7 Chondrosarcoma of the Appendicular Skeleton

Erik J. Geiger and Nicholas M. Bernthal

Epidemiology

Chondrosarcoma is a cartilage-forming malignant tumor of bone and is the second most common primary bone sarcoma after osteosarcoma. It typically forms in the medullary cavity of bone and grows outward (conventional chondrosarcoma) but can also arise from a preexisting benign cartilage lesion such as an enchondroma or osteochondroma (secondary chondrosarcoma). The anatomic distribution of these tumors favors the pelvis, the proximal appendicular skeleton, and the distal femur. Chondrosarcoma of the distal extremities is uncommon, and it is even more rarely found in the hands and feet. It is most commonly found in adults aged 40–60; patients younger than 25 are at significantly lower risk of developing a malignant cartilage tumor unless associated with syndromes of multiple cartilage lesions such as Ollier's or Maffucci's [1].

Most bone sarcomas – like osteosarcomas and Ewing sarcomas – are high grade and present with a correspondingly fulminant, rapidly progressive course. But this progression is less common in chondrosarcoma because the biologic spectrum it presents within is much broader. Chondrosarcoma histologic

E. J. Geiger · N. M. Bernthal (✉)
Department of Orthopaedic Surgery, University of California, Los Angeles, Santa Monica, CA, USA
e-mail: Egeiger@mednet.ucla.edu; Nbernthal@mednet.ucla.edu

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grade is assigned 1–3 in a system based on nuclear size, hyperchromasia, cellularity, and mitotic count [2]. Accurately determining chondrosarcoma grade in practice proves to be very challenging and subject to high interobserver variability, but it is critical to disease management since grade is the most important prognostic predictor for postoperative disease recurrence or metastasis and is a significant predictor of survival [3]. Most treatment teams can readily differentiate a benign cartilage lesion from a high-grade chondrosarcoma, but distinguishing an intermediate (grade 2) lesion from a high-grade (grade 3) or, more critically, distinguishing a benign enchondroma from a low-grade (grade 1) chondrosarcoma is much more subtle. The terms atypical cartilaginous tumor and low-grade cartilage neoplasm have been introduced as a synonym to grade 1 chondrosarcoma to reflect the unique clinical behavior of grade 1 tumors, which are locally aggressive but carry essentially no risk of metastasis and have a correspondingly excellent prognosis with 5-year survival of 83–99%. A worse prognosis is associated with grade 2 and 3 disease, which carry higher rates of metastasis (approximately 10 and 70%, respectively) and lower 5-year survival rates of between 60–70% and 30–50%, respectively [2].

Histologic Subtypes

There are multiple chondrosarcoma variants known to exist including dedifferentiated, mesenchymal, secondary, and clear cell. A concerning feature of low-grade chondrosarcoma lesions is that they have the ability to dedifferentiate or undergo conversion from a low- to a high-grade neoplasm. Dedifferentiated chondrosarcomas – comprising about 10% of malignant cartilage tumors – are biologically aggressive and histologically demonstrate two different components: one a well-differentiated cartilage lesion like an enchondroma or a grade 1 chondrosarcoma juxtaposed to a high-grade spindle cell lesion that can have features of osteosarcoma, fibrosarcoma, or an undifferentiated sarcoma [1]. This histologic change is typically accompanied by a clinical change with a notable increase in tumor size or increase in

pain. The outcomes of this tumor are poor, with reported 5-year survival rates ranging from 7% to 24%. Despite the dedifferentiated component's histologic similarity to more common primary bone sarcomas, there remains no consensus regarding the efficacy of adjuvant chemotherapy for this disease [4, 5].

Mesenchymal chondrosarcomas represent <2% of all malignant cartilage tumors but are notable because of their aggressive nature and small round cell components on histology. These high-grade tumors affect younger patients on average than typical chondrosarcoma and carry a substantial risk of local recurrence after surgical treatment and distant metastasis. Up to 15% of patients can have lung or other bone metastases at presentation. The overall survival rate for patients with this diagnosis is ~50% at 5 years [6]. Gross total resection remains the standard treatment but given the poor prognosis and unique histologic features of this disease, some argue for adjuvant anthracycline-based chemotherapy. Large European cooperatives and single institutional series have supported improved overall and progression-free survival in patients treated with chemotherapy (anthracycline plus alkylating agents) [7, 8]. A 2014 report out of MD Anderson also supported the use of radiation therapy to improve local control rates after surgical resection of mesenchymal chondrosarcoma [9]. Despite these reports, a recent large meta-analysis including 18 publications and 107 patients did not find the use of chemotherapy or radiation to be associated with improved overall or event-free survival [10]. Clearly, the use of adjuvant therapies is controversial in the management of mesenchymal chondrosarcoma but should be considered in medically fit patients.

Secondary chondrosarcomas are a distinct tumor that originates from a benign cartilaginous lesion. Most commonly, the precursor lesion is an osteochondroma, although secondary chondrosarcomas can arise from enchondromas, particularly as a sequalae of hereditary conditions like Ollier's disease or Maffucci's syndrome [1]. A sudden increase in size of an osteochondroma's cartilage cap – particularly in a skeletally mature patient – should raise concern about secondary chondrosarcoma development, although an exact size cutoff has not been established. Secondary chondrosarcomas do need to be distinguished

from dedifferentiated chondrosarcomas, but while the latter are high-grade lesions, the former are most often low to intermediate grade. As such, metastasis from secondary chondrosarcomas are rare, and the outcomes of these tumors are quite good with 5-year overall survival approaching 90%. Treatment is by wide surgical resection [11].

Finally, clear cell chondrosarcoma is an extremely rare variant of chondrosarcoma and is so named because of the vacant cell cytoplasm seen on light microscopy. This lesion is notable because it is one of the few epiphyseal-based tumors, commonly in the proximal femur. These tumors are low grade and have a good prognosis (80% 10-year survival) when treated adequately with wide resection. However, they have a propensity for local recurrence and late metastasis emphasizing the importance of appropriate local control and long-term surveillance [12].

Diagnosis and Staging

Initial Workup

The approach to a patient with suspected bone sarcoma from initial examination through histologic diagnosis is called staging and is composed of a medical history, physical examination, imaging studies, and, lastly, biopsy [13]. Although these steps are common themes throughout musculoskeletal oncology, the collaborative, multidisciplinary clinical-radiographic-histologic correlation is perhaps most important to the accurate diagnosis within chondrosarcoma.

The most common presenting symptom of patients with chondrosarcoma is pain. In a study by Marco et al., 60% of patients had pain at rest and another 20% endorsed vague regional pain [14]. Although a 20–30% of enchondromas can also be associated with pain, pain at night is particularly concerning for malignancy. It should be noted that a fraction of patients with chondrosarcoma can present without any pain at all. History taking should focus on the timing, duration, and intensity of symptoms, as well as the association with any other systemic signs of cancer such as fevers,

night sweats, and weight loss. Although a recent injury is commonly reported in patients who have musculoskeletal tumors, trauma does not rule out a sarcoma. A pathologic fracture can be the presenting sign of chondrosarcoma in up to 10% of patients, and any low-energy fracture should raise suspicion. A complete history will also note any personal or family history of cancer or cancer predisposition syndromes. Physical exam may identify long bone tenderness if cortical integrity is compromised, but a palpable mass will only be identified if the tumor has progressed through the cortex and periosteum [13].

Imaging

After a thorough history and physical examination, the next step is radiographic evaluation of the involved extremity. It is very difficult to differentiate enchondromas from low-grade intramedullary chondrosarcomas as they share many features. Enchondromas are classically diaphyseal or metaphyseal medullary lesions with a chondroid matrix containing "ring and arc" or "popcorn" calcification patterns. On MRI, a clearly lobulated growth pattern is evident with T1-hypointense cartilage with bright foci of displaced yellow marrow. The same hyaline cartilage is bright on T2 images because of its high water content [15]. There are some imaging features, however, which when taken together can help identify a malignant cartilage lesion. First, larger lesions carry a greater risk of malignancy. In a comparative study by Murphey et al. looking at 92 enchondromas and 95 chondrosarcomas, benign lesions averaged 5 cm in size, while malignant lesions averaged 8 cm [16]. For most authors, lesion size over 6 cm raises the index of suspicion for malignancy [17].

Advanced imaging is indicated to better evaluate symptomatic cartilage tumors. While some degree of endosteal scalloping and cortical expansion can be seen in both enchondroma and chondrosarcoma, Murphey et al. found endosteal scalloping of greater than two-thirds of cortical thickness on an axial CT slice to be particularly discriminatory as 90% of chondrosarcomas exhibited this feature compared to only 10% of benign lesions. Endosteal

scalloping to any degree for greater than two-thirds the longitudinal length of the lesion was also indicative of a malignant process. When the endosteal scalloping perforated the cortex, an odds ratio of 86 predicted chondrosarcoma over enchondroma and was even more dramatic in the presence of a soft tissue mass. However, an overt soft tissue mass is typically a sign of a high-grade process, and the difficultly differentiating this from a benign cartilage tumor is obviated. Periosteal reaction and cortical thickening were also observed more frequently in chondrosarcomas [16].

So, while standard MRI sequences are useful for delineating soft tissue extension of these typically intramedullary tumors and identifying other characteristics of high-grade malignancy, they are of limited value in differentiating enchondroma from intramedullary chondrosarcoma. Some authors have recommended using dynamic, contrast-enhanced MR modalities to aid in these subtle diagnoses, but such sequences are poorly sensitive [18]. Others have advocated for the use of bone scans in diagnosing cartilage tumors, but while high-grade lesions will demonstrate a high degree of activity, this modality is similarly limited in its ability to differentiate enchondroma and low-grade chondrosarcoma [16]. Therefore, few centers will consistently employ contrast-enhanced MRI or bone scans in clinical practice for low-grade cartilage lesions.

Based on the abundance of literature on imaging findings of cartilage tumors, Parlier-Cuau proposed a means of classifying radiologic findings as aggressive, active, or quiescent to help guide clinicians as to when biopsy was indicated [17]. They specified aggressive criteria (suggestive of grade 2 or 3 chondrosarcoma) that included pathologic fracture, periosteal reaction, permeative osteolysis, cortical destruction, and presence of a soft tissue mass. Any lesion with at least one aggressive feature should be biopsied, specifically in the area of the tumor that appeared most aggressive (if nonuniform). In the absence of aggressive radiologic features, then active features should be assessed and considered in the context of clinical pain. These active features included endosteal scalloping of more than two-thirds of the diaphyseal cortex or along more than two-thirds of lesion length, cortical thickening, cortical remodeling or enlargement of the

medullary canal, intense radiotracer uptake on bone scan, or early and exponential contrast enhancement on dynamic gadolinium-enhanced MRI. Lesions with two or more active features should be biopsied in the area of greatest activity as these could represent an area of low-grade chondrosarcoma. When only one active criterion was identified on standard X-ray, CT scan, and standard MRI, then bone scan or dynamic contrast-enhanced MRI should be pursued. Additional active features would then lead to biopsy, but if no other active feature is identified, then the lesions are termed quiescent and radiographic surveillance at 3–6 months and then annually was recommended [17].

Biopsy and Histology

Although clinical history and imaging characteristics can identify cartilage lesions in need of biopsy, they are themselves insufficient for determining tumor grade. Since histologic grade is the most important factor guiding surgical management and prognosis, accurate preoperative tumor grading is critical. This is routinely done via image-guided core needle biopsy. Unfortunately, there is a high rate of discordance between the histologic diagnosis obtained after preoperative core needle biopsy and the final surgical pathologic diagnosis after review of the entire specimen. Discordance in up to one-quarter of cases has been described with a majority of these discrepancies resulting from core needle biopsy under-grading the tumor [19, 20]. This phenomenon is likely due to tumor heterogeneity and sampling error. Although a lot of weight is placed on histology, it alone is a poor surrogate for biology, and the diagnostic inaccuracy inherent to pathologic specimen review may be even worse for axial lesions compared to appendicular samples.

All chondrosarcomas regardless of grade show malignant characteristics such as hypercellularity, mitoses, pleomorphism, binucleate lacunae, and cellular atypia [1]. Tumor grades 1–3 progress subtly along a continuum with more numerous and severe versions of these features. Differentiating low- from high-grade tumors is straightforward. Grade 1 chondrosarcoma is

pauci-cellular with abundant hyaline cartilage matrix, while grade 3 tumors are highly cellular within a mucomyxoid matrix exhibiting bizarre mitoses [21]. Differentiating an enchondroma from a grade 1 chondrosarcoma histologically, conversely, is nearly impossible, although a hallmark of malignancy is cartilage cells that replace marrow fat entrapping lamellar bone [14].

The possibility of biopsy sampling errors and the interobserver variability inherent to histologic review of cartilage lesions is concerning and emphasizes that even histology cannot be used independent of clinical and imaging data when working up these tumors. Since conventional chondrosarcoma is resistant to both chemotherapy and radiation, accurate preoperative diagnosis critically informs the surgical management of this disease. The challenge to the treating surgeon is balancing surgical morbidity with the risk of local recurrence and the potential for metastatic disease.

Chondrosarcoma Treatment

The treatment of chondrosarcoma can be as varied as its clinical, radiographic, and histologic presentation. However, because of its relative radio- and chemoresistance, surgery is a unifying factor. Once the decision to treat a cartilage lesion has been made, the surgeon will need to determine the type of surgical intervention. Enneking described the possible oncologic surgical margins and the plane of dissection that achieves them: an intralesional procedure is a cytoreductive technique that grossly debulks the tumor typically through a cortical window and is performed within the tumor mass itself. It conceivably leaves microscopic (if not macroscopic) disease behind. Intralesional margins can be extended by the use of mechanical and chemical adjuvants such as high-speed burr, phenol, liquid nitrogen, argon beam, or others. Alternatively, a marginal excision is a procedure performed to remove the tumor extracapsularly through the reactive zone of the tumor, possibly leaving microsatellites of disease behind. A wide resection margin is performed when the tumor is removed with a cuff of normal tissue beyond the reactive zone. This should render

the resection bed tumor-free, though the definition of an adequate cuff of tissue remains ill-defined to this day. Finally, a radical resection, as originally described by Enneking – in which the entire compartment of origin is removed along with the tumor – is not routinely performed in modern oncologic surgery [14, 22].

Treatment of Grade 1 Disease

Once a grade 1 chondrosarcoma has been differentiated from an enchondroma as described above, there is no doubt that it should be treated. However, controversy remains over the optimal surgical treatment. Historically, all chondrosarcomas were treated with wide or radical resection requiring limb reconstruction, which resulted in oncologically effective disease control but at considerable functional disability. As understanding of the biology and behavior of grade 1 chondrosarcoma has evolved – prompting some to omit the "sarcoma" designation all together in favor of "atypical cartilage tumors" – the most effective surgical intervention has been debated. Though these tumors cause pain and are locally aggressive, they almost never metastasize. Thus, some favor a more limited, intralesional approach sparing adjacent joints.

It is clear that chondrosarcomas of different grades are quite different diseases and, thus, an adequate margin for the surgical treatment of one grade may not be the same as that needed to treat a different grade. Thus, the best studies designed to address treatment controversies will restrict inclusion criteria by tumor grade. Mohler et al. retrospectively reviewed 46 patients with either grade 1 chondrosarcoma or painful enchondromas in the long bones treated with intralesional curettage plus liquid nitrogen cryosurgery with average 4-year follow-up. Two patients had a local recurrence (4.3%) which was subsequently removed by wide excision. Those patients were then tumor-free as of 3 years postoperative. Mean MSTS scores were high at 27 [23].

Additional retrospective studies have been performed that compare intralesional curettage plus local adjuvants to wide local resection for grade 1 chondrosarcoma. Aaraons et al. reviewed 32

cases of grade 1 intracompartmental chondrosarcomas of the long bones comparing 15 resections with 17 intralesional procedures combined with differing adjuvants such as phenol, liquid nitrogen, or PMMA cement. One local recurrence occurred in each group for a 5-year recurrence-free survival estimate of 93% and 94%, respectively. Neither recurrence transitioned grades, and there were no metastases. The mean MSTS scores were 29.5 versus 25.1 in favor of the intralesional cohort, and complications were observed more frequently after resection and reconstruction (7 of 15 patients) than with extended intralesional treatment (1 of 17 patients) concluding that intralesional procedures were oncologically safe, had better functional outcomes, and decreased complication rates for these tumors [24].

Campanacci et al. reviewed 85 cases of central grade 1 chondrosarcoma. In 65 cases, intralesional curettage plus phenol adjuvant was performed, while in 21 cases with more "aggressive radiological patterns" a wide resection was performed. Postsurgical complications were much higher in the resection group in which five patients did have to return to the operating room for management. There were two instances of local recurrence without metastasis, and although the intergroup difference was not statistically significant, both recurrences were in the intralesional cohort. One patient who did recur did so as a grade 2 lesion. Additionally, it should be emphasized that even grade 1 lesions can occur along a spectrum, and the authors choosing wide resection for lesions that had more concerning features such as bone enlargement, periosteal reaction, or presence of a soft tissue mass adds ambiguity to their results, which should be interpreted with caution [25]. Leerapun et al. published a similar study conceptually that found no survival difference between an intralesional group and a wide resection group of grade 1 chondrosarcoma, but, again, more radiographically aggressive lesions were treated with more extensive surgery [26].

Understanding the risk of local recurrence from these very different surgical procedures is important. Schwab et al. investigated whether local recurrence after treatment of grade 1 chondrosarcoma negatively influenced survival [27]. They reviewed 164 patients treated surgically for grade 1 chondrosarcoma of long

bones with median 9.5-year follow-up. Surgical treatment included all forms of procedures from intralesional to amputation. Twenty-one patients (13%) experienced a recurrence, and overall survival for patients with recurrence after primary treatment was worse than those without recurrence (10-year survival estimates of 79% versus 90%). Six patients in the study died from disease – all of these were in the recurrence group – and 4 of the 21 had progression of tumor grade upon recurrence. Local recurrence and tumor metastasis were factors independently associated with death (HR 10.8, $p < 0.001$). Of note, recurrences were noted up to 9 years after the index procedure, emphasizing the need for prolonged follow-up in studies investigating surgical treatment outcomes of this disease [27].

So, the literature is clearly mixed regarding the appropriateness of intralesional treatment for grade 1 chondrosarcoma. In the absence of randomized studies comparing intralesional curettage plus adjuvant treatment to wide resection, multiple systematic reviews and meta-analyses have tried to amalgamate the retrospective data available [28–30]. In 2019, Dierselhuis et al. published a systematic review out of the Cochrane Library comprised of retrospective comparative studies and case series on the treatment of central low-grade chondrosarcoma of long bones. The primary outcome was recurrence-free survival, and the secondary outcomes included function as assessed by the MSTS score and incidence of complications. Eighteen studies were included although data abstraction could only be performed in 14. Meta-analysis of data from 238 participants across the seven comparative studies demonstrated no difference in recurrence-free survival after intralesional treatment versus wide resection (risk ratio (RR) 0.98, CI 0.92–1.04). This was graded as "low-certainty" evidence. MSTS scores were slightly better after intralesional surgery (mean 93% vs. 78%) with a mean difference of 12% (95% CI 2.82–22.55, $p < 0.001$). Major complications across six studies (203 patients) were lower in the intralesional cohort (5 in 125 cases) compared to the wide resection group (18 in 78 cases) with a RR = 0.23 (CI 0.10–0.55). In four patients (0.5% of total), local recurrence presented as a grade 2 or higher lesion. Two of these were treated with wide resection and were free of disease at final

follow-up, and two patients died from chondrosarcoma. Overall, there was a 96% recurrence-free survival after resection compared to a 94% recurrence-free survival after intralesional treatment after maximum follow-up of over 20 years. It must be noted that only evidence of low and very low certainty according to the GRADE system was available for inclusion in this review [31]. Thus, although event-free survival appears equivalent between intralesional treatment and wide resection, while favoring intralesional treatment for patient function and postoperative complications, these results should be interpreted with caution since such conclusions are based on low-quality evidence. Clearly, shared decision-making and the application of available data to individualize patient care recommendations is paramount in the treatment of this disease.

Treatment of High-Grade and Dedifferentiated Chondrosarcoma

Treatment of high-grade chondrosarcoma (grade 2 or 3 or dedifferentiated) of the appendicular skeleton is much less controversial, as these lesions require wide resection to achieve oncologically safe margins and ensure best possible patient survival [3]. Lee et al. reported on 227 patients managed with chondrosarcoma and followed for a mean of 6 years at a single institution from 1972 to 1994 [32]. One hundred forty-one tumors were considered high grade, wherein 103 were grade 2 and 38 were grade 3, dedifferentiated, or had components of each. Three patients were treated with amputation and the rest with wide resection. Of the 141 high-grade tumors, 15 patients underwent resection with intralesional margins and 19 had marginal margins because of anatomic constraints and patient preference to spare critical structures instead of undergoing an ablative procedure. The authors found that patients managed with wide margins had a significantly higher rate of survival than those managed with either an intralesional or marginal margin. All 19 patients managed with a marginal resection died of their disease during study follow-up. Predictors of metastasis and death with high-grade tumors included local recur-

rence and higher tumor grade. Of note, adjuvant chemotherapy and/or radiotherapy did not help survival outcomes when it was used [32].

Grimer et al. orchestrated a multi-institutional study of the rare dedifferentiated subtype of chondrosarcoma, the survival from which is fairly dismal with median patient survival of 1.4 years [33]. Two hundred sixty-six patients with nonmetastatic disease were reviewed, 254 of which underwent surgery (73% achieved adequate wide margins, while 23% had inadequate marginal resections). The nonmetastatic cohort had 5-year survival of 28%, but inadequate margin was one of the factors predictive of death in their multivariate model (HR = 0.55, 95% CI 0.37–0.82; p = 0.003 for clear margins) [33]. Other studies have similarly confirmed the very high risk of local recurrence that exists when high-grade chondrosarcoma resection margins are inadequate and how that adversely affects patient survival [34].

But while the need for wide surgical resection should be considered standard for high-grade conventional and dedifferentiated chondrosarcoma, the role of adjuvant modalities is less clear. Miao et al. retrospectively reviewed their single institution cohort of 72 patients with dedifferentiated chondrosarcoma treated in the 1990s and 2000s. Though median overall survival was just 13.9 months (95% CI: 6.4–21.5 months) for the entire cohort, chemotherapy was associated with improved overall survival (HR 0.23, 95% CI: 0.12–0.44, p = 0.002) and improved progression-free survival (HR 0.43, 95% CI: 0.24–0.77, p = 0.005) [5]. Unfortunately, treatment regimens were highly heterogeneous. Conversely, in another single institution review of 123 patients, the percentage and specific histologic subtype of the dedifferentiated component affected patient survival, but the use of neoadjuvant or adjuvant chemotherapy did not. The median survival of patients treated with chemotherapy was 23 months (95% CI: 12–34 months) versus 18 months (95% CI: 11–25 months) (p = 0.88) for those treated with surgery alone [4]. This ambiguity argues for multicentered trials on the use of chemotherapy as adjuvant treatment for dedifferentiated chondrosarcoma to meet larger patient accrual targets in order to help clarify this clinical controversy. Similarly, interest in adjuvant therapies has extended

beyond traditional cytotoxic chemotherapies. The small molecule inhibitors and immunotherapies that have become exciting fields of study in modern solid organ and hematopoietic oncology have also become of interest to sarcoma specialists, particularly for high-grade or unresectable disease. While some targeted therapies have demonstrated modest survival benefits in sarcoma, the results of trials with immunotherapies have been largely disappointing to date [35–40]. Clearly, while ablative surgery remains the primary means by which to treat high-grade chondrosarcoma, more work needs to be done to provide patients with local and systemic control options when surgical resection is not curative.

Treatment of Recurrent Chondrosarcoma

It is clear that an inadequate margin in the treatment of high-grade chondrosarcoma carries a substantial risk of local recurrence and, with that, a risk in progression of tumor grade and/or tumor metastasis. Suggested management of locally recurrent chondrosarcoma is debated in the literature. Recurrent tumor either presents as the same histologic grade or, in a minority of patients, at a higher grade. If the recurrent tumor presents again as grade 1 chondrosarcoma and is identified early while entirely intramedullary, an argument can be made for treatment with another intralesional procedure [21]. However, recurrent disease – even if recurrently low grade – argues that the patient's cancer is biologically aggressive, and recurrent low-grade tumors treated with an intralesional procedure are at a high rate of re-recurrence [27]. Laitinen et al. reported on 126 patients diagnosed with locally recurrent chondrosarcoma of the pelvis or limb. In patients without metastases prior to or at the time of local recurrence, significant factors affecting disease-specific survival after univariate analysis were grade of tumor and wide margins compared to marginal or intralesional margins. Although these associations did not achieve statistical significance in the multivariate model, this group still argued for wide margins in the treatment of locally recurrent chondrosarcoma and in the rare circumstances of multiply-recurrent disease. Understandably,

metastasis was a poor prognostic sign as 50% of patients died within 8 months of disseminated disease. Surgical treatment of the local recurrence among patients with metastasis at or prior to the recurrence did not improve their survival arguing against aggressive resections of recurrent disease in patients with metastases [41]. Recommendation against aggressive surgery for patients with synchronous metastatic disease in favor of palliative options has been supported by other authors [42].

Treatment of Appendicular Chondrosarcoma with Pathologic Fracture

The incidence of long bone pathologic fracture in patients with primary bone sarcoma is about 10% [43]. Fracture risk is related to the mechanical impact of bone destruction by the tumor, subsequent necrosis from neoadjuvant treatment, and even mechanical weakness from a biopsy procedure. In the past, the occurrence of pathologic fracture was a contraindication to limb salvage surgery because of the concern for tumor contamination of adjacent joints, nerves, vessels, and other soft tissues. Additionally, fracture was felt to increase the risk of metastasis because of microvascular damage and tumor seeding [43]. However, modern oncologic surgery has begun to change the treatment paradigm. Twenty years ago, Scully et al. studied pathologic fracture in osteosarcoma patients and found that although fracture portended a higher risk of local recurrence and death from disease compared to patients without pathologic fracture, limb salvage surgery could be performed safely and without incurring additional oncologic risk to the patient [44]. Osteosarcoma, critically, can be very responsive to chemotherapy, which provides a framework for understanding how limb salvage can be possible in the face of fracture-contaminated compartments. Chondrosarcoma, on the other hand, does not have effective local or systemic adjuvant options, and thus limb salvage after pathologic fracture has been more controversial.

First, Albergo et al. reported a retrospective case-control study on 182 patients with femoral chondrosarcoma treated at their

institution, 39 of which presented with a pathologic fracture. They analyzed cancer-specific survival, development of local recurrence, and metastasis over a mean nearly 10-year follow-up. Similar to the report by Scully, the pathologic fracture group had worse overall 5-year disease-specific survival (49% versus 75%, $p = 0.0001$). Interestingly, when the groups were stratified by histologic grade, survival was significantly worse for grade 1 disease with pathologic fracture compared to grade 1 disease without fracture, but there was no difference in survival with or without associated pathologic fracture at higher chondrosarcoma grades. There was no association between fracture and the development of metastases [45]. These authors did not investigate the impact of local control options on outcome.

Chandrasekar et al. performed a retrospective review of 72 patients with nonosteogenic primary bone sarcomas of the proximal femur – all of whom had associated pathologic femur fractures – including 34 patients with chondrosarcoma [46]. This represented 29% of all proximal femoral chondrosarcoma patients treated at their referral hospital in a 30-year period. The authors assessed patient, tumor, and treatment factors in relation to patient survival, and local treatment options ranged from limb salvage with endoprosthetic reconstruction to amputation at the hip or hindquarter level. Interestingly, survival outcomes were dictated almost exclusively by tumor histology. The 5-year survival outcome for fracture patients with Ewing sarcoma was 60%, for conventional chondrosarcoma it was 57%, and for dedifferentiated chondrosarcoma it was 0%. This difference between dedifferentiated chondrosarcoma and other histologies was statistically significant. For the whole group, there was no difference in survival related to the timing of fracture, patient age, surgical margin, or limb salvage versus amputation. Local recurrence rate was 24%, and this also did not affect survival. The incidence of metastasis at diagnosis was 10/72 fracture patients, which represented an equivalent proportion to all patients treated for primary bone sarcomas during the study period institutionally. The authors argued that pathologic fracture is not a contraindication to limb salvage as amputation does not provide a survival benefit [46].

Similarly, Bramer et al. reviewed the influence of pathologic fracture on surgical management and outcomes of a large cohort of primary bone sarcomas that included 152 higher grade extremity chondrosarcomas. Thirteen patients presented with metastasis in the fracture group, which was not statistically significantly different than that in the non-fractured group (13% versus 7%, $p = 0.3$). One-third of the remaining 130 localized chondrosarcomas presented with a fracture, but there was no significant difference in local recurrence rates between the patients selected for amputation and those treated with limb salvage (39% versus 20%, $p = 0.28$). Though overall survival in the fracture group was lower (35% at 10 years) than the controls (63%, $p = 0.04$), amputation provided no survival benefit. In fact, in multivariate analyses, only grade 3 and dedifferentiated tumor subtypes were predictive of survival [47].

Overall, although pathologic fracture is a sign of a biologically aggressive bone sarcoma carrying a higher risk of local recurrence and death from disease, limb salvage surgery does not appear to significantly impact these outcomes and, thus, is appropriate for local control if adequate tumor margins can be achieved around the tumor and fracture beds.

Oncologic Reconstruction

The reconstruction options in the surgical treatment of cartilage tumors are as vast as the clinical spectrum of presentation is wide. We previously discussed that controversy exists as to the surgical management of low-grade (grade 1) chondrosarcoma, or atypical cartilage tumors, but intralesional curettage plus the use of local adjuvants such as phenol/ethanol, liquid nitrogen cryosurgery, argon beam, high-speed burr, or PMMA cement can be as effective as extralesional resection. After the resulting curettage cavity is filled either by cement or a bone graft, plate and screw internal fixation constructs can be added depending on the size of the lesion and amount of cortex removed in an attempt to decrease the postoperative fracture risk [14, 48, 49]. Intramedullary devices

are not recommended for stabilization as they increase the risk of spreading tumor cells within the bone and adjacent soft tissues.

The surgical treatment for high-grade primary bone malignancies, historically, was limb amputation. The development of multi-agent neoadjuvant chemotherapeutic regimens effectively changed the prognosis of osteosarcoma and bought time for the fabrication of custom prostheses so that surgeons could save a patient's limb during tumor resection [50–52]. Additional advances in surgical techniques and implants have made limb-sparing surgery the standard of care for extremity sarcomas since 1990 without compromising oncologic outcomes [53, 54]. The rest of the section will provide an overview of reconstructive options when wide resection is employed to achieve an adequate tumor margin. In this instance, reconstruction options for chondrosarcoma are similar to those available after resection of other high-grade primary bone sarcomas and depend on the tumor location within the long bone, its proximity to a joint surface, and patient factors such as age, overall health, and activity level. Adjuvant therapies such as radiation and chemotherapy – not typically indicated for chondrosarcoma except rare subtypes as noted previously – must also be considered in the reconstructive decisions if they are to be employed in the adjuvant setting.

Allograft and Allograft-Prosthetic Composite

Various methods have been described for reconstructing the large skeletal defect that can result from bone tumor resection including allograft – osteoarticular allografts, allograft-prosthetic composites, and intercalary allografts – allograft plus vascularized fibulas, and endoprostheses. Allografts theoretically offer the advantage of preserving bone stock, incorporate directly to host bone, and provide superior soft tissue attachments for periarticular reconstruction. However, allograft use also carries risks of degenerative joint disease (if osteoarticular), host-allograft junction nonunion, allograft fracture, and infectious disease transmission [55–58]. Endoprostheses allow immediate weight bearing with either intercalary segment or joint reconstruction but

carry disadvantages of lifetime risks of infection, loosening, and component wear [59–61]. What is clear is that each reconstruction method has its inherent advantages and disadvantages without a clear superiority in terms of longevity, function, and revision.

Fox et al. published their large institutional experience on 137 patients treated with fresh frozen proximal femoral allografts after bone tumor resection, 45 of which were for chondrosarcoma, with mean follow-up of 7.8+/−5.6 years (maximum 28 years). Their series included 38 osteoarticular allografts, 69 allograft-prosthetic composites, 22 intercalary allografts, and 8 allograft arthrodeses. Postoperatively, patients were kept non-weight bearing for at least 2 months. If the eight patients with tumor recurrence were excluded, then 103 of 129 (80%) had an excellent or good outcome, meaning the patients were pain-free with no or moderate activity restriction. Twenty-one patients (16%) experienced a non-tumor-related failure requiring allograft removal or amputation. Graft and complication type substantially impacted outcomes. Osteoarticular allografts and allograft arthrodeses had the lowest success rates of around 60% (23 of 38 and 5 of 8 successful grafts, respectively). Allograft-prosthetic composites and intercalary allografts did much better with success rates of over 80% each. There were 74 total complications in 54 patients. All 15 patients who suffered infection experienced failure, while half of the 26 allograft fractures and 85% of the 20 nonunions were successfully salvaged. Of the 83 patients who did not experience a complication, the graft survival was over 90% [62].

Much of an allograft's failings can be attributed to its lack of a blood supply. Rodolfo Capanna sought to address this critical issue by combining structural allograft shells used for metadiaphyseal tumor reconstruction with a centrally placed free vascularized fibular graft (VFG) and first described his technique in 1988 [63]. Dr. Capanna's group went on to publish the largest series to date of VFG/allograft reconstructions for the femur in 2018 [64]. Twenty-three patients who had undergone VFG/allograft reconstruction of the femur were retrospectively reviewed at an average 141 months (24–313 months) follow-up. The mean MSTS score in 22 surviving patients was 94% (73–100) at final follow-up. Partial weight bearing was allowed at

1 month, but full weight bearing without a brace was 1 year. There were eight major complications requiring seven reoperations including five fractures (22%) and three nonunions (13%). Revision-free survival of the reconstructions with failure due to fracture or nonunion requiring surgery as the endpoints was 72% at 5 years; overall survival with graft removal or amputation as the endpoints was 94% at 15 years. There were no complications seen after 5 years from surgery implying that, provided the reconstruction heals, it is durable [64].

Whether or not the added complexity of the Capanna technique enhances allograft outcome is debatable as few studies have compared these reconstructions directly. Houdek et al. did retrospectively compare 11 intercalary allograft reconstructions with 18 allograft/VFG reconstructions in a pediatric population from a single institution [65]. Reoperation to address a complication was needed in 86% of patients, and the most common indication for reoperation (delayed union requiring bone autograft) was no different between the two groups. However, there were only two deep infections and only three cases that required allograft removal for infection or fracture – these cases were in the non-supplemented cohort. The authors concluded based on their work that allograft supplementation with a vascularized fibula does reduce the risk of allograft failure.

Free Fibula Grafts

Vascularized free fibular grafts alone without allograft are also an attractive means of reconstructing extremity defects after tumor resection because of the fibula's length (up to 25 cm can be harvested from an average adult), cylindrical shape, predictable vascular pedicle, and its ability to hypertrophy under load bearing. Its vascularized nature should also theoretically provide enhanced likelihood of union and infection resistance [66, 67]. The free fibula graft is particularly attractive for upper extremity reconstructions that are placed under less mechanical stress compared to those of the femoral diaphysis. Chen et al. reported on 25 consecutive patients who underwent free fibula reconstruction after

limb-sparing tumor resection at Memorial Sloan Kettering between 1991 and 2002. Reconstructed areas included bones of the upper and lower extremities; six patients had chondrosarcoma. All flaps survived over the 3- to 117-month follow-up period, and full weight bearing was achieved at 12 months postoperatively. There were three instances of infection and three cases of non-union, but each was addressed with either operative debridement or bone grafting, respectively, and all flaps were salvaged. Functional assessment was quite limited in this cohort due to disease progression in some and poor follow-up in others. The authors had MSTS scores on 14 patients, all of which were rated as "good" [68].

Endoprosthetic Reconstruction

The use of allografts and vascularized fibulas fall under the umbrella category of biologic reconstructions, meant to augment host bone stock and provide a durable reconstruction after time if healing occurs. A separate category includes endoprosthetic reconstructions, which are modular metal and polyethylene implants designed to replace whole joints or intercalary limb segments capable of immediate fixation, patient mobilization, and functional recovery but which carry the concern of wear or infection failure over a prolonged period of time. These implants can be cemented into the medullary cavities of the recipient bone or "press-fit" without cement. A clear advantage of these reconstructive techniques is the immediate weight bearing that most endoprostheses allow a patient, and the fixation of cemented stems is not impacted by adjuvant treatment modalities, if employed.

However, the enhanced survivorship of modern cancer patients can challenge the longevity of endoprosthetic reconstructions; thus, long-term outcome studies of these implants are important. Henderson et al. wrote up a retrospective, multi-institution review of 2174 endoprostheses used for reconstruction after tumor resection over a 34-year period (1974 to 2008) investigating the most common reasons for failure. He identified and classified the five most common modes of failure: soft tissue failures (type 1), asep-

tic loosening (type 2), structural failures (type 3), infection (type 4), and tumor progression (type 5). They also performed a literature review based on a separate 4359 patients. Infection proved to be the most common mode of failure in the multi-institutional cohort, while aseptic loosening proved to be most commonly cited issue in the literature. Critically, both the mode of and time to failure depended heavily on the anatomic location of the reconstruction. Soft tissue failures were more common around the shoulder and hip, while aseptic loosening was more common around hinged joints like the elbow and knee. The authors emphasized that outcome studies on endoprostheses should ideally be stratified by anatomic location to best understand specific failure risks. Also, of note, the overall failure rate of endoprostheses dropped significantly over the course of the study period [69]. It is reasonable to expect modern endoprostheses to again outperform those currently captured in long-term follow-up studies as refinements have been made in everything from implant metallurgy to intraoperative cementation technique.

The very-long-term outcomes of these reconstructions are even more challenging to study in large numbers. Despite this challenge, Grimer et al. conducted a retrospective study on endoprosthetic replacements performed at their institution with at least 25-year follow-up, comprising 230 patients (24 of which had chondrosarcoma). Only 18% of the original implants remained in place at this length of follow-up, but it should be noted that all patients were treated with what would now be called a first-generation endoprosthesis. Over this long study period, there were an additional 2.7 operations per patient – although even smaller procedures like bushing changes were counted. The median time to a first revision was 5 years and, by 10 years, 67% of patients had required further surgery. The most common reasons for reoperation were aseptic loosening (112 cases), structural implant failures (48 cases), and infection (25 cases). A notable issue is that the risk of infection persisted for the life of the prosthesis at 1% per year, and infection led to double the average reoperation rate for an infected patient. Despite this, overall limb salvage was high, and functional outcomes were largely excellent as judged by MSTS scores [70]. Other long-term outcome studies

have confirmed that despite a fairly high rate of revision surgery for endoprostheses, there is a very high rate of ultimate limb salvage with correspondingly good functional scores [71, 72].

However, none of these studies have reviewed prosthetic survival by patients' tumor stage, a major factor in providing prognostic information to the individual patient. Bernthal et al. retrospectively focused on a single anatomic location and reported survival of the implant and patient according to tumor stage in an effort to provide the clearest interpretation of relative longevity [73]. They included 86 cemented proximal femoral replacements used for tumor reconstruction from 1982 to 2008 at a single institution followed for 64 months (range 3–291 months). Primary diagnoses included 43 high-grade localized sarcomas (Enneking stage IIA/IIB), 20 low-grade tumors (IA/IB), and 23 with metastatic disease (III). Only 5 of 86 patients required revision of the femoral component (5.8%). The 5-, 10-, and 20-year implant survivorships were 97%, 84%, and 56%, respectively. Among the causes for revision, there were three instances of aseptic loosening and one deep infection. For patients with low-grade disease, there was 100% survival at 20 years. The 5-, 10, and 20- year survival for patients with stage IIA/IIB disease were 54%, 50%, and 44%, respectively. No patients with stage III disease survived 10 years. Thus, based on this work, well-performed cemented endoprosthetic reconstructions after tumor resection can be expected to outlive patients with metastatic disease, while patients with low-grade disease and long-term survivors of stage IIA/IIB disease should expect at least one revision procedure in their lifetime [73].

Since endoprostheses accrue increased rates of revision in the medium to long term, these long-term studies are particularly informative. However, it should be again emphasized that the quality of implants and their surgical techniques have evolved since many of these implants being studied over long intervals were first implanted. Schwartz et al. have already shown that modular implants have performed better with longer survivorship than the historic standard of custom-fabricated implants [74]. While patient function is undoubtedly reliable with endoprosthetics, it remains to be seen if their shortcomings can be further mit-

igated by technological advancements in component design, wear characteristics, fixation methods, and infection resistance.

Bone Transport and Distraction Osteogenesis

The ideal reconstruction technique after tumor resection would demonstrate biologic affinity with the host, have resistance to infection, have sufficient immediate biomechanical strength, demonstrate long-term durability, and preserve articular anatomy when possible. Given the limitations of allograft and endoprosthetic reconstructions, alternative biologic solutions using bone transport and distraction osteogenesis are being considered to address challenges posed by improved patient survival and modern quality of life demands. The use of these techniques has been avoided by many surgeons because of infection concerns and uncertainty regarding the impact of neoadjuvant treatments on bone callus regenerates [75]. However, since chemotherapy and radiation are rarely indicated for chondrosarcoma, these techniques are reasonable to consider. One of the first proof-of-concept studies on bone transport for bone defect reconstruction after tumor resection was published by Tsuchiya et al. [76]. They looked at 19 patients with osteosarcoma, chondrosarcoma, or giant cell tumor and found nearly all patients could achieve an excellent or good functional outcome on the Enneking scale. Ten minor complications occurred but only one instance of deep infection; limbs were salvaged in all cases [76]. This group has also published long-term functional outcome studies on a cohort of 22 patients followed for a mean of 202 months. Final follow-up MSTS scores were 90%, and 14 of the 22 patients could play sports actively [77]. However, the up-front cost of these techniques should be emphasized as, historically, patients have had to spend up to a year in an external fixator device. Technologies are similarly evolving in this space, though, that should shorten external transport times. More studies are needed to determine if the initial challenges inherent to these biologic techniques are outweighed by the longevity, function, and durability of the limb reconstructions [75].

In summary, while it is important to understand the wide variety of reconstruction options available to orthopedic oncologists for use in any case, appendicular chondrosarcoma is notable in that all reconstruction methods detailed above can be reasonably indicated as the chemotherapy and radiotherapy protocols often cited as complicating factors affecting the outcomes of allograft, bone transport, and endoprostheses alike are rarely used. So, while osteosarcoma and Ewing sarcoma patients often comprise the bulk of patients in studies on limb salvage, treating patients with chondrosarcoma represents a unique opportunity for outcome studies to focus on factors inherent to the reconstructive method of choice.

Chondrosarcoma of the Hand and Foot

Chondrosarcoma of the Hand

Chondrosarcoma of the hands and feet presents its own challenges, specifically related to its diagnosis and surgical treatment, owed in part to its relative rarity (generally only around 5% of all chondrosarcomas will occur in the hands or feet). Most reports on chondrosarcoma of the hands and feet are found in small retrospective case series, from which conclusions must be drawn [78, 79]. The difficulty in differentiating enchondroma from low-grade chondrosarcoma is well described, generally, but takes on added importance considering enchondroma is the most common bone tumor in the hands and feet [15]. It can be an even more vexing problem because of the propensity for enchondromas in the small tubular bones to display cytologic atypia [80]. Some authors have suggested that essential to the differentiation of malignancy are radiographic features of cortical destruction, permeative growth, and a soft tissue mass. Pain is also a common presenting symptom of malignancy, but this cannot be used to reliably differentiate chondrosarcoma in the hand from benign lesions [80, 81].

Though more challenging, the problem of diagnosis may be arguably less important in the hand because the biology of chondrosarcoma there appears to be unique. Del Pino reported on the treatment of 17 cases of grade 1 chondrosarcoma of the hands –

six of which were referral cases for local recurrence – with minimum follow-up of 9 years. Nine patients were treated with intralesional curettage and grafting, and eight were treated with wide resection when finger function could not be salvaged because of local tissue compromise. There was a nonsignificant difference in local recurrence rates (22% versus 13% favoring wide resection), but, critically, there were no instances of metastasis or death from disease [82]. Similarly, Mittermayer et al. reported on 13 patients with low-grade disease of the hand, eight treated with curettage and grafting versus five treated with wide resection. There was only one instance of local recurrence after intralesional curettage. With a relapse rate of 12% and no distant metastasis noted for mean follow-up of almost 10 years (range 26–293 months), the authors concluded intralesional curettage is the preferred treatment of low-grade chondrosarcoma of the hand allowing patients to preserve near-normal hand function [83].

Critically, similar results have been reported for higher grade chondrosarcoma in the hand. Patil et al. reported on 23 cases of phalangeal chondrosarcoma, all of which were grade 2 or 3 except one case. Curettage was performed in eight cases, and ray resection or amputation was performed for 15. Though five out of eight patients locally recurred after curettage during median 8-year follow-up (range 2–19 years) – compared to 0 patients who had been treated with wide resection – there were no cases of metastasis [84]. Additionally, Bovee et al. have confirmed that intralesional procedures performed for even high-grade chondrosarcoma of the phalanges do create a high rate of local recurrence but incur no risk of metastasis [85]. These authors have not found any deaths attributable to malignancy in their series, arguing that chondrosarcoma of the hands is a different disease with different biology than similar grade lesions in the more proximal extremities.

Chondrosarcoma of the Foot

Chondrosarcoma of the foot, conversely, does not adhere to the same set of rules as that in the hand. Again, gleaning robust data for patient prognosis and treatment decisions from the literature is challenging because of the rarity of these presentations. When

Toepfer et al. reviewed almost 7500 bone and soft tissue tumors, only 5% were tumors of the foot and ankle. Of these, 266 tumors involved the bone (64%), but only 35 tumors were malignant (13%). Of malignant bone tumors of the foot in adults, chondrosarcoma is the most common, representing half of all cases, but this is an incredibly small absolute number of patients [86]. Within the foot, these authors did find the hindfoot to be more commonly involved than the midfoot or forefoot, and this is helpful because enchondromas have rarely been found in the hindfoot. Other authors have similarly suggested that if a purely cartilaginous lesion is found in the talus or calcaneus, it is much more likely to be a chondrosarcoma [80].

Yang et al. performed a retrospective 30-year review of malignant bone tumors at a supraregional tumor referral center and identified 55 primary malignant tumors of the foot [87]. Given the population they serve, this came out to 0.12 cases of a primary osseous foot malignancy per one million people. Of their total, 25 (or 46%) were chondrosarcoma, and this was the most common primary bone tumor in adults. In contrary to Toepfer et al., the forefoot was more commonly involved. Interestingly, the average time to diagnosis of a malignant tumor was 1 year in the study cohort. Perhaps because of its more indolent course, chondrosarcoma had an even longer duration of symptoms prior to diagnosis (median 104 weeks, range 52–156 weeks). Three low-grade tumors in the whole cohort were treated with intralesional curettage, and the rest of the higher-grade tumors were treated with wide resection (this took the form of below knee amputation in 18 patients). Despite this, six patients developed local recurrence and another seven developed metastasis. Eight of these patients with local or systemic disease recurrence died within the study period [87]. Patil et al. also noted that 3 out of 12 patients in their series experienced local recurrence after intralesional or wide resection of chondrosarcoma of the foot. All three of these patients went on to die of metastatic disease [88].

Thus, while chondrosarcoma of the hand appears to be biologically unique and does not appear to commonly represent a systemic threat to the patient, chondrosarcoma of the foot can represent life-threating disease and needs to be treated accordingly. There is characteristically a long delay in diagnosis, particularly

for cartilage tumors in the foot. A long duration of symptoms should not be reassuring, and instead index of suspicion needs to remain high for malignancy. Though chondrosarcoma of the hand can reliably be treated with an intralesional procedure, the best mode of treatment for chondrosarcoma of the foot is controversial. Only small series are available to inform this decision. Given the real risk of local and systemic disease recurrence, chondrosarcoma of the foot is likely best treated with wide resection in the form of ray resection for forefoot disease and below knee amputation for tumors in the hindfoot.

Conclusion

Chondrosarcoma is the most common primary bone sarcoma in adults. It presents along a continuum from indolent, minimally symptomatic disease to a rapidly progressive malignancy. This spectrum corresponds directly to tumor grade. Establishing the grade of any cartilage lesion requires the musculoskeletal oncologist to work in close concert with colleagues in pathology and radiology. Even then, clear tumor stratification may be elusive, but it is critical for guiding patient prognosis and treatment. Surgery remains the cornerstone of treatment as most subtypes are resistant to both chemotherapy and radiation. Once the decision to treat has been made, a surgeon has a range of tools at his or her disposal with which to reconstruct the bone defect from bone allograft to endoprosthetic implants to distraction osteogenesis. Each of these techniques has their advantages and disadvantages, making individualized treatment decisions important to maximize the oncologic and functional outcomes of each patient.

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