzamy, Dr. Wilson, and Dr. Rajani.

The views expressed in this publication are those of the author(s) and do not reflect the official policy or position of William Beaumont Army Medical Center, Department of the Army, Defense Health Agency, or the US Government.

JAAOS Glob Res Rev 2022;6: e22.00097

DOI: 10.5435/JAAOSGlobal-D-22-00097

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Benign Osseous Conditions With Delayed Malignant Transformation

Osteochondroma

Solitary osteochondromas are the most common benign lesions of bone accounting for approximately 30% of all benign bone lesions (Table 2).¹¹ These are often referred to as exostoses and can arise in any bone of the body, but

Table 1. Premalignant Conditions, Associated Mutated Protein, and Protein Function

Condition	Associated Mutated Protein (Gene)	Protein Function
Osteochondroma	Exostosin-1,2,3 (<i>EXT1, EXT2, EXT3</i>)	Heparan sulfate biosynthesis
Enchondroma	Isocitrate dehydrogenase-1&2 (<i>IDH1&2</i>)	Tricarboxylic acid cycle
Paget disease of bone	Sequestosome-1 (<i>SQSTM1</i>)	Autophagosome cargo protein
Fibrous dysplasia	G-protein (<i>GNAS</i>)	Signal transduction protein
Synovial chondromatosis	No associated gene mutation	
Chondroblastoma	H3.3 histone B (<i>H3F3B</i>)	Nucleosome structure and genetic integrity
Giant cell tumor of bone	H3.3 histone A (<i>H3F3A</i>)	Nucleosome structure and genetic integrity
Osteoblastoma	c-Fos (<i>cFOS</i>)	Proto-oncogene, target gene promotor and enhancer
Retinoblastoma	Retinoblastoma (<i>RB1</i>)	Tumor suppressor gene, cell-cycle checkpoint regulation
Li-Fraumeni	Tumor protein p53 (<i>TP53</i>)	Tumor suppressor gene, cell-cycle checkpoint regulation
Rothmund-Thompson	RecQ helicase (<i>RECQL4</i>)	Telomerase maintenance protein
Bloom syndrome	RecQ helicase (<i>BLM</i>)	Telomerase maintenance protein
Werner syndrome	RecQ helicase (<i>WRN</i>)	Telomerase maintenance protein
Osteomyelitis	No associated gene mutation	
Postradiation sarcoma	Cyclin dependent kinase inhibitor 2A&B (<i>CDKN2A&B</i>)	Tumor suppressor gene, cell-cycle checkpoint regulation

most often develop in areas of notable growth, such as the distal femur, proximal tibia, and proximal humerus. The true incidence of osteochondromas is likely under-represented because they often present as incidental findings on imaging studies.¹² These exostoses are characterized as pedunculated or sessile bony masses in direct continuity of the medullary canal with an overlying cartilage cap¹³ (Figure 1, A–C). Histologically, these “mushroom” shaped lesions show a cartilaginous cap composed of mature hyaline cartilage with normal underlying bone that includes trabecular bone and marrow contents (Figure 1D). Malignant transformation can occur within the cartilage cap with degeneration to chondrosarcoma and occurs in approximately 1% of benign cases.^{14,15} The exception to this low rate of

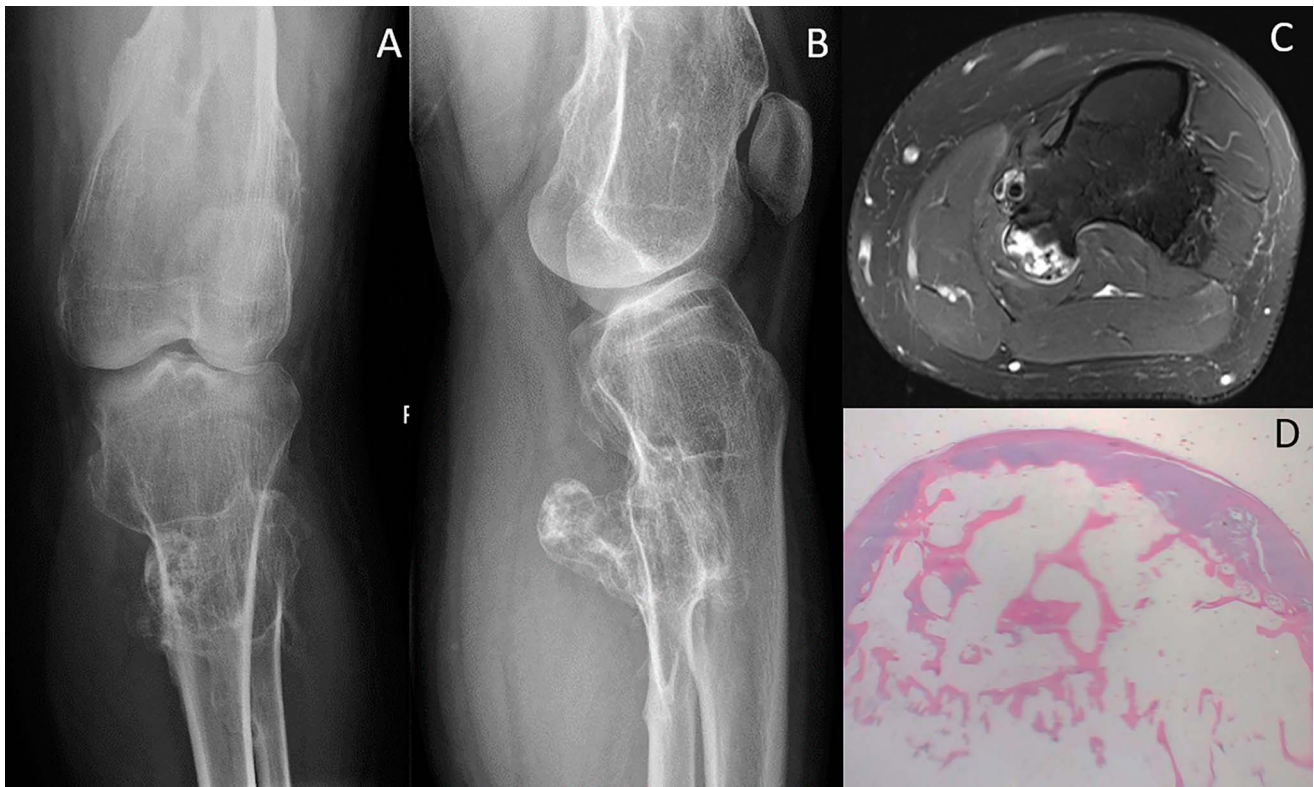
malignant transformation in osteochondromas is found in patients with multiple hereditary exostoses (MHE). These patients have a notably increased whole-body risk of osteochondroma degeneration to chondrosarcoma with references rates as high as 35%.^{16,17} More recent MHE studies, however, suggest much lower rates of malignant transformation at around 2% to 5%.^{13,18–21}

MHE is an autosomal dominant genetic predisposition to the development of multiple diffuse osteochondromas.^{22,23} Mutations in the *EXT1*, *EXT2*, and *EXT3* genes have been attributed to this condition.²⁴ All three *EXT* gene proteins function in heparin sulfate proteoglycan biosynthesis with loss of function mutations resulting in dysregulated growth.²⁵ While occurring almost equally between male and female patients, the

Table 2. Summary of Key Points

No	Benign Osseous Conditions
1	Osteochondromas and enchondromas are benign cartilaginous lesions of bone with low rates of malignant degeneration which is increased in conditions characterized by multiple lesions
2	Paget disease of bone and fibrous dysplasia are disorders of disorganized or dysplastic bone formation and can develop osteosarcoma secondarily
3	Synovial chondromatosis is a metaplastic process with low rates of chondrosarcomagenesis
4	Chondroblastoma and giant cell tumor of bone are benign bone tumors associated with lung metastases and rarely develop malignant transformation posttreatment of an initial lesion

Figure 1



Diagrams showing multiple hereditary exostoses: (A and B) demonstrate AP and lateral radiographs with characteristic exostoses with secondary deformity of the knee joint. C, Axial T2 MRI cut with signal intense cartilaginous cap. D, Complete resection of this lesion shows a cartilaginous cap with underlying trabecular bone and marrow contents.

more severe phenotype predominates in male patients.¹⁸ Common symptomatology among these patients includes localized nerve compression, limb-length discrepancies, and genu valgum.²⁶

Malignant transformation of an osteochondroma is associated with several symptoms. Previously dormant lesions that insidiously continue growing, particularly after skeletal maturity, can be suggestive of malignant transformation.²⁷ This is especially true if the lesion becomes painful without a clear etiology.²⁷ In addition, osteochondromas with a cartilage cap greater than 2 cm by radiographic imaging are associated with the development of chondrosarcoma.²⁸ This cartilage cap may be measured using MRI or CT scan images with higher interobserver reliability for measurements obtained on CT imaging.²⁸

When this malignant transformation does occur, it is most often to low-grade chondrosarcoma that can often be treated effectively with wide excision alone and with a good prognosis at >90% survival.^{17,27,29} Patients with chondrosarcoma arising from osteochondromas in the axial skeleton, particularly in the pelvis, may have worse outcomes due to delays in identification and subsequent treatment.^{27,30}

Enchondroma

Characterized as benign intramedullary hyaline cartilaginous tumors, enchondromas are one of the most common primary bone tumors in the body³¹ (Figure 2, A and B). They account for 3% of all bone tumors and 13% of all benign bone tumors.³² The exact incidence is unknown because these are typically asymptomatic and found incidentally.³³ As these lesions are benign, treatment is most often with observation alone when found. Tumors that do present, often present secondarily to a pathologic fracture, because they can create a relative area of weakness in the bone.

Malignant transformation is of notable concern in patients who have enchondromatosis.^{31,34} Two main subtypes of enchondromatosis include Ollier disease and Maffucci syndrome. Both disorders are nonhereditary, and the malignant transformation occurs most often during the fourth decade of life.³⁵ Isolated enchondromas, Ollier disease, and Maffucci syndrome are all associated with mutations in *IDH1* and *IDH2* genes, encoding proteins involved in the tricarboxylic acid cycle with downstream effects on histone modification and DNA hypermethylation.^{36,37} Rates of malignant

Figure 2

Diagrams showing enchondroma. **A**, AP and **(B)** lateral radiographs of a small finger middle phalanx base enchondroma. Often these lesions are purely lytic and expansile when present in the small bones of the hand. **C**, Hyaline cartilage is seen with variable atypia. In this case, the atypia is minimal, but sometimes the atypia may resemble low-grade chondrosarcoma due to hypercellularity, nuclear atypia, and myxoid changes.

transformation are 10% to 40% for Ollier disease and up to 15% to 50% for Maffucci syndrome.^{35,38,39} Other malignancies can occur as well in these patients including astrocytoma, gliomas, and mesenchymal ovarian tumors.^{39,40}

Although uncommon, the most common secondary malignancy to occur in the setting of an enchondroma is dedifferentiation into chondrosarcoma. Differentiating a benign enchondroma from low-grade chondrosarcoma can be difficult, both on radiographic evaluation and biopsy analysis.^{38,41} Signs and symptoms of malignant transformation include the development of a mass in the region of a previously known enchondroma or, very importantly, new-onset pain. Radiographic findings include periosteal reaction, endosteal scalloping, soft-tissue invasion, and poorly demarcated lesions.⁴² Microscopically, they show lobules of hyaline cartilage that are often encased by bone or fibrous perichondrium (Figure 2C). Treatment for low-grade chondrosarcomas of the extremities and symptomatic enchondromas is the same and usually entails marginal curettage excision, bone grafting, and/or polymethylmethacrylate augmentation.³⁸ Low-grade pelvic chondrosarcomas and all higher-grade chondrosarcomas should be treated with wide resection.⁴³ Prognosis is best when enchondromas occur in the short bones of the body.³⁵

Paget Disease of Bone

Paget disease of bone, also referred to as osteitis deformans, is a metabolic disorder characterized by osteoclast-mediated disorganized bone remodeling,⁴⁴ typically found in patients aged older than 55 years.^{45,46} It most often affects people of European descent with a predilection for the axial skeleton. Although the exact mechanism is not understood, it is thought to be secondary to multiple environmental factors, including nutrition, infection, and activity level of the patients.⁴⁷ Radiographically, it is characterized by osteolytic extension from epiphysis toward metaphysis with a widening of the affected bone with coarsened trabeculae and cortical thickening⁴⁸ (Figure 3A–D). The histology varies based on the temporal phase of this lesion: osteolytic phase, mixed osteoclastic/osteoblastic phase, or osteosclerotic phase. The earlier presentation shows woven bone and a mosaic pattern (or jigsaw puzzle) appearance of lamellar bone along cement lines, (Figure 3E), while the later stages show thick bone trabeculae with myelofibrosis.

A genetic predisposition for Paget disease of bone has been established as displayed through a mutation in the ubiquitin-associated domain of the *SQSTM1* gene; this resulting mutation displays autosomal dominance with variable penetrance.⁴⁹ Paget osteosarcoma, often referred to as Paget sarcoma, is a devastating complication of

Figure 3



Diagrams showing polyostotic Paget disease of bone. **A**, Proximal humerus and **(B)** proximal femur and pelvic involvement with classic moth-eaten appearance. **B**, Varus deformity can develop secondary to proximal femoral involvement. Technicium-99 bone scan **(C)** anterior and **(D)** posterior showing increased metabolic activity in bilateral proximal humeri, the right clavicle, and right hip. **E**, This microscopic image shows trabecular bone with a mosaic (or jigsaw puzzle) pattern, along prominent cement lines.

Paget disease of bone with poor outcomes.^{50–54} Although osteosarcoma is the most common subtype of Paget-associated tumor, chondrosarcoma and fibrosarcoma are also documented.⁵⁵ This malignant transformation thankfully occurs in only approximately 1% to 3% of cases.^{56,57} The rate of transformation is higher in severe polyostotic Paget patients at 5% to 10%.⁴⁸ Symptoms of transformation include acute-onset pain or sudden increase in a previously stable chronic pain. Additional signs can include swelling or the development of a soft-tissue mass. Radiographically, malignancy is characterized by invasive growth within the medullary canal, cortical destruction, and soft-tissue expansion.⁵⁷ The

femur, humerus, and skull are most often affected by the sarcomatous transformation.

Diagnosis and treatment, when a malignant transformation is suspected, should be confirmed with a biopsy and followed with early aggressive treatment. Overall prognosis with Paget sarcoma is poor with 80% to 90% of patients dying within 3 years.^{48,58,59} These poor survival rates may be secondary to the frank malignant disease on presentation or simply due to its occurrence in older, more medically comorbid patients who cannot tolerate the aggressive chemotherapeutic and surgical treatment options. Treatment can include surgery, chemotherapy, and radiation therapy and is largely dependent on the

sarcoma that develops.⁶⁰ Fortunately, the rates of Paget sarcoma seem to be declining overall.⁵⁸

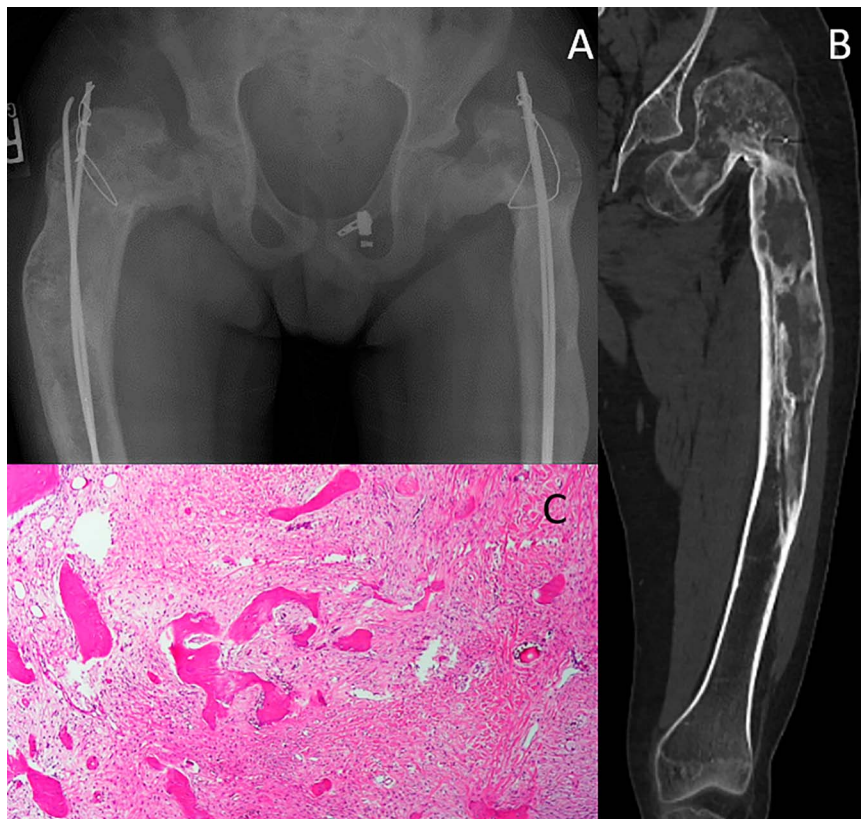
Fibrous Dysplasia

As a relatively common lesion, fibrous dysplasia (FD) has been well described in the literature. Occurring as both mono-ostotic and polyostotic, FD is a disorder where fibro-osseous bone forms in lieu of native bone marrow with cancellous bone. The etiology for FD is a *GNAS* gene mutation with downstream constitutive activation of cAMP production and activation of the parathyroid hormone receptor.⁶¹ Monostotic FD comprises 75% of cases,⁶² often presenting in the second to fourth decades of life secondary to pain or pathologic fracture. Polyostotic patients often present earlier and are more likely to have an associated limb deformity present. On radiographic examination, the affected bone has a classically coined ground glass appearance (Figure 4, A and B). Histologically, the lesion shows thin trabecular bone in a background of fibroblast-like spindle cells (Figure 4C). These irregular-shaped trabeculae typically lack conspicuous

osteoblastic rimming. These osseous locations most commonly affected in descending order include the femur, tibia, pelvis, foot, and facial bones.⁶³

There are two major associated genetic disorders with FD, which include McCune-Albright and Mazabraud syndrome. First described by Albright and colleagues, McCune-Albright is known to display a classic triad of polyostotic FD, café-au-lait spots, and precocious puberty, although only roughly half of patients will phenotypically display the triad.⁶⁴ Mazabraud syndrome is polyostotic FD with intramuscular myxomas. Similar to Paget disease, FD most commonly undergoes malignant transformation to osteosarcoma, chondrosarcoma, and fibrosarcoma at a rate of approximately 1%.⁶⁵ However, malignant transformation is more common with polyostotic involvement with rates of around 4% in both McCune-Albright and Mazabraud patients.^{61,66} The most common locations for malignant transformation are, unsurprisingly, the proximal femur, humerus, and pelvis. Historically, one of the contributing factors to malignancy has been the treatment of FD with radiation

Figure 4



Diagrams showing polyostotic fibrous dysplasia. **A**, AP pelvis x-ray demonstrating bilateral expansile and ground-glass appearing lesions with secondary varus deformity of the proximal femur. **B**, CT of the patient's left femur after hardware removal with Sheppard crook deformity. **C**, These lesions typically show irregular shaped, thin bone trabeculae in a background of fibroblast-like spindle cells, which lack conspicuous osteoblastic rimming.

Figure 5

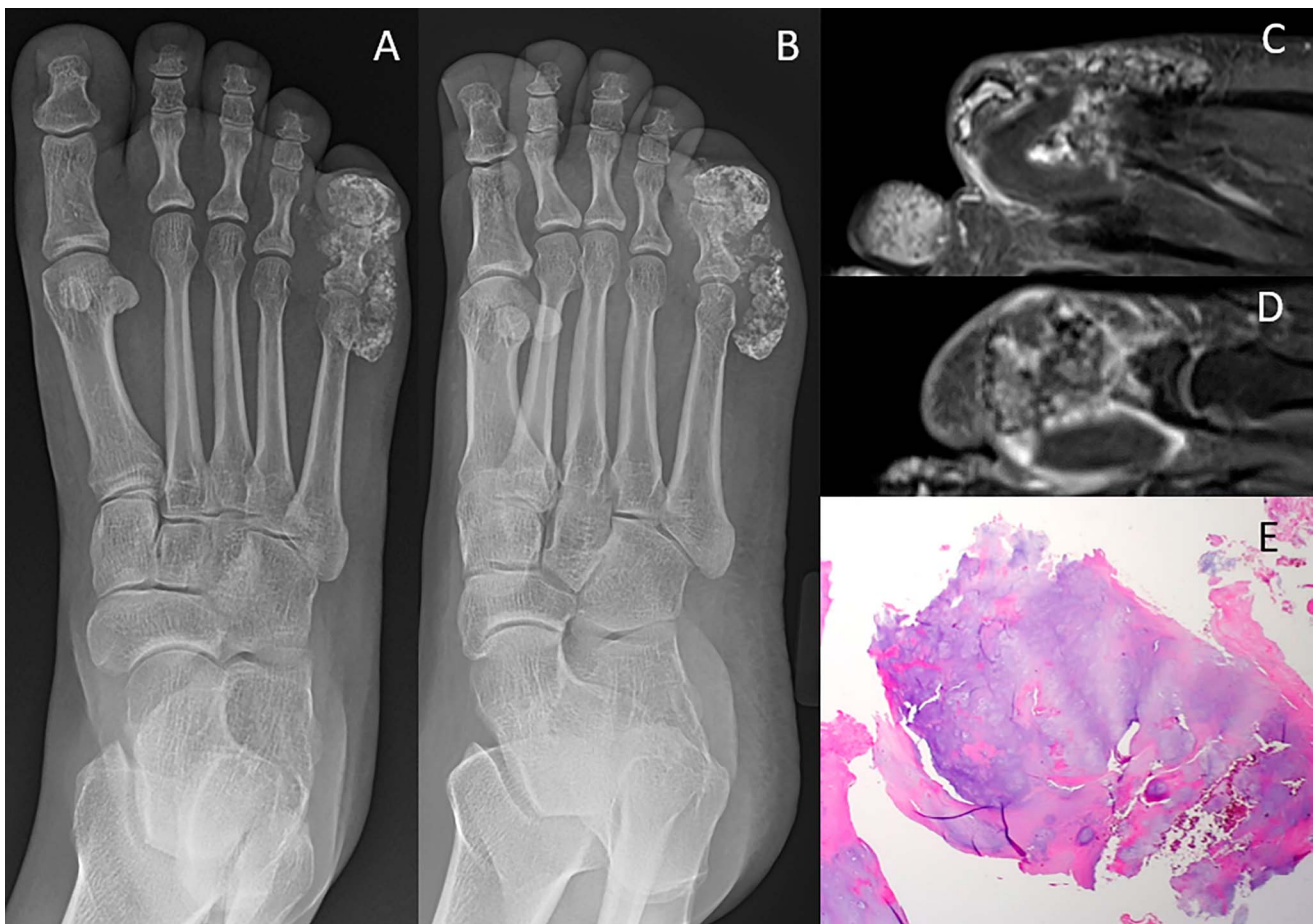


Diagram showing synovial chondromatosis. **A** and **B**, Soft-tissue ossifications around fifth toe. **C** and **D**, Sequential coronal T1 postcontrast MRI with multiple bodies with peripheral enhancement. **E**, Nodules of mature hyaline cartilage are seen with variable degrees of cellularity and nuclear atypia.

therapy,⁶⁷ and thankfully, more conservative approach to FD has become the standard of care.

Radiographically, malignant transformation should be suspected when poorly marginated, mineralized, and osteolytic lesions are identified.⁶⁸ Treatment can include surgery, chemotherapy, and radiation therapy. Transformation often occurs during the fifth decade of life.^{66,68}

Synovial Chondromatosis

The formation of cartilaginous and osteochondral bodies by synovium is the hallmark of synovial chondromatosis. This rare, benign condition can occur in any joint of the body. It often presents nonspecifically and can have a delayed diagnosis of up to 5 years after the onset of symptoms.^{69,70} There is a predilection for weight-bearing joints, with the most common locations being the knee followed by the hip, shoulder, elbow, and ankle.⁴⁴ Overall, it is believed to be a metaplastic process of hyaline cartilaginous with loose body production (Figure 5A–D)

that microscopically forms nodules of mature hyaline cartilage with variable cellularity and nuclear atypia (Figure 5E). Typical symptoms include pain, swelling, catching, popping, or crepitus within the affected joint.

Although malignant transformation of synovial chondromatosis is rare, there have been multiple case reports and series.^{70–74} These small sample-sized studies postulate the rate of chondrosarcomatous transformation of up to 6.3%; however, the authors caution that this may be a high estimate because many cases of synovial chondromatosis are asymptomatic.⁷⁰ Typically, low-grade or intermediate-grade chondrosarcoma arises from a range of 2 to 39 years after initial diagnosis, with an average of 20 years.⁷⁰ Clinically differentiating primary synovial chondromatosis from secondary chondrosarcoma can be very difficult,⁷⁵ so clinical suspicion should be raised based on lesion recurrence alone. As is typical of chondrosarcoma treatment, radiation and chemotherapy have limited

roles in these patients and surgical intervention is the mainstay of treatment.⁷⁶ Surgical treatment is often wide resection or, if necessary for adequate control, amputation³⁸

Chondroblastoma

Occurring most specifically within the epiphysis of long bones, chondroblastoma is a rare benign primary bone tumor with a frequently aggressive nature.^{77,78} It is most often diagnosed in the second or third decade of life due to pain and often has associated joint symptoms due to its periarticular location. Radiographically, these are seen as well-circumscribed, lytic lesions in the epiphysis. Histologically, there is the proliferation of round chondroblasts in a background of a pink chondroid matrix, interspersed giant cells, and mature cartilage.⁷⁷ Pericellular lace-like calcification is often seen in degenerative chondroblasts. Mutations in the *H3F3B* gene are found in up to 70% of patients with chondroblastoma⁷⁹ and can help differentiate it from other giant-cell containing tumors. Treatment options include radiofrequency ablation in small lesions or local surgical excision with curettage.⁸⁰ Chondroblastoma exhibits a relatively low recurrence rate of approximately 5% to 8%.^{81,82}

Although chondroblastoma has metastatic potential itself, with 2% metastasizing to the lung,⁸³ more aggressive chondroblastoma may represent its own category of malignant chondroblastoma. However, there is some dispute in malignant chondroblastoma being a separate entity but rather an initial misdiagnosis.⁷⁷ Other malignancies have been found in the setting of chondroblastoma as well, including osteosarcoma and malignant fibrous histiocytoma.^{82,83} Nearly all malignant chondroblastomas occur in patients who have had a previous resection that later develops recurrence of their lesions.^{77,82,83} Prognosis of malignant chondroblastoma is difficult to assess because it is rare and not fully understood; however, metastatic lesions in the setting of benign chondroblastoma portend a poor prognostic implication.^{82,84}

Giant Cell Tumor of Bone

As a benign tumor, giant cell tumor of bone (GCTB) is known to display locally aggressive features with an underrecognized metastatic potential, most often to the lungs.^{85,86} These tumors most often affect the epiphyseal and metaphyseal regions of long bones and are characterized by their classic histologic mononuclear stromal cells with frequent multinucleated giant cells. Bone destruction is mediated through overexpression of RANK ligand, which stimulates precursor monocytes to

become the aforementioned osteoclastic giant cells.^{87,88} Mutations in *H3F3A* are present in most GCTB cases, which affects the histone H3.3.^{89,90} The size and overall localized tumor burden of GCTB considerably vary as does the proposed treatment modalities. Systemic adjuvant medical treatment with diphosphonate therapy has been shown to promote apoptosis of the stromal component in GCTB and stabilize inoperable disease.^{91,92} Bisphosphonates may also help prevent local recurrence.⁹³ Surgery with extended intralesional curettage, with or without local adjuvant options, is considered the primary treatment modality and the benchmark.⁹⁴ Denosumab, an antibody against receptor activator of nuclear factor- κ B-ligand, is a recent treatment option, which has been shown to prevent disease progression in up to 96% of patients in one clinical trial at 13 months.⁹⁵ The overall benefit of denosumab is being called into question, with recent studies showing possible association with malignant transformation^{96,97} and local recurrence in patients undergoing curettage.⁹⁸

Although benign in nature, GCTB does have an ability to metastasize to the lungs, commonly in the setting of recurrent disease or primary axial skeletal location.^{99–101} Lung metastases are often indolent but can be aggressive and fatal.¹⁰² The metastatic rate in benign tumors is approximately 1% to 9%, although this may not change the long-term outcomes or mortality in these patients.^{103,104} Importantly, the pulmonary metastases are histologically identical to the primary bone lesion.^{105,106} Treatment is usually satisfactory with resection of the pulmonary metastasis.^{85,104}

Malignant transformation of GCTB is broken into primary or secondary. Primary malignant GCTB is defined by an area of highly pleomorphic cells within an otherwise benign GCTB, whereas secondary GCTB occurs in an area of previously treated GCTB.¹⁰⁷ Most malignant GCTBs are secondary to radiation therapy, accounting for up to 75% of all cases.¹⁰⁷ Comparing malignant versus benign primary GCTB can be very difficult, with only one study finding that benign GCTB was more likely to have well-defined margins and the presence of a thin rim of bone.¹⁰⁸ Other factors evaluated in the study found that there were no other differences between malignant and benign. Genetic mutations involving *TP53* and *H-RAS* have been identified in secondary malignant GCTB which occur in nonpreviously irradiated patients.¹⁰⁹ Mortality is influenced by previous radiation therapy, with postirradiation malignancy increasing 5-year mortality from 13% in nonirradiated patients to 72% or greater in postirradiated patients.^{107,108}

Osteblastoma

Osteblastoma is a lytic fibro-osseous tumor of bone that produces an osteoid matrix. They were first described as a lesion related to osteoid osteoma, however, with greater growth potential.¹¹⁰ Osteblastoma is differentiated from osteoid osteoma by its larger size (>1.5 cm) and lack of nocturnal night pain relieved by nonsteroidal anti-inflammatory drugs.¹¹¹ However, both entities share similar histology, consisting of trabecular woven bone that is rimmed by plump osteoblasts in a vascularized stroma. As benign neoplasms of bone, osteblastomas are maybe found incidentally and however are more classically symptomatic.¹¹² There is a predilection for the axial spine location with male patients between ages 10 and 25 years being the most common patient cohort.^{113–115} Although benign, these can be locally aggressive with variable clinical course.¹¹² These can be differentiated from osteoid osteomas usually by their size, location, and their aggressive nature.¹¹⁴ However, both osteoid osteomas and osteoblastomas often carry a *c-FOS* mutation and have other similarities in microscopic morphology.¹¹⁶ Treatment is typically with curettage and bone grafting or resection, and prognosis is excellent. There is a 15% to 25% recurrence rate after treatment, typically with curettage and grafting.¹¹⁷

Malignant transformation of osteblastoma to osteosarcoma has been described, most commonly into osteosarcoma after postsurgical resection recurrence.^{118–121} These case reports however have been called into question as possible initial misdiagnosis due to the similarities in histologic examination.¹¹³ This counter-argument to true malignant degeneration has been supported by genomic examination.¹²¹

Genetic Predisposition

Retinoblastoma

The tumor suppressor gene retinoblastoma (*RB1*) serves as a cell-cycle checkpoint regulator (Table 3). Lack of the

allele, *RB1*, displays Mendelian inheritance patterns in an autosomal dominant fashion. Due to the mutation with subsequent loss of this tumor suppressor gene, various neoplasms can result including osteosarcoma, melanoma, breast, and supratentorial primitive neuroectodermal tumors.^{122,123} Although *RB1* mutation results in classic retinoblastoma of the eye,¹²² osteosarcoma remains the second most common malignancy in this patient cohort.¹²⁴ Screening for retinoblastomas is done in neonates with red reflex testing before discharge from the neonatal nursery.¹²⁵

Secondary malignancies in patients with retinoblastoma, including osteosarcoma, are common, particularly in the setting of radiation therapy which historically was part of the treatment algorithm.^{3,126} Rates of development are around 13.1% to 38.5% at 30 years or longer after irradiation.^{127,128} However, current rates of secondary malignancy are likely decreasing today because radiation therapy is becoming less frequently used in these patients from 30.5% to 2.6% of cases.¹²⁸ Screening for sarcoma development in patients with heritable retinoblastoma has not been shown to have benefit.¹²⁹

Li-Fraumeni

Another predisposition syndrome, Li-Fraumeni, has a high association with numerous malignancies. Like *RB1* dysfunction, *TP53* serves as a cell-cycle checkpoint regulator and inherited loss of function mutations displays Mendelian inheritance characteristics in an autosomal dominant fashion.¹²⁴ Heterozygous germline variation in the *TP53* allele results in a lifetime cancer risk of $\geq 90\%$ for women and $\geq 70\%$ for men.¹³⁰ The five most common malignancies in these patients are adrenocortical carcinomas, breast cancer, central nervous system tumors, osteosarcomas, and soft-tissue sarcomas.¹³¹

These patients tend to develop malignancies early in life with 41% occurring before age 18 years,¹³³ with osteosarcoma occurring in approximately 12% of individuals.¹³² Families with Li-Fraumeni syndrome do demonstrate anticipation as well, likely secondary to telomerase shortening.¹³³ Overall, 3% of osteosarcoma

Table 3. Summary of Key Points

No	Genetic Predisposition
1	Retinoblastoma is secondary to loss of tumor suppressor gene <i>RB1</i> with classically ocular retinoblastoma formation and often osteosarcoma formation
2	Li-Fraumeni syndrome is characterized by loss of <i>p53</i> tumor suppressor gene and lifetime cancer risk greater of 70% to 90%
3	Rothmund-Thompson, Bloom, and Werner syndromes have mutations in genes associated with DNA replication and are at risk for several forms of cancer

Table 4. Summary of Key Points

No	Extrinsic Conditions
1	Chronic osteomyelitis with an associated nonhealing wound can result in a Marjolin ulcer or carcinoma formation at the site of the nonhealing wound
2	Postradiation sarcoma is rare but can result in osteosarcoma or soft-tissue sarcomas after doses of 45–60 Gy
3	Extrinsic conditions typically result in secondary malignant transformation 15 + years after radiation or the development of osteomyelitis
4	Chronic osteomyelitis with an associated nonhealing wound can result in a Marjolin ulcer or carcinoma formation at the site of the nonhealing wound

cases are found in Li-Fraumeni patients.¹³⁴ Cancer-screening guidelines for these patients have been described by multiple organizations.^{135–140} Screening includes whole-body MRI, laboratory studies, and endoscopy. The Toronto protocol for screening has been shown to have improved overall survival compared with no surveillance.¹³⁸

Rothmund-Thompson

Because of a mutation of *RECQL4*, a telomerase maintenance protein, Rothmund-Thompson is an autosomal recessive disorder characterized by rash, sparse hair, small size, skeletal and dental abnormalities, and juvenile cataracts.^{141,142} These patients also have an increased risk of cancers, usually osteosarcoma which occurs in 30% to 60% of patients.^{133,134,143} The average age of patients who develop their first malignancy is 15 years, although those who develop osteosarcoma typically do so at an earlier age around 11 years.^{143,144}

Bloom Syndrome

Congenital telangiectatic erythema, or Bloom syndrome, is an autosomal recessive disorder. Genomic instability results from mutations in the *BLM* gene, a RecQ helicase, and patients are predisposed to all types of cancers.^{133,145,146} There is a higher rate of Bloom syndrome in the Ashkenazi Jewish population, accounting for approximately 25% of all cases.¹⁴⁷ Besides malignancy, these patients often have small stature with proportional bodies, sunlight sensitivities, insulin resistance, and immune abnormalities.¹⁴⁸

The mean age of death in patients with Bloom syndrome is 26 years, and typically due to complications of malignancy.^{145,146} The most common malignancies in this syndrome are leukemia and lymphoma accounting for 44% of cases with osteosarcoma occurring in approximately 2% of cases.¹⁴⁵

Werner Syndrome

Patients with Werner syndrome present with premature aging, bilateral cataracts, short stature, osteoporosis, and hypogonadism.¹⁴⁹ It is more commonly seen in the Japanese population and is usually caused by mutations in the *WRN* gene, which encodes a RecQ Helicase.¹³³ This genetic mutation predisposes these patients to malignancy, often including thyroid neoplasms (16.7% of cases), but also soft-tissue sarcomas (10.1%) and osteosarcomas (7.7%).¹⁵⁰ When osteosarcoma does develop, it is often in unusual locations such as the foot, ankle, or patella.¹³³

Extrinsic Conditions

Osteomyelitis

Chronic nonhealing wounds are a well-known risk factor for the development of malignancy, referred to as Marjolin ulcers (Table 4).¹⁵¹ They have an incidence of approximately 1.6% to 23% in the setting of chronic osteomyelitis.¹⁵² Osteomyelitis is the etiology in only 2.6% of Marjolin ulcers however with burns accounting for the vast majority at 76.5%.¹⁵³ The latency period from ulcer development to malignancy is on average 29 to 43 years.^{153–155} The most common location is the lower extremity.^{153,155}

Although squamous cell carcinoma is the most common type of malignancy to develop in this patient population, other malignancies have been identified such as fibrosarcoma, angiosarcoma, osteosarcoma, adenocarcinoma, basal cell carcinoma, and malignant fibrous histiocytoma.¹⁵² Malignant degeneration may have occurred whether the patient reports worsening pain, increased drainage, enlargement, or lymphadenopathy.^{152,154} Unfortunately, the prognosis in these patients is poor, predominately due to late diagnosis of the malignancy. Metastasis is found in 10% to 27% of

patients on initial diagnosis.^{153,156} Treatment has often been with amputation proximal to the tumor,^{156–158} although wide excision with reconstruction may also be a viable option dependent on patient and tumor-specific characteristics.¹⁵²

Postradiation Sarcoma

Ionizing radiation is a known risk factor for the development of malignancy. Presentation of postradiation sarcoma is on average 15 to 16 years after radiation exposure and most often develops as a bone sarcoma, specifically osteosarcoma.^{159–161} The most common soft-tissue sarcoma to develop is undifferentiated pleomorphic sarcoma.^{161,162} Rates of sarcoma formation after radiation are low at roughly 0.03% to 0.9%.^{162,163} Prior radiation doses of 45 to 60 Gy are often found in these patients, but sarcomas can still arise in lower doses such as 30 Gy.^{159,161} Other risk factors for development are younger age at the time of radiation treatment and concurrent chemotherapy with alkylating agents.^{164,165} Genetic mutations are similar between sporadic and postradiation sarcomas, such as RB1 involvement; however, postradiation sarcomas are more likely to have *CDKN2A* and *CDKN2B*.¹⁶⁶ The survival rate in these patients is variable in the literature with an average 5-year overall survival of 33% to 68.2%.^{159–162} Patients presenting without metastatic disease at the time of diagnosis when treated with surgery and chemotherapy may have similar outcomes to primary sarcoma; however, those treated with surgery alone or present with the metastatic disease already present have worse outcomes.¹⁶⁷

Conclusion

Multiple factors and conditions that affect bone can predispose patients to the later development of malignancy including benign neoplasms, genetic conditions, and extrinsic factors. Although malignant transformation is rare in many of these conditions, a high index of suspicion must be kept when evaluating and following these patients to provide aggressive appropriate treatment if malignancy develops. Often malignant transformation will present as new-onset pain or mass formation in these patients and should trigger further workup and evaluation for these patients.

References

1. Vasquez L, Silva J, Chavez S, et al: Prognostic impact of diagnostic and treatment delays in children with osteosarcoma. *Pediatr Blood Cancer* 2020;67:e28180.

2. Levine AJ, Momand J, Finlay CA: The p53 tumour suppressor gene. *Nature* 1991;351:453-456.
3. Rodriguez-Galindo C, Orbach DB, VanderVeen D: Retinoblastoma. *Pediatr Clin North Am* 2015;62:201-223.
4. Knudson AG Jr: Mutation and cancer: Statistical study of retinoblastoma. *Proc Natl Acad Sci U S A* 1971;68:820-823.
5. Jhiang SM: The RET proto-oncogene in human cancers. *Oncogene* 2000;19:5590-5597.
6. Kroemer G: The proto-oncogene Bcl-2 and its role in regulating apoptosis. *Nat Med* 1997;3:614-620.
7. Prescott JD, Zeiger MA: The RET oncogene in papillary thyroid carcinoma. *Cancer* 2015;121:2137-2146.
8. Kovac M, Woolley C, Ribí S, et al: Germline RET variants underlie a subset of paediatric osteosarcoma. *J Med Genet* 2021;58:20-24.
9. Coultas L, Strasser A: The role of the Bcl-2 protein family in cancer. *Semin Cancer Biol* 2003;13:115-123.
10. Weinberg RA: Oncogenes and tumor suppressor genes. *CA Cancer J Clin* 1994;44:160-170.
11. Bozzola M, Gertosio C, Gnoli M, et al: Hereditary multiple exostoses and solitary osteochondroma associated with growth hormone deficiency: To treat or not to treat? *Ital J Pediatr* 2015;41:53.
12. Siegal GP, Bloem JL, Cates JMM: *Soft Tissue and Bone Tumours*. Lyon, France, International Agency for Research on Cancer, 2020.
13. Tong K, Liu H, Wang X, et al: Osteochondroma: Review of 431 patients from one medical institution in South China. *J Bone Oncol* 2017; 8:23-29.
14. Wicklund CL, Pauli RM, Johnston D, Hecht JT: Natural history study of hereditary multiple exostoses. *Am J Med Genet* 1995;55:43-46.
15. Lamovec J, Špiler M, Jevtić V: Osteosarcoma arising in a solitary osteochondroma of the fibula. *Arch Pathol Lab Med* 1999;123: 832-834.
16. Florez B, Monckeberg J, Castillo G, Beguiristain J: Solitary osteochondroma long-term follow-up. *J Pediatr Orthop* 2008;17: 91-94.
17. Ahmed AR, Tan TS, Unni KK, Collins MS, Wenger DE, Sim FH: Secondary chondrosarcoma in osteochondroma: Report of 107 patients. *Clin Orthop Relat Res* 2003;193-206.
18. Pedrini E, Jennes I, Tremosini M, et al: Genotype-phenotype correlation study in 529 patients with multiple hereditary exostoses: Identification of "protective" and "risk" factors. *J Bone Joint Surg Am* 2011;93:2294-2302.
19. Fei L, Ngoh C, Porter DE: Chondrosarcoma transformation in hereditary multiple exostoses: A systematic review and clinical and cost-effectiveness of a proposed screening model. *J Bone Oncol* 2018;13:114-122.
20. Jurik AG, Jørgensen PH, Mortensen MM: Whole-body MRI in assessing malignant transformation in multiple hereditary exostoses and enchondromatosis: Audit results and literature review. *Skeletal Radiol* 2020;49:115-124.
21. Legeai-Mallet L, Munnich A, Maroteaux P, Le Merrer M, Munnich A: Incomplete penetrance and expressivity skewing in hereditary multiple exostoses. *Clin Genet* 1997;52:12-16.
22. Jurik AG: Multiple hereditary exostoses and enchondromatosis. *Best Pract Res Clin Rheumatol* 2020;34:101505.
23. Beltrami G, Ristori G, Scoccianti G, Tamburini A, Capanna R: Hereditary multiple exostoses: A review of clinical appearance and metabolic pattern. *Clin Cases Miner Bone Metab* 2016;13:110-118.

24. Stieber JR, Dormans JP: Manifestations of hereditary multiple exostoses. *J Am Acad Orthop Surg* 2005;13:110-120.
25. Jennes I, Pedrini E, Zuntini M, et al: Multiple osteochondromas: Mutation update and description of the multiple osteochondromas mutation database (MOdb). *Hum Mutat* 2009;30:1620-1627.
- 26. Wells M, Birchard Z: A 40-year-old male presenting with hereditary multiple exostosis: Management and considerations. Case Rep Orthop** 2019;2019:4793043-4793044.
27. Lin PP, Moussallem CD, Deavers MT: Secondary chondrosarcoma. *J Am Acad Orthop Surg* 2010;18:608-615.
28. Bernard SA, Murphey MD, Flemming DJ, Kransdorf MJ: Improved differentiation of benign osteochondromas from secondary chondrosarcomas with standardized measurement of cartilage cap at CT and MR imaging. *Radiology* 2010;255:857-865.
29. Altay M, Bayrakci K, Yildiz Y, Ereku S, Saglik Y: Secondary chondrosarcoma in cartilage bone tumors: Report of 32 patients. *J Orthop Sci* 2007;12:415-423.
- 30. Bus MPA, Campanacci DA, Albergio JI, et al: Conventional primary central chondrosarcoma of the pelvis: Prognostic factors and outcome of surgical treatment in 162 patients. J Bone Joint Surg Am** 2018;100:316-325.
31. Herget GW, Strohm P, Rottenburger C, et al: Insights into Enchondroma, Enchondromatosis and the risk of secondary Chondrosarcoma. Review of the literature with an emphasis on the clinical behaviour, radiology, malignant transformation and the follow up. *Neoplasma* 2014;61:365-378.
- 32. Mulligan ME: How to diagnose enchondroma, bone infarct, and chondrosarcoma. Curr Probl Diagn Radiol** 2019;48:262-273.
33. Adler C-P: *Bone Diseases: Macroscopic, Histological, and Radiological Diagnosis of Structural Changes in the Skeleton*, Freiburg, Germany, Springer, 2000, Vol. 588.
34. Sassoon AA, Fitz-Gibbon PD, Harmsen WS, Moran SL: Enchondromas of the hand: Factors affecting recurrence, healing, motion, and malignant transformation. *J Hand Surg Am* 2012;37:1229-1234.
35. Verdegaal SHM, Bovée JVMG, Pansuriya TC, et al: Incidence, predictive factors, and prognosis of chondrosarcoma in patients with Ollier disease and Maffucci syndrome: An International Multicenter Study of 161 patients. *Oncologist* 2011;16:1771-1779.
36. Amary MF, Damato S, Halai D, et al: Ollier disease and Maffucci syndrome are caused by somatic mosaic mutations of IDH1 and IDH2. *Nat Genet* 2011;43:1262-1265.
37. Pansuriya TC, Van Eijk R, D'Adamo P, et al: Somatic mosaic IDH1 and IDH2 mutations are associated with enchondroma and spindle cell hemangioma in Ollier disease and Maffucci syndrome. *Nat Genet* 2011;43:1256-1261.
- 38. Wells ME, Eckhoff MD, Kafchinski LA, Polfer EM, Potter BK: Conventional cartilaginous tumors: Evaluation and treatment. JBJS Rev** 2021;9.
- 39. El Abiad JM, Robbins SM, Cohen B, et al: Natural history of Ollier disease and Maffucci syndrome: Patient survey and review of clinical literature. Am J Med Genet** 2020;182:1093-1103.
40. Amary MF, Bacsi K, Maggiani F, et al: IDH1 and IDH2 mutations are frequent events in central chondrosarcoma and central and periosteal chondromas but not in other mesenchymal tumours. *J Pathol* 2011;224:334-343.
- 41. Weinschenk RC, Wang WL, Lewis VO: Chondrosarcoma. J Am Acad Orthop Surg** 2021;29:553-562.
42. Lubahn JD, Bachoura A: Enchondroma of the hand: Evaluation and management. *J Am Acad Orthop Surg* 2016;24:625-633.
- 43. Bus MPA, Campanacci DA, Albergio JI, et al: Conventional primary central chondrosarcoma of the pelvis: Prognostic factors and outcome of surgical treatment in 162 patients. J Bone Joint Surg Am** 2018;100:316-325.
44. Biermann JS, Siegel GW, American Academy of Orthopaedic Surgeons: *Orthopaedic knowledge update Musculoskeletal tumors*. Rosemont, IL, American Academy of Orthopaedic Surgeons, pp 528.
45. Van Staa TP, Selby P, Leufkens HGM, Lyles K, Sprafka JM, Cooper C: Incidence and natural history of Paget's disease of bone in England and Wales. *J Bone Miner Res* 2002;17:465-471.
46. Ralston SH: Clinical practice. Paget's disease of bone. *N Engl J Med* 2013;368:644, 650.
47. Layfield R: The molecular pathogenesis of Paget disease of bone. *Expert Rev Mol Med* 2007;9:1-13.
48. Smith SE, Murphey MD, Motamedi K, Mulligan ME, Resnik CS, Gannon FH: From the archives of the AFIP: Radiologic spectrum of paget disease of bone and its complications with pathologic correlation. *Radiographics* 2002;22:1191-1216.
49. Harvey L, Gray T, Beneton MNC, Douglas DL, Kanis JA, Russell RGG: Ultrastructural features of the osteoclasts from Paget's disease of bone in relation to a viral aetiology. *J Clin Pathol* 1982;35:771-779.
50. Schajowicz F, Santini Araujo E, Berenstein M: Sarcoma complicating Paget's disease of bone. A clinicopathological study of 62 cases. *J Bone Joint Surg Br* 1983;65:299-307.
51. Shaylor PJ, Peake D, Grimer RJ, Carter SR, Tillman RM, Spooner D: Paget's osteosarcoma - No cure in sight. *Sarcoma* 1999;3:191-192.
52. Frassica FJ, Sim FH, Frassica DA, Wold LE: Survival and management considerations in postirradiation osteosarcoma and Paget's osteosarcoma. *Clin Orthop Relat Res* 1991:120-127.
53. Dray MS, Miller MV: Paget's osteosarcoma and post-radiation osteosarcoma: Secondary osteosarcoma at Middlemore Hospital, New Zealand. *Pathology* 2008;40:604-610.
54. Calabrò T, Mavrogenis AF, Ruggieri P: Osteoblastic osteosarcoma in monostotic Paget's disease. *Musculoskelet Surg* 2011;95:37-40.
55. López C, Thomas DV, Davies AM: Neoplastic transformation and tumour-like lesions in Paget's disease of bone: A pictorial review. *Eur Radiol* 2003;13(Suppl 4):L151-L163.
56. Colina M, La Corte R, De Leonardi F, Trotta F: Paget's disease of bone: A review. *Rheumatol Int* 2008;28:1069-1075.
57. Seitz S, Priemel M, Zustin J, et al: Paget's disease of bone: Histologic analysis of 754 patients. *J Bone Miner Res* 2009;24:62-69.
58. Mangham DC, Davie MW, Grimer RJ: Sarcoma arising in Paget's disease of bone: Declining incidence and increasing age at presentation. *Bone* 2009;44:431-436.
59. Mirabello L, Troisi RJ, Savage SA: Osteosarcoma incidence and survival rates from 1973 to 2004: Data from the surveillance, epidemiology, and end results program. *Cancer* 2009;115:1531-1543.
60. Mankin HJ, Hornicek FJ: Paget's sarcoma: A historical and outcome review. *Clin Orthop Relat Res* 2005;438:97-102.
61. Leet AI, Collins MT: Current approach to fibrous dysplasia of bone and McCune-Albright syndrome. *J Child Orthop* 2007;1:3-17.
62. Riddle ND, Bui MM: Fibrous dysplasia. *Arch Pathol Lab Med* 2013;137:134-138.
63. Most MJ, Sim FH, Inwards CY: Osteofibrous dysplasia and adamantinoma. *J Am Acad Orthop Surg* 2010;18:358-366.
64. Parekh SG, Donthineni-Rao R, Ricchetti E, Lackman RD: Fibrous dysplasia. *J Am Acad Orthop Surg* 2004;12:305-313.

65. Boyce AM, Florenzano P, de Castro LF, Collins MT: **Fibrous Dysplasia/McCune-Albright Syndrome**. Leiden, the Netherlands, Leiden University, 2019.
66. Ruggieri P, Sim FH, Bond JR, Unni KK: Malignancies in fibrous dysplasia. *Cancer* 1994;73:1411-1424.
67. Stanton RP, Ippolito E, Springfield D, Lindaman L, Wientroub S, Leet A: The surgical management of fibrous dysplasia of bone. *Orphanet J Rare Dis* 2012;7(suppl 1):1-9.
68. Qu N, Yao W, Cui X, Zhang H: Malignant transformation in monostotic fibrous dysplasia: Clinical features, imaging features, outcomes in 10 patients, and review. *Medicine (Baltimore)* 2015;94:e369.
69. Neumann JA, Garrigues GE, Brigman BE, Eward WC: Synovial chondromatosis. *JBJS Rev* 2016;4:e2.
70. Evans S, Boffano M, Chaudhry S, Jeys L, Grimer R: Synovial chondrosarcoma arising in synovial chondromatosis. *Sarcoma* 2014;2014:647939.
71. Kenan S, Abdelwahab IF, Klein MJ, Lewis MM: Case report 817: Synovial chondrosarcoma secondary to synovial chondromatosis. *Skeletal Radiol* 1993;22:623-626.
72. Sachinis NP, Sinopidis C, Baliaka A, Givissis P: Odyssey of an elbow synovial chondromatosis. *Orthopedics* 2015;38:e62-e67.
73. Davis RI, Hamilton A, Biggart JD, Hamilton A: Primary synovial chondromatosis: A clinicopathologic review and assessment of malignant potential. *Hum Pathol* 1998;29:683-688.
74. Bhadra AK, Pollock R, Tirabosco RP, et al: Primary tumours of the synovium: A report of four cases of malignant tumour. *J Bone Joint Surg Br* 2007;89:1504-1508.
75. Murphey MD, Vidal JA, Fanburg-Smith JC, Gajewski DA: From the archives of the AFIP: Imaging of synovial chondromatosis with radiologic-pathologic correlation. *Radiographics* 2007;27:1465-1488.
76. Gelderblom H, Hogendoorn PCW, Dijkstra SD, et al: The clinical approach towards chondrosarcoma. *Oncologist* 2008;13:320-329.
77. Chen W, DiFrancesco LM: Chondroblastoma: An update. *Arch Pathol Lab Med* 2017;141:867-871.
78. Ramappa AJ, Lee FY, Tang P, Carlson JR, Gebhardt MC, Mankin HJ: Chondroblastoma of bone. *J Bone Joint Surg Am* 2000;82:1140-1145.
79. Clevon AHG, Höcker S, Braire-De Bruijn I, Suzhai K, Cleton-Jansen AM, Bovée JMMG: Mutation analysis of H3F3A and H3F3B as a diagnostic tool for giant cell tumor of bone and chondroblastoma. *Am J Surg Pathol* 2015;39:1576-1583.
80. Rybak LD, Rosenthal DI, Wittig JC: Chondroblastoma: Radiofrequency ablation—alternative to surgical resection in selected cases. *Radiology* 2009;251:599-604.
81. Xu H, Nugent D, Monforte HL, et al: Chondroblastoma of bone in the extremities: A multicenter retrospective study. *J Bone Joint Surg Am* 2015;97:925-931.
82. Lin PP, Thenappan A, Deavers MT, Lewis VO, Yasko AW: Treatment and prognosis of chondroblastoma. *Clin Orthop Relat Res* 2005;438:103-109.
83. Narhari MD, Haseeb A, Lee S, Singh V: **Spontaneous conventional osteosarcoma transformation of a chondroblastoma: A case report and literature review**. *Indian J Orthop* 2018;52:87-90.
84. Laitinen MK, Stevenson JD, Evans S, et al: **Chondroblastoma in pelvis and extremities- A single centre study of 177 cases**. *J Bone Oncol* 2019;17:100248.
85. Raskin KA, Schwab JH, Mankin HJ, Springfield DS, Hornicek FJ: Giant cell tumor of bone. *J Am Acad Orthop Surg* 2013;21:118-126.
86. Sobti A, Agrawal P, Agarwala S, Agarwal M: Giant cell tumor of bone - An overview. *Arch Bone Joint Surg* 2016;4:2-9.
87. Kim Y, Nizami S, Goto H, Lee FY: Modern interpretation of giant cell tumor of bone: Predominantly osteoclastogenic stromal tumor. *Clin Orthop Surg* 2012;4:107-116.
88. Wu PF, Tang JY, Li KH: RANK pathway in giant cell tumor of bone: Pathogenesis and therapeutic aspects. *Tumour Biol* 2015;36:495-501.
89. Yamamoto H, Ishihara S, Toda Y, Oda Y: **Histone H3.3 mutation in giant cell tumor of bone: An update in pathology**. *Med Mol Morphol* 2020;53:1-6.
90. Behjati S, Tarpey PS, Presneau N, et al: Distinct H3F3A and H3F3B driver mutations define chondroblastoma and giant cell tumor of bone. *Nat Genet* 2013;45:1479-1482.
91. Chang SS, Suratwala SJ, Jung KM, et al: Bisphosphonates may reduce recurrence in giant cell tumor by inducing apoptosis. *Clin Orthop Relat Res* 2004;426:103-109.
92. Balke M, Campanacci L, Gebert C, et al: Bisphosphonate treatment of aggressive primary, recurrent and metastatic giant cell tumour of bone. *BMC Cancer* 2010;10:462.
93. Tse LF, Wong KC, Kumta SM, Huang L, Chow TC, Griffith JF: Bisphosphonates reduce local recurrence in extremity giant cell tumor of bone: A case-control study. *Bone* 2008;42:68-73.
94. **Network NCC. Bone Cancer 2022**. https://www.nccn.org/professionals/physician_gls/pdf/bone.pdf.
95. Chawla S, Henshaw R, Seeger L, et al: Safety and efficacy of denosumab for adults and skeletally mature adolescents with giant cell tumour of bone: Interim analysis of an open-label, parallel-group, phase 2 study. *Lancet Oncol* 2013;14:901-908.
96. Park A, Cipriano CA, Hill K, Kyriakos M, McDonald DJ: Malignant transformation of a giant cell tumor of bone treated with denosumab: A case report. *JBJS Case Connect* 2016;6:e78.
97. Hasenfratz M, Mellert K, Marienfeld R, et al: **Profiling of three H3F3A-mutated and denosumab-treated giant cell tumors of bone points to diverging pathways during progression and malignant transformation**. *Sci Rep* 2021;11:5709.
98. Asano N, Saito M, Kobayashi E, et al: **Preoperative denosumab therapy against giant cell tumor of bone is associated with an increased risk of local recurrence after curettage surgery**. *Ann Surg Oncol* 2022;29:3992-4000, doi:
99. Niu X, Zhang Q, Hao L, et al: Giant cell tumor of the extremity: Retrospective analysis of 621 Chinese patients from one institution. *J Bone Joint Surg Am* 2012;94:461-467.
100. Kremen TJ, Bernthal NM, Eckardt MA, Eckardt JJ: Giant cell tumor of bone: Are we stratifying results appropriately?. *Clin Orthop Relat Res* 2012;470:677-683.
101. Chan CM, Adler Z, Reith JD, Gibbs CP: Risk factors for pulmonary metastases from giant cell tumor of bone. *J Bone Joint Surg Am* 2015;97:420-428.
102. Balke M, Schrempfer L, Gebert C, et al: Giant cell tumor of bone: Treatment and outcome of 214 cases. *J Cancer Res Clin Oncol* 2008;134:969-978.
103. Rosario M, Kim HS, Yun JY, Han I: Surveillance for lung metastasis from giant cell tumor of bone. *J Surg Oncol* 2017;116:907-913.
104. Viswanathan S, Jambhekar NA: Metastatic giant cell tumor of bone: Are there associated factors and best treatment modalities? *Clin Orthop Relat Res* 2010;468:827-833.
105. Kay RM, Eckardt JJ, Seeger LL, Mirra JM, Hak DJ: Pulmonary metastasis of benign giant cell tumor of bone. Six histologically confirmed cases, including one of spontaneous regression. *Clin Orthop Relat Res* 1994;219-230.

106. Tubbs WS, Brown LR, Beabout JW, Rock MG, Unni KK: Benign giant-cell tumor of bone with pulmonary metastases: Clinical findings and radiologic appearance of metastases in 13 cases. *AJR Am J Roentgenol* 1992;158:331-334.
107. Palmerini E, Picci P, Reichardt P, Downey G: Malignancy in giant cell tumor of bone: A review of the literature. *Technol Cancer Res Treat* 2019;18:1533033819840000.
108. Domovitev SV, Healey JH: Primary malignant giant-cell tumor of bone has high survival rate. *Ann Surg Oncol* 2010;17:694-701.
109. Oda Y, SAKAmoto A, SaiTo T, et al: Secondary malignant giant-cell tumour of bone: Molecular abnormalities of p53 and H-ras gene correlated with malignant transformation. *Histopathology* 2001;39:629-637.
110. Lichtenstein L, Sawyer WR: Benign Osteoblastoma. Further observations and report of twenty additional cases. *J Bone Joint Surg Am* 1964;46:755-765.
111. Gitelis S, Schajowicz F: Osteoid osteoma and osteoblastoma. *Orthop Clin North Am* 1989;20:313-325.
112. Yalcinkaya U, Doganavsargil B, Sezak M, et al: Clinical and morphological characteristics of osteoid osteoma and osteoblastoma: A retrospective single-center analysis of 204 patients. *Ann Diagn Pathol* 2014;18:319-325.
113. Limaïem F, Byerly DW, Singh R, Osteoblastoma. *StatPearls*, 2021. <https://www.ncbi.nlm.nih.gov/books/NBK536954/>.
114. Atesok KI, Alman BA, Schemitsch EH, Peyser A, Mankin H: Osteoid osteoma and osteoblastoma. *J Am Acad Orthop Surg* 2011; 19:678-689.
115. Arkader A, Dormans JP: Osteoblastoma in the skeletally immature. *J Pediatr Orthop* 2008;28:555-560.
116. Amary F, Flanagan AM, O'Donnell P: Benign bone-forming tumors. *Surg Pathol Clin* 2021;14:549-565.
117. Berry M, Mankin H, Gebhardt M, Rosenberg A, Hornicek F: Osteoblastoma: A 30-year study of 99 cases. *J Surg Oncol* 2008;98:179-183.
118. Lucas DR, Unni KK, McLeod RA, O'Connor MI, Sim FH: Osteoblastoma: Clinicopathologic study of 306 cases. *Hum Pathol* 1994;25:117-134.
119. Mayer L: Malignant degeneration of so-called benign osteoblastoma. *Bull Hosp Joint Dis* 1967;28:4-13.
120. Görgün O, Salduz A, Kebudi R, Özger H, Bilgiç B: Malignant transformation of aggressive osteoblastoma to osteosarcoma. *Ekleml Hastalıklar Cerrahisi* 2016;27:108-112.
121. Geller DS, Levine NL, Hoang BH, et al: Genomic analysis does not support malignant transformation of osteoblastoma to osteosarcoma. *JCO Precis Oncol* 2019;3:1-7.
122. Dimaras H, Kimani K, Dimba EAO, et al: Retinoblastoma. *Lancet* 2012;379:1436-1446.
123. Kleinerman RA, Tucker MA, Tarone RE, et al: Risk of new cancers after radiotherapy in long-term survivors of retinoblastoma: An extended follow-up. *J Clin Oncol* 2005;23:2272-2279.
124. Ito M, Barys L, O'Reilly T, et al: Comprehensive mapping of p53 pathway alterations reveals an apparent role for both SNP309 and MDM2 amplification in sarcomagenesis. *Clin Cancer Res* 2011;17:416-426.
125. Retinoblastoma. *Am Acad Pediatr*, 2020. <https://aapos.org/glossary/retinoblastoma>.
126. Wong FL, Boice JD, Abramson DH, et al: Cancer incidence after retinoblastoma. Radiation dose and sarcoma risk. *JAMA* 1997;278: 1262-1267.
127. Kleinerman RA, Tucker MA, Abramson DH, Seddon JM, Tarone RE, Fraumeni JF: Risk of soft tissue sarcomas by individual subtype in survivors of hereditary retinoblastoma. *J Natl Cancer Inst* 2007;99:24-31.
128. Shinohara ET, DeWees T, Perkins SM: Subsequent malignancies and their effect on survival in patients with retinoblastoma. *Pediatr Blood Cancer* 2014;61:116-119.
129. Tonorezos ES, Friedman DN, Barnea D, et al: Recommendations for long-term follow-up of adults with heritable retinoblastoma. *Ophthalmology* 2020;127:1549-1557.
130. Schneider K, Zelle K, Nichols KE, Garber J, Li-Fraumeni Syndrome. *GeneReviews*(), 2019. <http://europepmc.org/books/NBK1311>.
131. Bougeard G, Renaux-Petel M, Flaman JM, et al: Revisiting Li-Fraumeni syndrome from TP53 mutation carriers. *J Clin Oncol* 2015;33: 2345-2352.
132. Mirabello L, Yeager M, Mai PL, et al: Germline TP53 variants and susceptibility to osteosarcoma. *J Natl Cancer Inst* 2015;107:101.
133. Hameed M, Mandelker D: Tumor syndromes predisposing to osteosarcoma. *Adv Anat Pathol* 2018;25:217-222.
134. Ottaviani G, Jaffe N: The epidemiology of osteosarcoma. *Cancer Treat Res* 2009;152:3-13.
135. Ballinger ML, Mitchell G, Thomas DM: Surveillance recommendations for patients with germline TP53 mutations. *Curr Opin Oncol* 2015;27: 332-337.
136. McBride KA, Ballinger ML, Killick E, et al: Li-Fraumeni syndrome: Cancer risk assessment and clinical management. *Nat Rev Clin Oncol* 2014;11:260-271.
137. Daly MB, Pilarski R, Axilbund JE, et al.: NCCN clinical practical guidelines in oncology genetic/familial high-risk assessment: Breast and ovarian. *Natl Compr Cancer Netw* 2017. https://www.nccn.org/professionals/physician_gls/f_guidelines.asp#genetics_screening.
138. Villani A, Shore A, Wasserman JD, et al: Biochemical and imaging surveillance in germline TP53 mutation carriers with Li-Fraumeni syndrome: 11 year follow-up of a prospective observational study. *Lancet Oncol* 2016;17:1295-1305.
139. Villani A, Tabori U, Schiffman J, et al: Biochemical and imaging surveillance in germline TP53 mutation carriers with Li-Fraumeni syndrome: A prospective observational study. *Lancet Oncol* 2011;12:559-567.
140. Kratz CP, Achatz MI, Brugieres L, et al: Cancer screening recommendations for individuals with Li-Fraumeni syndrome. *Clin Cancer Res* 2017;23:e38-e45.
141. Wang LL, Plon SE, Rothmund-Thomson Syndrome. *GeneReviews*. 2020. <https://www.ncbi.nlm.nih.gov/books/NBK1237/>.
142. Ghosh AK, Rossi ML, Singh DK, et al: RECQL4, the protein mutated in Rothmund-Thomson syndrome, functions in telomere maintenance. *J Biol Chem* 2012;287:196-209.
143. Wang LL, Gannavarapu A, Kozinetz CA, et al: Association between osteosarcoma and deleterious mutations in the RECQL4 gene in Rothmund-Thomson syndrome. *J Natl Cancer Inst* 2003;95:669-674.
144. Simon T, Kohlhase J, Wilhelm C, Kochanek M, De Carolis B, Berthold F: Multiple malignant diseases in a patient with Rothmund-Thomson syndrome with RECQL4 mutations: Case report and literature review. *Am J Med Genet* 2010;152A:1575-1579.
145. German J: Bloom's syndrome. XX. The first 100 cancers. *Cancer Genet Cytogenet* 1997;93:100-106.
146. Hafi W, Badri T, Rice AS. Bloom Syndrome. *StatPearls*. 2021. <https://www.ncbi.nlm.nih.gov/books/NBK448138/>.
147. Li L, Eng C, Desnick RJ, German J, Ellis NA: Carrier frequency of the Bloom syndrome b1mAsh mutation in the Ashkenazi Jewish population. *Mol Genet Metab* 1998;64:286-290.
148. Flanagan M, Cunniff C. Bloom Syndrome. *NCBI Bookshelf*. 2019. <http://europepmc.org/books/NBK1398>.

149. Oshima J, Sidorova JM, Monnat RJ: Werner syndrome: Clinical features, pathogenesis and potential therapeutic interventions. *Ageing Res Rev* 2017;33:105-114.
150. Lauper JM, Krause A, Vaughan TL, Monnat RJ: Spectrum and risk of neoplasia in werner syndrome: A systematic review. *PLoS One* 2013;8:e59709.
151. Multhoff G, Molls M, Radons J: Chronic inflammation in cancer development. *Front Immunol* 2011;2:98.
152. Panteli M, Puttaswamaiah R, Lowenberg DW, Giannoudis PV: Malignant transformation in chronic osteomyelitis: Recognition and principles of management. *J Am Acad Orthop Surg* 2014;22:586-594.
153. Kerr-Valentic MA, Samimi K, Rohlen BH, Agarwal JP, Rockwell WB: Marjolin's ulcer: Modern analysis of an ancient problem. *Plast Reconstr Surg* 2009;123:184-191.
154. Bauer T, David T, Rimareix F, Lortat-Jacob A, Lortat-Jacob A: Marjolin's ulcer in chronic osteomyelitis: Seven cases and a review of the literature [in French]. *Rev Chir Orthop Reparatrice Appar Mot* 2007;93:63-71.
155. Onah II, Olaitan PB, Ogbonnaya IS, Onuigbo WIB: Marjolin's ulcer (correction of ulcer) at a Nigerian hospital (1993-2003). *J Plast Reconstr Aesthet Surg* 2006;59:565-566.
156. Altay M, Arıkan M, Yildiz Y, Sağlık Y: Squamous cell carcinoma arising in chronic osteomyelitis in foot and ankle. *Foot Ankle Int* 2004;25:805-809.
157. Alami M, Mahfoud M, El Bardouni A, Berrada MS, El Yaacoubi M: Squamous cell carcinoma arising from chronic osteomyelitis. *Acta Orthop Traumatol Turc* 2011;45:144-148.
158. Pandey M, Kumar P, Khanna AK: Marjolin's ulcer associated with chronic osteomyelitis. *J Wound Care* 2009;18:504-506.
159. Inoue YZ, Frassica FJ, Sim FH, Unni KK, Petersen IA, McLeod RA: Clinicopathologic features and treatment of postirradiation sarcoma of bone and soft tissue. *J Surg Oncol* 2000;75:42-50.
160. Mavrogenis AF, Pala E, Guerra G, Ruggieri P: Post-radiation sarcomas. Clinical outcome of 52 Patients. *J Surg Oncol* 2012;105:570-576.
- 161. Joo MW, Kang YK, Ogura K, et al: Post-radiation sarcoma: A study by the Eastern Asian Musculoskeletal Oncology Group. *PLoS One* 2018;13:e0204927.**
162. Bjerkehagen B, Smeland S, Walberg L, et al.: Radiation-induced sarcoma: 25-year experience from the Norwegian radium hospital. *Acta Oncologica* 2008;47:1475-1482.
163. Kim KS, Chang JH, Choi N, et al: Radiation-induced sarcoma: A 15-year experience in a single large tertiary referral center. *Cancer Res Treat* 2016;48:650-657.
164. Virtanen A, Pukkala E, Auvinen A: Incidence of bone and soft tissue sarcoma after radiotherapy: A cohort study of 295, 712 Finnish cancer patients. *Int J Cancer* 2006;118:1017-1021.
165. Menu-Branthomme A, Rubino C, Shamsaldin A, et al: Radiation dose, chemotherapy and risk of soft tissue sarcoma after solid tumours during childhood. *Int J Cancer* 2004;110:87-93.
- 166. Lesluyes T, Baud J, Pérot G, et al: Genomic and transcriptomic comparison of post-radiation versus sporadic sarcomas. *Mod Pathol* 2019;32:1786-1794.**
167. Shaheen M, Deheshi BM, Riad S, et al: Prognosis of radiation-induced bone sarcoma is similar to primary osteosarcoma. *Clin Orthop Relat Res* 2006;450:76-81.