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. 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. 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. 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. Activation of proto-oncogenes results in unchecked growth and proliferation of cells, which can lead to papillary thyroid carcinoma, osteosarcoma, and lymphoma. Often tumor suppressor gene mutations are inherited, while proto-oncogene mutations are acquired. Table 1 presents all conditions included in this review and their associated protein mutations.

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). These are often referred to as exostoses and can arise in any bone of the body, but
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 underrepresented because they often present as incidental findings on imaging studies. These exostoses are characterized as pedunculated or sessile boney masses in direct continuity of the medullary canal with an overlying cartilage cap (Figure 1A–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. 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%. More recent MHE studies, however, suggest much lower rates of malignant transformation at around 2% to 5%.

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

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

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

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. This is especially true if the lesion becomes painful without a clear etiology. In addition, osteochondromas with a cartilage cap greater than 2 cm by radiographic imaging are associated with the development of chondrosarcoma. This cartilage cap may be measured using MRI or CT scan images with higher interobserver reliability for measurements obtained on CT imaging.

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. 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.

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.

Enchondroma

Characterized as benign intramedullary hyaline cartilaginous tumors, enchondromas are one of the most common primary bone tumors in the body (Figure 2, A and B). They account for 3% of all bone tumors and 13% of all benign bone tumors. The exact incidence is unknown because these are typically asymptomatic and found incidentally. 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. 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. 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. Rates of malignant
transformation are 10% to 40% for Ollier disease and up to 15% to 50% for Maffucci syndrome. Other malignancies can occur as well in these patients including astrocytoma, gliomas, and mesenchymal ovarian tumors.

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. 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. 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. Low-grade pelvic chondrosarcomas and all higher-grade chondrosarcomas should be treated with wide resection. Prognosis is best when enchondromas occur in the short bones of the body.

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, typically found in patients aged older than 55 years. 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. Radiographically, it is characterized by osteolytic extension from epiphysis toward metaphysis with a widening of the affected bone with coarsened trabeculae and cortical thickening (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, 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. Paget osteosarcoma, often referred to as Paget sarcoma, is a devastating complication of...
Paget disease of bone with poor outcomes.\textsuperscript{50–54} Although osteosarcoma is the most common subtype of Paget-associated tumor, chondrosarcoma and fibrosarcoma are also documented.\textsuperscript{55} This malignant transformation thankfully occurs in only approximately 1\% to 3\% of cases.\textsuperscript{56,57} The rate of transformation is higher in severe polyostotic Paget patients at 5\% to 10\%.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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

\textbf{Figure 3}

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

**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. Monostotic FD comprises 75% of cases, 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.

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. 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%. However, malignant transformation is more common with polyostotic involvement with rates of around 4% in both McCune-Albright and Mazabraud patients. 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](image-url)

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.
therapy,\textsuperscript{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.\textsuperscript{68} Treatment can include surgery, chemotherapy, and radiation therapy. Transformation often occurs during the fifth decade of life.\textsuperscript{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.\textsuperscript{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.\textsuperscript{64} 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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{70} Clinically differentiating primary synovial chondromatosis from secondary chondrosarcoma can be very difficult,\textsuperscript{75} so clinical suspicion should be raised based on lesion recurrence alone. As is typical of chondrosarcoma treatment, radiation and chemotherapy have limited

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**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.
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, amputation.38

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 epiphysial and metaphysial 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-κb-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 transformation96,97 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
Osteoblastoma

Osteoblastoma 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. Osteoblastoma is differentiated from osteoid osteoma by its larger size (>1.5 cm) and lack of nocturnal night pain relieved by nonsteroidal anti-inflammatory drugs. 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, osteoblastomas are maybe found incidentally and however are more classically symptomatic. There is a predilection for the axial spine location with male patients between ages 10 and 25 years being the most common patient cohort. Although benign, these can be locally aggressive with variable clinical course. These can be differentiated from osteoid osteomas usually by their size, location, and their aggressive nature. However, both osteoid osteomas and osteoblastomas often carry a c-FOS mutation and have other similarities in microscopic morphology. 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.

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

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. Heterozygous germline variation in the TP53 allele results in a lifetime cancer risk of 90% for women and 70% for men. The five most common malignancies in these patients are adrenocortical carcinomas, breast cancer, central nervous system tumors, osteosarcomas, and soft-tissue sarcomas. These patients tend to develop malignancies early in life with 41% occurring before age 18 years, with osteosarcoma occurring in approximately 12% of individuals. Families with Li-Fraumeni syndrome do demonstrate anticipation as well, likely secondary to telomerase shortening. Overall, 3% of osteosarcoma

Table 3. Summary of Key Points

| No | Genetic Predisposition |
|----|------------------------|
| 1  | Retinoblastoma is secondary to loss of tumor suppressor gene RB1 with classically ocular retinoblastoma formation and often osteosarcoma formation |
| 2  | Li-Fraumeni syndrome is characterized by loss of p53 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 |
cases are found in Li-Fraumeni patients. Cancer-screening guidelines for these patients have been described by multiple organizations. 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.

**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. These patients also have an increased risk of cancers, usually osteosarcoma which occurs in 30% to 60% of patients. 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.

**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. These patients also have an increased risk of cancers, usually osteosarcoma which occurs in 30% to 60% of patients. 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.

**Werner Syndrome**

Patients with Werner syndrome present with premature aging, bilateral cataracts, short stature, osteoporosis, and hypogonadism. It is more commonly seen in the Japanese population and is usually caused by mutations in the *WRN* gene, which encodes a RecQ Helicase. 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%). When osteosarcoma does develop, it is often in unusual locations such as the foot, ankle, or patella.

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**Extrinsic Conditions**

**Osteomyelitis**

Chronic nonhealing wounds are a well-known risk factor for the development of malignancy, referred to as Marjolin ulcers (Table 4). They have an incidence of approximately 1.6% to 23% in the setting of chronic osteomyelitis. Extrinsic conditions typically result in secondary malignant transformation 15 + years after radiation or the development of osteomyelitis. Chronic osteomyelitis with an associated nonhealing wound can result in a Marjolin ulcer or carcinoma formation at the site of the nonhealing wound.
patients on initial diagnosis.\textsuperscript{153,156} Treatment has often been with amputation proximal to the tumor,\textsuperscript{156–158} although wide excision with reconstruction may also be a viable option dependent on patient and tumor-specific characteristics.\textsuperscript{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 sarcomas, specifically osteosarcoma.\textsuperscript{159–161} The most common soft-tissue sarcoma to develop is undifferentiated pleomorphic sarcoma.\textsuperscript{161,162} Rates of sarcoma formation after radiation are low at roughly 0.03\% to 0.9\%.\textsuperscript{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.\textsuperscript{159,161} Other risk factors for development are younger age at the time of radiation treatment and concurrent chemotherapy with alkylating agents.\textsuperscript{164,165} Genetic mutations are similar between sporadic and post-radiation sarcomas, such as RB1 involvement; however, postradiation sarcomas are more likely to have CDKN2A and CDKN2B.\textsuperscript{166} The survival rate in these patients is variable in the literature with an average 5-year overall survival of 33\% to 68.2\%.\textsuperscript{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.\textsuperscript{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.

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Premalignant Conditions of Bone

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