Chondrosarcoma

Biology and Clinical Management

Francis J. Hornicek
Editor

Springer

Chondrosarcoma

Francis J. Hornicek
Editor

Chondrosarcoma

Biology and Clinical Management

Springer

Editor
Francis J. Hornicek
Department of Orthopaedic Surgery
David Geffen School of Medicine at UCLA
Los Angeles, CA
USA

ISBN 978-3-030-74571-4 ISBN 978-3-030-74572-1 (eBook)
https://doi.org/10.1007/978-3-030-74572-1

This Springer imprint is published by the registered company Springer Nature Switzerland AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

Foreword

Inspired by the biblical admonition, "*If the blind lead the blind, all will fall into the ditch*" (Matthew 15:14), the Flemish Renaissance master Pieter Brueghel the Elder portrayed a scene from a sixteenth-century century village. Depicted is a line of sight impaired men who, by following their blind leader, appear to be dragged one by one over an edge. Prophetic then and still true today, if we do not get the initial diagnosis correct, then everyone, especially the patient, may experience an adverse outcome.

Critical and central to the proper management of any neoplastic condition is the correct diagnosis. This cannot be left solely to the surgical pathologist who, of course, is critical, central, and pivotal in this process. Pathologists knowledgeable with bone and soft tissue tumors are rare, and the best of the best have a real passion for the field. The accuracy of their diagnoses often is dependent on the pertinent clinical and diagnostic information being shared with them. We have found this to be best achieved by collaborative consultation, in real time, to include the pathologist, the radiologists, and the physicians and surgeons. The radiologists add very important information as to location and extent of disease, as well as their independent differential diagnosis, which often correlates with the histologic diagnosis. The physicians and surgeons who are tasked with carrying out all subsequent treatment add their own differential based on the patient's presenting signs and symptoms. It is imperative that this occur not only at presentation, but throughout the patient's course.

At the University of California, Los Angeles, we endeavor to achieve this through participation in a multidisciplinary "tumor board." This board convenes weekly. New patients are discussed at presentation and are followed throughout their course of treatment. The multidisciplinary tumor board reviews all the information to determine the location, the pathologic diagnosis including stage and grade, and the clinical setting, and then discusses all potential surgical and medical treatment options. At subsequent meetings there is a review of the surgical margins, the effectiveness of any medical adjuvant treatment that may have been rendered, as well as recommendations for future medical or surgical intervention.

The multidisciplinary musculoskeletal tumor board at UCLA was initiated in 1984. The original four participants consisted of Fredrick R. Eilber, M.D. (surgical oncology), Jeffrey J. Eckardt, M.D. (orthopedic oncology), Joseph M. Mirra, M.D. (surgical pathology), and Richard H. Gold, M.D. (radiology). Today, in 2020, there are 22 members representing 8 disciplines: 5 orthopedic oncologists, 3 surgical oncologists, 3 musculoskeletal radiologists, 4 medical oncologists, 2 surgical (sarcoma) pathologists, 2 pediatric oncologists, 2 thoracic oncologists, and 1 gynecologic oncologist. The meetings are regularly attended by the majority, with generally 30–45 new and follow-up cases reviewed each week. Not only is it rigorous and educational, but it is also fun. Getting it right is paramount. Difficult or questionable diagnoses and/or treatments are sent out for second or third opinions without hesitation. Pride does not have a seat on this board.

Dr. Hornicek has assembled an outstanding and renowned group of clinicians, clinician- scientists, and researchers to address and review the presentation, the clinical management, and current research endeavors of benign and malignant cartilage neoplasms. This includes chondrosarcoma's primary and secondary bone locations, as well as the rare soft tissue presentations. Different diagnostic modalities, surgical techniques, and the various adjuvant methods of treatment are thoroughly discussed. Ongoing protocols are presented along with their rationales.

Differentiating chondrosarcomas from other benign or even non-neoplastic conditions has proven difficult and can be one of the most difficult diagnoses to make. Much has been written on

this topic. Chondrosarcoma's varying clinical presentations and pathology were first elucidated in articles by Dr. Dallas Phemister in 1930, followed by Dr. Louis Lichtenstein and Dr. Henry L. Jaffe in 1943. Subsequent books and articles are referenced:

- *Jaffe, Henry L.: Tumors and Tumorous Conditions of the Bones and Joints. Lea & Febiger, 1958.*
- *Unni, K. Krishnan, Dahlin, David Carl: Dahlin's Bone Tumors: General Aspects and Data on 11,087 Cases. 5th ed., Lippincott-Raven, 1996.*
- *Mirra, Joseph M., Picci, Piero, Gold, Richard H. "Intramedullary cartilage and chondroid producing tumor." Bone Tumors: Clinical, Radiographic and Pathologic Correlations. Vol. 1, Lea & Febiger, 1989;439–690.*
- *Mirra JM, Gold R, Downs J, Eckardt JJ. A new histologic approach to the differentiation of enchondroma from chondrosarcoma of the bones. A clinicopathologic analysis of 51 cases. Clin Orth Rel Res. 1985;201:214–37*
- *Murphey MD, Flemming DJ, Boyea SR, Bojescul JA, Sweet, DE, Temple T. From the Archives of the AFIP. Enchondroma versus Chondrosarcoma in the Appendicular Skeleton: Differentiating Features. RSNA. 1998;18:1213–1237*

There are many neoplastic and non-neoplastic conditions that contain cartilage. These conditions need to be recognized for what they are. Differentiating chondrosarcoma from the other cartilage lesions can be challenging, with the surgical pathologist's role pivotal. This publication by Dr. Francis J. Hornicek, M.D., Ph.D., and the use of a multidisciplinary review board should prove helpful in achieving this goal.

Jeffrey J. Eckardt, M.D.
Distinguished Professor
and Chair Emeritus,
Department of Orthopaedic surgery
UCLA David Geffen School
of Medicine at Los Angeles,
Los Angeles, CA, USA
February 1, 2020

Preface

This book focuses on chondrosarcoma biology, pathogenesis, and emerging treatment strategies. While this rare and malignant cartilage-forming tumor tends to occur within the bones, it can also arise within various soft tissues. Unlike other bone sarcomas that predominantly affect the young, chondrosarcomas are more often diagnosed in the adult population. In addition to being highly resistant to available chemotherapies and radiotherapies, management guidelines have been difficult to refine as low-grade and benign tumors are challenging to differentiate. Along with anatomic location and spread, tumor grade is a primary determinant of adjuvant therapy. Low-grade or grade 1 lesions are either observed or undergo surgical resection, with grade 2 or 3 tumors often receiving chemotherapeutic regimens. Clinical trials have been hindered by limited study participants robust pre-clinical evidence.

Although some progress has been made in characterizing chondrosarcoma pathogenesis, its genetic and epigenetic mechanisms are poorly described, and no known effective systemic therapy exists. There is, therefore, an urgent need to identify the underlying molecular mechanisms of chondrosarcoma for targeted therapies in prospective clinical trials. Recent studies have explored inhibitors that combat aberrant metabolic pathways, such as isocitrate dehydrogenase (IDH), an enzyme whose gene is frequently mutated in chondrosarcoma. COL2A1, a gene that encodes the α-chain of type II collagen fibers and the major contributor of collagen matrix and articular cartilage, is another frequently mutated gene chondrosarcoma. Other promising thera-

peutic targets include the EXT gene seen in hereditary multiple osseocartilaginous exostoses, as well as p16 and p53 alterations that transform enchondroma to chondrosarcoma. Tumorigenic gene signaling pathways including Hedgehog, CDK4, and TGF-beta/Sox have also been described in these cancers. Although preclinical studies have shown the targetability of these genetic pathways in chondrosarcoma therapy, follow-up clinical trials are needed to establish their utility within the clinic. In addition to these works, immunotherapies have generated considerable attention for their success in various human cancers and have led to emerging results in chondrosarcoma.

This book draws from impactful papers as well as the decades of experience from the contributing authors in the laboratory and treating patients in high-volume sarcoma centers. I have previously worked with several of the named authors in writing a book on bone pathology.

This book provides practical coverage of chondrosarcoma biology and therapy for medical students, residents, fellows, practicing physicians, and researchers. I hope our passion in caring for these patients comes through while reading this text.

Los Angeles, CA, USA Francis J. Hornicek, M.D., Ph.D.

Acknowledgement

I would like to thank all the contributors to this in-depth book on chondrosarcoma. Moreover, I would like to thank Dr. Jeffery Eckardt and the members of the UCLA sarcoma team.

Contents

Part I Biology of Chondrosarcoma

1 Pathology of Chondrosarcoma 3
Muhammad Omar Hakim and Andrew Eric Rosenberg

2 Advances in the Molecular Biology of Chondrosarcoma 27
Zhenfeng Duan, Dylan C. Dean, Susan Bukata, and Francis J. Hornicek

3 Imaging Features of Chondrosarcoma 53
Jonathan Lin, Benjamin D. Levine, and Leanne L. Seeger

Part II Skeletal and Extraskeletal Chondrosarcoma

4 Chondrosarcomas: Conventional and Secondary . . . 77
Christopher M. Hart, Zachary Burke, Alex Nobori, and Bennett L. Davis

5 Primary Soft Tissue Chondrosarcoma 93
Brooke Crawford

Part III Management of Chondrosarcoma

6 Chondrosarcoma of the Axial Skeleton 113
Akash A. Shah, Howard Young Park, Gideon Blumstein, and Don Young Park

7 Chondrosarcoma of the Appendicular Skeleton 133
Erik J. Geiger and Nicholas M. Bernthal

8 Chondrosarcoma of the Hand 169
Karren Takamura and Neil Ford Jones

9 Chondrosarcoma of the Clavicle 187
Tang Liu, Chao Tu, and Zhihong Li

10 Radiation Therapy for Chondrosarcoma 203
Ting Martin Ma, Thomas DeLaney, and Anusha Kalbasi

11 Systemic Therapy for Chondrosarcoma 255
Arun S. Singh, Jomjit Chantharasamee, and Francis J. Hornicek

12 Vascular Issues in Complex Surgical Resection of Chondrosarcoma 269
Rhusheet Patel and Donald T. Baril

Part IV The Future of Chondrosarcoma Research and Treatment

13 The Future of Chondrosarcoma Research and Treatment 283
Pichaya Thanindratarn, Dylan C. Dean, Francis J. Hornicek, and Zhenfeng Duan

Index 299

Contributors

Donald T. Baril, MD Division of Vascular Surgery, Cedars-Sinai, Los Angeles, CA, USA

Nicholas M. Bernthal, MD Department of Orthopaedic Surgery, University of California, Los Angeles, Santa Monica, CA, USA

Gideon Blumstein, MD UCLA Department of Orthopaedic Surgery, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA

Susan Bukata, MD Department of Orthopaedic Surgery, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA

Zachary Burke, MD Department of Orthopaedic Surgery, UCLA, Los Angeles, CA, USA

Jomjit Chantharasamee, MD Division of Hematology and Oncology, Department of Medicine, University of California Los Angeles, Los Angeles, CA, USA

Division of Medical Oncology, Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand

Brooke Crawford, MD Department of Orthopaedic Surgery, UCLA, Santa Monica, CA, USA

Bennett L. Davis, MD Department of Radiology, UCLA, Los Angeles, CA, USA

Dylan C. Dean, MD Department of Orthopaedic Surgery, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA

Thomas DeLaney, MD Department of Radiation Oncology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

Zhenfeng Duan, MD, PhD Department of Orthopaedic Surgery, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA

Erik J. Geiger, MD Department of Orthopaedic Surgery, University of California, Los Angeles, Santa Monica, CA, USA

Muhammad Omar Hakim, MD Department of Pathology, University of Miami, Miller School of Medicine, Miami, FL, USA

Christopher M. Hart, MD Department of Orthopaedic Surgery, UCLA, Los Angeles, CA, USA

Francis J. Hornicek, MD, PhD Department of Orthopaedic Surgery, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA

Neil Ford Jones, MD Department of Orthopaedic Surgery, University of California, Los Angeles, Santa Monica, CA, USA

Anusha Kalbasi, MD Department of Radiation Oncology, Jonsson Comprehensive Cancer Center, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, CA, USA

Benjamin D. Levine, MD Department of Radiology, UCLA Health System, Los Angeles, CA, USA

Zhihong Li, MD Department of Orthopaedics, The Second Xiangya Hospital of Central South University, Changsha, Hunan Province, China

Jonathan Lin, MD Department of Radiology, UCLA Health System, Los Angeles, CA, USA

Tang Liu, MD Department of Orthopaedics, The Second Xiangya Hospital of Central South University, Changsha, Hunan Province, China

Ting Martin Ma, MD, PhD Department of Radiation Oncology, Jonsson Comprehensive Cancer Center, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, CA, USA

Alex Nobori, MD Department of Pathology, UCLA, Los Angeles, CA, USA

Don Young Park, MD UCLA Department of Orthopaedic Surgery, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA

Howard Young Park, MD UCLA Department of Orthopaedic Surgery, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA

Rhusheet Patel, MD Division of Vascular Surgery, UCLA Medical Center, Los Angeles, CA, USA

Andrew Eric Rosenberg, MD Department of Pathology, University of Miami, Miller School of Medicine, Miami, FL, USA

Leanne L. Seeger, MD, FACR Department of Radiology, UCLA Health System, Los Angeles, CA, USA

Akash A. Shah, MD UCLA Department of Orthopaedic Surgery, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA

Arun S. Singh, MD Division of Hematology and Oncology, Department of Medicine, University of California Los Angeles, Los Angeles, CA, USA

Karren Takamura, MD Department of Orthopaedic Surgery, University of California, Los Angeles, Santa Monica, CA, USA

Pichaya Thanindratarn, MD Department of Orthopaedic Surgery, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA

Chao Tu, MD Department of Orthopaedics, The Second Xiangya Hospital of Central South University, Changsha, Hunan Province, China

Part I

Biology of Chondrosarcoma

1 Pathology of Chondrosarcoma

Muhammad Omar Hakim
and Andrew Eric Rosenberg

Introduction

Chondrosarcoma is the second most common primary bone sarcoma following osteosarcoma and comprises 25% of skeletal sarcomas [1–5]. In adults, it accounts for 40% of bone sarcomas, whereas, in children, it is uncommon and represents 6% of tumors. The SEER data (National Cancer Institute Surveillance Epidemiology and End results) from 2013 to 2017 shows that the age adjusted incidence per 100,000 individuals in adults is 0.7 for males and 0.5 for females in the United States [6].

Chondrosarcoma is classified according to its location, morphology, grade, and whether it is primary or secondary. The different histological types are conventional hyaline and/or myxoid, dedifferentiated, clear cell, and mesenchymal variants. Except for mesenchymal chondrosarcoma, they are graded using a three-tier scheme based on cellularity, atypia, mitotic activity, and necrosis; mesenchymal chondrosarcoma is not graded and is considered high grade (grade 3) [2, 3, 7]. The tumors can arise in the medullary

M. O. Hakim · A. E. Rosenberg (✉)
Department of Pathology, University of Miami, Miller School of Medicine, Miami, FL, USA
e-mail: ARosenberg@med.miami.edu

F. J. Hornicek (ed.), *Chondrosarcoma*,
https://doi.org/10.1007/978-3-030-74572-1_1

cavity (central) or on the surface (peripheral) and may be de novo (primary) or arise in diseased bone or a preexisting benign tumor such as enchondroma or osteochondroma (secondary) [8]. Most chondrosarcomas are primary, central, conventional, and low to intermediate grade [5]. Grade 1 conventional chondrosarcoma has a very low risk for developing metastases; therefore, in the appendicular skeleton, the WHO fifth edition recommends that they it be designated atypical cartilaginous tumor, whereas in the axial skeleton and flat bones the term conventional chondrosarcoma, grade 1, is retained because of potential local aggressive growth and biological transformation [9–11].

The pathological diagnosis of chondrosarcoma should always include careful correlation of the morphology with the clinical and radiological findings [12–17]. The morphological heterogeneity of chondrosarcoma can be challenging, and pathologists need to be aware of diagnostic pitfalls and the implications of their diagnosis [13, 18, 19]. If the diagnosis is expected to be rendered on needle biopsy, the specimen should include a minimum of three tumor-bearing cores of tissue, as well as the diagnostic considerations of the clinical team.

There have been significant advances in the discovery of the mutational landscape of chondrosarcoma, and the aberrations can be of diagnostic utility. IDH1 or IDH2 mutations are present in the majority of conventional primary and secondary central chondrosarcomas and are also commonplace in dedifferentiated variants [8, 20–25]. IDH mutation status can help distinguish conventional and dedifferentiated chondrosarcoma from mimics such as chondroblastic osteosarcoma and fibrosarcoma, as the latter lack these mutations, and IDH aberrations are also absent in peripheral, clear cell, and mesenchymal chondrosarcomas [10, 11, 26, 27]. The *HEY1–NCOA2* gene fusion is the driver mutation in mesenchymal chondrosarcoma and is pathognomonic [28]. Gene copy number changes, mutations in *Tp53* [29] and *CDKN2a*, epigenetic changes [11], and dysregulation of micro-RNA also play a role in the biology of these neoplasms.

Currently, most chondrosarcomas are managed with surgery; atypical cartilaginous tumors are aggressively curetted with the addition of an adjuvant, and the remainder are resected en bloc

with widely negative margins, if possible. All of the different types of chondrosarcoma can locally recur, especially if they are removed with positive margins [30], and local recurrence of conventional chondrosarcoma and clear cell chondrosarcoma may be associated with biological transformation into a higher grade neoplasm [31, 32]. Systemic therapy is often used to manage patients with dedifferentiated and mesenchymal chondrosarcoma. The incidence of metastasis of chondrosarcoma is related to tumor type and grade, and the overall 5-year survival rate is 75% [33]. Common sites of metastatic spread are the skeleton and lungs.

Primary Conventional Chondrosarcoma (80–90% of Chondrosarcomas)

Central conventional chondrosarcoma is the most common type of primary chondrosarcoma (90%) [11] and arises in the axial skeleton and the proximal portions of the large tubular bones [14]. The pelvis, scapulae, ribs, femur, tibia, and humerus are favored sites. Unlike enchondroma, chondrosarcoma of the short tubular bones of hands and feet are uncommon. Approximately 70–80% of conventional chondrosarcomas are low-grade sarcomas [4, 5].

Tumors composed of hyaline cartilage manifest as a solid, multinodular, firm blue-white mass with scattered, gritty, white flecks (Fig. 1.1). Myxoid tumors are mucinous and slimy and may undergo cystic change. Histologically, they usually grow with a permeative pattern with replacement of the marrow, encasement of preexisting lamellar bone, and growth into the Haversian systems of the cortex [1–5, 34] (Fig. 1.2).

Hyaline matrix is characterized by round or oval neoplastic cells of variable size residing in lacunar spaces embedded in a solid-appearing basophilic or eosinophilic sheet-like matrix. In myxoid cartilage, the cells are not in lacunar spaces and are bipolar or stellate shaped and enmeshed in a flocculent bubbly matrix [1–3, 5, 34].

Atypical cartilaginous tumor/grade 1 chondrosarcoma (50–70% of conventional chondrosarcoma) is hypo- to moderately cellular, and the chondrocytes exhibit mild cytologic atypia in the

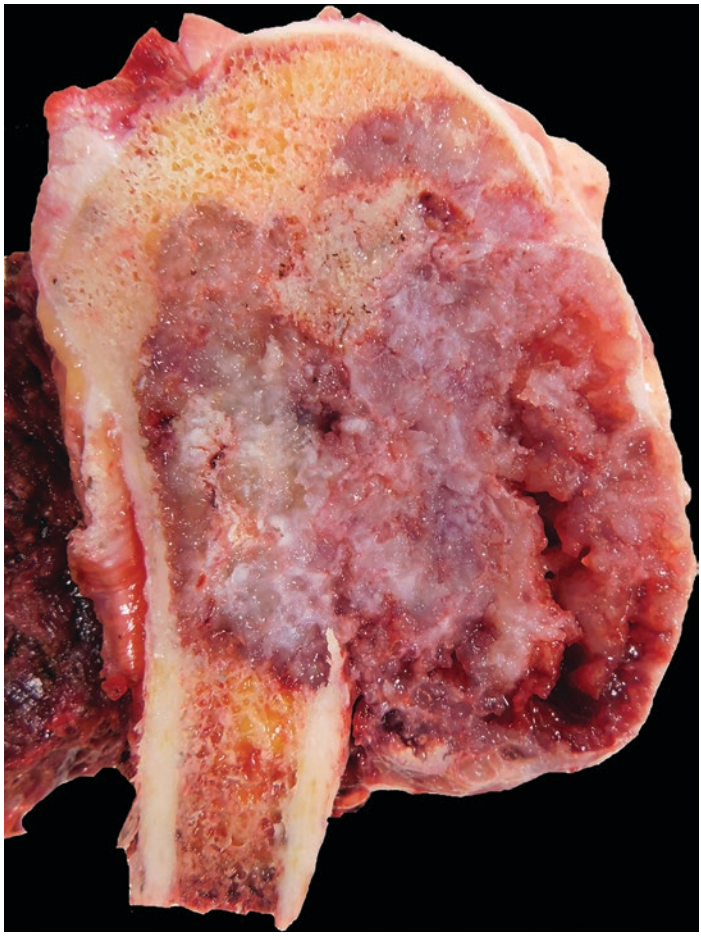

Fig. 1.1 Conventional chondrosarcoma of humeral head with intramedullary gray-blue glistening cartilage lobules showing cortical destruction, medially, with extension into soft tissue forming a sizable mass

form of nuclear enlargement, fine chromatin, and small nucleoli. Scattered cells may be binucleate, and there are no or rare mitoses. The matrix may be focally calcified and undergo enchondral ossification (Fig. 1.3). The neoplastic features may overlap with

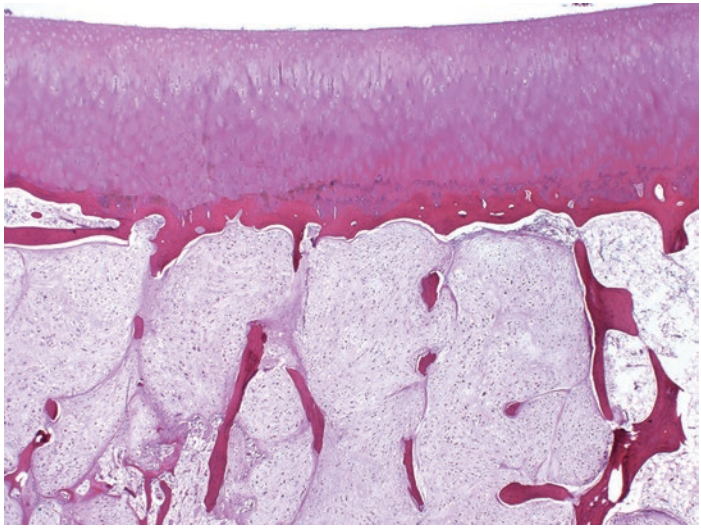

Fig. 1.2 Conventional chondrosarcoma growth pattern: neoplastic hyaline cartilage replaces the marrow and entrapsping the preexisting cancellous bone trabeculae. The tumor is more cellular than the overlying articular cartilage

enchondroma, and an essential characteristic that distinguishes between these types of neoplasms is the presence of infiltration [1, 5, 18, 35].

Grade 2 chondrosarcoma (25–40% of conventional chondrosarcoma) shows moderate cellularity and moderate cytological atypia. The nuclei are large, may have irregular contours, and are hyperchromatic. Some cells may be trinucleate, and mitoses are uncommon. The amount of matrix calcification and enchondral ossification is limited (Fig. 1.4). Many myxoid chondrosarcomas are grade 2 [4, 7, 9, 18, 35–37].

Grade 3 chondrosarcoma (5–15% of conventional chondrosarcoma) is highly cellular and exhibits severe pleomorphism and mitotic activity, including atypical forms (Fig. 1.5). This type of chondrosarcoma should raise the differential diagnosis of chondroblastic osteosarcoma, and genetic studies in search of mutations in IDH are helpful as it is not present in osteosarcoma [4, 7, 18, 36–38].

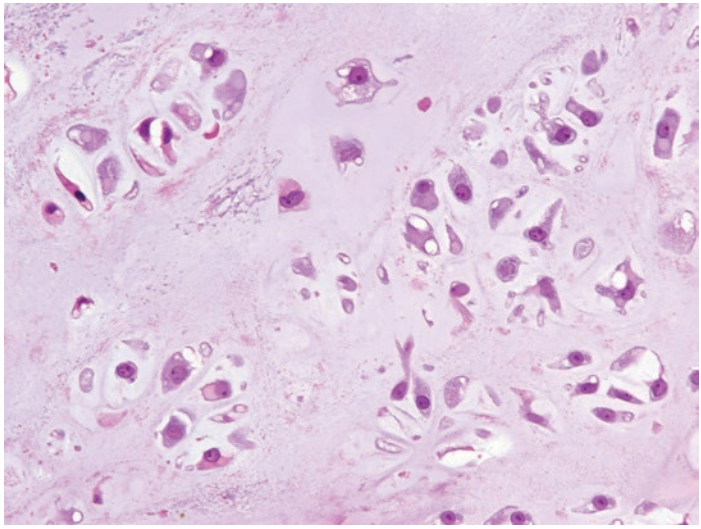

Fig. 1.3 Grade 1 chondrosarcoma: Minimally hypercellular neoplastic hyaline cartilage with clustered chondrocytes displaying mild nuclear enlargement, mostly round nuclei, some with open and others with condensed chromatin, occasional nucleoli, and minimal nuclear size variability. No mitoses are present

The prognosis of grade 1 chondrosarcoma is very good with over 90% survival at 5 years and 89–95% survival at 10 years. Grade 2 chondrosarcoma is associated with a 70–80% 5-year survival and 58–86% 10-year survival. Grade 3 chondrosarcoma has 0–77% 5-year survival and 30% 10-year survival rate [7, 9, 30, 36, 37].

Secondary Chondrosarcoma

Secondary chondrosarcoma refers to a chondrosarcoma that develops in abnormal bone that may be a benign neoplasm, irradiated bone, or bone affected by Paget's disease. Morphologically, the vast majority of secondary chondrosarcomas are conventional chondrosarcoma, and most arise in benign neoplasms, especially enchondroma and osteochondroma [11, 39] (Figs. 1.6, 1.7, and 1.8).

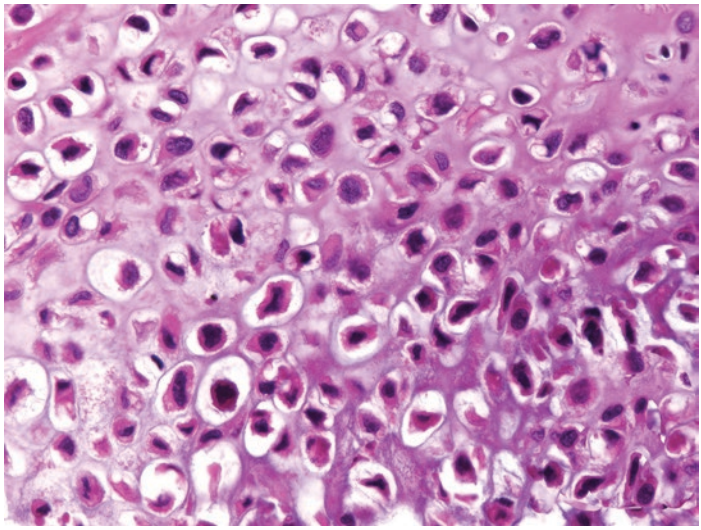

Fig. 1.4 Conventional chondrosarcoma, grade 2: Hypercellular malignant hyaline cartilage that has irregular hyperchromatic nuclei that vary in size

In fact, in our experience, many conventional chondrosarcomas have radiological or histological evidence of an underlying enchondroma; therefore, one can argue that secondary conventional chondrosarcoma is more common than primary variants. The risk of malignant transformation of solitary enchondroma or osteochondroma is a small fraction of 1% and is greater in the setting of syndromes associated with multiple lesions such as hereditary multiple osteochondromatosis (1–25%) and the Ollier disease and Maffucci syndrome (5–50%) [4, 9, 16, 40]. The basis for the great variability in rates of malignant transformation is related to morphological definition of malignancy.

Dedifferentiated Chondrosarcoma

Dedifferentiated chondrosarcoma is a biphasic tumor and composed of a high-grade, non-cartilage-forming sarcoma arising in the background of an enchondroma or grade 1 or grade 2 conven-

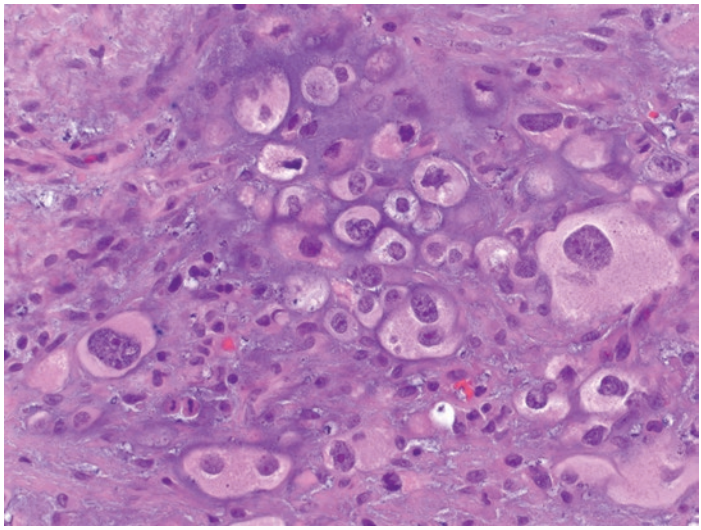

Fig. 1.5 Grade 3 conventional chondrosarcoma: Striking nuclear pleomorphism with marked variation in nuclear size and scattered mitoses

tional or clear cell chondrosarcoma. Approximately 10% of conventional chondrosarcomas show dedifferentiation [14]. The skeletal distribution is femur (30%), pelvis (20%), humerus (16%), ribs (7%), and scapula (7%) [14]. This type of chondrosarcoma is the most aggressive variant of chondrosarcoma, and it often exhibits rapid growth with pathological fracture and soft tissue extension in half of cases. Approximately 20% of cases have metastases at presentation, and 60–90% subsequently develop systemic spread (Fig. 1.10).

The dedifferentiated tumor is solid and has fleshy, pink-tan regions admixed with nodules of opalescent blue-gray cartilage that may have specks of gritty white calcifications (Fig. 1.9). The dedifferentiated component usually has the morphology of pleomorphic fibrosarcoma and is composed of pleomorphic spindle cells with eosinophilic cytoplasm that are enmeshed in a collagenous stroma and arranged in intersecting fascicles (Fig. 1.10). However, the dedifferentiated element may have protean appear-

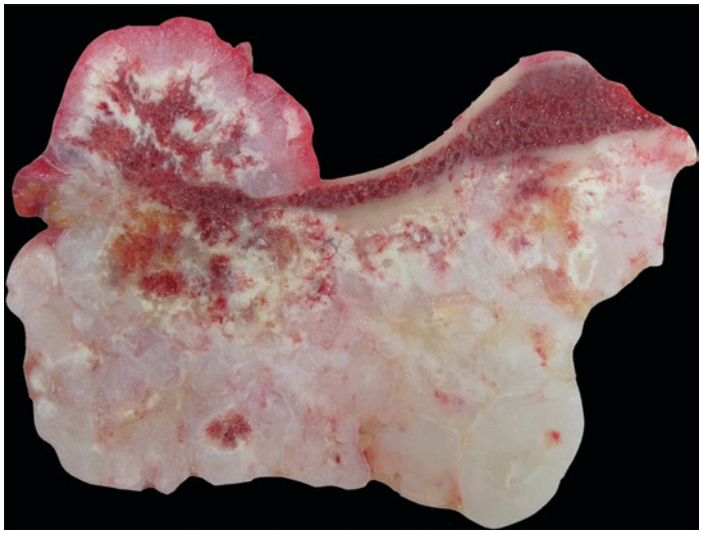

Fig. 1.6 Secondary chondrosarcoma arising in an osteochondroma, a remnant of which is seen on the left, that is replaced by chondrosarcoma. Fibrous bands dissect through the neoplastic myxo-hyaline cartilage lobules imparting an irregular configuration

ances and consist of epithelioid cells or exhibit heterologous differentiation such as osteosarcoma, rhabdomyosarcoma, angiosarcoma, and rarely carcinoma [41]. Diagnostic difficulties and misinterpretation may occur if both components of the tumor are not recognized or present which most commonly occurs in the setting of limited small core biopsies or FNA material. Mutational analysis for IDH1/IDH2 genes is valuable in instances where no low-grade cartilaginous component is identified as the vast majority (87%) of tumors bear an IDH1/IDH2 mutation. Immunohistochemistry is helpful in confirming a specific lineage of the dedifferentiated component, and in the appropriate setting metastatic spindle cell carcinoma or melanoma may be in the differential diagnosis. Overall survival of patients is dismal as the 5-year survival rate is 24% and most fatalities occur within in 1–2 years after diagnosis [3, 4, 9, 38, 42–45].

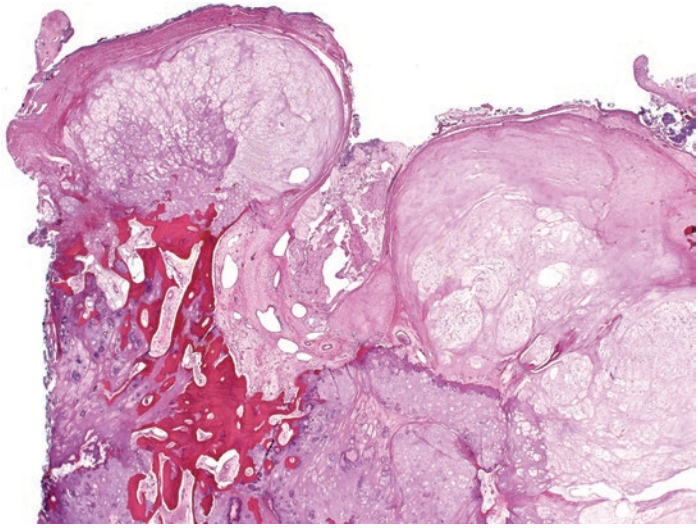

Fig. 1.7 Chondrosarcoma secondarily arising in the cartilaginous cap of an osteochondroma. The malignant component is low grade and composed of nodules of cellular hyaline cartilage delineated by fibrous bands

Clear Cell Chondrosarcoma

Clear cell chondrosarcoma is very uncommon and accounts for 2% of chondrosarcomas. It typically arises in the epiphysis or epiphyseal equivalent in the long tubular bones such as the proximal femur and humerus, and in the axial skeleton it has a propensity to develop in the ribs and vertebrae. Grossly the tumor is lobulated and gray-tan and may have hemorrhagic and cystic change (Fig. 1.11).

Histologically, the tumor contains small areas of low-grade conventional chondrosarcoma, and the majority is composed of groups and sheets of large polygonal chondrocytes that have vesicular nuclei and abundant clear to palely eosinophilic cytoplasm. Deposited throughout these areas are small trabeculae of

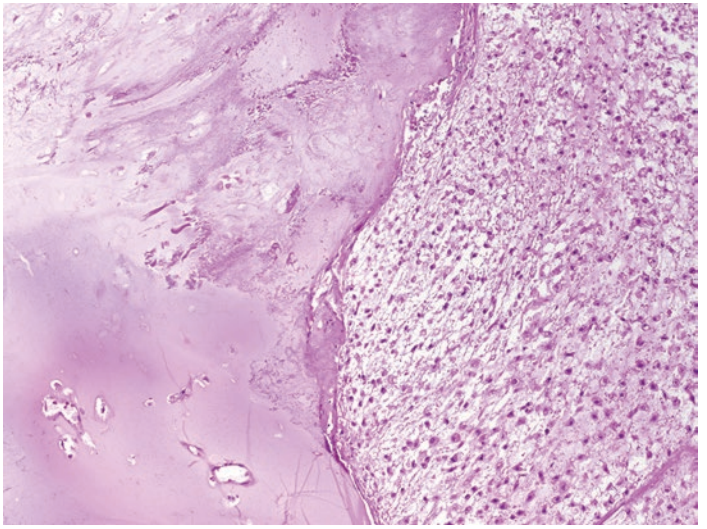

Fig. 1.8 Secondary chondrosarcoma arising in the Ollier disease: hypercellular homogenously myxoid chondrosarcoma that has flocculent stroma in contrast with the hypocellular, hyaline cartilage of the adjoining enchondroma

woven bone that are focally rimmed by nonneoplastic osteoblasts and occasional osteoclasts (Figs. 1.12, 1.13, and 1.14)

Immunohistochemistry shows that both clear cell and conventional chondrosarcoma components are positive for SOX-9 and S-100; a significant number of cases also stain with a variety of molecular weight keratins. Unlike conventional chondrosarcoma, IDH1 or IDH2 mutations are not present. Clear cell chondrosarcoma is more aggressive than conventional low-grade conventional chondrosarcoma, and the tumor is excised en bloc with negative margins – the local recurrence rate is 16–20%, and metastases develop in 20–25% of cases, usually over a period of many years following diagnosis [9, 42]. Very rarely dedifferentiation occurs, and this complication is associated with a more aggressive clinical course.

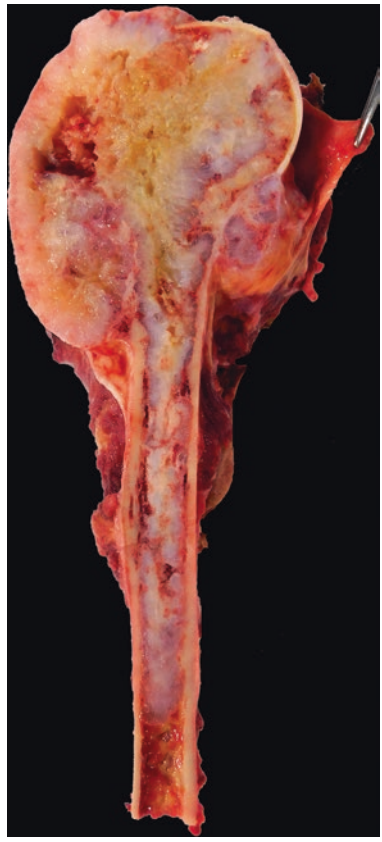

Fig. 1.9 Dedifferentiated chondrosarcoma composed of fish flesh - like, gray-tan, soft tissue mass with necrotic foci and cavitation (dedifferentiated component) arising in the humeral head. The conventional component fills the proximal diaphysis and consists of homogenous iridescent cartilaginous lobules of hyaline cartilage

Mesenchymal Chondrosarcoma

Mesenchymal chondrosarcoma is a high-grade malignancy that is responsible for 1–10% of chondrosarcomas. The tumor harbors a specific HEY-1-NICOA2, in-frame, gene fusion [1]. Most cases arise in the skeleton (40–78%), where it affects individuals 20–30 years old, whereas in the soft tissues, patients (22–60%) are often 40 years or older. The North American experience using the SEER database estimates 60% of mesenchymal chondrosarcomas

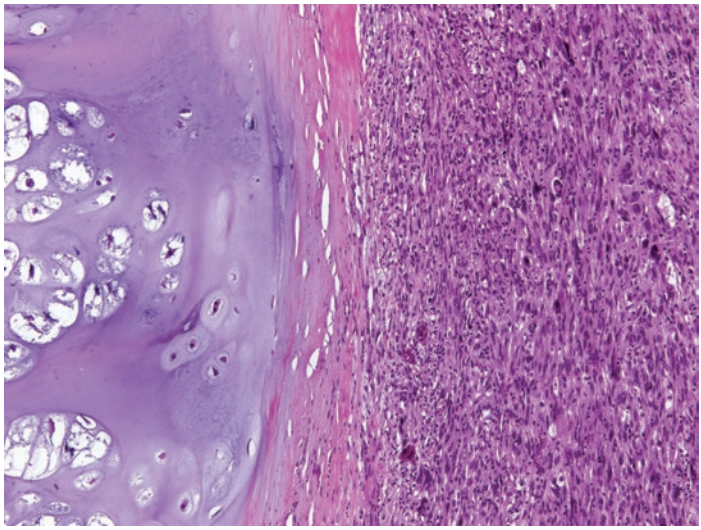

Fig. 1.10 Dedifferentiated chondrosarcoma: Biphasic appearance with relatively hypocellular hyaline cartilage and low-grade chondrocyte atypia in conventional chondrosarcoma (left half of image) adjacent to markedly hypercellular pleomorphic spindle cell sarcoma

arise in soft tissues, whereas in a large European series it is estimated 36% arise in soft tissues [46, 47]. In bone the tumor involves the maxilla, mandible, vertebrae, ribs, pelvis, and humerus. The appendicular skeleton is less frequently involved [29].

The tumors are usually large and are solitary, solid, gray-tan, fleshy masses. The neoplasm is composed of primitive small round and short spindle cells and islands of well-differentiated fibro-hyaline cartilage. The round cells may grow in a sheet-like pattern and often contains a staghorn-like supportive vascular tree. The cartilage is deposited in islands that are moderately cellular, and the chondrocytes exhibit mild cytological atypia (Figs. 1.15 and 1.16).

Cortical bone destruction with an associated soft tissue mass occurs in 50% of cases. Immunohistochemistry shows that the round cells are positive for Sox 9, CD99, and Fli1, and a minority cells may express desmin and myogenin [48–50].

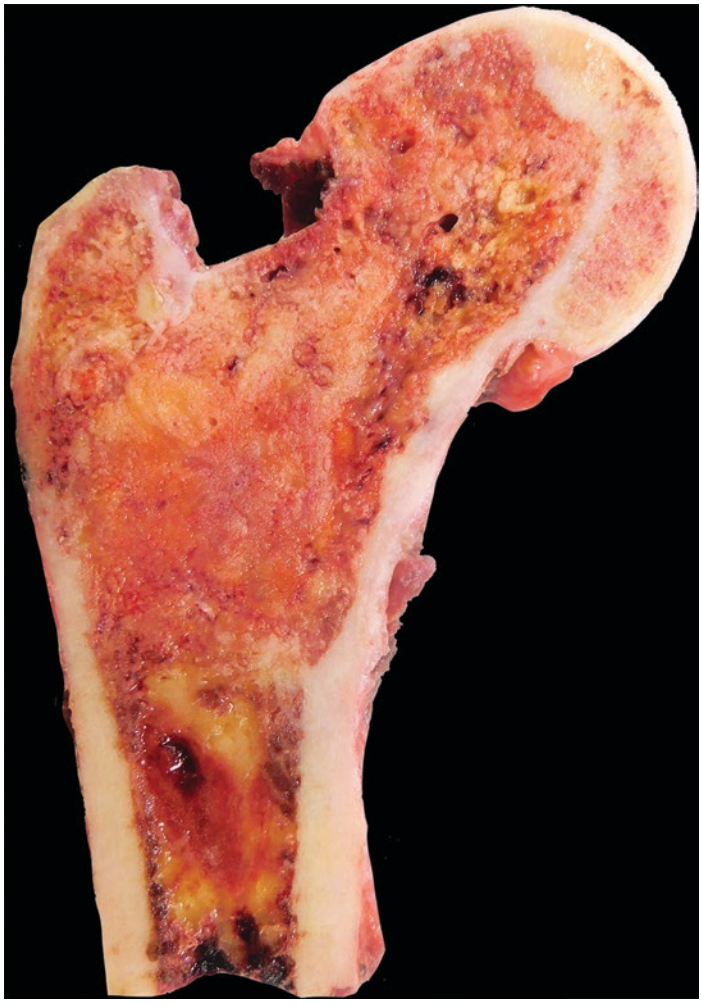

Fig. 1.11 Proximal femur involved by clear cell chondrosarcoma that is pink-tan gray and extends up to the base of the articular surface

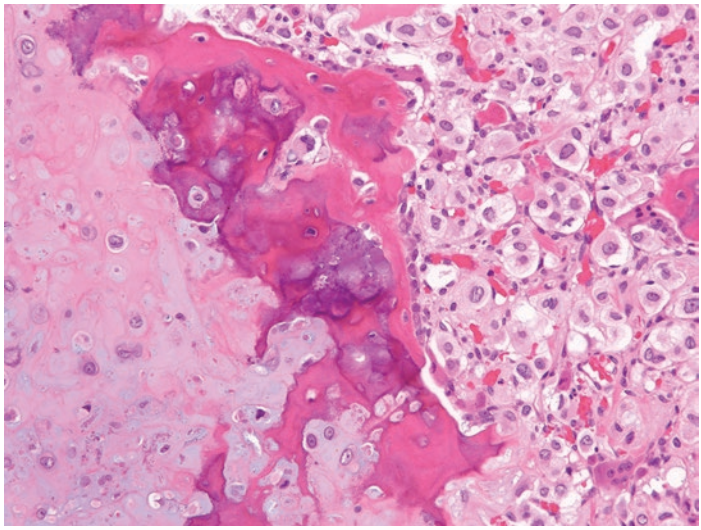

Fig. 1.12 Conventional chondrosarcoma showing relatively hypocellular hyaline neoplastic cartilage (left half of image) juxtaposed to groups of clear cell chondrosarcoma (right half of image). The large clear cells surround a central trabeculum of metaplastic woven bone that shows osteoblastic rimming (nonneoplastic bone)

The differential diagnosis includes Ewing sarcoma and other translocation-associated round cell sarcomas, rhabdomyosarcoma, small cell osteosarcoma, and lymphoma [28]. The treatment is systemic therapy and wide resection with negative margins. The local recurrence rate reported ranges from 13% to 75%, and 10.6% of cases show metastases at initial presentation [47, 51]. The overall 5- and 10-year survival rates reported in recent SEER data review are 51% and 43% [46] with older literature reporting 55% and 26% [52], respectively. There are, however, significant 5-year survival differences noted in axial, appendicular, and cranial sites as they are 37%, 50%, and 74%, respectively [46]. Some metastases occur years after initial diagnosis [9, 42, 46, 47, 51].

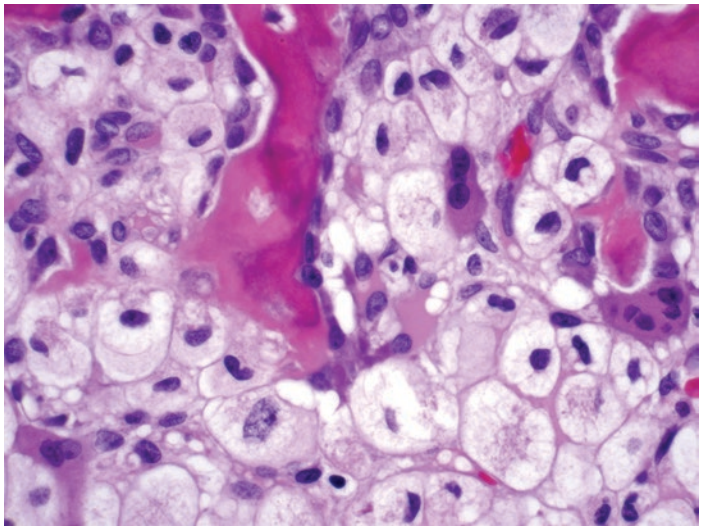

Fig. 1.13 Large polyhedral chondrocytes with abundant clear cytoplasm, well-defined cytoplasmic membranes, and generally vesicular nuclei, some with distinct nucleoli, surround a centrally located fragment of metaplastic, reactive woven bone, rimmed by osteoblasts. Scattered multinucleated non-tumoral giant cells also present

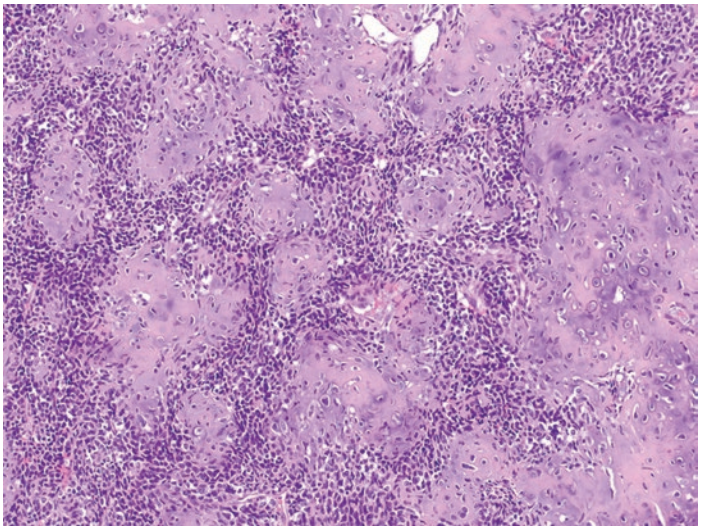

Fig. 1.14 Mesenchymal chondrosarcoma composed of pink-blue, well-demarcated islands of hyaline cartilage, vaguely archipelagic, within a "busy" hypercellular small round to focally spindled tumor

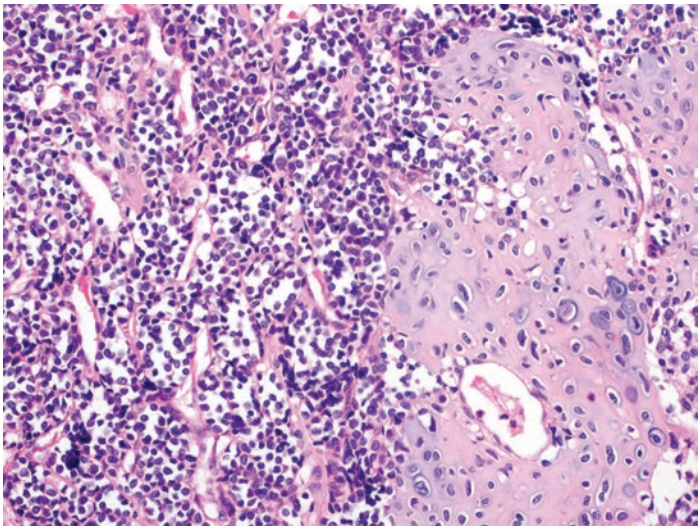

Fig. 1.15 Biphasic tumor composed of a hypercellular small blue round cell tumor with abrupt interface with a neoplastic nodule of hyaline cartilage – typical of mesenchymal chondrosarcoma. Note pink hue of the cartilage matrix. A staghorn-like vascular pattern is present in the round cell component

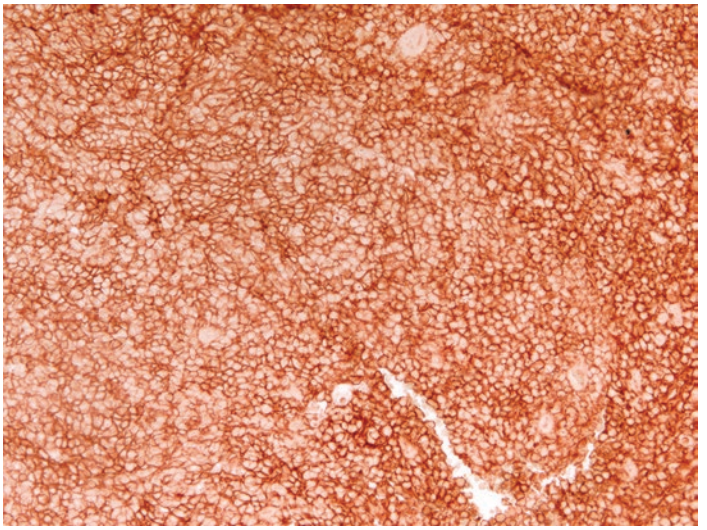

Fig. 1.16 Membranous CD99 immunostaining in mesenchymal chondrosarcoma. A diagnostic pitfall for misclassification as other round cell sarcomas are positive for CD99

References

1. Nielsen GP, Rosenberg AE. Diagnostic pathology: bone. 1600 JFK Blvd. Philadelphia, PA 19103-2899: Elsevier Health Sciences; 2017.
2. Unni KK, Inwards CY. Dahlin's bone tumors: general aspects and data on 10,165 cases. Philadelphia: Lippincott Williams & Wilkins; 2010.
3. Unni KK. Cartilaginous lesions of bone. J Orthop Sci. 2001;6(5):457–72. https://doi.org/10.1007/s007760170015.
4. Czerniak B. Dorfman and Czerniak's bone tumors E-book: 1600 JFK Blvd.Philadelphia, PA 19103-2899: Elsevier Health Sciences; 2015.
5. Krishnan Unni K, Inwards CY. Dahlin's bone tumors: general aspects and data on 10,165 cases. Philadelphia: Lippincott Williams and Wilkins; 2010.
6. Howlader N, Noone A, Krapcho M, Miller D, Brest A, Yu M, et al. SEER Cancer Statistics Review, 1975–2017, National Cancer Institute. Bethesda. 2020.
7. Nota SP, Braun Y, Schwab JH, van Dijk CN, Bramer JA. The identification of prognostic factors and survival statistics of conventional central chondrosarcoma. Sarcoma. 2015;2015:623746. https://doi.org/10.1155/2015/623746.
8. Afonso PD, Isaac A, Villagran JM. Chondroid tumors as incidental findings and differential diagnosis between enchondromas and low-grade chondrosarcomas. Semin Musculoskelet Radiol. 2019;23(1):3–18. https://doi.org/10.1055/s-0038-1675550.
9. Amer KM, Munn M, Congiusta D, Abraham JA, Basu MA. Survival and prognosis of chondrosarcoma subtypes: SEER database analysis. J Orthop Res. 2020;38(2):311–9. https://doi.org/10.1002/jor.24463.
10. Chow WA. Chondrosarcoma: biology, genetics, and epigenetics. F1000Res. 2018;7. https://doi.org/10.12688/f1000research.15953.1.
11. Boehme KA, Schleicher SB, Traub F, Rolauffs B. Chondrosarcoma: a rare misfortune in aging human cartilage? The role of stem and progenitor cells in proliferation, malignant degeneration and therapeutic resistance. Int J Mol Sci. 2018;19(1). https://doi.org/10.3390/ijms19010311.
12. Verdegaal SH, van Rijswijk CS, Brouwers HF, Dijkstra PD, van de Sande MA, Hogendoorn PC, et al. MRI appearances of atypical cartilaginous tumour/grade I chondrosarcoma after treatment by curettage, phenolisation and allografting: recommendations for follow-up. Bone Joint J. 2016;98-B(12):1674–81. https://doi.org/10.1302/0301-620X.98B12.36970.
13. Suster D, Hung YP, Nielsen GP. Differential diagnosis of cartilaginous lesions of bone. Arch Pathol Lab Med. 2020;144(1):71–82. https://doi.org/10.5858/arpa.2019-0441-RA.
14. Disler DG, Rosenberg AE, Springfield D, O'Connell JX, Rosenthal DI, Kattapuram SV. Extensive skeletal metastases from chondrosarcoma without pulmonary involvement. Skelet Radiol. 1993;22(8):595–9. https://doi.org/10.1007/BF00197142.

15. Gelderblom H, Hogendoorn PC, Dijkstra SD, van Rijswijk CS, Krol AD, Taminiau AH, et al. The clinical approach towards chondrosarcoma. Oncologist. 2008;13(3):320–9. https://doi.org/10.1634/theoncologist.2007-0237.
16. Gitto S, Cuocolo R, Albano D, Chianca V, Messina C, Gambino A, et al. MRI radiomics-based machine-learning classification of bone chondrosarcoma. Eur J Radiol. 2020;128:109043. https://doi.org/10.1016/j.ejrad.2020.109043.
17. Logie CI, Walker EA, Forsberg JA, Potter BK, Murphey MD. Chondrosarcoma: a diagnostic imager's guide to decision making and patient management. Semin Musculoskelet Radiol. 2013;17(2):101–15. https://doi.org/10.1055/s-0033-1342967.
18. Eefting D, Schrage YM, Geirnaerdt MJ, Le Cessie S, Taminiau AH, Bovee JV, et al. Assessment of interobserver variability and histologic parameters to improve reliability in classification and grading of central cartilaginous tumors. Am J Surg Pathol. 2009;33(1):50–7. https://doi.org/10.1097/PAS.0b013e31817eec2b.
19. Mavrogenis AF, Angelini A, Vottis C, Palmerini E, Rimondi E, Rossi G, et al. State-of-the-art approach for bone sarcomas. Eur J Orthop Surg Traumatol. 2015;25(1):5–15. https://doi.org/10.1007/s00590-014-1468-2.
20. Amary MF, Bacsi K, Maggiani F, Damato S, Halai D, Berisha F, et al. IDH1 and IDH2 mutations are frequent events in central chondrosarcoma and central and periosteal chondromas but not in other mesenchymal tumours. J Pathol. 2011;224(3):334–43. https://doi.org/10.1002/path.2913.
21. Tinoco G, Wilky BA, Paz-Mejia A, Rosenberg A, Trent JC. The biology and management of cartilaginous tumors: a role for targeting isocitrate dehydrogenase. Am Soc Clin Oncol Educ Book. 2015:e648–55. https://doi.org/10.14694/EdBook_AM.2015.35.e648.
22. Sharma H. Development of novel therapeutics targeting isocitrate dehydrogenase mutations in cancer. Curr Top Med Chem. 2018;18(6):505–24. https://doi.org/10.2174/1568026618666180518091144.
23. Golub D, Iyengar N, Dogra S, Wong T, Bready D, Tang K, et al. Mutant isocitrate dehydrogenase inhibitors as targeted cancer therapeutics. Front Oncol. 2019;9:417. https://doi.org/10.3389/fonc.2019.00417.
24. Li L, Paz AC, Wilky BA, Johnson B, Galoian K, Rosenberg A, et al. Treatment with a small molecule mutant IDH1 inhibitor suppresses tumorigenic activity and decreases production of the oncometabolite 2-hydroxyglutarate in human chondrosarcoma cells. PLoS One. 2015;10(9):e0133813. https://doi.org/10.1371/journal.pone.0133813.
25. Li L, Hu X, Eid JE, Rosenberg AE, Wilky BA, Ban Y, et al. Mutant IDH1 depletion downregulates integrins and impairs chondrosarcoma growth. Cancers (Basel). 2020;12(1). https://doi.org/10.3390/cancers12010141.
26. Nicolle R, Ayadi M, Gomez-Brouchet A, Armenoult L, Banneau G, Elarouci N, et al. Integrated molecular characterization of chondrosar-

coma reveals critical determinants of disease progression. Nat Commun. 2019;10(1):4622. https://doi.org/10.1038/s41467-019-12525-7.
27. Chow WA. Update on chondrosarcomas. Curr Opin Oncol. 2007;19(4):371–6. https://doi.org/10.1097/CCO.0b013e32812143d9.
28. Evola FR, Costarella L, Pavone V, Caff G, Cannavo L, Sessa A, et al. Biomarkers of osteosarcoma, chondrosarcoma, and ewing sarcoma. Front Pharmacol. 2017;8:150. https://doi.org/10.3389/fphar.2017.00150.
29. Mohammadinezhad C. Chondrosarcoma of the jaw. J Craniofac Surg. 2009;20(6):2097–100. https://doi.org/10.1097/SCS.0b013e3181bec5d3.
30. Evans HL, Ayala AG, Romsdahl MM. Prognostic factors in chondrosarcoma of bone: a clinicopathologic analysis with emphasis on histologic grading. Cancer. 1977;40(2):818–31. https://doi.org/10.1002/1097-0142(197708)40:2<818::aid-cncr2820400234>3.0.co;2-b.
31. Stevenson JD, Laitinen MK, Parry MC, Sumathi V, Grimer RJ, Jeys LM. The role of surgical margins in chondrosarcoma. Eur J Surg Oncol. 2018;44(9):1412–8. https://doi.org/10.1016/j.ejso.2018.05.033.
32. Laitinen MK, Stevenson JD, Parry MC, Sumathi V, Grimer RJ, Jeys LM. The role of grade in local recurrence and the disease-specific survival in chondrosarcomas. Bone Joint J. 2018;100-B(5):662–6. https://doi.org/10.1302/0301-620X.100B5.BJJ-2017-1243.R1.
33. National Cancer Institute. Surveillance/Epidemiology and end results (SEER) program (2000–2010) 2019. http://seer.cancer.gov/data.
34. Duckworth LV, Reith JD. Well-differentiated central cartilage tumors of bone: an overview. Surg Pathol Clin. 2012;5(1):147–61. https://doi.org/10.1016/j.path.2011.12.001.
35. Rosenberg AE, Nielsen GP, Keel SB, Renard LG, Fitzek MM, Munzenrider JE, et al. Chondrosarcoma of the base of the skull: a clinicopathologic study of 200 cases with emphasis on its distinction from chordoma. Am J Surg Pathol. 1999;23(11):1370–8. https://doi.org/10.1097/00000478-199911000-00007.
36. Thorkildsen J, Taksdal I, Bjerkehagen B, Norum OJ, Myklebust TA, Zaikova O. Risk stratification for central conventional chondrosarcoma of bone: a novel system predicting risk of metastasis and death in the Cancer Registry of Norway cohort. J Surg Oncol. 2020;121(7):1115–25. https://doi.org/10.1002/jso.25883.
37. Welkerling H, Werner M, Delling G. [Histologic grading of chondrosarcoma. A qualitative and quantitative analysis of 74 cases of the Hamburg bone tumor register]. Pathologe. 1996;17(1):18–25. https://doi.org/10.1007/s002920050130.
38. Gao Z, Lu T, Song H, Gao Z, Ren F, Ouyang P, et al. Prognostic factors and treatment options for patients with high-grade chondrosarcoma. Med Sci Monit. 2019;25:8952–67. https://doi.org/10.12659/MSM.917959.
39. Tsuchiya T, Osanai T, Ogose A, Tamura G, Chano T, Kaneko Y, et al. Methylation status of EXT1 and EXT2 promoters and two mutations of

EXT2 in chondrosarcoma. Cancer Genet Cytogenet. 2005;158(2):148–55. https://doi.org/10.1016/j.cancergencyto.2004.08.031.
40. Beltrami G, Ristori G, Scoccianti G, Tamburini A, Capanna R. Hereditary Multiple Exostoses: a review of clinical appearance and metabolic pattern. Clin Cases Miner Bone Metab. 2016;13(2):110–8. https://doi.org/10.11138/ccmbm/2016.13.2.110.
41. Zhang Y, Paz Mejia A, Temple HT, Trent J, Rosenberg AE. Squamous cell carcinoma arising in dedifferentiated chondrosarcoma proved by isocitrate dehydrogenase mutation analysis. Hum Pathol. 2014;45(7):1541–5. https://doi.org/10.1016/j.humpath.2014.02.016.
42. Bongers MER, Karhade AV, Setola E, Gambarotti M, Groot OQ, Erdogan KE, et al. How does the skeletal oncology research group algorithm's prediction of 5-year survival in patients with chondrosarcoma perform on international validation? Clin Orthop Relat Res. 2020. https://doi.org/10.1097/CORR.0000000000001305.
43. Lee FY, Mankin HJ, Fondren G, Gebhardt MC, Springfield DS, Rosenberg AE, et al. Chondrosarcoma of bone: an assessment of outcome. J Bone Joint Surg Am. 1999;81(3):326–38. https://doi.org/10.2106/00004623-199903000-00004.
44. Lex JR, Evans S, Stevenson JD, Parry M, Jeys LM, Grimer RJ. Dedifferentiated chondrosarcoma of the pelvis: clinical outcomes and current treatment. Clin Sarcoma Res. 2018;8:23. https://doi.org/10.1186/s13569-018-0110-1.
45. Grimer RJ, Gosheger G, Taminiau A, Biau D, Matejovsky Z, Kollender Y, et al. Dedifferentiated chondrosarcoma: prognostic factors and outcome from a European group. Eur J Cancer. 2007;43(14):2060–5.
46. Schneiderman BA, Kliethermes SA, Nystrom LM. Survival in mesenchymal chondrosarcoma varies based on age and tumor location: a survival analysis of the SEER database. Clin Orthop Relat Res. 2017;475(3):799–805. https://doi.org/10.1007/s11999-016-4779-2.
47. Frezza AM, Cesari M, Baumhoer D, Biau D, Bielack S, Campanacci DA, et al. Mesenchymal chondrosarcoma: prognostic factors and outcome in 113 patients. A European Musculoskeletal Oncology Society study. Eur J Cancer. 2015;51(3):374–81. https://doi.org/10.1016/j.ejca.2014.11.007.
48. Wehrli BM, Huang W, De Crombrugghe B, Ayala AG, Czerniak B. Sox9, a master regulator of chondrogenesis, distinguishes mesenchymal chondrosarcoma from other small blue round cell tumors. Hum Pathol. 2003;34(3):263–9. https://doi.org/10.1053/hupa.2003.41.
49. Lee AF, Hayes MM, Lebrun D, Espinosa I, Nielsen GP, Rosenberg AE, et al. FLI-1 distinguishes Ewing sarcoma from small cell osteosarcoma and mesenchymal chondrosarcoma. Appl Immunohistochem Mol Morphol. 2011;19(3):233–8. https://doi.org/10.1097/PAI.0b013e3181fd6697.

50. Granter SR, Renshaw AA, Fletcher CD, Bhan AK, Rosenberg AE. CD99 reactivity in mesenchymal chondrosarcoma. Hum Pathol. 1996;27(12):1273–6. https://doi.org/10.1016/s0046-8177(96)90336-6.
51. Mendenhall WM, Reith JD, Scarborough MT, Stechmiller BK, Mendenhall NP. Mesenchymal chondrosarcoma. Int J Part Ther. 2016;3(2):300–4. https://doi.org/10.14338/IJPT-16-00019.1.
52. Nakashima Y, Unni KK, Shives TC, Swee RG, Dahlin DC. Mesenchymal chondrosarcoma of bone and soft tissue. A review of 111 cases. Cancer. 1986;57(12):2444–53. https://doi.org/10.1002/1097-0142(19860615)57:12<2444::aid-cncr2820571233>3.0.co;2-k.

2 Advances in the Molecular Biology of Chondrosarcoma

Zhenfeng Duan, Dylan C. Dean, Susan Bukata, and Francis J. Hornicek

Introduction

Chondrosarcoma (CS) is a heterogeneous cartilage-producing tumor and the second most common primary bone cancer after osteosarcoma [1, 2]. It accounts for more than 20% of all primary bone malignancies. Although CS is proposed to arise from the chondrocyte lineage of mesenchymal cells, its exact cellular origin remains unknown [3]. Unlike osteosarcoma, which tends to affect children and adolescents, CS occurs in all ages with a predilection for the hip and femur [4]. Given its heterogeneity, pathologic and radiographic data are often combined in order to distinguish CS subtypes and inform treatment [5].

CS is classified into low, intermediate, or high grade according to histopathological cellularity, nuclear atypia, and pleomorphism [6]. Progression from low to high grade is reflected by increased muco-myxoid matrix and vascularization in addition to cellularity and nuclear atypia. A classification change was approved in 2013 by the World Health Organization (WHO),

Z. Duan (✉) · D. C. Dean · S. Bukata · F. J. Hornicek
Department of Orthopaedic Surgery, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA
e-mail: zduan@mednet.ucla.edu

F. J. Hornicek (ed.), *Chondrosarcoma*,
https://doi.org/10.1007/978-3-030-74572-1_2

whereby grade 1 (low-grade) CS was renamed "atypical cartilaginous tumor" [6, 7]. Because grade 1 CS rarely metastasizes, it is considered a locally aggressive neoplasm rather than malignant sarcoma. Additionally, the 5-year survival rate for grade 1 is relatively good at 85–95%. Grade 2 (intermediate-grade) CSs are comparatively more cellular with less chondroid matrix than grade 1. While mitoses are present, they are widely scattered. The chondrocyte nuclei are enlarged and either vesicular or hyperchromatic. Between the low- and high-grade subtypes, the metastatic potential is intermediate at approximately 10–15%. Grade 2 CS has a 5-year survival rate of approximately 70–85%. The vast majority (85%) of conventional (primary and secondary) CSs are grade 1 or 2. Grade 3 (high-grade) CSs are hypercellular with nuclear pleomorphism, detected mitoses, and a sparse to absent chondroid matrix. High-grade CSs have high rates of metastasis up to 70% and a dismal prognosis when surgical resection is used alone. Five-year survival rates for grade 3 CS are less than 20%, largely a result of early disseminated metastases. In most cases, the histological grade of recurrent CS mimics the primary tumor; however, up to 13% of recurrences form a higher comparative grade. In addition to grade, CS is divided into subgroups, where 90% are conventional CS and the remaining 10% include the dedifferentiated, clear cell, mesenchymal, periosteal, or myxoid CS subtypes [6, 7]. As diagnostics and sequencing technologies advance, the pathogenic biology and sensitivities between subtypes have gained increased attention with therapeutic selection.

CS is notorious for its resistance to traditional chemotherapy and radiation treatment [8] and has more recently shown robust resistance to several lauded targeted and immune therapies [9]. Extensive surgical resection has, therefore, remained the primary treatment modality, with prognosis a function of histological grade and negative surgical margins. Given the limitations of treatment for inoperable or metastatic CS, these patients maintain the shortest median survival times at less than 12 months. And while low-grade CS rarely metastasizes and can often be managed with surgery alone, high-grade CS is often recurrent, metastatic to the lung, liver, kidney, brain and frequently lethal [3, 8].

Differentiating these two major subtypes and subsequently managing patient expectations are complicated as no validated predictive or prognostic biomarkers for CS exist [10]. Additionally, as few therapeutics are used within the clinic, outcomes over the last several decades have plateaud and relied primarily on surgery. There is, therefore, an urgent need to identify novel CS treatments. Clearly, the efficacy of future therapies will necessitate a deeper understanding of the molecular biology of CS, perhaps with increased attention to subtype tailored management, so that newer and more precise targets are investigated in this heterogeneous and resistant cancer.

Although great strides have been made in understanding the pathology and morphology of CSs, many genetic and epigenetic mechanisms underlying their pathogenesis are poorly characterized. The current understanding is that CS develops in multistep fashion in which precursor mesenchymal stem cells (MSCs) exponentially accumulate genetic and pathway alterations, which encourage an increasingly more malignant histological phenotype [1, 3]. CS has been referred to as a sarcoma with a complex cytogenetic signature. Historically, comparative genomic hybridization (CGH), fluorescence in situ hybridization (FISH), methylation assays, single-nucleotide polymorphism (SNP) microarrays, and coding and noncoding RNA arrays were the major detection techniques of CS genomic and epigenomic alterations [1, 3]. More recently, an emergence of large-scale next-generation sequencing (NGS) studies have discovered a vast array of DNA amplification/deletions, somatic mutations, and epigenetic changes [1, 3]. Simply put, these technologies have significantly improved our understanding of the molecular landscape that drives CS. The NGS technology has revolutionized our understanding through its variants such as whole genome sequencing (WGS), whole exosome sequencing (WES), and RNA sequencing (RNA-Seq). WGS is more comprehensive, as it can reveal an unbiased landscape of somatic mutations in noncoding and unannotated regions of the whole genome. WES is the preferred method for uncovering genetic variants in known protein-coding regions of the exosome across an entire genome. Finally, RNA-Seq can characterize an entire transcriptome, including protein-coding messenger RNAs

(mRNAs) and noncoding RNAs (ncRNAs). This article reviews the most recent and relevant discoveries of the molecular biology driving CS, with a specific focus on the novel biomarkers and targets for prognostics and therapeutics.

Frequently Amplified or Deleted Genes in CS

DNA copy-number alterations such as gene amplification or deletions represent a core mechanism of cancer pathogenesis. As a heterogeneous cancer, the CS genome displays comparatively more DNA amplifications and deletions than other tumors. Past CGH and more recent NGS investigations have highlighted these changes and reflect the chromosomal instability which drives CS initiation and progression. In a CGH study of 67 CS cases, a remarkable 59 displayed abnormal DNA copy numbers. Specific and recurrent amplifications included 8q24.21-q24.22 and11q22.1-q22.3. The amplified region of 8q24.21-q24.22 contains the noteworthy genes MYC, MLZE, FAM49B, DDEF1, and ADCY8. The MYC oncogene has been shown to be frequently amplified in grade 2 and 3 CS and correlates with shorter overall survival. In contrast, no MYC amplification was found in lower grade samples of enchondroma or grade 1 CS [11]. Homozygous deletions of 9p21.3, 8q24.11, and 11p11.2, which contain CDKN2A (p16) as well as exostosin glycosyltransferase genes (EXT1 and EXT2), are present in some CSs [12]. The EXT genes encode glycosyltransferases involved in the biosynthesis of heparan sulfate (HS) chains at HS proteoglycans (HSPGs). These HSPGs are important in the diffusion of IHH, PTHLH, and fibroblast growth factor (FGF), all of which promote chondrocyte proliferation and differentiation. Therefore, EXT deletions are able to affect hedgehog signaling by defective HS. Similar results have been reported in skull base CS [13]. Another CGH array was used to investigate the copy-number changes in CS that initiate genetic events related to tumor progression. This same study showed genomic imbalances were rare in grade 1 CS tumors yet much more frequent in high-grade CS [14]. In total,

22 chromosome regions were imbalanced in ≥25% of the high-grade CS tumors, with three of those regions located on chromosome 12 containing the PTPRF-interacting protein-binding protein 1 (PPFIBP1) gene [14]. Loss of chromosome 6 and gain of 12q12 were associated with higher grade. Importantly, array CGH with cDNA expression showed gene amplification of chromosomal region 12q13 correlated with expression of the cyclin-dependent kinase 4 (CDK4) gene [14]. RNA expression analysis revealed higher expression of CDK4 in the CSs with this region being amplified. Loss of p16 occurs in 75% of high-grade central CSs and no low-grade CSs [15]. Another study showed loss of heterozygosity (LOH) at chromosomal band 9p21 is one of the few consistent genetic aberrations found in CS [16]. This locus harbors two cell-cycle regulators, p16 and INK4A-p14ARF (p14), which are inactivated in various human malignancies [16]. Loss of p16 protein expression was detected by immunohistochemistry in 12 of 73 central CSs and correlated with increasing histological grade. However, LOH at 9p21 was found in 15 of 39 CSs (38%) but did not correlate with loss of p16 protein expression [16]. Single-strand conformation polymorphism (SSCP) analysis of p16 did not reveal any mutations in the 47 cases. To investigate whether an epigenetic mechanism was responsible for loss of p16 protein expression, methylation-specific PCR was used to detect p16 promotor methylation, which it found in 5 of the 30 tumors. Of note, p16 promotor methylation did not correlate with p16 protein expression or LOH at 9p21 [16]. These studies suggest that although alterations exist in the general DNA sequence and its promoter regions, the absence of correlation between LOH, promotor methylation, and protein expression indicates a locus outside p16 is the likely target of LOH at 9p21 [16, 17]. The correlation between p16 protein expression and tumor grade indicates that a loss of p16 protein expression is an important event of CS progression [16]. This is supported by other studies as well, where loss of p16 protein expression also correlated with histological grade. In dedifferentiated, mesenchymal, clear cell, and periosteal CS, p16 aberrations were common and occurred in 85%, 70%, 95%, and 50% of the cases, respectively [18].

Frequently Mutated Genes and Signaling Pathways in CS

Gene mutations are often the nidus for cancer initiation. CS is no different, as multiple mutations, either germline or somatic, have been identified [3, 18]. The most commonly mutated genes in CS include isocitrate dehydrogenase (IDH) 1 and 2, COL2A1, p53, the tumor suppressor retinoblastoma protein (Rb), and hedgehog-associated genes (Table 2.1).

IDH Somatic mutations of IDH1 and IDH2 were first discovered in gliomas and then in acute myeloid leukemia (AML) [19]. IDH1 and IDH2 mutations were the first common genetic abnormalities identified in CS and occur in 50–75% of CSs, with frequency varying by CS subtype and grade [20–23]. Similar to gliomas and AML, these mutations occur early on in CS tumourigenesis [23]. In a mutational analysis including 25 high-grade CSs, 61% of the cases (14/23) harbored a somatic mutation in IDH1/2, with the majority (86%) of mutations occurring in the IDH1 gene. IDH1/2 mutation analysis is a promising distinguishing biomarker between CS and chondroblastic osteosarcoma [22]. These mutations are quite specific, as the point mutations of IDH1 and IDH2 in CS are often different from the mutations in other tumor types including AML and glioma. CS predominantly harbors

Table 2.1 Most frequently mutated genes in CS

Gene	Location	Class	DNA size (kb)	mRNA size (kb)	Signaling pathway
IDH1/2	2q34/15q26	Enzymes	29.8	2.5	Cell metabolism
COL2A1	12q13	Collagen	52.3	5.0	Cartilage
p53	17p13	Tumor suppressor	25.8	2.6	p53
Rb1	13q14	Tumor suppressor	29.6	4.7	Cell cycle/ apoptosis
Hedgehog	7q36	Hedgehog genes	12.4	4.6	Sonic hedgehog

R132C mutations in IDH1, whereas glioma has mainly R132H mutations in IDH1 and AML has R140Q mutations in IDH2. Caution is advised diagnostically, however, as these mutations are not entirely exclusive, suggesting the IDH1 and IDH2 mutations share tumorigenic pathways in cancers [22]. In another study with 102 tissues from 37 CS patients, which included both primary and recurrent samples, researchers found that detection of an IDH1 mutation in a primary CS would also present in any locally recurrent or metastatic tumors [15].

IDH1 and IDH2 have similar enzymatic functions in the tricarboxylic acid cycle (TCA cycle), where they normally convert isocitrate to α-ketoglutarate (α-KG). Mutant IDH loses this function and instead causes accumulation of δ-2-hydroxyglutarate (D2HG) [24]. Different IDH1 and IDH2 mutations produce variable levels of this oncogenic metabolite. R132C is a strong D2HG producer, whereas R132H and R140Q are weak producers. D2HG functions as an oncometabolite by mimicking the α-KG structure and therefore inhibiting α-KG-dependent dioxygenases involved in DNA and histone demethylation. This ultimately produces a hypermethylated state of DNA and histones [24, 25] (Fig. 2.1). IDH mutations also affect metabolism, cell growth, signaling pathways, and DNA damage repair [25]. Studies have shown introduction or imitation of IDH mutations in mesenchymal stem cells impairs osteogenic differentiation and promotes chondrogenic differentiation *in vitro*. Thus, DNA copy-number alterations and IDH1/IDH2 mutations likely represent early initiating events in CS. Subsequent mutations CS may acquire such COL2A1 and p53 further drive CS tumorigenesis.

In addition to their roles in malignant CS, mutated IDHs are found in benign cartilaginous enchondromas [26]. A wide range of mutations have been reported in these neoplasms, including the IDH1-R132Q mutation. Mice with IDH1-R132Q in a single allele with concomitant COL2A1 expression form a disordered growth plate, with persistence of type X-expressing chondrocytes. Chondrocyte cultures from these animals showed increased proliferation and expression of genes characteristic of hypertrophic chondrocytes, including IDH1-R132Q. COL2A1-Cre; IDH1-R132Q mutant knock-in mice (mutant allele expressed in

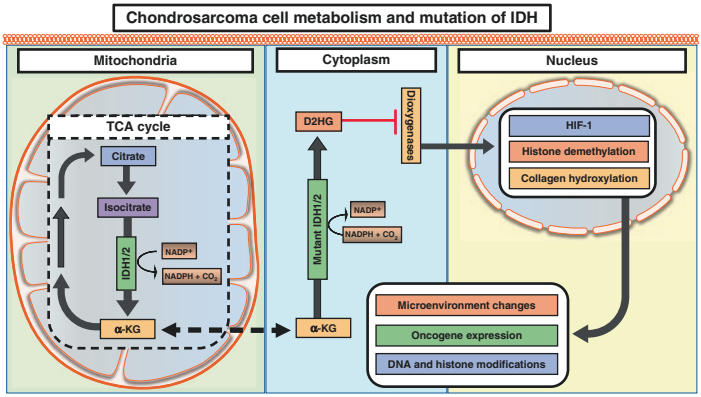

Fig. 2.1 Chondrosarcoma cell metabolism and mutation of IDH. The IDH enzyme family includes three proteins: IDH1, IDH2, and IDH3. IDH1 and IDH2 catalyze the oxidative decarboxylation of isocitrate to α-KG, which is dependent on reversible NADP+. IDH3 catalyzes isocitrate to α-KG in the TCA cycle, and dependent on NAD+. Mutant IDH1/2 enzymes catalyze NADPH and α-KG to NADP+ and D2HG. D2HG is a competitive inhibitor of α-KG-dependent dioxygenases, which are involved in various cellular processes and act as oncometabolites. Superfluous D2HG can lead to increased histone methylation, oncogene expression, and impaired cell differentiation. *Abbreviations*: D2HG δ-2-hydroxyglutarate, IDH isocitrate dehydrogenase, NAD nicotinamide adenine dinucleotide, NADP nicotinamide adenine dinucleotide phosphate, TCA cycle tricarboxylic acid cycle, αKG alpha ketoglutarate

chondrocytes) did not survive after the neonatal stage [26]. COL2A1-Cre/ERT2; IDH1-R132 Q mutant conditional knock-in mice developed multiple enchondroma-like lesions. Taken together, these findings suggest mutant IDH causes a persistence of chondrocytes, giving rise to growth-plate cells that form in the bone as enchondromas [26].

COL2A1 A comprehensive WES analysis by the Cancer Genome Project was conducted with 49 CS cases and their paired normal tissues, including 30 central, 4 peripheral, 14 dedifferentiated, and 1 synovial chondromatosis. In total, 1428 somatic mutations were identified, with a somatic mutation burden ranging from 1 to 115.

These mutations comprised 944 missense, 61 nonsense, 37 essential splice, 80 indel, and 301 synonymous changes [27]. The somatic mutation burden was significantly associated with increasing grade. In fact, high-grade CS (grade 2, 3, and dedifferentiated) contained more than double the somatic mutations per sample of grade 1 CS. The most striking finding of this study was the discovery of COL2A1 mutations via insertions, deletions, and rearrangements, which were identified in 37% of the CS cases. The mutation patterns were selective for those variants more likely to impair normal collagen biosynthesis [27]. As CS is an extracellular matrix (ECM)-rich sarcoma and collagen is the major component of the ECM, the aberrant ECM collagen in CS is likely driven by these COL2A1 mutations [28, 29]. COL2A1 encodes the α-chain of type II collagen fibers and is the major contributor to this collagen matrix and articular cartilage. Indeed, if normal collagen production is affected by mutant COL2A1, there is opportunity for therapeutic strategies which upregulate the cellular and endoplasmic reticulum stress responses geared toward managing misfolded proteins as a natural defense mechanism. The entire COL2A1 gene has also been sequenced in osteosarcomas, chordomas, and meningiomas to compare mutation patterns. The results showed specificity for the COL2A1 in CS [27]. As an ECM component, type II collagen matrix restores cartilaginous features of human primary chondrocytes greater than type I collagen matrix [30]. COL2A1 mutations likely represent hallmark alterations of CS matrix deposition and signaling and are therefore attractive oncogenic targets.

P53 and Rb1 Tumor suppressor genes p53 and Rb1 are the most commonly mutated genes in human cancer, and their pathways are pivotal in the control of cell cycle progression and apoptosis. As expected, mutated p53 is also observed in CS [2, 27, 31]. A significant correlation exists between p53 overexpression or alteration and tumor histological grade and metastasis in CS [32, 33]. Additionally, p53 protein inactivation may occur by binding with the protein mouse double minute 2 homolog (MDM2, 18). Overexpression of MDM2 was evidenced by immunohistochemistry (IHC) in 33% of high-grade CSs and correlated with increas-

ing histological grade. These results warrant the development of strategies which block the p53–MDM2 interaction in order to restore normal p53 function in CS. The other prominent tumor suppressor, Rb, prevents progression from the G1 to S phase of the cell cycle by binding and inhibiting E2 factor (E2F). Cyclin-dependent kinase 4 or 6 (CDK4/6) phosphorylates Rb (pRb) and therefore switches off the tumor-suppressing function of Rb, hence releasing the E2F complex. In short, the pRb is unable to restrict cell cycle progression in its phosphorylated form [34]. Over-activation and expression of CDK4 complexes exist in CS and similarly disrupt cell cycle breakpoints and enable uncontrolled cell proliferation [35]. Complete deletion or low expression of the Rb gene has been found in a majority of high-grade CSs. One study reported the Rb pathway is aberrant in a remarkable 96% of high-grade CSs, either via decreased tumor suppressor p16 (48%) or increased CDK4 (55%) or cyclin D1 (62%) [36].

Hedgehog Three hedgehog-related genes have been reported and include sonic hedgehog (SHH), desert hedgehog (DHH), and Indian hedgehog (IHH). They all undergo similar processing, cell secretion, and share signaling pathways within the cells. Once produced, HH proteins are first cleaved in order to become functional signal molecules. After this posttranslational processing, the protein is secreted from the cell before binding to membrane protein patched (PTH). The signal is received by another membrane protein, Smoothened (SMO), and then transduced into the nucleus by the transcription factor Gli. The stability and activity of Gli are modified by scaffold protein suppressor of fused (SUFU). This complex hedgehog signaling pathway is instrumental in chondrocyte proliferation and bone development [37]. WES has revealed 18% of CS tumors contain mutations in hedgehog signaling genes. High-grade CS is notable for its high expression of hedgehog pathway factors. Mutations of SHH-associated genes (hedgehog receptor PTCH1, Gli2/3) constitutively activate hedgehog signaling, resulting in benign cartilaginous neoplasms including enchondroma, osteochondroma, chondroblastoma, periosteal chondroma, and chondromyxoid fibroma [27, 38, 39]. These growths, while benign, can be precursor lesions to malignant

CS. Four PTCH1 mutations have been identified via an exome screen (2 missense and 2 truncating), and inactivating SUFU mutations and GLI1 amplifications also exist in CS [27].

Fusion Genes in CS

Fusion genes are rare compared to DNA amplifications, deletions, and mutations in CS**.** Of those that exist, the two fusion genes HEY1-NCOA2 and IRF2BP2-CDX1 have been reported in mesenchymal CS [40, 41]. HEY1-NCOA2, which was the first fusion gene identified in CS, is a promising diagnostic marker of mesenchymal CS as it is quite specific for this subtype [42]. HEY1, the 5′ partner of the HEY1-NCOA2 fusion gene, is a downstream effector of Notch signaling [1]. NCOA2 is a member of the p160 nuclear hormone receptor transcriptional coactivator family. The C-terminal portion of HEY1 can be replaced by the NCOA2 AD1/CID and AD2 domains while retaining the HEY1 bHLH DNA-binding/dimerization domain, thus resulting in the fusion gene HEY1-NCOA2. Further functional studies of the HEY1-NCOA2 fusion gene are required to delineate its significance in mesenchymal CS pathogenesis and whether its targeting affects cancer hallmarks. Lastly, the NR4A3-FUS fusion gene has been reported in extra-skeletal myxoid CS [43], but follow-up studies are limited.

Epigenetic Alterations in CS

A variety of epigenetic mechanisms can be disturbed in cancer, which has prompted their emergence in cancer detection and therapy. Several epigenetic alterations, especially DNA methylation and ncRNAs, have garnered recent attention for their roles in CS [44].

DNA Methylation Hypermethylation primarily occurs at the promoter CpG islands of tumor suppressor genes, hence inactivating their expression. Affected tumor suppressor genes include p16 and Runt-related transcription factor 3 (RUNX3), which also double as potential prognostic indicators for CS [44].

Hypermethylation of the promoter CpG island of Wnt inhibitory factor 1 (WIF1) has been observed in the CS cell lines CS-1 and SW1353 as well as tumor tissues [45]. WIF1 encodes a lipid-binding protein to Wnt proteins which ultimately prevents its canonical signaling cascade and its various downstream oncogene effectors [46, 47]. The Wnt proteins comprise a large family of secreted cysteine-rich glycoproteins with important roles in cancer pathogenesis [48], with each member defined by its amino acid sequence rather than function. The majority of Wnt cancer research has focused on its β-catenin and canonical signaling [48, 49]. Ordinarily, Wnt ligands bind to the frizzled and low-density lipoprotein receptor-related protein-5/6 (LRP-5/6) which in turn activates the intracellular protein Dishevelled (Dvl). Wnt antagonists, including WIF1, collapse this pathway by inhibiting binding of Wnt ligands to receptor complexes, followed by β-catenin phosphorylation and degradation, and finally blockage of TCF/LEF transcription of various oncogenes. Dysregulated Wnt signaling has been observed in bone sarcomas such as osteosarcoma and Ewing sarcoma as well as cartilaginous CS [45, 49]. Western blot analysis has confirmed loss WIF1 expression and activation of Wnt pathway proteins (Wnt5a/b, LRP6, and Dvl2) in CS. Statistical follow-up analysis revealed high levels of WIF1 methylation were associated with shorter overall survival and progression-free survival rates in CS patients. Multivariate Cox hazard analysis supported detection of hypermethylation of WIF1 as an independent prognostic factor in overall survival and progression-free survival in CS [45]. Another tumor-suppressor gene, p73, has also shown promoter hypermethylation in CS [50]. The recently discovered transcription factor p73 is a new member of the p53 family, with a DNA sequence containing significant homology to p53. The level of p73 methylation is positively correlated with CS histological grade. In addition, loss of p73 protein expression was correlated with heightened methylation of the p73 promoter. Furthermore, p73 expression could be restored in CS cell lines after exposure to a DNA demethylating drug.

NcRNAs ncRNAs are functional RNA molecules that do not form a protein. Epigenetic-related ncRNAs include miRNA,

lncRNA, and circular RNAs. Among these subclasses, miRNAs (miRs) are the best known and most extensively studied in human cancer. Expression of altered miR can be instrumental in tumor progression. Several miRs including miR-30a, miR-100, miR-145, miR-181a, and miR-221 are dysregulated in CS [51–54]. Regarding lncRNAs, expression of HOTAIR (a lncRNA) is upregulated in CS tissues and cell lines, with heightened expression correlating with CS tumor stage and poor prognosis. Furthermore, HOTAIR knockdown leads to growth inhibition of CS cells *in vitro* and *in vivo* [55]. BCAR4, another lncRNA, has also shown to be upregulated in CS tissues and cell lines [56] and an inducer of proliferation and migration. The mTOR signaling pathway is epigenetically activated by BCAR4-induced hyperacetylation of histone H3. Several *in vivo* experiments have further confirmed BCAR4 overexpression accelerates CS tumor growth and, conversely, that knockdown of BCAR4 inhibits CS growth. In summary, BCAR4 promotes chondrosarcoma cell proliferation and migration through activation of the mTOR signaling pathway and is a potential therapeutic target [56].

Integrated Genomic Approaches in CS

A variety of sequencing methods have highlighted the genomic complexity and heterogeneity of CS, including variations in DNA sequences/mutations, copy numbers, epigenetics, and gene expression. Compared to implementing a single sequencing method such as WGS, WES, RNA-Seq, or a methylation study, more integrated genomic profiling platforms are able to more completely identify copy-number alterations, somatic mutations, gene fusions, gene expression, and epigenetic alterations (DNA methylation and ncRNA). Through the integration of multiple genomic data platforms, researchers have created a fuller molecular biology picture, with less bias and more interplay of the genome, epigenome, and transcriptome. In an integrated multiplatform (DNA, mRNA, miRNA, and methylation) molecular approach to CS, three major molecular features have emerged as principally important to CS pathogenesis: high mitotic state, loss

of chromosomal region 14q32, and IDH mutations leading to genome-wide DNA hypermethylation [57]. These three elements were able to subclassify CS with superior accuracy than currently administered grading techniques.

Mouse Models of CS

Cancer mouse models enable preclinical studies to take the next step toward clinical application, as the abnormalities from patient tissues and cell lines can undergo another round of vigorous testing *in vivo* before a clinical trial. Mouse xenograft models, either through xenotransplantation of cancer cell lines or patient-derived tumor xenografts (PDXs) in immune-deficient mice, have been the gold standard method in this endeavor. Although relatively few CS mouse models have been developed, some athymic nude mice have allowed for reliable human xenograft transplantation, and several human CS cell lines have been successfully used to generate tumors within the mice to date [58, 59]. Although preclinical *in vitro* effectiveness has been demonstrated in a number of antitumor agents, the lack of representative orthotopic CS mouse models has hindered subsequent clinical trial work. Genetically engineered CS mouse models have been tested by conditional loss of expression of p53 or Ink4a/Arf. However, subsequent tumor location was unpredictable and varied, making confident conclusions and functional assessment of the model challenging [60]. Gli2 and p53 cooperatively regulate insulin-like growth factor (IGF)-mediated chondrocyte signaling in the progression from benign neoplasm to malignant CS in mouse models. Mice having enchondromas with overexpression of Gli2 in chondrocytes were crossed with mice deficient in p53 and were subsequently found to develop lesions similar to low-grade CS [61].

Genetic Pathways and Targets in CS

Treatment of unresectable and metastatic CS is hindered by resistance to standard chemotherapy regimens. Newer targeted therapies have also been evaluated in CS, including inhibitors of

AKT-PI3K, mTOR, and PDGFR with disappointing results [1–3]. In recent years, however, superior genomic studies have identified promising targetable genes and related driver pathways in CS. Specific targets include alterations in IDH, Hh, Rb, and CDK4 signaling pathways (Table 2.2). And while preclinical studies have shown favorable outcomes in CS inhibition [62–64], follow-up clinical trials are needed to cement their utility in CS therapy.

IDH Whereas the normal IDH protein produces α-KG in the TCA cycle, the mutant IDH protein uses α-KG as a substrate for conversion into the oncometabolite D2HG (Fig. 2.1). While the exact functions of IDH mutations in CS are unclear, emerging works have shown its mechanisms. In a study which implemented CRISPR/Cas9 to knockout mutant IDH1 in two CS cell lines, D2HG production, anchorage-independent growth, and cell

Table 2.2 Potential genetic pathways and targets in CS

Gene and target	Agent and inhibitor	Mechanism	Preclinical and clinical results
IDH	AG-120, AG-221	Mutant IDH inhibitor	D2HG reduction, acceptable safety profile, and clinical activity
Hedgehog	IPI-926	Smoothened (Smo) inhibitor, a hedgehog antagonist	Hedgehog pathway downregulation, decreased in vivo tumor growth
Rb and CDK4	Palbociclib	Kinase inhibition	Reduced CDK4 and tumor burden
Sox2, Sox9	siRNA	Target mRNA	Apoptosis
COX2	Celecoxib	COX2 inhibition	Decreased CS cell viability
AKT/PI3K	SF2523	Kinase inhibition	Decreased CS cell growth
Src	Dasatinib	Kinase inhibition	Decreased CS cell proliferation
HIF	siRNA and inhibitor	mRNA or HIF protein targeting	Decreased CS cell invasion
IGF	IGF-1R inhibitor or antibody	IGF-1R inhibition	Apoptosis

migration were significantly decreased. Loss of mutant IDH1 also led to reduced CS formation and D2HG production in a xenograft model. In addition, RNA-Seq analysis of the mutant IDH1 knockout cells revealed downregulation of several integrin genes. This was quite significant, as deregulation of integrin-mediated processes contributed to the tumorigenicity of mutant IDH1 CS cells. Overall, this study showed IDH1 contributes to CS genesis through integrin modulation and can be successfully targeted by gene editing. Therefore, integrins are promising candidates for activity modulation alongside mutant IDH1 inhibitors in CS treatment [65]. Of note, the two mutant IDH inhibitors enasidenib (AG-221) and ivosidenib (AG-120) were recently approved by the FDA for IDH-mutant relapsed or refractory acute myeloid leukemia (AML). Based on promising phase 1 safety and efficacy data, they continue to be studied in trials focused on hematologic malignancies, gliomas, cholangiocarcinoma, and even CS. Finally, preclinical studies have demonstrated AG-120 reduces several cancer hallmarks in addition to D2HG reduction with demonstrated inhibition of migration and invasion in CS cell lines [24].

Hedgehog CS expresses high levels of the hedgehog target genes PTCH1 and GLI1 [66, 67]. Quantitative changes in CS cultures have shown significance in preclinical models. Cultures with increased hedgehog protein showed heightened proliferation, while an inoculation with hedgehog signaling inhibitor caused decreased proliferation [68]. CS xenografts from 12 different human tumors were established in NOD-SCID mice. Treatment with triparanol, an inhibitor of hedgehog signaling, resulted in a 60% decrease in tumor volume, 30% decrease in cellularity, and a 20% reduction in proliferation rate. These results support hedgehog signaling as a contributor to CS proliferation [66]. Saridegib (IPI-926) is a potent, orally delivered small molecule inhibitor of the hedgehog signaling pathway that functions via binding to Smoothened (SMO). IPI-926 administration downregulates the hedgehog pathway in primary CS xenografts, as is demonstrated by reduced hedgehog target genes GLI1 and PTCH1 alongside depressed tumor growth [67]. Mechanistically, CS exhibits autocrine and paracrine hedgehog signaling, both of

which are affected by IPI-926. Treatment also resulted in characteristic histopathologic changes of calcification and tumor cell loss. Subsequent gene profiling studies highlighted several important genes differentially expressed in CS following IPI-926 treatment, including ADAMTSL1, which regulates CS proliferation [67]. These studies showcase the roles of the hedgehog pathway in CS and provide a rationale for its targeting in CS.

Rb and CDK4 Several studies have shown increased expression of the cell cycle regulatory protein CDK4 in human CS tissues, which correlates with genomic amplification on 12q13 [14]. The hyperexpression of CDK4 is associated with metastasis and poor patient prognosis [35, 36]. Knockdown of CDK4 by shRNA in CS cell lines significantly decreases viability, proliferation, and clonogenicity *in vitro* [35, 36]. Several works have followed these findings, including treatment of CS cell lines with the potent CDK4 inhibitor palbociclib. Researchers found treatment induced a state of cell cycle arrest within the G1 phase, as well as decreased cell migration and invasion via modulating the CDK4/Rb signaling pathway. Administration of palbociclib *in vivo* could also reduce CS tumor burden [35]. In a phase I dose-defining study of the heat shock protein 90 inhibitor alvespimycin, a patient with CS maintained disease stability for more than 6 months alongside a concomitant reduction of CDK4 levels [69]. These results support CDK inhibitors as potential treatment strategies for patients with high-grade CS.

Other Pathways Although several common mutations and pathways have been identified in CS such as COL2A1, p53, p16, Rb, and MDM2, their novel targeted therapies have yet to be successful in clinic [70]. There are several other attractive pathway targets, however, including those with Sox2, Sox9, COX2, IGF, HIF-1, and AKT/PI3K [3, 71–73]. As an example, the Sox2 and Sox9 transcriptional factors are vital throughout the chondrocyte cell lineage, with roles in chondrogenesis, chondrocyte differentiation, and proliferation. Furthermore, Sox2 and Sox9 activate transcripts of many cartilage-specific genes such as COL2A1, COL9A1, COL11A2, aggrecan, and cartilage link protein genes.

Aside from their roles in physiologic cartilage growth, high levels of Sox9 and type II collagen have been detected in CS [71]. Mechanistically, Sox9 enhances transcriptional activities of the AKT/PI3K pathway via promoter binding. There is evidence that Sox9 knockdown promotes apoptosis of CS cells and a subsequent reduction of AKT phosphorylation [74]. Hence, there is growing interest in Sox2 and Sox9, as they may play vital roles in CS progression and are also amenable to targeting. Although it can be active in normal cartilaginous tissue, COX2 overexpression is specifically associated with higher histological grade and shorter survival in CS [75]. Another transcription factor, HIF-1, is expressed in high-grade CS and may also contribute to its chemoresistance [76]. At present, there are several inhibitors of AKT/PI3K, Src, and HIF-1 signaling pathways with clinical development and promise in CS therapy. One leading candidate is SF2523, a highly selective and potent inhibitor of PI3K, which has been shown to inhibit CS cell growth *in vitro* and *in vivo* [77].

Immunotherapy of CS

Emerging immunotherapies have generated considerable attention for their success in a variety of human cancers, which has led to studies assessing their potential in various sarcomas such as CS. Of the immunogenic target antigens, cancer testis antigens (CTAs) have been especially prominent in CS work and include MAGE, NY-ESO-1, TRAG-3/CSAGE, and PRAME [78]. As an example, specific CD8+ T cells are able to lyse chondrosarcoma cell lines which express these antigens [78–80]. Recent preclinical studies have focused on immune checkpoint proteins including programmed cell death receptor-1 (PD-1) and its associated ligand (PD-L1) in CS [9]. Increased expression of PD-1 has been observed in CS tissues compared to healthy bone tissue controls [81]. Several studies have stratified PD-L1 expression according to CS subtype. In one study, PD-L1 expression was observed in 41% of dedifferentiated CS samples. A more recent study revealed a PD-L1 expression of 67.8% and PD-L2 expression of 42.4% in 59 conventional CS tissue samples. In addition to simply being

expressed, PD-L1 correlated with worse tumor grade and recurrence [43]. Although these studies support anti-PD-1 blockade therapy for CS treatment, immune checkpoint inhibitor studies in CS remain sparse at the clinical trial level, and confident conclusions on their efficacy would be premature. The majority of data thus far has been drawn from clinical trials on diverse sarcoma types, without a specific focus on CS. In the SARC028 clinical trial, one of five CS patients treated with the PD-1 antibody pembrolizumab (KEYTRUDA®) had an objective response [82]. Another study showed a partial response in a 74-year-old patient with dedifferentiated CS after six cycles of the PD-1 antibody nivolumab (OPDIVO®) [83]. The recent favorable clinical results seen in chimeric antigen receptor T cell (CAR-T) immunotherapy for hematologic malignancies may lead to an expansion of studies utilizing this therapy for CS, both at the preclinical and clinical levels [84].

Conclusion

CS is a relatively common cartilaginous tumor of bone with an especially dismal prognosis for those patients with unresectable or metastatic disease, as it is highly resistant to currently used chemotherapies. This has garnered an expansion of advanced NGS studies, which have revealed a variety of targets and pathways that will guide future diagnostic and therapeutic intervention. Current efforts integrate genomic, epigenetic, transcriptomic, and metabolomic technologies into a single dataset across CS subtypes and have highlighted the most robust oncogenic drivers amenable to targeted therapy. The molecular spectrum across CS subtypes has become clearer, each with their own underlying biology and treatment sensitivity. Within the next few years, the catalogue of genetic alterations and pathways that drive CS will become even more defined, largely due to the work of large-scale efforts through the NGS, TCGA, the International Cancer Genome Consortium, and others. Furthermore, single-cell-based NGS may further clarify CS heterogeneity. Given the low incidence and high diversity of CS subtypes, global multicenter studies with

larger CS sample cohort sizes are required. Additional discoveries focused on the molecular biology underlying CS will enable a selection of therapy according to an individual tumor sensitivity. By identifying the targeted therapies as well as the prognostic and predictive biomarkers most effective in inoperable or recurrent disease, CS subtypes can be confidently analyzed, and tailored management can overcome current therapeutic barriers.

Acknowledgment This work was supported, in part, by the Department of Orthopaedic Surgery at UCLA.

References

1. Baumhoer D, Amary F, Flanagan AM. An update of molecular pathology of bone tumors. Lessons learned from investigating samples by next generation sequencing. Genes Chromosomes Cancer. 2019;58(2):88–99.
2. Chow WA. Chondrosarcoma: biology, genetics, and epigenetics. F1000Res. 2018;7.
3. Mery B, Espenel S, Guy JB, Rancoule C, Vallard A, Aloy MT, et al. Biological aspects of chondrosarcoma: leaps and hurdles. Crit Rev Oncol Hematol. 2018;126:32–6.
4. Whelan JS, Davis LE. Osteosarcoma, chondrosarcoma, and chordoma. J Clin Oncol. 2018;36(2):188–93.
5. de Andrea CE, San-Julian M, Bovee J. Integrating morphology and genetics in the diagnosis of cartilage tumors. Surg Pathol Clin. 2017;10(3):537–52.
6. Rosenberg AE. WHO classification of soft tissue and bone, fourth edition: summary and commentary. Curr Opin Oncol. 2013;25(5):571–3.
7. Jo VY, Doyle LA. Refinements in sarcoma classification in the current 2013 World Health Organization classification of tumours of soft tissue and bone. Surg Oncol Clin N Am. 2016;25(4):621–43.
8. Leddy LR, Holmes RE. Chondrosarcoma of bone. Cancer Treat Res. 2014;162:117–30.
9. Thanindratarn P, Dean DC, Nelson SD, Hornicek FJ, Duan Z. Advances in immune checkpoint inhibitors for bone sarcoma therapy. J Bone Oncol. 2019;15:100221.
10. Jeong W, Kim HJ. Biomarkers of chondrosarcoma. J Clin Pathol. 2018;71(7):579–83.
11. Morrison C, Radmacher M, Mohammed N, Suster D, Auer H, Jones S, et al. MYC amplification and polysomy 8 in chondrosarcoma: array com-

parative genomic hybridization, fluorescent in situ hybridization, and association with outcome. J Clin Oncol. 2005;23(36):9369–76.
12. Hallor KH, Staaf J, Bovee JV, Hogendoorn PC, Cleton-Jansen AM, Knuutila S, et al. Genomic profiling of chondrosarcoma: chromosomal patterns in central and peripheral tumors. Clin Cancer Res. 2009;15(8):2685–94.
13. Kanamori H, Kitamura Y, Kimura T, Yoshida K, Sasaki H. Genetic characterization of skull base chondrosarcomas. J Neurosurg. 2015;123(4):1036–41.
14. Rozeman LB, Szuhai K, Schrage YM, Rosenberg C, Tanke HJ, Taminiau AH, et al. Array-comparative genomic hybridization of central chondrosarcoma: identification of ribosomal protein S6 and cyclin-dependent kinase 4 as candidate target genes for genomic aberrations. Cancer. 2006;107(2):380–8.
15. Amary MF, Ye H, Forbes G, Damato S, Maggiani F, Pollock R, et al. Isocitrate dehydrogenase 1 mutations (IDH1) and p16/CDKN2A copy number change in conventional chondrosarcomas. Virchows Arch. 2015;466(2):217–22.
16. van Beerendonk HM, Rozeman LB, Taminiau AH, Sciot R, Bovee JV, Cleton-Jansen AM, et al. Molecular analysis of the INK4A/INK4A-ARF gene locus in conventional (central) chondrosarcomas and enchondromas: indication of an important gene for tumour progression. J Pathol. 2004;202(3):359–66.
17. Bovee JV, Cleton-Jansen AM, Kuipers-Dijkshoorn NJ, van den Broek LJ, Taminiau AH, Cornelisse CJ, et al. Loss of heterozygosity and DNA ploidy point to a diverging genetic mechanism in the origin of peripheral and central chondrosarcoma. Genes Chromosomes Cancer. 1999;26(3):237–46.
18. Meijer D, de Jong D, Pansuriya TC, van den Akker BE, Picci P, Szuhai K, et al. Genetic characterization of mesenchymal, clear cell, and dedifferentiated chondrosarcoma. Genes Chromosomes Cancer. 2012;51(10):899–909.
19. Taylor BS, Barretina J, Maki RG, Antonescu CR, Singer S, Ladanyi M. Advances in sarcoma genomics and new therapeutic targets. Nat Rev Cancer. 2011;11(8):541–57.
20. Tinoco G, Wilky BA, Paz-Mejia A, Rosenberg A, Trent JC. The biology and management of cartilaginous tumors: a role for targeting isocitrate dehydrogenase. Am Soc Clin Oncol Educ Book. 2015:e648–55.
21. Gao P, Seebacher NA, Hornicek F, Guo Z, Duan Z. Advances in sarcoma gene mutations and therapeutic targets. Cancer Treat Rev. 2018;62:98–109.
22. Kerr DA, Lopez HU, Deshpande V, Hornicek FJ, Duan Z, Zhang Y, et al. Molecular distinction of chondrosarcoma from chondroblastic osteosarcoma through IDH1/2 mutations. Am J Surg Pathol. 2013;37(6):787–95.

23. Amary MF, Bacsi K, Maggiani F, Damato S, Halai D, Berisha F, et al. IDH1 and IDH2 mutations are frequent events in central chondrosarcoma and central and periosteal chondromas but not in other mesenchymal tumours. J Pathol. 2011;224(3):334–43.
24. Golub D, Iyengar N, Dogra S, Wong T, Bready D, Tang K, et al. Mutant isocitrate dehydrogenase inhibitors as targeted cancer therapeutics. Front Oncol. 2019;9:417.
25. Tommasini-Ghelfi S, Murnan K, Kouri FM, Mahajan AS, May JL, Stegh AH. Cancer-associated mutation and beyond: the emerging biology of isocitrate dehydrogenases in human disease. Sci Adv. 2019;5(5):eaaw4543.
26. Hirata M, Sasaki M, Cairns RA, Inoue S, Puviindran V, Li WY, et al. Mutant IDH is sufficient to initiate enchondromatosis in mice. Proc Natl Acad Sci U S A. 2015;112(9):2829–34.
27. Tarpey PS, Behjati S, Cooke SL, Van Loo P, Wedge DC, Pillay N, et al. Frequent mutation of the major cartilage collagen gene COL2A1 in chondrosarcoma. Nat Genet. 2013;45(8):923–6.
28. Gao S, Shen J, Hornicek F, Duan Z. Three-dimensional (3D) culture in sarcoma research and the clinical significance. Biofabrication. 2017;9(3):032003.
29. Totoki Y, Yoshida A, Hosoda F, Nakamura H, Hama N, Ogura K, et al. Unique mutation portraits and frequent COL2A1 gene alteration in chondrosarcoma. Genome Res. 2014;24(9):1411–20.
30. Chiu LH, Chen SC, Wu KC, Yang CB, Fang CL, Lai WF, et al. Differential effect of ECM molecules on re-expression of cartilaginous markers in near quiescent human chondrocytes. J Cell Physiol. 2011;226(8):1981–8.
31. Kim MJ, Cho KJ, Ayala AG, Ro JY. Chondrosarcoma: with updates on molecular genetics. Sarcoma. 2011;2011:405437.
32. Terek RM, Healey JH, Garin-Chesa P, Mak S, Huvos A, Albino AP. p53 mutations in chondrosarcoma. Diagn Mol Pathol. 1998;7(1):51–6.
33. Dobashi Y, Sugimura H, Sato A, Hirabayashi T, Kanda H, Kitagawa T, et al. Possible association of p53 overexpression and mutation with high-grade chondrosarcoma. Diagn Mol Pathol. 1993;2(4):257–63.
34. Zhou Y, Shen JK, Yu Z, Hornicek FJ, Kan Q, Duan Z. Expression and therapeutic implications of cyclin-dependent kinase 4 (CDK4) in osteosarcoma. Biochim Biophys Acta Mol Basis Dis. 2018;1864(5 Pt A):1573–82.
35. Ouyang Z, Wang S, Zeng M, Li Z, Zhang Q, Wang W, et al. Therapeutic effect of palbociclib in chondrosarcoma: implication of cyclin-dependent kinase 4 as a potential target. Cell Commun Signal. 2019;17(1):17.
36. Schrage YM, Lam S, Jochemsen AG, Cleton-Jansen AM, Taminiau AH, Hogendoorn PC, et al. Central chondrosarcoma progression is associated with pRb pathway alterations: CDK4 down-regulation and p16 overexpression inhibit cell growth in vitro. J Cell Mol Med. 2009;13(9A):2843–52.
37. Cannonier SA, Sterling JA. The role of hedgehog signaling in tumor induced bone disease. Cancers (Basel). 2015;7(3):1658–83.

38. Bruce SJ, Butterfield NC, Metzis V, Town L, McGlinn E, Wicking C. Inactivation of Patched1 in the mouse limb has novel inhibitory effects on the chondrogenic program. J Biol Chem. 2010;285(36):27967–81.
39. Wuelling M, Vortkamp A. Transcriptional networks controlling chondrocyte proliferation and differentiation during endochondral ossification. Pediatr Nephrol. 2010;25(4):625–31.
40. Panagopoulos I, Gorunova L, Bjerkehagen B, Boye K, Heim S. Chromosome aberrations and HEY1-NCOA2 fusion gene in a mesenchymal chondrosarcoma. Oncol Rep. 2014;32(1):40–4.
41. Nyquist KB, Panagopoulos I, Thorsen J, Haugom L, Gorunova L, Bjerkehagen B, et al. Whole-transcriptome sequencing identifies novel IRF2BP2-CDX1 fusion gene brought about by translocation t(1;5)(q42;q32) in mesenchymal chondrosarcoma. PLoS One. 2012;7(11):e49705.
42. Wang L, Motoi T, Khanin R, Olshen A, Mertens F, Bridge J, et al. Identification of a novel, recurrent HEY1-NCOA2 fusion in mesenchymal chondrosarcoma based on a genome-wide screen of exon-level expression data. Genes Chromosomes Cancer. 2012;51(2):127–39.
43. Broehm CJ, Wu J, Gullapalli RR, Bocklage T. Extraskeletal myxoid chondrosarcoma with a t(9;16)(q22;p11.2) resulting in a NR4A3-FUS fusion. Cancer Genet. 2014;207(6):276–80.
44. Liu P, Shen JK, Xu J, Trahan CA, Hornicek FJ, Duan Z. Aberrant DNA methylations in chondrosarcoma. Epigenomics. 2016;8(11):1519–25.
45. Liu P, Shen JK, Hornicek FJ, Liu F, Duan Z. Wnt inhibitory factor 1 (WIF1) methylation and its association with clinical prognosis in patients with chondrosarcoma. Sci Rep. 2017;7(1):1580.
46. Rubin EM, Guo Y, Tu K, Xie J, Zi X, Hoang BH. Wnt inhibitory factor 1 decreases tumorigenesis and metastasis in osteosarcoma. Mol Cancer Ther. 2010;9(3):731–41.
47. Poggi L, Casarosa S, Carl M. An eye on the Wnt inhibitory factor Wif1. Front Cell Dev Biol. 2018;6:167.
48. Martin-Orozco E, Sanchez-Fernandez A, Ortiz-Parra I, Ayala-San Nicolas M. WNT signaling in tumors: the way to evade drugs and immunity. Front Immunol. 2019;10:2854.
49. Haseeb M, Pirzada RH, Ain QU, Choi S. Wnt signaling in the regulation of immune cell and cancer therapeutics. Cells. 2019;8(11):1380.
50. Liu P, Garbutt C, Hornicek FJ, Liu F, Duan Z. Aberration of p73 promoter methylation in chondrosarcoma. Anticancer Res. 2017;37(6):2939–45.
51. Palmini G, Marini F, Brandi ML. What is new in the miRNA world regarding osteosarcoma and chondrosarcoma? Molecules. 2017;22(3):417.
52. Nugent M. microRNA and bone cancer. Adv Exp Med Biol. 2015;889:201–30.
53. Chang L, Shrestha S, LaChaud G, Scott MA, James AW. Review of microRNA in osteosarcoma and chondrosarcoma. Med Oncol. 2015;32(6):613.

54. Sun X, Chen Y, Yu H, Machan JT, Alladin A, Ramirez J, et al. Anti-miRNA oligonucleotide therapy for chondrosarcoma. Mol Cancer Ther. 2019;18(11):2021–9.
55. Bao X, Ren T, Huang Y, Sun K, Wang S, Liu K, et al. Knockdown of long non-coding RNA HOTAIR increases miR-454-3p by targeting Stat3 and Atg12 to inhibit chondrosarcoma growth. Cell Death Dis. 2017;8(2):e2605.
56. Shui X, Zhou C, Lin W, Yu Y, Feng Y, Kong J. Long non-coding RNA BCAR4 promotes chondrosarcoma cell proliferation and migration through activation of mTOR signaling pathway. Exp Biol Med (Maywood). 2017;242(10):1044–50.
57. Nicolle R, Ayadi M, Gomez-Brouchet A, Armenoult L, Banneau G, Elarouci N, et al. Integrated molecular characterization of chondrosarcoma reveals critical determinants of disease progression. Nat Commun. 2019;10(1):4622.
58. Clark JC, Dass CR, Choong PF. Development of chondrosarcoma animal models for assessment of adjuvant therapy. ANZ J Surg. 2009;79(5):327–36.
59. Meohas W, Granato RA, Guimaraes JAM, Dias RB, Fortuna-Costa A, Duarte MEL. Patient-derived xenografts as a preclinical model for bone sarcomas. Acta Ortop Bras. 2018;26(2):98–102.
60. Jacques C, Renema N, Ory B, Walkley CR, Grigoriadis AE, Heymann D. Murine models of bone sarcomas. Methods Mol Biol. 1914;2019:331–42.
61. Ho L, Stojanovski A, Whetstone H, Wei QX, Mau E, Wunder JS, et al. Gli2 and p53 cooperate to regulate IGFBP-3- mediated chondrocyte apoptosis in the progression from benign to malignant cartilage tumors. Cancer Cell. 2009;16(2):126–36.
62. Polychronidou G, Karavasilis V, Pollack SM, Huang PH, Lee A, Jones RL. Novel therapeutic approaches in chondrosarcoma. Future Oncol. 2017;13(7):637–48.
63. Speetjens FM, de Jong Y, Gelderblom H, Bovee JV. Molecular oncogenesis of chondrosarcoma: impact for targeted treatment. Curr Opin Oncol. 2016;28(4):314–22.
64. Jamil N, Howie S, Salter DM. Therapeutic molecular targets in human chondrosarcoma. Int J Exp Pathol. 2010;91(5):387–93.
65. Li L, Hu X, Eid JE, Rosenberg AE, Wilky BA, Ban Y, et al. Mutant IDH1 depletion downregulates integrins and impairs chondrosarcoma growth. Cancers (Basel). 2020;12(1):141.
66. Tiet TD, Hopyan S, Nadesan P, Gokgoz N, Poon R, Lin AC, et al. Constitutive hedgehog signaling in chondrosarcoma up-regulates tumor cell proliferation. Am J Pathol. 2006;168(1):321–30.
67. Campbell VT, Nadesan P, Ali SA, Wang CY, Whetstone H, Poon R, et al. Hedgehog pathway inhibition in chondrosarcoma using the smoothened inhibitor IPI-926 directly inhibits sarcoma cell growth. Mol Cancer Ther. 2014;13(5):1259–69.

68. Bovee JV, Hogendoorn PC, Wunder JS, Alman BA. Cartilage tumours and bone development: molecular pathology and possible therapeutic targets. Nat Rev Cancer. 2010;10(7):481–8.
69. Pacey S, Wilson RH, Walton M, Eatock MM, Hardcastle A, Zetterlund A, et al. A phase I study of the heat shock protein 90 inhibitor alvespimycin (17-DMAG) given intravenously to patients with advanced solid tumors. Clin Cancer Res. 2011;17(6):1561–70.
70. Schrage YM, Briaire-de Bruijn IH, de Miranda NF, van Oosterwijk J, Taminiau AH, van Wezel T, et al. Kinome profiling of chondrosarcoma reveals SRC-pathway activity and dasatinib as option for treatment. Cancer Res. 2009;69(15):6216–22.
71. Li J, Shen J, Wang K, Hornicek F, Duan Z. The roles of Sox family genes in sarcoma. Curr Drug Targets. 2016;17(15):1761–72.
72. Xix Congresso Nazionale S.I.C.O.O.P. Societa' Italiana Chirurghi Ortopedici Dell'Ospedalita' Privata A, Capasso L, Florio M, Lillo M, Basilico M, De Santis V, et al. Vascular endothelial growth factor expression as a biomarker of prognosis in patients with chondrosarcoma, Ewing's sarcoma and osteosarcoma. Current concepts. J Biol Regul Homeost Agents. 2019;33(2 Suppl. 1):39–43.
73. Lin C, McGough R, Aswad B, Block JA, Terek R. Hypoxia induces HIF-1alpha and VEGF expression in chondrosarcoma cells and chondrocytes. J Orthop Res. 2004;22(6):1175–81.
74. Ikegami D, Akiyama H, Suzuki A, Nakamura T, Nakano T, Yoshikawa H, et al. Sox9 sustains chondrocyte survival and hypertrophy in part through Pik3ca-Akt pathways. Development. 2011;138(8):1507–19.
75. Endo M, Matsumura T, Yamaguchi T, Yamaguchi U, Morimoto Y, Nakatani F, et al. Cyclooxygenase-2 overexpression associated with a poor prognosis in chondrosarcomas. Hum Pathol. 2006;37(4):471–6.
76. Sun X, Wei L, Chen Q, Terek RM. CXCR4/SDF1 mediate hypoxia induced chondrosarcoma cell invasion through ERK signaling and increased MMP1 expression. Mol Cancer. 2010;9:17.
77. Zhu JX, Xiao JR. SF2523 inhibits human chondrosarcoma cell growth in vitro and in vivo. Biochem Biophys Res Commun. 2019;511(3):559–65.
78. Wei R, Dean DC, Thanindratarn P, Hornicek FJ, Guo W, Duan Z. Cancer testis antigens in sarcoma: expression, function and immunotherapeutic application. Cancer Lett. 2020;479:54–60.
79. Bluman EM, Coulie PG, Xiaojuan S, Machan J, Lin C, Meitner PA, et al. Lysis of human chondrosarcoma cells by cytolytic T lymphocytes recognizing a MAGE-A3 antigen presented by HLA-A1 molecules. J Orthop Res. 2007;25(5):678–84.
80. Pollack SM, Li Y, Blaisdell MJ, Farrar EA, Chou J, Hoch BL, et al. NYESO-1/LAGE-1s and PRAME are targets for antigen specific T cells in chondrosarcoma following treatment with 5-Aza-2-deoxycitabine. PLoS One. 2012;7(2):e32165.

81. Torabi A, Amaya CN, Wians FH Jr, Bryan BA. PD-1 and PD-L1 expression in bone and soft tissue sarcomas. Pathology. 2017;49(5):506–13.
82. Tawbi HA, Burgess M, Bolejack V, Van Tine BA, Schuetze SM, Hu J, et al. Pembrolizumab in advanced soft-tissue sarcoma and bone sarcoma (SARC028): a multicentre, two-cohort, single-arm, open-label, phase 2 trial. Lancet Oncol. 2017;18(11):1493–501.
83. Paoluzzi L, Cacavio A, Ghesani M, Karambelkar A, Rapkiewicz A, Weber J, et al. Response to anti-PD1 therapy with nivolumab in metastatic sarcomas. Clin Sarcoma Res. 2016;6:24.
84. Thanindratarn P, Dean DC, Nelson SD, Hornicek FJ, Duan Z. Chimeric antigen receptor T (CAR-T) cell immunotherapy for sarcomas: from mechanisms to potential clinical applications. Cancer Treat Rev. 2020;82:101934.

3 Imaging Features of Chondrosarcoma

Jonathan Lin, Benjamin D. Levine, and Leanne L. Seeger

Introduction

Chondrosarcoma is a malignant tumor of hyaline cartilage. It can be classified as primary or secondary (arising from a benign osteochondroma or enchondroma). Primary chondrosarcoma is the third most common primary malignant bone tumor [1]. Chondrosarcoma can be further divided into different subtypes that include central, clear cell, periosteal, mesenchymal, myxoid, and dedifferentiated.

The purposes of imaging malignant bone tumors are to aid in diagnosis, evaluate local tumor extent, plan and guide biopsy sampling, and direct medical and surgical management. Initial workup for a suspected bone tumor begins with plain radiography. Plain radiographs can reveal the presence and type of matrix mineralization, aggressive bony destruction, and pathologic fractures. Advanced, cross-sectional imaging with CT and/or MRI should then be obtained. Both modalities can help determine local extent of tumor and plan biopsy sampling. The use of intravenous contrast with either modality may reveal specific enhancement patterns that may further aid in tumor characterization and help identify tumor necrosis, fluid collections, and soft tissue extent.

J. Lin (✉) · B. D. Levine · L. L. Seeger
Department of Radiology, UCLA Health System, Los Angeles, CA, USA
e-mail: jolin@mednet.ucla.edu; blevine@mednet.ucla.edu; lseeger@mednet.ucla.edu

F. J. Hornicek (ed.), *Chondrosarcoma*,
https://doi.org/10.1007/978-3-030-74572-1_3

Central Chondrosarcoma

Central chondrosarcoma, also known as intramedullary chondrosarcoma, is the most common chondrosarcoma subtype. It commonly presents in the fourth to fifth decades of life and occurs twice as frequently in males as in females [1]. Histologically, central chondrosarcoma can be classified as low, intermediate, or high grade. Aggressive imaging features typically correspond with the grading classification. Higher grade lesions generally have higher risk of local recurrence and metastasis [1].

Long bones of the appendicular skeleton are most commonly involved with central chondrosarcoma, with up to 35% of cases occurring in the femur, followed by the humerus and tibia [1, 2]. Of long bone lesions, half occur at the metaphysis, followed by the diaphysis (36%) and epiphysis (16%) [3]. Lesions can also occur proximally and along the axial skeleton, most commonly in the pelvis (25%) and less frequently in the ribs, scapula, and sternum [1]. Central chondrosarcoma of the pelvis is often large at presentation and commonly occurs at the region of the fused triradiate cartilage [1, 2]. Cases involving ribs typically occur at the anterior costochondral junctions [1]. Rarely does central chondrosarcoma occur in the bones of hands and feet. Differentiation between a low-grade chondrosarcoma and an enchondroma of the hands or feet is challenging on imaging, as both entities may display endosteal scalloping [3]. An associated soft tissue mass and clear cortical destruction are suggestive of malignancy [3].

On plain radiographs, central chondrosarcoma appears as a mixed lytic and sclerotic lesion (Fig. 3.1). As with most benign and malignant cartilaginous lesions, central chondrosarcoma often demonstrates the characteristic ring-and-arc chondroid matrix mineralization pattern [1]. Low-grade lesions may appear geographic with lobular margins. Endosteal scalloping, cortical penetration, and a soft tissue mass may also be seen. Moth-eaten or permeative bony destructive patterns are aggressive radiologic features that suggest high-grade chondrosarcoma or dedifferentiation [1]. Pathologic fractures are seen in up to 17% of cases [1] (Fig. 3.2).

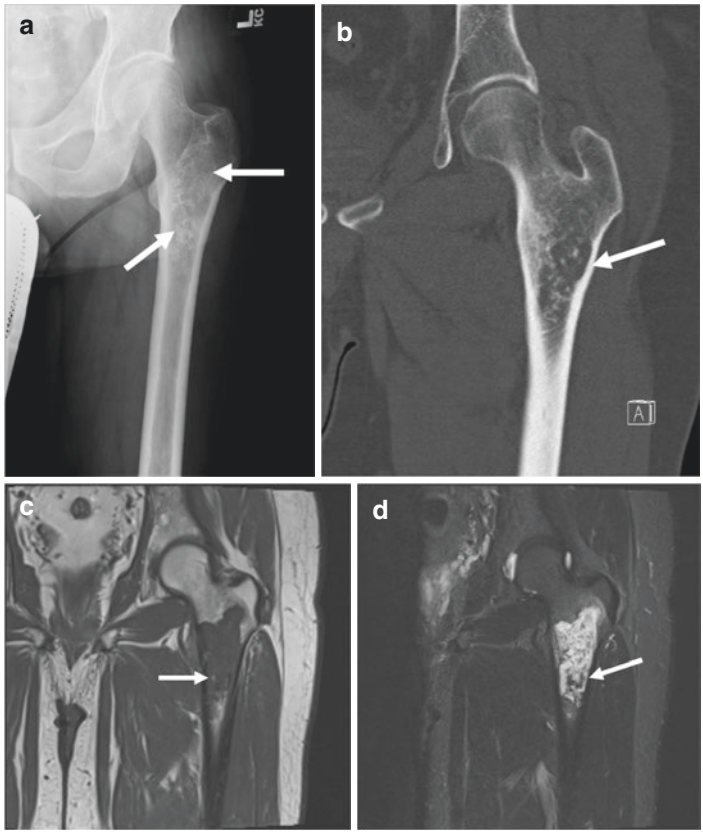

Fig. 3.1 Central chondrosarcoma, grade 2: 64-year-old man with a mixed lytic and sclerotic lesion of the proximal femur. (**a**) AP radiograph of the femur shows cartilaginous mineralization in the proximal femur (arrows). (**b**) Coronal CT image also demonstrates cartilaginous mineralization and mild endosteal scalloping of the cortex (arrow). (**c**) Coronal T1W MR image shows a hypointense lobulated mass with subtle speckled hyperintense foci of trapped bone marrow fat (arrow). (**d**) Coronal STIR MR image shows a heterogeneously hyperintense mass with hypointense cartilaginous calcifications (arrow)

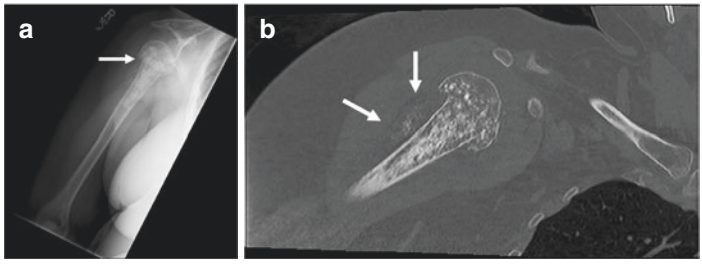

Fig. 3.2 Central chondrosarcoma, grade 1: 61-year-old female with a pathologic fracture of the humerus. (**a**) AP radiograph of the humerus shows a fracture of the surgical neck (arrow) with sclerotic regions in the proximal humerus and adjacent soft tissue. (**b**) Coronal CT image further characterizes the areas of sclerosis as cartilaginous calcifications and shows an adjacent soft tissue mass with similar calcifications (arrows)

On both MRI and CT, central chondrosarcoma appears as a lobulated mass with cartilaginous features. On MRI, there is typically low to intermediate signal intensity on T1-weighted imaging. Within the lesion, there may be small speckled foci of T1 hyperintensity, representing trapped yellow marrow [1, 4]. On T2-weighted imaging, hyperintense lobules of hyaline cartilage separated by low-intensity fibrovascular septae are commonly seen [1]. Matrix mineralization will appear dark in all MR sequences. CT imaging is useful in characterizing matrix mineralization that would be typical of cartilage, extent of cortical destruction, and presence of soft tissue involvement. Contrast-enhanced CT and MRI typically show mild peripheral and septal enhancement [1] (Fig. 3.3).

Aggressive features on cross-sectional imaging include cortical destruction and the presence of a soft tissue mass (Fig. 3.4). On MRI, loss of the lobular architecture and of the entrapped yellow marrow suggest higher grade chondrosarcoma [4]. Aggressive lesions may also demonstrate central non-enhancing areas, which correspond to hemorrhagic cystic changes or necrosis [4].

Bone scintigraphy and [^{18}F]fluoro-2-deoxy-D-glucose positron emission tomography (^{18}FDG-PET) imaging may also be used to distinguish chondrosarcoma from a benign chondral lesion. On scintigraphy, chondrosarcoma often demonstrates heterogeneous uptake that is greater than that of the anterior iliac crest [3]. On

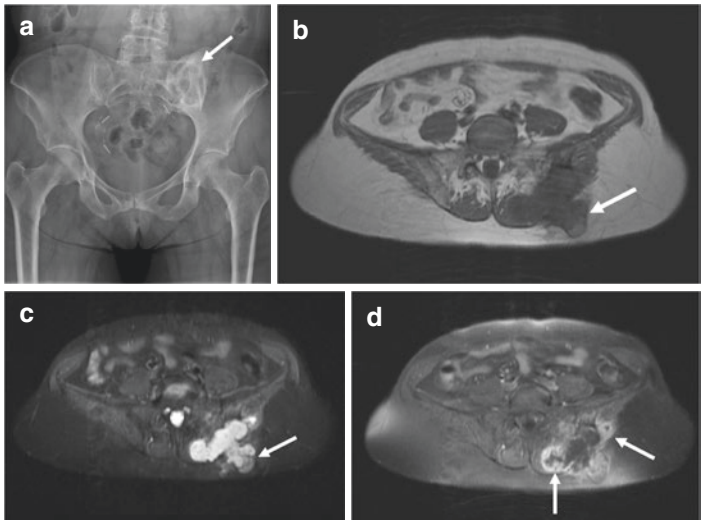

Fig. 3.3 Central chondrosarcoma, grade 2: 60-year-old female with focal sclerosis of a left iliac bone lesion. (**a**) AP radiograph of the pelvis shows a predominantly sclerotic mass centered along left sacroiliac joint (arrow). (**b**, **c**) Axial T1W and STIR MR images show a lobulated mass arising from the posterior iliac bone with cortical destruction and extension into the adjacent soft tissue (arrows). The high STIR signal suggests a cartilaginous lesion. (**d**) Axial contrast-enhanced T1W FS MR image shows the characteristic peripheral and lobular enhancement pattern of a cartilaginous tumor (arrows)

^{18}FDG-PET imaging, chondrosarcoma has a maximum standardized uptake value (SUV) greater than 2.0 [5]. Higher SUV is associated with higher grade lesions and may correspond to an increased rate of recurrence or metastasis [6].

Secondary Chondrosarcoma

Secondary chondrosarcoma arises from a preexisting benign chondral lesion (Fig. 3.5), usually an osteochondroma or enchondroma [1, 2].

Osteochondroma is the most common benign chondral bone neoplasm and usually develops along the bone growth plate [7]. Malignant transformation into chondrosarcoma occurs in 1% of

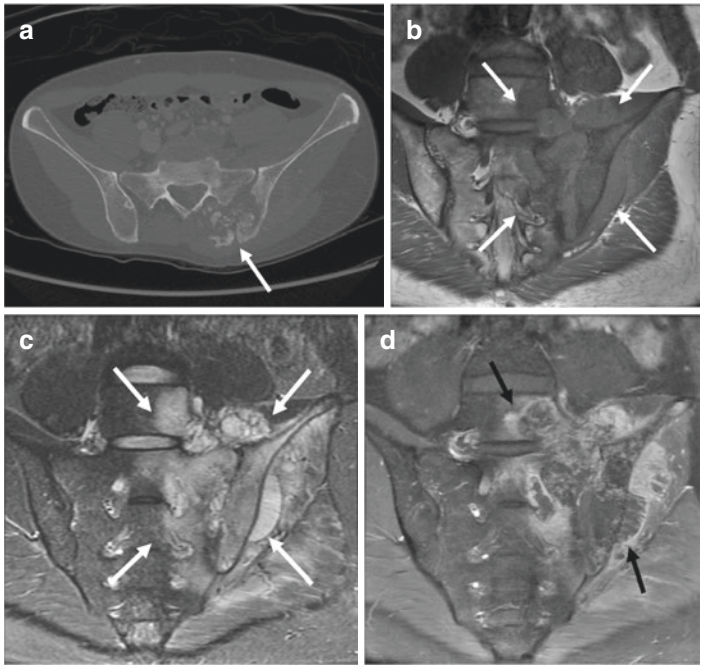

Fig. 3.4 Central chondrosarcoma, grade 3. 32-year-old male with an aggressive osseous lesion of the sacrum. (**a**) Axial CT image shows an osseous lesion in the left sacrum and posterior iliac bone, with cartilaginous mineralization and cortical destruction (arrow). (**b**), (**c**), and (**d**) Oblique coronal T1W, STIR, and contrast-enhanced T1W FS MR images of the sacrum show tumor extent, involving the adjacent osseous and soft tissue structures (white arrows). Signal characteristics are that of a cartilaginous lesion, hyperintense on STIR and with peripheral, lobular enhancement (black arrows)

solitary osteochondromas and 3–5% in hereditary multiple exostoses [7]. A majority of these transformed chondrosarcomas are of low histologic grade. Malignant transformation more frequently occurs in lesions of the pelvis, hips, and shoulders [7].

On radiographs, growth of a preexisting osteochondroma in a skeletally mature individual, cortical loss, and focal radiolucencies within the lesion suggest malignant change [7]. On CT and MRI, a thickened cartilage cap of greater than 3 cm is a highly sensitive

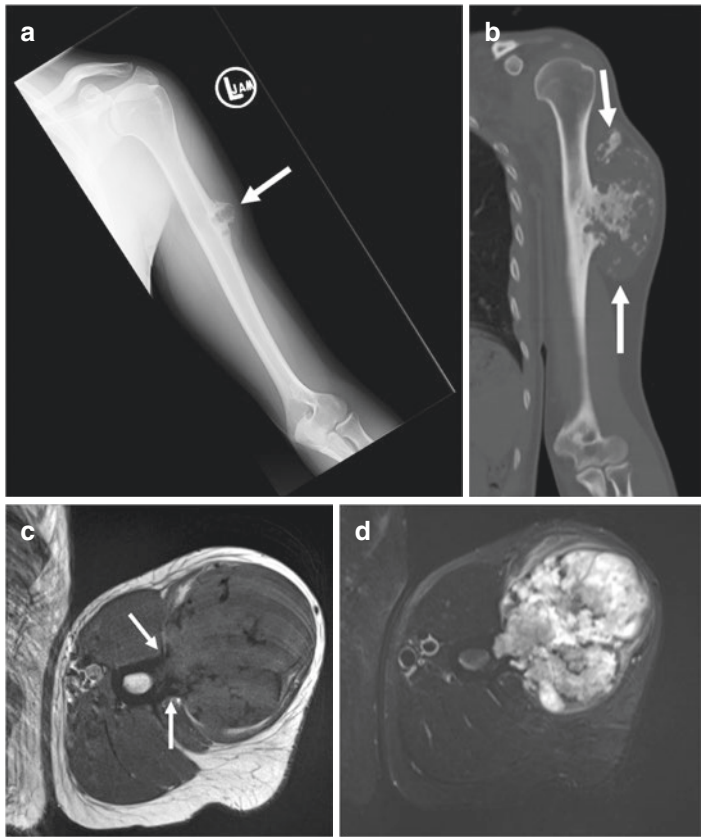

Fig. 3.5 Secondary periosteal chondrosarcoma: 20-year-old female with an enlarging humeral diaphyseal lesion. (**a**) AP radiograph of the humerus shows a cortically based, expansile diaphyseal lesion (arrow). Biopsy pathology showed features consistent with juxtacortical chondroma. (**b**) Coronal CT image obtained 12 years later demonstrates interval growth with the cartilaginous calcified mass extending into the surrounding soft tissue (arrows). (**c**) and (**d**) Axial T1W and T2W FS MR images show a cartilaginous lesion arising from the cortex (arrows). These findings are consistent with periosteal chondrosarcoma, secondary from the original chondroma

and specific distinguishing feature of a secondary chondrosarcoma [8]. Though transformed lesions will have increased tracer uptake on bone scintigraphy, they cannot be distinguished from benign osteochondromas with active osteochondral formation [7].

Enchondromas are the second most common benign chondral lesion of bone and can also transform into secondary chondrosarcomas [1, 9] (Fig. 3.6). Enchondromas most commonly occur in the bones of the hands but also within appendicular long bones and small

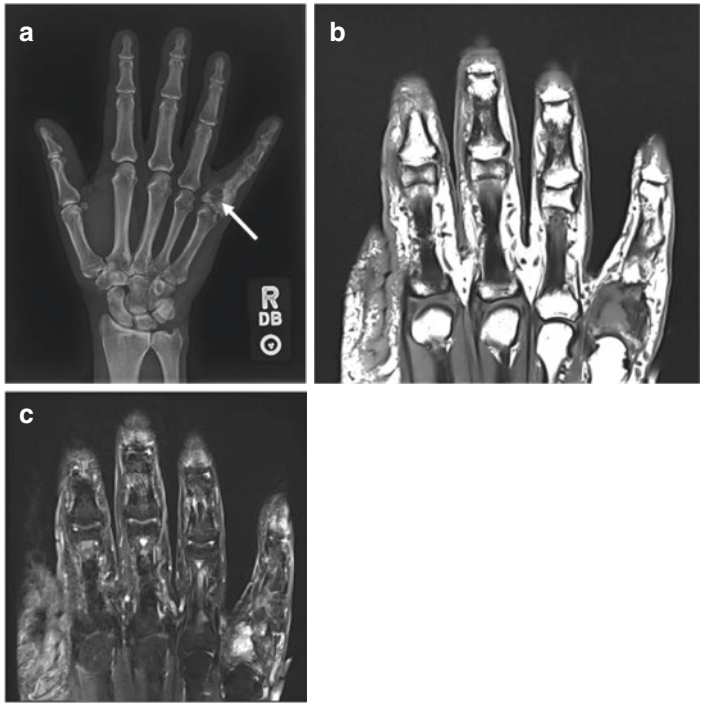

Fig. 3.6 Secondary chondrosarcoma, grade 2: 65-year-old male with history of an excised enchondroma of fifth proximal phalanx with a recurrent mass. (**a**) PA radiograph of the right hand shows an expansile lytic lesion of the fifth proximal phalanx with thinned surrounding cortex (arrow). (**b**) and (**c**) Coronal T1W and T2W FS MR images show a lobulated, expansile lesion with high T2 signal extending through the cortex. Given history of an excised enchondroma and new cortical involvement, findings suggest secondary chondrosarcoma

bones of the feet [9]. Like chondrosarcoma, the majority of enchondromas of the long bones occur in the diaphysis or metaphysis [3]. Given their common locations and similar appearances, reliably differentiating between a low-grade chondrosarcoma and an enchondroma may be challenging both with imaging and histology [10, 11].

There are several characteristic imaging features that can help distinguish chondrosarcomas from enchondromas. Chondrosarcomas are typically larger, with a mean size of 8 cm, compared to enchondromas, with a mean size of 5 cm [3]. Deep endosteal scalloping of greater than two thirds of the cortical thickness suggests chondrosarcoma; however, extensive scalloping can also be seen in eccentrically located enchondromas [3, 12]. Bone scintigraphy has been reported to assist in differentiation, as enchondromas demonstrate homogeneous uptake similar or less than that of the anterior iliac crest, while tracer uptake of chondrosarcomas is greater and heterogeneous in appearance [3].

Clear Cell Chondrosarcoma

Clear cell chondrosarcoma is a low-grade subtype and represents 2% of all chondrosarcomas [1]. Histologically, it demonstrates abundant clear cytoplasm and a lobulated architecture [1, 13]. It presents in the third to fifth decades and affects males twice as frequently [1, 13]. Clear cell chondrosarcoma is most commonly an epiphyseal lesion of the long bones, occurring in the femur in up to 68% of cases, followed by the proximal humerus (23%) [13]. Clear cell chondrosarcoma uncommonly occurs in the flat bones of the axial skeleton [1, 13].

On radiographs, clear cell chondrosarcoma typically appears as a well-defined geographic epiphyseal lytic lesion that can extend to the metaphysis [1, 13] (Fig. 3.7). A sclerotic rim may be present in 20% of cases [1]. About one third of lesions demonstrate typical chondroid matrix mineralization [1]. Lesions of the proximal humerus may appear mildly expansile and show indistinct margination and pathologic fractures [13].

Clear cell chondrosarcoma on T1-weighted MR images demonstrates heterogeneous low signal intensity. There may be areas

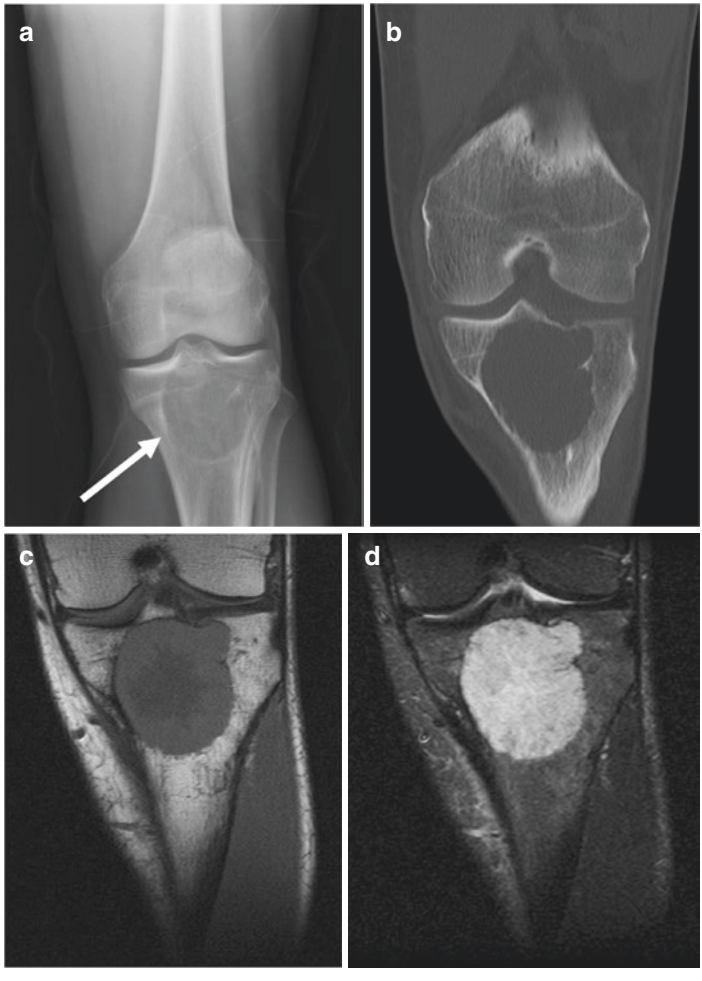

Fig. 3.7 Clear cell chondrosarcoma: 49-year-old male with a proximal tibial lytic lesion. (**a**) AP radiograph of the knee shows a geographic lytic lesion of the proximal tibial epiphysis and metaphysis (arrow). (**b**) Coronal CT image shows cortical thinning. There is no significant matrix mineralization. (**c**) and (**d**) Coronal T1W and STIR MR images show a lobulated high STIR signal mass with peripheral small lobulations and without significant bone marrow edema. (**e**) Coronal contrast-enhanced T1W FS MR image shows intense enhancement and central necrosis (arrow)

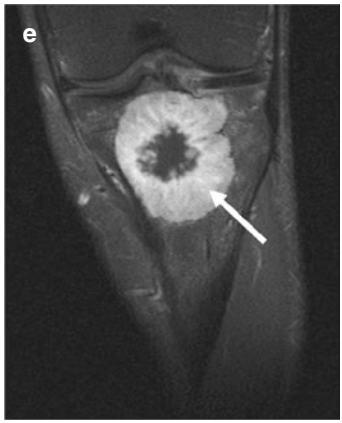

Fig. 3.7 (continued)

of T1 hyperintensity, representing intralesional hemorrhage [13]. On T2-weighted imaging, the lesions are heterogeneously bright with areas of intralesional cystic changes [13]. The enhancement pattern is typically heterogeneous [13]. There may be secondary aneurysmal bone cystic change [13].

Periosteal Chondrosarcoma

Periosteal chondrosarcoma arises from the surface of the bone and represents up to 4% of all chondrosarcomas [1]. It presents in the second to fourth decades and has a slight male predominance [1]. About half of cases are located in the femur, commonly at the posterior aspect of the distal femoral metaphysis or metadiaphysis [2, 14]. Periosteal chondrosarcoma less commonly occurs in the humerus (24%) and tibia (14%) and rarely in the pelvis, fibula, and rib [2].

Radiographs commonly depict a mass arising from the surface of the bone with characteristic chondroid matrix mineralization [14] (Fig. 3.5). Though thickening or thinning of the underlying cortex is commonly seen, periosteal chondrosarcoma does not demonstrate complete cortical destruction [14]. Periosteal buttressing of the involved cortex can be present [15]. The tumor may demonstrate a calcified shell [14].

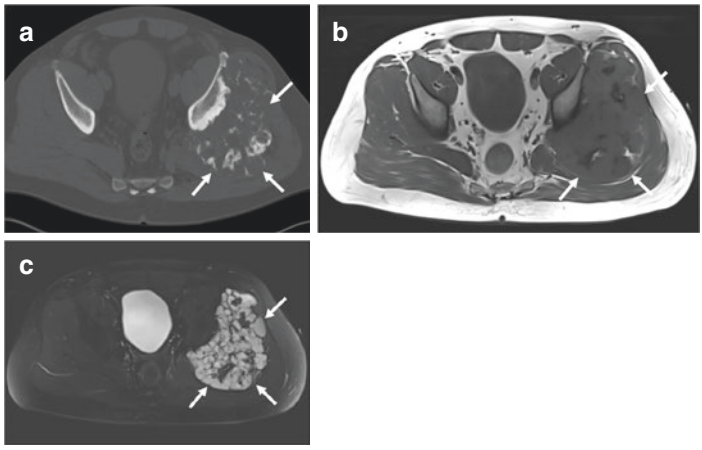

Fig. 3.8 Periosteal chondrosarcoma: 35-year-old male with history of a left gluteal mass. (**a**) Axial CT image shows a large soft tissue mass with cartilaginous mineralization arising from the iliac wing cortex (arrows). (**b**) and (**c**) Axial T1W and T2W FS MR images show a large, lobulated and septated cartilaginous mass (arrows) arising from the cortex of the iliac bone with otherwise normal underlying bone marrow

On CT imaging, periosteal chondrosarcoma appears as a round- or oval-shaped mass adjacent to a thickened or thinned but intact cortex [14, 15] (Fig. 3.8). Chondroid matrix mineralization is typically well appreciated on CT, and the noncalcified portions of the tumor are of low attenuation [1].

Periosteal chondrosarcoma has the characteristic signal intensity and internal architecture of a low-grade cartilaginous lesion on MRI. It presents with low to intermediate heterogeneous T1 signal intensity and T2 hyperintense lobulations separated by hypointense septae [1, 15]. Periosteal chondrosarcoma demonstrates peripheral and septal enhancement on contrast-enhanced imaging [15]. Intramedullary extension is rare [14].

Mesenchymal Chondrosarcoma

Mesenchymal chondrosarcoma represents 2–13% of all chondrosarcomas [1]. It presents in the second to fourth decades and equally affects males and females [1, 16]. Mesenchymal chondrosarcoma

can arise from bone or within soft tissue, with 25–70% originating from bone [1]. Unlike central chondrosarcoma, mesenchymal chondrosarcoma more commonly affects the axial skeleton. Up to 30% of cases occur in the craniofacial region, specifically the maxilla and mandible. Within the appendicular skeleton, the femur is most commonly affected, in 15–23% of cases [1].

Skeletal mesenchymal chondrosarcoma demonstrates aggressive radiographic features, including ill-defined margins and moth-eaten or permeative bony destruction [1, 2] (Fig. 3.9). Two thirds of lesions demonstrate cartilaginous matrix mineralization [1, 2]. On CT imaging, there may be foci of low attenuation within the tumor that may represent internal necrosis [1].

Skeletal mesenchymal chondrosarcoma has low to intermediate T1 and intermediate T2 signal intensity on MRI [1]. A distinguishing feature from other chondrosarcomas is the enhancement

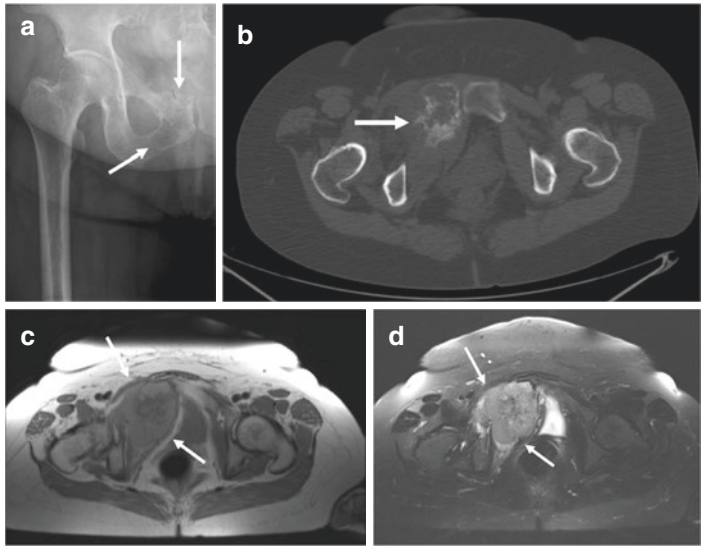

Fig. 3.9 Skeletal mesenchymal chondrosarcoma: 48-year-old female with a right pelvic lesion. (**a**) AP radiograph of the right hip shows a subtle ill-defined lucency in the right parasymphyseal pubic bone with expansion (arrows). (**b**) Axial CT image shows a destructive lytic lesion with cartilaginous mineralization (arrow). (**c**) and (**d**) T1W and T2W FS MR images show the lobulated, destructive pubic bone mass (arrows)

pattern. Enhancement is diffuse, either homogeneous or heterogeneous, which is different from the typical septal and peripheral enhancement pattern of other chondrosarcomas [1] (Fig. 3.10). Unlike other subtypes, mesenchymal chondrosarcoma may also have serpentine vessel flow voids within the lesion [1].

Extraskeletal mesenchymal chondrosarcoma has been reported to occur within head and neck, including the orbits and meninges as well as the soft tissues of the lower extremity, specifically the thigh [1]. Imaging typically depicts a nonspecific soft tissue mass with variable patterns of internal calcifications [16–18] (Fig. 3.11).

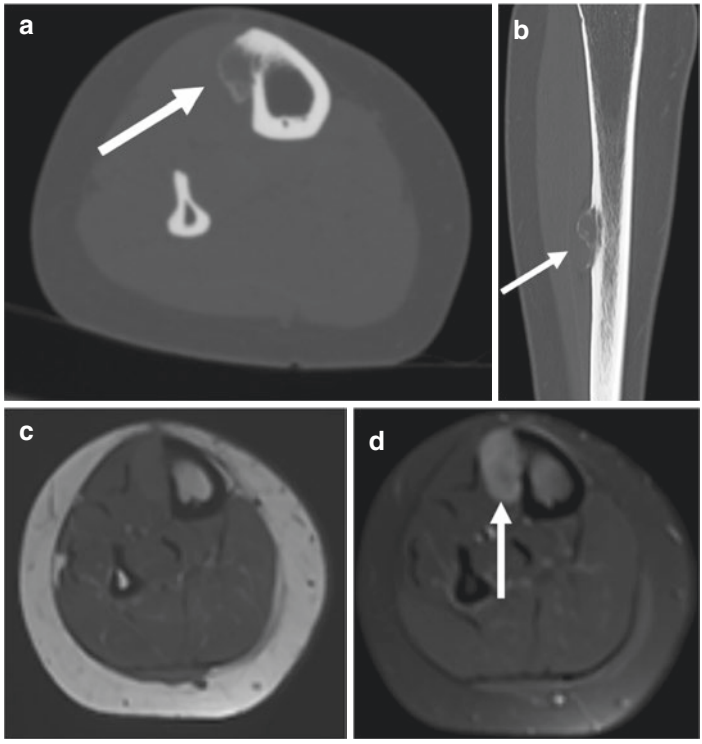

Fig. 3.10 Skeletal mesenchymal chondrosarcoma: 21-year-old female with a tibial mass. (**a**) and (**b**) Axial and coronal CT images show an aggressive juxtacortical lesion along the mid tibial shaft (arrows). (**c**) and (**d**) Axial T1W and contrast-enhanced T1W FS MR images show uniform enhancement of the lesion (arrow), a characteristic finding of mesenchymal chondrosarcoma

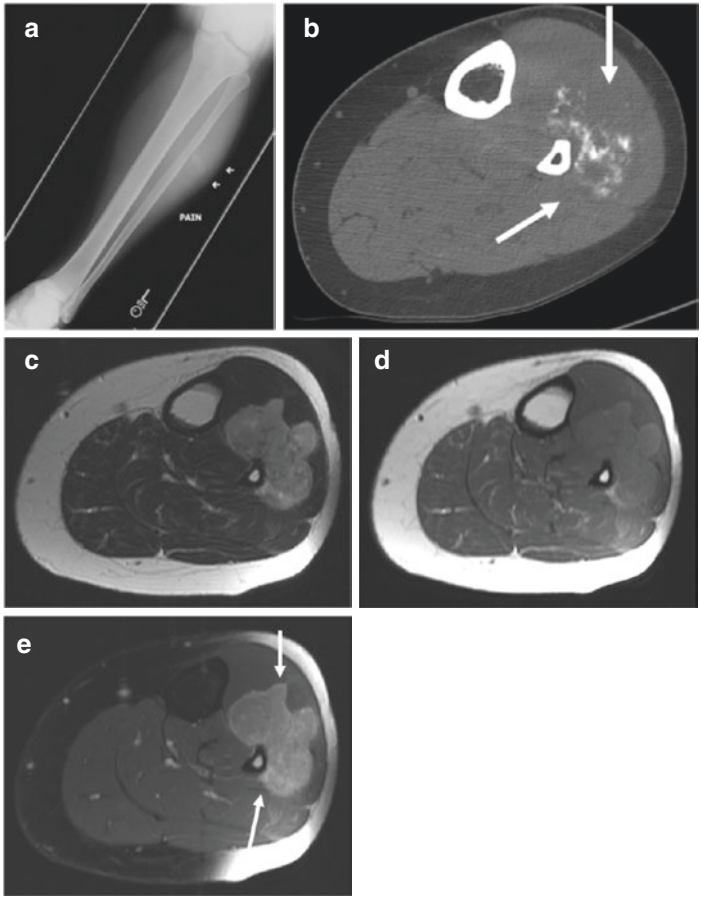

Fig. 3.11 Extraskeletal mesenchymal chondrosarcoma: 32-year-old female with a mass of the left lower leg. (**a**) AP radiograph of the lower leg shows a soft tissue mass with amorphous calcification. (**b**) Axial CT image better characterizes the punctate and course calcifications within the anterior muscle compartment (arrows). The underlying tibia and fibula are normal. (**c**) Axial T2W MR image shows a heterogeneously hyperintense mass surrounding the fibula. (**d**) and (**e**) Axial T1W and contrast-enhanced T1W FS MR images show mildly heterogeneous but diffuse enhancement (arrows), a characteristic finding of mesenchymal chondrosarcoma

Noncalcified portions are isodense on CT imaging. These extraskeletal tumors generally show low T1 and high T2 signal intensity but are heterogeneous in appearance due to variable amounts of low signal matrix mineralization [17, 18]. A limited number of published cases with contrast-enhanced MR imaging depict diffuse heterogeneous enhancement [1, 18].

Myxoid Chondrosarcoma

Myxoid chondrosarcoma is a rare intermediate-grade subtype of chondrosarcoma that occurs either within soft tissue or bone [1]. It is the most common extraskeletal chondrosarcoma and frequently occurs within the soft tissues of the proximal extremities, particularly within the thigh [1]. The mean age for presentation is 50 years, and there is a male predominance [1]. Myxoid chondrosarcoma of the bone is much less common. When occurring within the bone, the femur is most often affected [1].

Myxoid chondrosarcoma is composed of myxoid and gelatinous nodules separated by fibrous septae and often demonstrates intratumoral hemorrhage [19]. MR imaging features correlate with the histologic composition and architecture (Figs. 3.12 and 3.13). Of extraskeletal myxoid chondrosarcoma, the intratumoral hemorrhage often results in a heterogeneous intermediate to high T1 signal intensity [19]. On T2-weighted images, these tumors are predominantly hyperintense, due to the high water content of the myxoid nodules [1, 19]. Enhancement pattern is peripheral and septal but can also appear heterogeneous [1, 19].

Dedifferentiated Chondrosarcoma

Dedifferentiated chondrosarcoma is a subtype of chondrosarcoma with an associated high-grade non-cartilaginous component. It is theorized that a portion of the tumor undergoes anaplastic transformation into a non-cartilaginous lesion [1, 20]. The high-grade non-cartilaginous component is osteosarcoma in 70% of cases, followed by fibrosarcoma [20].

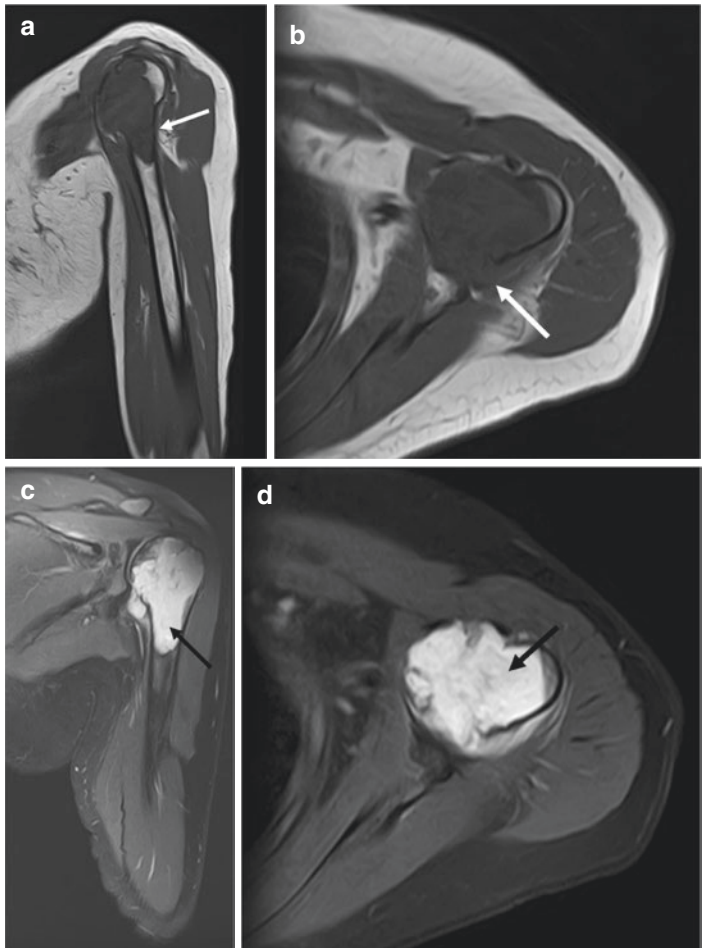

Fig. 3.12 Skeletal myxoid chondrosarcoma: 26-year-old female with a left proximal humeral lesion. (**a**) and (**b**) Sagittal and axial T1W; (**c**) and (**d**) coronal and axial T2W FS MR images show an expansile lobulated mass causing cortical thinning (white arrows). The prominent T2 hyperintense signal is likely due to the high water content of the myxoid component (black arrows)

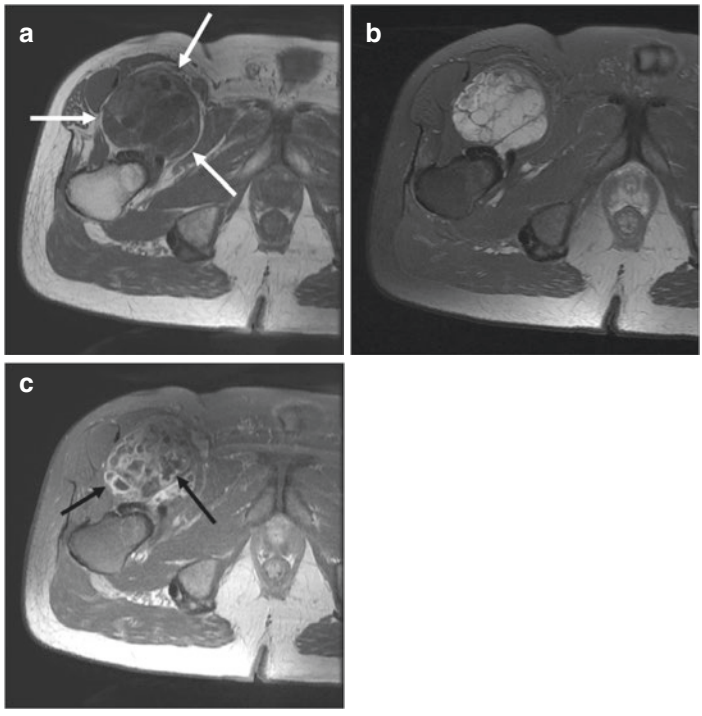

Fig. 3.13 Extraskeletal myxoid chondrosarcoma: 67-year-old male with a proximal thigh mass. (**a**) and (**b**) Axial T1W and proton density FS MR images show a large intramuscular lobulated mass with multiple septations (white arrows). There is no involvement of the underlying femur. (**c**) Axial contrast-enhanced T1W FS MR image shows a peripheral and septal pattern of enhancement (black arrows). The MR signal characteristics are that of a cartilaginous lesion

Dedifferentiated chondrosarcoma represents up to 10% of all chondrosarcomas [1]. It presents in the fifth to seventh decades and occurs equally in males and females [1, 20]. The femur is the most common location, in up to 55% of cases, followed by the pelvis (23%) and humerus (10%) [20]. Almost all cases of dedifferentiated chondrosarcoma occur within the medullary bone [1, 20].

The imaging appearance of dedifferentiated chondrosarcoma is variable, depending on the extent of the high-grade non-cartilaginous lesion [1]. An aggressive cartilaginous lesion with cortical destruction is frequently seen [20]. A majority of dedif-

ferentiated chondrosarcomas show areas of chondroid matrix mineralization, reflecting the underlying cartilaginous component [20]. Pathologic fractures occur in about a third of cases [1, 20].

Tumor bimorphism is a key distinguishing feature of dedifferentiated chondrosarcoma. It is defined as a cartilaginous tumor with an associated region that shows non-cartilaginous features [20] (Fig. 3.14). Common appearances include a dominant lytic focus or soft tissue mass with little mineralization adjacent to or

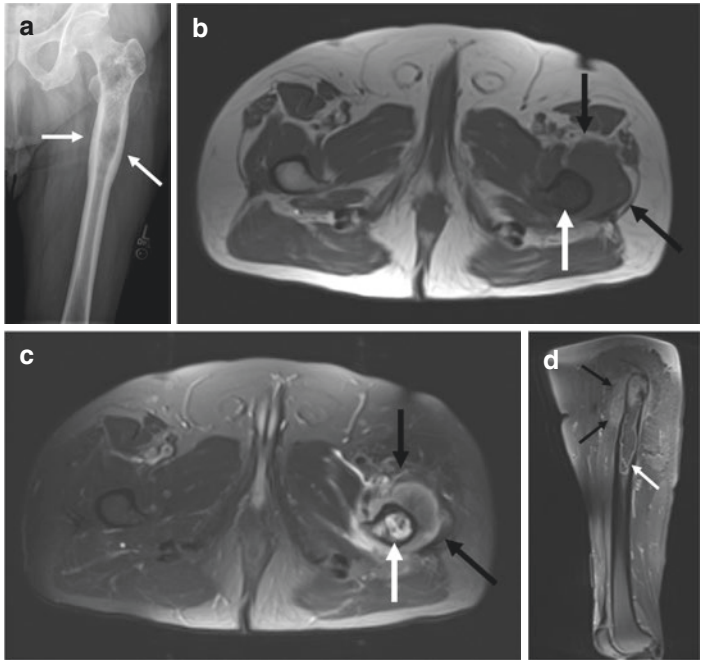

Fig. 3.14 Dedifferentiated chondrosarcoma with an osteosarcoma component: 69-year-old male with worsening left thigh pain. (**a**) AP radiograph of the left femur shows an ill-defined mixed lytic and sclerotic expansile lesion with cortical thickening (white arrows). (**b**) and (**c**) Axial T1W and T2W FS MR images show an intramedullary cartilaginous mass (white arrows) with an associated soft tissue component (black arrows). (**d**) Sagittal contrast-enhanced T1W MR image shows peripheral enhancement of the intramedullary cartilaginous component (white arrow) and uniform enhancement of the soft tissue mass (black arrows). The difference in enhancement patterns is suggestive of tumor bimorphism with a non-cartilaginous component

within a chondral tumor [20, 21]. Portions of the tumor representing chondrosarcoma will demonstrate the characteristic cartilaginous T2 hyperintensity, while non-cartilaginous components will have variable signal intensity. Contrast-enhanced imaging shows the typical cartilaginous septal and peripheral enhancement adjacent to a region of diffuse enhancement, representing the non-cartilaginous component [1].

References

1. Murphey MD, Walker EA, Wilson AJ, Kransdorf MJ, Temple HT, Gannon FH. From the archives of the AFIP: imaging of primary chondrosarcoma: radiologic-pathologic correlation. Radiographics. 2003;23(5):1245–78.
2. Douis H, Saifuddin A. The imaging of cartilaginous bone tumours. II. Chondrosarcoma. Skeletal Radiol. 2013;42(5):611–26.
3. Murphey MD, Flemming DJ, Boyea SR, Bojescul JA, Sweet DE, Temple HT. Enchondroma versus chondrosarcoma in the appendicular skeleton: differentiating features. Radiographics. 1998;18(5):1213–37; quiz 44–5.
4. Yoo HJ, Hong SH, Choi JY, Moon KC, Kim HS, Choi JA, et al. Differentiating high-grade from low-grade chondrosarcoma with MR imaging. Eur Radiol. 2009;19(12):3008–14.
5. Feldman F, Van Heertum R, Saxena C, Parisien M. 18FDG-PET applications for cartilage neoplasms. Skelet Radiol. 2005;34(7):367–74.
6. Brenner W, Conrad EU, Eary JF. FDG PET imaging for grading and prediction of outcome in chondrosarcoma patients. Eur J Nucl Med Mol Imaging. 2004;31(2):189–95.
7. Murphey MD, Choi JJ, Kransdorf MJ, Flemming DJ, Gannon FH. Imaging of osteochondroma: variants and complications with radiologic-pathologic correlation. Radiographics. 2000;20(5):1407–34.
8. Bernard SA, Murphey MD, Flemming DJ, Kransdorf MJ. Improved differentiation of benign osteochondromas from secondary chondrosarcomas with standardized measurement of cartilage cap at CT and MR imaging. Radiology. 2010;255(3):857–65.
9. Douis H, Saifuddin A. The imaging of cartilaginous bone tumours. I. Benign lesions. Skeletal Radiol. 2012;41(10):1195–212.
10. Eefting D, Schrage YM, Geirnaerdt MJ, Le Cessie S, Taminiau AH, Bovée JV, et al. Assessment of interobserver variability and histologic parameters to improve reliability in classification and grading of central cartilaginous tumors. Am J Surg Pathol. 2009;33(1):50–7.

11. Group SLICaEDSS. Reliability of histopathologic and radiologic grading of cartilaginous neoplasms in long bones. J Bone Joint Surg Am. 2007;89(10):2113–23.
12. Bui KL, Ilaslan H, Bauer TW, Lietman SA, Joyce MJ, Sundaram M. Cortical scalloping and cortical penetration by small eccentric chondroid lesions in the long tubular bones: not a sign of malignancy? Skelet Radiol. 2009;38(8):791–6.
13. Collins MS, Koyama T, Swee RG, Inwards CY. Clear cell chondrosarcoma: radiographic, computed tomographic, and magnetic resonance findings in 34 patients with pathologic correlation. Skelet Radiol. 2003;32(12):687–94.
14. Vanel D, De Paolis M, Monti C, Mercuri M, Picci P. Radiological features of 24 periosteal chondrosarcomas. Skelet Radiol. 2001;30(4):208–12.
15. Chaabane S, Bouaziz MC, Drissi C, Abid L, Ladeb MF. Periosteal chondrosarcoma. AJR Am J Roentgenol. 2009;192(1):W1–6.
16. Nakashima Y, Unni KK, Shives TC, Swee RG, Dahlin DC. Mesenchymal chondrosarcoma of bone and soft tissue. A review of 111 cases. Cancer. 1986;57(12):2444–53.
17. Shapeero LG, Vanel D, Couanet D, Contesso G, Ackerman LV. Extraskeletal mesenchymal chondrosarcoma. Radiology. 1993;186(3):819–26.
18. Hashimoto N, Ueda T, Joyama S, Araki N, Beppu Y, Tatezaki S, et al. Extraskeletal mesenchymal chondrosarcoma: an imaging review of ten new patients. Skelet Radiol. 2005;34(12):785–92.
19. Tateishi U, Hasegawa T, Nojima T, Takegami T, Arai Y. MRI features of extraskeletal myxoid chondrosarcoma. Skelet Radiol. 2006;35(1):27–33.
20. Littrell LA, Wenger DE, Wold LE, Bertoni F, Unni KK, White LM, et al. Radiographic, CT, and MR imaging features of dedifferentiated chondrosarcomas: a retrospective review of 174 de novo cases. Radiographics. 2004;24(5):1397–409.
21. MacSweeney F, Darby A, Saifuddin A. Dedifferentiated chondrosarcoma of the appendicular skeleton: MRI-pathological correlation. Skelet Radiol. 2003;32(12):671–8.

Part II

Skeletal and Extraskeletal Chondrosarcoma

4 Chondrosarcomas: Conventional and Secondary

Christopher M. Hart, Zachary Burke, Alex Nobori, and Bennett L. Davis

Introduction

Chondrosarcoma is a malignant cartilage-forming tumor of bone. It represents a spectrum of disease defined by histologic confirmation of a cartilaginous neoplasm in the correct clinical and radiographic context. These tumors range from locally aggressive, low-grade cartilaginous tumors to highly malignant dedifferentiated chondrosarcoma. Accurate diagnosis of these tumors, particularly low-grade lesions which can histologically resemble benign cartilaginous tumors, can be challenging and requires a combination of clinical, radiologic, and histologic findings.

Chondrosarcomas are classified as primary if they arise de novo from bone and secondary if they develop from the malignant transformation of a preexisting benign lesion. The most common

C. M. Hart (✉) · Z. Burke
Department of Orthopaedic Surgery, UCLA, Los Angeles, CA, USA
e-mail: chart@mednet.ucla.edu; zburke@mednet.ucla.edu

A. Nobori
Department of Pathology, UCLA, Los Angeles, CA, USA
e-mail: anobori@mednet.ucla.edu

B. L. Davis
Department of Radiology, UCLA, Los Angeles, CA, USA
e-mail: bldavis@mednet.ucla.edu

F. J. Hornicek (ed.), *Chondrosarcoma*,
https://doi.org/10.1007/978-3-030-74572-1_4

histopathologic type is termed "conventional," a primary tumor that usually arises in the axillary or proximal appendicular skeleton within the medullary canal. Conventional chondrosarcoma is the second most common malignant bone tumor. In addition to the conventional type, there are rare variants of primary chondrosarcoma, including clear cell, juxtacortical, mesenchymal, and dedifferentiated chondrosarcoma [1].

Tumor location is increasingly recognized as an important prognostic factor. In 2020, the World Health Organization adopted the designation of "central atypical cartilaginous tumor" when referring to tumors of the appendicular skeleton (long and short tubular bones) and reserved the term "chondrosarcoma grade 1" for tumors involving the axial skeleton, including the pelvis, scapula, and skull base [2]. The rationale underlying this nomenclature is that low-grade cartilaginous tumors of the appendicular skeleton behave in a locally aggressive manner and do not metastasize; in contrast, tumors of the axial skeleton have malignant potential and a worse prognosis. In contrast to other primary bone sarcomas such as osteosarcoma or Ewing sarcoma, chondrosarcomas are typically slowly progressing due the relative rarity of high-grade histology.

Conventional Chondrosarcoma

Conventional chondrosarcoma of bone accounts for roughly 85% of all chondrosarcomas and is characterized histologically by lobules of hyaline cartilage with variable degrees of cellularity, myxoid changes, and calcification [3, 4]. Higher grade tumors may have minimal discernable cartilage and are difficult to distinguish from other high-grade sarcomas. The majority of conventional chondrosarcomas arise within the medullary canal and may be referred to as central chondrosarcomas [3]. A minority of primary chondrosarcomas occur as peripheral tumors (<1%) at the surface of bone without a preexisting lesion and are designated juxtacortical or periosteal chondrosarcoma [5, 6].

Clinical Presentation

Conventional chondrosarcomas have a predilection for the proximal appendicular and axial skeleton. It occurs most commonly in the proximal femur, ilium, proximal humerus, distal femur, and ribs. Conventional chondrosarcoma most commonly occurs in patients over 50 with peak incidence in the fifth to seventh decades of life. It occurs more commonly in males, with a 2 to 1 male preponderance [4, 7].

Imaging Characteristics

Radiographs of cartilaginous lesions typically show characteristic changes often referred to as "popcorn" or "ringlet" calcifications in a pattern of "arcs and whorls." Findings suggestive of malignancy include cortical destruction, soft tissue extension, and permeative changes such as a "moth-eaten" pattern (Fig. 4.1) [4].

Pathology, Treatment, and Prognosis

Histopathologic grade remains the best prognostic indicator for chondrosarcoma [8]. Most authors grade chondrosarcomas from grade I to III: low, intermediate, and high [8–11]. Dedifferentiated chondrosarcoma is a unique histological entity that portends a poor prognosis. When evaluating a cartilaginous bone tumor, the critical histologic feature is the presence of lobules of cartilage permeating through and entrapping native bone trabeculae. Other features, including increased cellularity and mitotic activity, may also be seen. However, even low-grade chondrosarcomas can show a cytologic appearance nearly identical to benign hyaline cartilage (Figs. 4.2 and 4.3). Therefore, correlation with imaging studies is essential. Grade 3 chondrosarcomas demonstrate more unique histologic findings, including increased cellularity, myxoid stroma, poorly differentiated spindle-cell morphology, and increased mitotic activity (Fig. 4.4). Approximately 90% of conventional

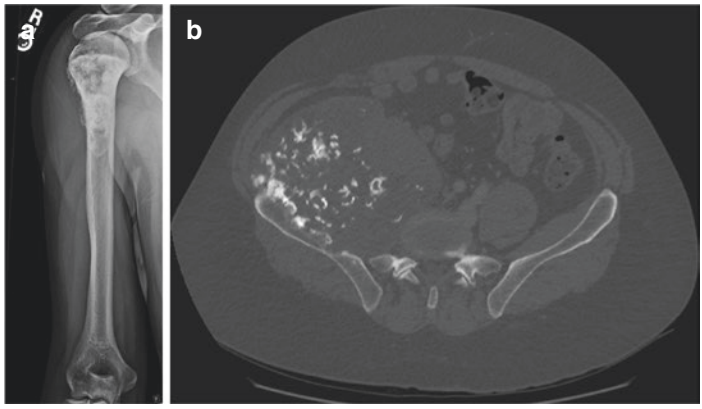

Fig. 4.1 Conventional chondrosarcoma. (**a**) Right humerus radiograph: Typical appearance of an intramedullary chondrosarcoma demonstrating endosteal scalloping, extraosseous extension, and internal chondroid matrix typified by a pattern of "arcs and whorls." (**b**) Axial CT image of the upper pelvis: Typical CT appearance of a chondrosarcoma. The aggressive soft tissue mass involving the right iliac wing extends anteriorly into the pelvis and demonstrates the "arcs and whorls" matrix typical of chondrosarcomas. Though clearly seen in this image, the matrix calcifications may be too subtle to be seen with conventional radiography making CT the modality of choice

chondrosarcomas are low- to intermediate-grade tumors [9]. Grade I lesions in the appendicular skeleton are considered to be locally aggressive without metastatic potential. In the axial skeleton, grade I lesions generally have a worse outcome, but individual prognosis is dependent on location [12, 13]. The mainstay of treatment is wide surgical resection. A 5-year survival for patients with grade I tumors is 89% compared to 57% for the combined group of patients with grade II and III lesions [4, 10]. Dedifferentiated chondrosarcoma has a reported 5-year survival of 18% [14].

Secondary Chondrosarcoma

Secondary chondrosarcomas arise from preexisting cartilaginous lesions. The most common precursor lesion is an osteochondroma, from which 88% of all secondary chondrosarcomas arise

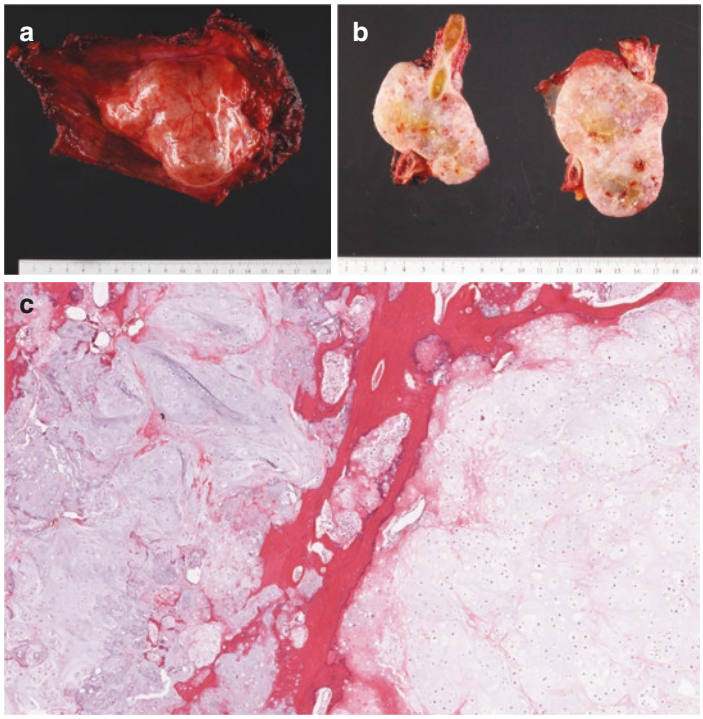

Fig. 4.2 Chondrosarcoma, grade 1. (**a**) Gross examination shows a well-demarcated mass arising from the left chest wall. (**b**) Cut sections of the tumor show variegated cut surfaces ranging from a yellow and gelatinous to a chalky, white appearance. Scattered foci of hemorrhage are seen. (**c**) Histologic sections show a lobulated proliferation of relatively bland hyaline cartilage permeating into and entrapping native bone, consistent with grade 1 chondrosarcoma

[15–20]. Secondary chondrosarcoma can also arise in Ollier disease (multiple enchondromas) and Maffucci syndrome (multiple enchondromas associated with soft tissue hemangioma) [20]. Other benign cartilaginous lesions that have been reported in case reports as precursor lesions for secondary chondrosarcoma include solitary enchondroma, synovial chondromatosis, and chondromyxoid fibroma [17, 21–23].

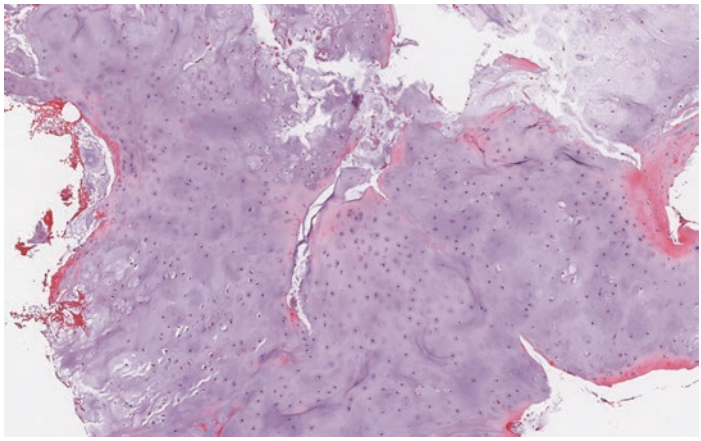

Fig. 4.3 Enchondroma. Similar to Fig. 4.2c, sections from this enchondroma show lobules of mildly cellular hyaline cartilage. Radiographic correlation together with the histologic appearance is required to make this diagnosis

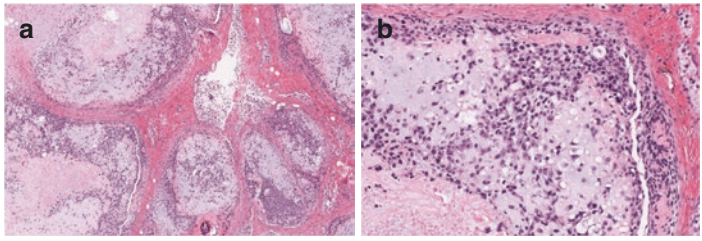

Fig. 4.4 Chondrosarcoma, grade 3. (**a**) In contrast to Figs. 4.2c and 4.3, a low power view of sections from this grade 3 chondrosarcoma shows a more cellular proliferation with foci of necrosis. Spindled tumor cells condense at the periphery of the lobules. (**b**) Higher power view shows poorly differentiated spindle cells set in a myxoid matrix. Mitotic activity is increased

Histologically, secondary chondrosarcoma resembles primary conventional chondrosarcoma. In both, the entire tumor is composed of cartilaginous tissue. However, there are important differences in both clinical presentation and behavior. Additionally, the development from a benign chondroid tumor may point to important genetic differences between primary and secondary chondro-

sarcomas. Therefore, despite histologic similarities between secondary and conventional chondrosarcoma, these two entities should be considered separately.

Clinical Presentation

The most common presenting clinical symptom is pain with a palpable mass [20]. New-onset pain and/or increasing size of a known osteochondroma (especially after skeletal maturity) raises the possibility of an enlarging cartilage cap and malignant transformation. The mean age of patients presenting with secondary chondrosarcoma is 34 years, which is notably younger than those who develop the primary conventional type [15–19]. The most common site of involvement is the pelvis, followed by proximal femur, scapula, and proximal humerus.

Imaging Characteristics

Imaging offers important clues in the diagnosis of secondary chondrosarcoma. On plain radiography, osteochondromas have clear bony borders, including along the subchondral bone beneath the cartilaginous cap. Malignant transformation of the cartilage cap in secondary chondrosarcomas may show surface irregularity and blurriness of the bone-cartilage interface reflecting the increased invasive nature of the lesion. Other radiographic markers that suggest malignant transformation include an osteochondroma larger than 5 cm, increase in size of an osteochondroma over time, and a cartilage cap >2 cm [20]. CT and MRI are important in demonstrating malignant features, especially in characterizing the features of the cartilage cap of osteochondromas. It is generally agreed upon that the malignant transformation occurs within the cartilage tissue of the cap and not the bony tissue that makes up the base or stalk of the osteochondroma. Plain radiography alone may fail to show the size of the cartilage cap and can lead to a missed diagnosis. It should be noted that the often cited >2 cm thickness of the cartilage cap as a marker of malignant

transformation should be considered as an average and not an absolute criterion for diagnosis. A wide range of cap thickness for secondary chondrosarcomas has been reported in the literature, including a series of 107 patients with a mean thickness of 3.9 cm (range, 0.5–15.0 cm) [15]. For this reason, a qualitative assessment in addition to a precise measurement of cap thickness is essential for an accurate diagnosis.

Pathology

The diagnosis of secondary chondrosarcoma is confirmed through histologic evaluation of biopsy material in the correct radiographic and clinical context. Grading is similar to primary chondrosarcomas and includes grades I–III. As with primary conventional chondrosarcoma, distinguishing benign lesions from low-grade cartilage tumors can be very difficult and often requires clinical and imaging characteristics to make the diagnosis. Histologic analysis alone has been shown to have a high rate of inter- and intraobserver variability in diagnosis further highlighting the importance of adjunct clinical and radiographic data [24]. The majority of secondary chondrosarcomas are low grade. In the largest case series reported in the literature, up to three fourths were grade I and nearly all the remainder grade II with only 1% of reported cases defined as grade III [15–20].

Genetics and Mutations

The genetic basis for the development of benign cartilaginous lesions may help elucidate subsequent malignant degeneration. Approximately 15% of patients with osteochondromas present with multiple lesions characteristic of the autosomal dominant multiple hereditary exostosis (MHE) genetic disorder [25]. The risk of development of secondary peripheral chondrosarcoma is estimated at less than 1% for sporadic osteochondroma and 5% for MHE [26]. Biallelic inactivation of the EXT1 and EXT2 genes is observed in the majority of both inherited and sporadic cases of

osteochondroma [27, 28]. The EXT proteins are required for polymerization of heparan sulfate chains forming hyaline cartilage. Interestingly, the majority of cells in secondary peripheral chondrosarcoma that develop from osteochondromas (which are EXT-negative) have been shown to be EXT-positive [29]. It is hypothesized that EXT-negative cells in osteochondroma create an extracellular mutation-promoting environment which leads to the development of malignant chondrosarcoma in adjacent EXT-positive cells [25]. This pathway has not been fully characterized and is not currently a target for therapeutic intervention.

Enchondromas are benign cartilaginous neoplasms that develop within the medullary canal, unlike osteochondromas which develop on the periphery. Mutations in the isocitrate dehydrogenase (IDH) 1 and 2 genes are present in 85% of the enchondromatosis-associated disorders Ollier disease and Maffucci syndrome and 50% of solitary enchondromas [30]. The risk of transformation into secondary central chondrosarcoma is approximately 40% for Ollier disease and up to 53% in Maffucci syndrome [25, 31]. It has also been shown that IDH mutations are present in 52–59% of central chondrosarcomas as well as 57% of dedifferentiated chondrosarcomas. IDH inhibitors are currently being investigated as treatment for advanced chondrosarcoma [32, 33].

Surveillance, Prognosis, and Treatment

There is little consensus regarding surveillance protocols for patients with benign cartilage tumors. Most authors agree that isolated enchondromas represent the lowest risk of malignant transformation and only require yearly radiographs in the absence of worsening pain or other symptoms [20]. Serial radiographic examination is generally recommended for patients with MHE, Ollier disease, and Maffucci syndrome [34, 35]. Patients with large, isolated osteochondromas located centrally such as in the pelvis should also be considered to be at higher risk and therefore candidates for surveillance. For appendicular osteochondromas without features concerning for transformation,

surveillance is often performed only in the setting of enlarging mass or new symptoms.

Treatment for secondary chondrosarcoma is wide surgical resection. Radiation and chemotherapy are not effective, and marginal resection has been shown to have a high rate of recurrence [18]. In general, the prognosis for secondary chondrosarcoma is very good, and these tumors rarely metastasize [36]. Overall survival at 5 years is approximately 90% [15, 16, 19].

Rare Chondrosarcoma Subtypes

In addition to conventional chondrosarcoma, there are several rare subtypes accounting for between 10% and 15% of all chondrosarcomas [3].

Dedifferentiated chondrosarcoma is characterized by a high-grade non-cartilaginous sarcoma immediately adjacent to a low-grade conventional chondrosarcoma. The average age of presentation is between 50 and 60 years. Imaging showing a cartilaginous component with an adjacent aggressive lytic lesion invading soft tissues is characteristic [4]. The prognosis is dismal, with a 5-year overall survival of just 18% [37]. The rare genetic reports on dedifferentiated chondrosarcoma show that the two components share identical genetic mutations, with additional aberrations in the anaplastic portion [38]. This suggests that both portions are derived from a common precursor cell before diverging [3]. Wide surgical resection is the primary treatment [3]. Chemotherapy may be considered and has been shown by some authors to be more effective than in low-grade chondrosarcoma [39].

Clear cell chondrosarcoma is a low-grade malignant tumor which derives its name from the clear and abundant cytoplasm seen on light microscopy (Fig. 4.5). The tumor accounts for 1–2% of all chondrosarcomas [4]. It affects males more often than females (2.6:1) and usually presents in the epiphysis of long bones, classically the femoral head. Metastases are rare but have been reported to occur up to 24 years following presentation, mandating the need for long-term follow-up [40]. A 5-year overall

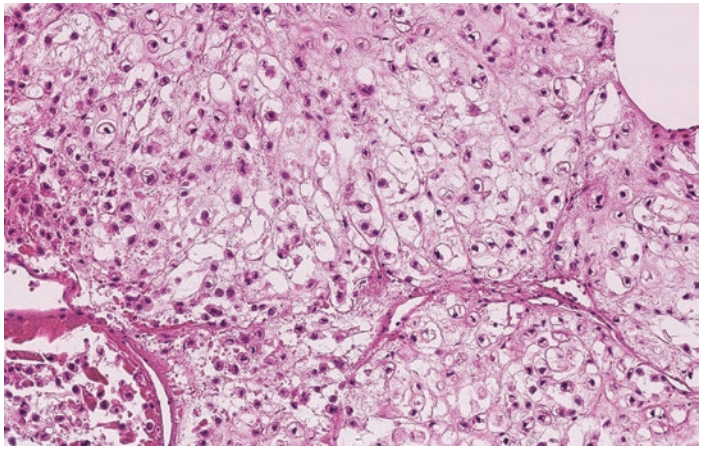

Fig. 4.5 Clear cell chondrosarcoma. Sections show a cellular proliferation composed of tumor cells with abundant clear to slightly eosinophilic cytoplasm. The cells contain distinct cytoplasmic membranes with large, centrally placed nuclei. By definition, this tumor is classified as low grade

survival has been reported at 62% [41]. Wide surgical resection is recommended.

Mesenchymal chondrosarcoma is a rare highly malignant tumor that arises in both bone and soft tissue. Peak incidence is in the second to third decades of life [42]. It can occur in both soft tissue and bone with a predilection for the axial skeleton, most commonly the craniofacial region, followed by the pelvis and vertebrae. Histologically, it is characterized by areas of well-differentiated hyaline cartilage mixed with undifferentiated small round blue cells [3]. By definition, it is considered a high-grade tumor and is not graded on a case-by-case basis by histologic features. A 5-year overall survival has been reported at 37% [41]. Chemotherapy may be considered and has been shown by some authors to be more effective than in low-grade chondrosarcoma [39].

Periosteal (juxtacortical) chondrosarcoma accounts for less than 2% of all chondrosarcomas and occurs on the surface of the bone [4]. Peak incidence is in the third to fourth decade of life,

and it commonly occurs in the metaphysis of long bones, especially the femur and humerus. Histologically, it is similar to conventional chondrosarcoma, usually grade 1 or grade 2. Invasion of the underlying cortex or size greater than 5 cm is required for diagnosis [2]. Prognosis is excellent with 5-year overall survival of approximately 83% [43].

References

1. Compton ML, Cates JM. Evidence-based tumor staging of skeletal chondrosarcoma. Am J Surg Pathol. 2020;44(1):111–9.
2. WHO Classification of Tumours Editorial Board. WHO classification of tumours of soft tissue and bone. 5th ed. Lyon: IARC Press; 2020.
3. Gelderblom H, Hogendoorn PCW, Dijkstra SD, et al. The clinical approach towards chondrosarcoma. Oncologist. 2008;13(3):320–9.
4. Ro JY, Kim MJ, Cho KJ, Ayala AG. Chondrosarcoma: with updates on molecular genetics. Sarcoma. 2011. https://doi.org/10.1155/2011/405437.
5. Schajowicz F. Juxtacortical chondrosarcoma. J Bone Jt Surg - Ser B. 1977. https://doi.org/10.1302/0301-620x.59b4.270475.
6. Schajowicz F, Sobin L. World Health Organization. International histological classification of tumors. Histological typing of bone tumors. 2nd Edi. Berlin: Spinger; 1993.
7. Leddy LR, Holmes RE. Chondrosarcoma of bone. Cancer Treat Res. 2014. https://doi.org/10.1007/978-3-319-07323-1_6.
8. Evans HL, Ayala AG, Romsdahl MM. Prognostic factors in chondrosarcoma of bone. A clinicopathologic analysis with emphasis on histologic grading. Cancer. 1977. https://doi.org/10.1002/1097-0142(197708)40:2<818::AID-CNCR2820400234>3.0.CO;2-B.
9. Mirra JM, Gold R, Downs J, Eckhardt JJ. A new histologic approach to the differentiation of enchondroma and chondrosarcoma of the bones. A clinicopathologic analysis of 51 cases. Clin Orthop Relat Res. 1985. https://doi.org/10.1097/00003086-198512000-00035.
10. Björnsson J, McLeod RA, Unni KK, Ilstrup DM, Pritchard DJ. Primary chondrosarcoma of long bones and limb girdles. Cancer. 1998. https://doi.org/10.1002/(SICI)1097-0142(19981115)83:10<2105::AID-CNCR9>3.0.CO;2-U.
11. Sanerkin NG. The diagnosis and grading of chondrosarcoma of bone a combined cytologic and histologic approach. Cancer. 1980. https://doi.org/10.1002/1097-0142(19800201)45:3<582::AID-CNCR2820450326>3.0.CO;2-#.
12. Fromm J, Klein A, Baur-Melnyk A, Knösel T, Lindner L, Birkenmaier C, Roeder F, Jansson V, Dürr HR. Survival and prognostic factors in conven-

tional central chondrosarcoma. BMC Cancer. 2018;18(1):849. https://doi.org/10.1186/s12885-018-4741-7.
13. Bindiganavile S, Han I, Yun JY, Kim HS. Long-term outcome of chondrosarcoma: a single institutional experience. Cancer Res Treat. 2015;47(4):897–903.
14. Strotman PK, Reif TJ, Kliethermes SA, Sandhu JK, Nystrom LM. Dedifferentiated chondrosarcoma: a survival analysis of 159 cases from the SEER database (2001-2011). J Surg Oncol. 2017;116(2):252–7.
15. Ahmed AR, Tan TS, Unni KK, Collins MS, Wenger DE, Sim FH. Secondary chondrosarcoma in osteochondroma: report of 107 patients. Clin Orthop Relat Res. 2003. https://doi.org/10.1097/01.blo.0000069888.31220.2b.
16. Altay M, Bayrakci K, Yildiz Y, Erekul S, Saglik Y. Secondary chondrosarcoma in cartilage bone tumors: report of 32 patients. J Orthop Sci. 2007. https://doi.org/10.1007/s00776-007-1152-z.
17. Coley BL, Higinbotham NL. Secondary chondrosarcoma. Ann Surg. 1954. https://doi.org/10.1097/00000658-195405000-00003.
18. Garrison RC, Unni KK, McLeod RA, Pritchard DJ, Dahlin DC. Chondrosarcoma arising in osteochondroma. Cancer. 1982. https://doi.org/10.1002/1097-0142(19820501)49:9<1890::AID-CNCR2820490923>3.0.CO;2-U.
19. Wuisman PIJM, Jutte PC, Ozaki T. Secondary chondrosarcoma in osteochondromas. Medullary extension in 15 of 45 cases. Acta Orthop Scand. 1997. https://doi.org/10.3109/17453679708996185.
20. Lin PP, Moussallem CD, Deavers MT. Secondary chondrosarcoma. J Am Acad Orthop Surg. 2010. https://doi.org/10.5435/00124635-201010000-00004.
21. Müller PE, Dürr HR, Nerlich A, Pellengahr C, Maier M, Jansson V. Malignant transformation of a benign enchondroma of the hand to secondary chondrosarcoma with isolated pulmonary metastasis. Acta Chir Belg. 2004. https://doi.org/10.1080/00015458.2004.11679569.
22. Sah AP, Geller DS, Mankin HJ, et al. Malignant transformation of synovial chondromatosis of the shoulder to chondrosarcoma. J Bone Jt Surg. 2007. https://doi.org/10.2106/jbjs.f.00511.
23. Peiper M, Zornig C. Chondrosarcoma of the thumb arising from a solitary enchondroma. Arch Orthop Trauma Surg. 1997. https://doi.org/10.1007/BF00393722.
24. Eefting D, Schrage YM, Geirnaerdt MJA, et al. Assessment of interobserver variability and histologic parameters to improve reliability in classification and grading of central cartilaginous tumors. Am J Surg Pathol. 2009. https://doi.org/10.1097/PAS.0b013e31817eec2b.
25. Chow WA. Chondrosarcoma: biology, genetics, and epigenetics. F1000Research. 2018. https://doi.org/10.12688/f1000research.15953.1.
26. Wicklund CL, Pauli RM, Johnston D, Hecht JT. Natural history study of hereditary multiple exostoses. Am J Med Genet. 1995. https://doi.org/10.1002/ajmg.1320550113.

27. Ahn J, Lüdecke HJ, Lindow S, et al. Cloning of the putative tumour suppressor gene for hereditary multiple exostoses (EXT1). Nat Genet. 1995. https://doi.org/10.1038/ng1095-137.
28. Stickens D, Clines G, Burbee D, et al. The EXT2 multiple exostoses gene defines a family of putative tumour suppressor genes. Nat Genet. 1996. https://doi.org/10.1038/ng0996-25.
29. De Andrea CE, Reijnders CMA, Kroon HM, et al. Secondary peripheral chondrosarcoma evolving from osteochondroma as a result of outgrowth of cells with functional EXT. Oncogene. 2012. https://doi.org/10.1038/onc.2011.311.
30. Amary MF, Damato S, Halai D, et al. Ollier disease and Maffucci syndrome are caused by somatic mosaic mutations of IDH1 and IDH2. Nat Genet. 2011. https://doi.org/10.1038/ng.994.
31. Schwartz HS, Zimmerman NB, Simon MA, Wroble RR, Millar EA, Bonfiglio M. The malignant potential of enchondromatosis. J Bone Jt Surg Am. 1987. https://doi.org/10.2106/00004623-198769020-00016.
32. Amary MF, Bacsi K, Maggiani F, et al. IDH1 and IDH2 mutations are frequent events in central chondrosarcoma and central and periosteal chondromas but not in other mesenchymal tumours. J Pathol. 2011. https://doi.org/10.1002/path.2913.
33. Urban DJ, Martinez NJ, Davis MI, et al. Assessing inhibitors of mutant isocitrate dehydrogenase using a suite of pre-clinical discovery assays. Sci Rep. 2017. https://doi.org/10.1038/s41598-017-12630-x.
34. Murphey MD, Choi JJ, Kransdorf MJ, Flemming DJ, Gannon FH. Imaging of osteochondroma: variants and complications with radiologic-pathologic correlation. Radiographics. 2000;20(5):1407–34.
35. Pierz KA, Womer RB, Dormans JP, Stanitski CL. Pediatric bone tumors: osteosarcoma, Ewing's sarcoma, and chondrosarcoma associated with multiple hereditary osteochondromatosis. J Pediatr Orthop. 2001. https://doi.org/10.1097/01241398-200105000-00028.
36. Merchan EC, Sanchez-Herrera S, Gonzalez JM. Secondary chondrosarcoma. Four cases and review of the literature. Acta Orthop Belg. 1993;59(1):76–80.
37. Strotman PK, Reif TJ, Kliethermes SA, Sandhu JK, Nystrom LM. Dedifferentiated chondrosarcoma: a survival analysis of 159 cases from the SEER database (2001–2011). J Surg Oncol. 2017. https://doi.org/10.1002/jso.24650.
38. Röpke M, Boltze C, Neumann HW, Roessner A, Schneider-Stock R. Genetic and epigenetic alterations in tumor progression in a dedifferentiated chondrosarcoma. Pathol Res Pract. 2003. https://doi.org/10.1078/0344-0338-00443.
39. Italiano A, Mir O, Cioffi A, Palmerini E, Piperno-Neumann S, Perrin C, Chaigneau L, Penel N, Duffaud F, Kurtz JE, Collard O. Advanced chondrosarcomas: role of chemotherapy and survival. Ann Oncol. 2013;24(11):2916–22.

40. Donati D, Yin JQ, Colangeli M, et al. Clear cell chondrosarcoma of bone: long time follow-up of 18 cases. Arch Orthop Trauma Surg. 2008. https://doi.org/10.1007/s00402-007-0353-4.
41. Amer KM, Munn M, Congiusta D, Abraham JA, Basu Mallick A. Survival and prognosis of chondrosarcoma subtypes: SEER database analysis. J Orthop Res. 2020. https://doi.org/10.1002/jor.24463.
42. Nakashima Y, Unni KK, Shives TC, Swee RG, Dahlin DC. Mesenchymal chondrosarcoma of bone and soft tissue. A review of 111 cases. Cancer. 1986. https://doi.org/10.1002/1097-0142(19860615)57:12<2444::AID-CNCR2820571233>3.0.CO;2-K.
43. Papagelopoulos PJ, Galanis EC, Mavrogenis AF, et al. Survivorship analysis in patients with periosteal chondrosarcoma. Clin Orthop Relat Res. 2006. https://doi.org/10.1097/01.blo.0000194684.40624.a8.

5 Primary Soft Tissue Chondrosarcoma

Brooke Crawford

Introduction

Chondrosarcoma is a primary bone tumor, with <1% occurrence of extraskeletal classic chondrosarcoma [27], unless there is a recurrence with soft tissue of a resection bed. Due to their histopathologic appearance, however, there are two soft tissue sarcomas that have been named chondrosarcoma, although they are distinct genetically and behaviorally. In this chapter, we will explore specifics of these primary soft tissue "chondrosarcomas," extraskeletal myxoid chondrosarcoma, and mesenchymal chondrosarcoma.

Mesenchymal Chondrosarcoma

History

Mesenchymal chondrosarcoma has the relatively unique quality of occurring as a primary soft tissue or bone tumor. It was originally described in 1959 by Lichtenstein and Bernstein as a primary bone tumor [2]. The first case of primary extraskeletal

B. Crawford (✉)
Department of Orthopaedic Surgery, UCLA, Santa Monica, CA, USA
e-mail: brookecrawford@mednet.ucla.edu

F. J. Hornicek (ed.), *Chondrosarcoma*,
https://doi.org/10.1007/978-3-030-74572-1_5

mesenchymal chondrosarcoma was reported in 1964; data now varies widely on the proportion of soft tissue occurrence, ranging from 14% to 73% although no prognostic difference has been detected between soft tissue and bony locations [27].

Epidemiology

Only 2–9% of chondrosarcomas are mesenchymal [27], with the extraskeletal tumors making up only 1% of all chondrosarcomas [2]. The 10-year overall survival rate has a wide range in the literature, from 20% to 67% [27], with better prognosis seen in young patients with tumors in the head and neck region [2], and median event-free survival has been documented as 57 months [32]. Most patients present in the second or third decade of life [20].

Presentation and Diagnosis

Patients usually present with localized swelling, pain, and rarely a pathologic fracture [26]. Soft tissue masses that are deep to fascia, over 5 cm, and growing rapidly need imaging and biopsy before intervention [7]. MRI is the axial imaging modality typically used for a soft tissue mass, but CT scan can be considered as well.

For primary soft tissue mesenchymal chondrosarcoma tumors, CT imaging shows a well-circumscribed mass [2] with granular, ring-and-arc calcifications in approximately one third of cases [20]. These calcifications, when present, are very helpful in diagnosis as biopsy can have sampling error showing only the round cell component, leading to difficulty in accurately classifying the tissue [26] (Fig. 5.1). T1 magnetic resonance imaging of the tumor reveals isointensity with muscle and hypointensity compared to fat, and T2 sequences show hyperintensity to muscle, heterogeneity and may have serpentine voids, correlating with a the vascular pattern seen on histology [20].

Biopsy is typically performed by image-guided core needle. Mesenchymal chondrosarcoma has a chondroprogenitor origin and displays a biphasic pattern [2, 20]. There are undifferentiated small round cells, which mimic other round cell sarcomas such as Ewing's and exhibit a hemangiopericytomatous vascular proliferation [2, 20]. The round cell component shows high cellularity,

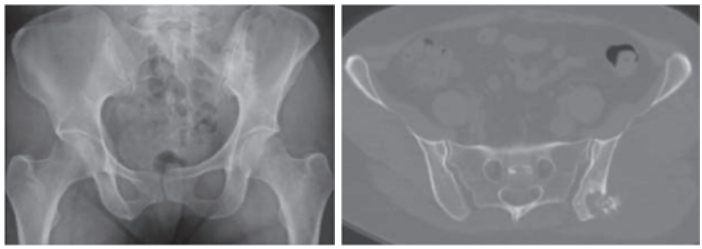

Fig. 5.1 A 49-year-old female with soft tissue mass in left upper gluteal region noticed after trauma. XR shows calcification in the corresponding location, and CT shows bony erosion, with accompanying soft tissue mass, ring, and arc calcifications consistent with cartilaginous lesion. Whether this was a primary bone tumor with soft tissue extension or soft tissue tumor with bony erosion is unknown

foci of necrosis, and frequent mitoses [26]. These small round cells are interspersed with islands of well-differentiated hyaline cartilage [20], which may show calcification, ossification, and osteoid production [26]. When the biphasic pattern is present in the biopsy tissue, diagnosis is much more straightforward, although with needle biopsy it is possible the tissue will only represent the round cell component of the tumor, and in these cases further workup is required for accurate interpretation (Fig. 5.2).

Immunohistochemistry staining shows positive SOX9, a master regulator of cartilage production [26], and S100, mostly within the chondrogenic islands [15]. The tumor demonstrates CD99 positivity but is negative for FLI-1, which helps distinguish it from Ewing's sarcoma [2]. INI-1 is retained in mesenchymal chondrosarcoma, ruling out INI-1 loss tumors from the differential such as atypical teratoid rhabdoid tumor in the central nervous system, epithelioid sarcoma, myoepithelial carcinoma, and extraskeletal myxoid chondrosarcoma [2].

Wang et al. used cytogenetics and molecular studies to recently show a novel and recurrent fusion, HEY1-NCOA2, in nearly 80% of mesenchymal chondrosarcoma tumors [2]. This fusion involves HEY1, a BHLH transcription factor with NCOA2, a transcriptional domain of nuclear receptor coactivator 2 [11]. NCOA2 fusions have also been described in spindle cell rhabdomyosarcoma

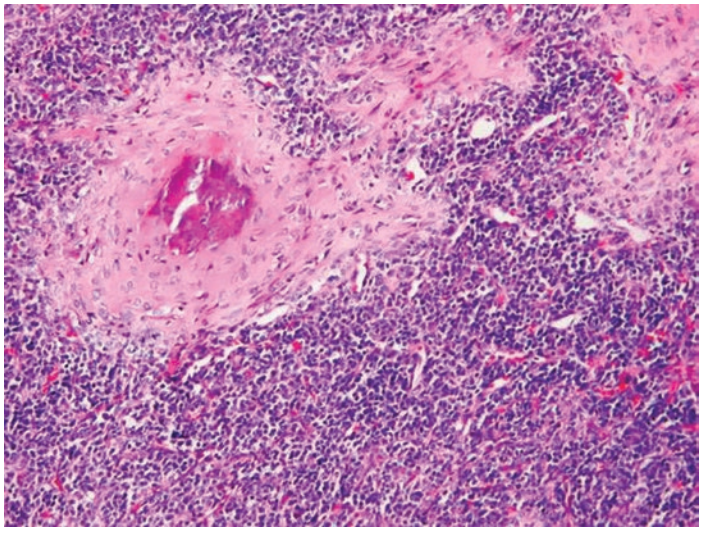

Fig. 5.2 H&E at 100× magnification showing a tumor composed of hyaline cartilage adjacent to a solid small blue round cell component with prominent vasculature

(SRF-NCOA2 and TEAD1-NCOA2) [11]. Another novel fusion that has recently been described in extraskeletal mesenchymal chondrosarcoma tumors is the IRF2BP2 gene with the transcription factor CDX1 [2, 20]. Both fusions may be useful in diagnosis, especially in biopsy specimens that do not contain the biphasic pattern. Also, IDH1 and 2 mutations are not detected in mesenchymal chondrosarcomas, distinguishing them from classic chondrosarcomas as IDH mutations are a hallmark of the latter [2].

In 2018, Folpe et al. noted that mesenchymal chondrosarcoma staining positive for MyoD1, myogenin, and desmin, especially in a biopsy where the biphasic pattern of cartilage interspersed in round blue cells was not demonstrated, was a diagnostic pitfall leading to misdiagnosis of rhabdomyoblastic tumors. They found that spindle cell/sclerosing rhabdomyosarcoma and mesenchymal chondrosarcoma that shows skeletal muscle differentiation are difficult to reliably distinguish and recommended clinical and morphologic clues to help with diagnosis: imaging studies that

show cartilaginous matrix in mesenchymal chondrosarcoma, epithelioid rhabdomyoblasts in spindle cell/sclerosing rhabdomyosarcoma, and demonstration of either the HEY1-NCOA2 (for mesenchymal chondrosarcoma) or MYOD1/PIKC34 (for rhabdomyosarcoma) mutations [15].

Staging

Once the diagnosis is confirmed to be a malignant mesenchymal neoplasm, staging can begin. In soft tissue sarcomas, staging is often limited to chest imaging unless there is a predilection of the particular tumor type to metastasize to other areas. For example, if rhabdomyosarcoma is high on the differential, regional lymph nodes can be imaged for staging with a PET scan, or by expanding an MRI of the extremity. If PET scan is not planned, a bone scan could be considered for mesenchymal chondrosarcoma diagnosis to evaluate for a mixed presentation of bone and soft tissue. Frezza et al. examined 113 patients from several centers, with 95 patients presenting with localized disease. Metastases developed in 45 (47%) of these patients, with 36% to lung alone, 27% to bone, and 17% to multiple sites [2, 16]. Therefore, with a certain diagnosis of extraosseous mesenchymal chondrosarcoma, full axial imaging of the soft tissue mass, a chest CT scan, and consideration of a bone scan would make up all of the staging studies needed to decide treatment.

As Ewing's is also on the differential for mesenchymal chondrosarcoma, a bone marrow biopsy may also be done as part of staging if final diagnosis has not yet been confirmed as mesenchymal chondrosarcoma.

Treatment

Systemic Therapy

Because of the small round blue cell component and high cellularity of mesenchymal chondrosarcoma, theoretically it should be more responsive to chemotherapy than conventional chondrosarcomas made up of slowly dividing cells. The evidence to support this theory, however, is mixed. In the early 1980s, it was shown that the high-grade, round cell component

of the tumor did respond better to chemotherapy (and radiation) [17]. Frezza's study, a large, retrospective review, confirmed that chemotherapy decreased risk of recurrence and improved overall survival in patients with localized disease [16]. Xu et al., in 2015, reviewed 107 patients in 18 different studies and found no correlation between adriamycin-based chemotherapy and survival [33].

Despite the inconsistent results in the literature, there are some promising pathways being explored to increase the response of mesenchymal chondrosarcomas to systemic therapy. De Jong et al. have shown pro- and antiapoptotic proteins of the Bcl-2 family promote chemotherapy resistance to doxorubicin. They created a mesenchymal chondrosarcoma (+HEY1-NCOA2 positive) cell line that demonstrated high Bcl-2 expression and inhibited it with a BH3 mimetic, ABT-737 [11]. Alone, Bcl-2 inhibition did not affect the viability of the cells, but when doxorubicin was added, there was a synergistic induction of apoptosis and reduction in cell viability [11].

Trabectedin is an antitumor agent found in ascidian, marine filter feeders that are sac-like in appearance [29]. In 2016, Morioka et al. examined the efficacy of trabectedin against both mesenchymal chondrosarcoma and extraskeletal myxoid chondrosarcoma in a randomized phase 2 trial, with the control group receiving best supportive care. Three mesenchymal chondrosarcoma patients were assigned to the treatment arm; at 22.7 months of follow-up, one of these patients showed partial response with tumor burden decreasing greater than 50%, and the others showed stable disease [23].

Radiation Therapy

Radiation treatment is a standard adjuvant in soft tissue sarcoma after literature has consistently shown rate reduction of local recurrence. Beane et al. in 2014 showed a soft tissue sarcoma recurrence rate of 25% in 71 patients with surgery alone, compared to a recurrence rate of 1.4% in another 71 patients who received surgery with radiation [3]. Interestingly, there is no convincing evidence that radiation prolongs survival, although

intuitively decreasing local recurrence would lead to prolonged disease-specific survival.

In extraskeletal mesenchymal chondrosarcoma, the role of radiation is not well defined, mostly because the largest studies are retrospective, multi-institutional database reviews, and indications, dose, and fractionation are not consistently recorded [2, 16]. Standard treatment for extraskeletal mesenchymal chondrosarcoma is therefore wide surgical resection and chemotherapy [2], with radiation administration used at the discretion of the treating physician, tumor board, or institution.

Surgery

Wide surgical resection is the mainstay of most sarcoma treatment, and soft tissue mesenchymal chondrosarcoma is no different [8]. Frezza et al. showed R1 resection to be a significant risk for local recurrence; in five patients who developed localized recurrence, four were treated with surgery and were alive and disease-free at the time of the study completion – one had died after being treated with only palliative chemotherapy [16]. Surgery is less effective in metastatic patients at presentation: five of six patients in this group were treated with chemotherapy, primary resection, and metastasectomy but ultimately succumbed to their disease [16].

These findings align with the standard of care approach to all soft tissue sarcomas, in that isolated or oligometastatic disease is resected, as well as isolated localized recurrence. Daigeler et al. showed a 5-year, post-recurrence survival rate of 53% after wide resection of soft tissue local recurrence [9]. Surgery in diffusely metastatic disease is most often palliative in nature, and radiation can be considered instead for local control of certain lesions in a metastatic situation.

Outcomes

Schneiderman et al. performed a Surveillance, Epidemiology, and End Results (SEER) database retrospective review on mesenchymal chondrosarcoma, finding 205 patients for analysis, of which 60% had extraskeletal tumors. Overall survival of the group was

51% and 43% for 5 and 10 years. Axial locations showed lower overall 5- and 10-year survival, 37% and 31%, respectively. Cranial location, in comparison, portended a 74% and 67% 5- and 10-year survival, although better for younger patients than older. Appendicular tumors had a 50% and 39% 5- and 10-year survival. Bone metastasis and 1 cm increase in tumor size were found to be predictors of death from disease [27]. Although histologic grade and margin status have been found in other studies to be related to survival, neither were uniformly reported in the database.

In the retrospective review by Frezza et al., chemotherapy administration was associated with a reduced risk of recurrence and death in patients with localized disease, with overall survival at 5 and 10 years reaching 84% and 80%, compared to overall survival in patients who didn't receive chemotherapy at 5 and 10 years at 73% and 46%. Approximately half of patients presenting with localized disease progressed to metastatic disease, usually to bone or lung [16]. Metastatic disease had an overall survival rate in this study of 3 years, with no apparent benefit with aggressive multi-modality treatment, as only one of six patients treated with chemotherapy and resection of multiple sites remained alive at the end of this study [16].

Extraskeletal Myxoid Chondrosarcoma

History

Originally, Dr. Stewart in 1948 described a "chordoid tumor" due to a resemblance to chordoma and lack of chondroid differentiation [32]. In 1953, Stout and Verner first reported on seven cases of extraskeletal myxoid chondrosarcoma [14]. As more were described in the literature, they were found to have a more favorable clinical course than primary bone chondrosarcomas, occur in a wide age range of 13–89 years old and more frequently in male patients, and localize to the extremities [14]. In 1972, Enzinger and Shiraki formally described extraskeletal myxoid chondrosarcoma as a distinctive entity [28]. Histologically, the specimens appeared lobular with rare mitotic figures, and cells were arranged in small nests and were accompanied by myxoid ground substance,

all of which "closely resembled those of chondroblastic tissue in early stages of cartilage development," [14] which is how its name came to be. However, the World Health Organization classifies it under uncertain differentiation due to lack of cartilaginous differentiation [18].

Epidemiology

Age distribution has remained wide from the first published studies, with ages ranging from under 20 years old to 89 years old, but the majority occur in adults from 20 to 69 years [6], with mean ages from 46 to 57 years [12]. Male preponderance is consistent with early literature, and lower extremity site of tumor is approximately 58–75% of cases [6, 12]. The tumor is quite rare, only about 2.3% of soft tissue sarcomas [12].

Presentation and Diagnosis

Typically, patients present with a slow-growing, deep, painless mass in the proximal extremity [22, 28]. Local pain and tenderness is less common but can occur in up to one third of patients [28]. Because of the deep level and slow growth, the duration before clinical presentation has a wide range, from 1 month to 3 years [28].

Ultrasound imaging will show a circumscribed mass of low echogeneity [28]. Although they cannot further characterize the mass, plain X-rays can show a soft tissue shadow, especially if the tumor is large which is often the case. Kapoor et al., in a study of 40 patients with extraskeletal myxoid sarcoma, showed an average tumor size of 9.3 cm. No tumors showed any calcifications and were lobular in nature with T1 showing isointensity to muscle and T2 showing hyperintensity to muscle with intralesional hypointense septa and peripheral and septal enhancement with contrast [18, 28] (Fig. 5.3). CT scan with enhancement shows slight hypodensity to muscle and may underestimate the tumor burden [18].

Grossly, primary tumors are well circumscribed within a pseudocapsule and lobulated [12, 28]. Classic extraskeletal myxoid chondrosarcomas show infrequent mitoses and a nodular architecture with uniform round to spindled cells forming

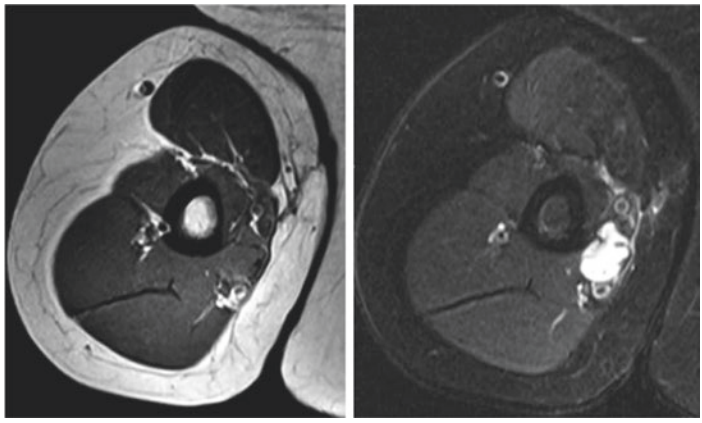

Fig. 5.3 Axial T1 and T2 FS MRI sequences showing muscle isointensity on T1. On T2, there is enhancement and a lobular appearance that is well encapsulated

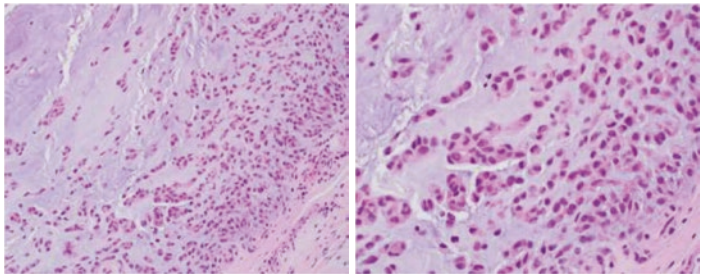

Fig. 5.4 Extraskeletal myxoid sarcoma at 200× and 400×. Both show the characteristic cords and nests of tumor cells with hyperchromatic nuclei and moderate amounts of eosinophilic cytoplasm in a myxoid background

interconnecting cords in a reticular pattern, widely separated by myxoid to chondromyxoid matrix which is consistent with expression of chondroitin sulfate [6, 12, 28] (Fig. 5.4). Intracytoplasmic vacuoles or eosinophilic cytoplasm is a prominent feature in most cases, and intralesional hemorrhage and necrosis often exist [12, 28]. Cellular variants have little or are completely devoid of myxoid stroma in areas, are composed of large epithelioid cells with

prominent nucleoli, and have several mitotic figures [28]. A rhabdoid variant also exists, which will be discussed further below [12].

Shao et al. did a study of 40 extraskeletal myxoid chondrosarcoma patients to examine their clinicopathologic features. Their immunohistochemistry studies showed consistently positive vimentin [28]. Partial expression was noted in synaptophysin (36%), S-100 (29%), and epithelial membrane antigen (11%) [28]. In the cellular variants, Ki-67 staining was >30% compared to 5–10% in classic tumors [28]. Another study by Agaram et al. found over half of 14 cases that underwent immunohistochemistry staining showed negative S-100 and epithelial membrane antigen. They also noted INI-1 was retained in 5 of 14 cases [1], indicating no particular stain or pattern is diagnostic of extraskeletal myxoid chondrosarcoma. In fact, the patterns are more consistent with neural or neuroendocrine differentiation [10].

Genetic studies have identified four chromosome translocations that pathologically occur in extraskeletal myxoid chondrosarcoma [4], all involving the NR4A3 gene. In 75% of cases, NR4A3 on chromosome 9 is fused to EWSR1 on chromosome 22 [4, 10]. This translocation is associated with tumors that are low in cellularity, mitotic counts, and under 40% necrosis [1]. Another NR4A3 translocation, this time to TAF15 (TATA binding protein-associated factor 15) also on chromosome 22, accounts for approximately 15% of extraskeletal myxoid chondrosarcomas; because the TAF15 gene and EWSR1 are homologous, the function of both these fusions is considered identical [4]; both fusions have been shown to be strong transcriptional activators [1]. NR4A3-TAF15 fusions lead to tumors that are less common in the thigh, with 80% showing moderate to increased cellularity and atypia, increased mitotic activity, and tumor necrosis of 15–90% [1]. The final two translocations identified are NR4A3 with the fused gene transcription factor 12 (TCF12) and the TRK-fused gene (TFG), both of which are also located on chromosome 22 [4].

Staging

Staging for extraskeletal myxoid chondrosarcoma is similar to staging for any soft tissue sarcoma, in that the most common loca-

tion for metastasis is pulmonary [10]. Axial imaging of the chest should therefore be performed at diagnosis and for surveillance, as there is a high rate of distant metastasis, up to 50% [10]. Imaging of the mass itself should clearly show the entire tumor as extracompartmental invasion has also recently been shown to correlate with development of metastasis [22].

Kapoor et al. looked at 13 patients with extraskeletal myxoid chondrosarcoma, and 12 patients developed lung metastases, 3 developed bone metastases, which were all lytic in nature, 2 each developed soft tissue metastases in abdominal/pelvic nodes, and one each developed mediastinal nodes and peritoneal metastases. PET/CT was performed for three patients, but each patient had different findings, one PET avid, one with mild tumor peripheral uptake, and one with no avidity [18]. Based on these findings, PET/CT should not be considered in staging but rather in avid disease may be used to survey an avid tumor or monitor treatment and progression.

Treatment

Systemic Therapy

Localized soft tissue sarcomas in general are not treated systemically with the exception of certain histologic diagnoses. This is true of extraskeletal myxoid chondrosarcoma; isolated disease is treated with local treatment only, as described in subsequent sections below.

In patients presenting with or who subsequently develop metastatic disease, however, local treatment is not enough for disease response. The standard chemotherapy for most sarcomatous cancers is anthracycline-based, and literature is mixed regarding its efficacy in extraskeletal myxoid sarcoma. McGory et al. reported two of six metastatic patients with response to multi-agent chemotherapy in 2001; one had partial response and eventually succumbed to disease, and the other had complete response and had no disease at 6 years post-metastatic presentation [19]. In 2008, Memorial Sloan Kettering looked at their 21 patients treated with different regimens, many anthracycline-based, and found stable disease in 25% of cases, with duration of response >6 months

[13]. However, MD Anderson did a retrospective review in 1995, in which ten patients were treated with doxorubicin and dacarbazine regimens without any response [19]. Another series of four metastatic patients were treated with ifosfamide and showed no response [25].

Unfortunately, the rarity of this disease prevents large numbers, and many of the regimens in the larger series were not standard. In 2013, Stacchiotti et al. published the Italian Rare Cancer Network experience on 11 patients who had received anthracycline-based chemotherapy for progressing, advanced, and molecularly confirmed extraskeletal myxoid chondrosarcoma [31]. Of their patients, 40% had partial response, and 30% had stable disease confirmed at 3 months after end treatment [31]. Median overall survival was 30 months, and median progression-free survival was 8 months, with half progression-free at 6 months [31]. They postulated that their better response rates were due to diagnostic criteria available to them that had not been available for the prior case series; specifically, they only looked at tumors with confirmed NR4A3 translocation-positive tumors [31].

This same group continued to investigate systemic therapies for metastatic extraskeletal myxoid chondrosarcomas, as resistance to cytotoxic chemotherapy is common, and in 2014 published their series on the activity of sunitinib in this tumor [30]. Ten patients were treated with the tyrosine-kinase inhibitor, and six had partial response, two had stable disease, and two progressed [30]. Responses were durable at 2 years, with no resistance noted, and all were in patients who had the NR4A3-EWSR1 translocation [30].

Radiation Therapy

Drilon et al. looked at 86 patients retrospectively from two referral centers and found, of the 76 patients presenting with localized disease, 22 (30%) had surgery with radiation. Patients receiving combined modality treatment tended toward high rates of both local and distant recurrences (41% for both) compared to surgery alone, which showed local and distant recurrence rates of 35% and 20%, respectively [13]. They concluded that patients with

more aggressive tumors had been selected for radiation combined with surgery [13].

Bishop et al. at MD Anderson more recently evaluated their experience with 41 patients with localized disease treatment. Eighty percent received radiation with surgery, with a median dose of 50 Gy [5]. Five patients developed local recurrence, four of which did not have radiation treatment [5]. This corresponds to prior literature regarding all soft tissue sarcomas that suggests radiation is a good local control adjuvant. Although there has been no definitive evidence showing radiation improves overall survival in soft tissue sarcoma, in Bishop's study, local recurrence was found to be associated with poorer distant metastatic disease-free survival in both univariate and multivariate analyses [5]. In this particular tumor type, neoadjuvant or adjuvant radiation should be given unless there are strong clinical reasons not to.

Surgery

Margin status, in the Bishop study, was not found to be associated with local recurrence or distant metastatic-free survival, despite six patients being classified as having margin positive or uncertain margin resections [5]. Yet another study by Minami examining the prognosis of extracompartmental invasion of extraskeletal myxoid chondrosarcoma showed no negative influence on overall survival based on margin status.

However, in the 2008 study by Drilon et al., 43 patients in whom margin status data was available showed only 2 of 24 (8%) patients with R0 resection, 3 of 12 (25%) patients with R1 resection, and 5 of 7 (71%) patients with R2 resection experienced local recurrence. Meis-Kindblom et al., in a large review of 117 cases, showed intralesional or marginal excisions of primary tumors lead to a higher incidence of local recurrence [21].

Surgical resection in soft tissue sarcoma should always attempt negative margin resection as a standard of care, and although margin status in extraskeletal myxoid sarcoma has shown questionable prognostic value in some smaller studies, R0 resection remains the goal in localized disease treatment.

Outcomes

Unfortunately, extraskeletal myxoid chondrosarcoma has a high local and distant recurrence rate overall. Local recurrence rates range from 37% to 48% in many studies [10, 28], and distant metastatic progression is from 26% to 50% [10, 28]. Despite high recurrence rates, survival is actually quite good, with patients living years after diagnosis and even after development of recurrence. Local recurrence-free survival at 5 and 10–20-years, for example, is >70% and >60% in 71 patients followed at Sloane Kettering over the course of 28 years [6]. The same study identified disease-specific survival at 5 years at 80%, 10 years at 65%, and 15 years at 55% [6]. Factors shown to influence prognosis include radiation in localized disease in one study [5], metastasis at presentation [22], and tumor size [5, 24].

References

1. Agaram NP, et al. Extraskeletal myxoid chondrosarcoma with non-EWSR1-NR4A3 variant fusions correlate with rhabdoid phenotype and high-grade morphology. Hum Pathol. 2014;45:1084–91.
2. Arora K, et al. Extraskeletal mesenchymal chondrosarcoma. Arch Pathol Lab Med. 2018;142:1421–4.
3. Beane JD, et al. Efficacy of adjuvant radiation therapy in the treatment of soft tissue sarcoma of the extremity: 20-year follow-up of a randomized prospective trial. Ann Surg Oncol. 2014;21:2484–9.
4. Benini S, et al. Diagnostic utility of molecular investigation in extraskeletal myxoid chondrosarcoma. J Mol Diagn. 2014;16:314–23.
5. Bishop AJ, et al. Extraskeletal myxoid chondrosarcomas: combined modality therapy with both radiation and surgery improves local control. Am J Clin Oncol. 2019;42:744–8.
6. Brennan MF, et al. Chapter 20: Extraskeletal myxoid chondrosarcoma. In: Management of soft tissue sarcoma. New York: Springer; 2013.
7. Casali PG, et al. Soft tissue and visceral sarcomas: ESMO-EURACAN Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2018;29(Suppl 4):iv51–67.
8. Cesari M, et al. Mesenchymal chondrosarcoma: an analysis of patients treated at a single institution. Tumori. 2007;93:423–7.
9. Daigeler A, et al. Long-term outcome after local recurrence of soft tissue sarcoma: a retrospective analysis of factors predictive of survival in 135

patients with locally recurrent soft tissue sarcoma. Br J Cancer. 2014;110:1456–64.
10. Davis EJ, et al. Next generation sequencing of extraskeletal myxoid chondrosarcoma. Oncotarget. 2017;8:21770–7.
11. De Jong Y, et al. Inhibition of Bcl-2 family members sensitizes mesenchymal chondrosarcoma to conventional chemotherapy: report on a novel mesenchymal chondrosarcoma cell line. Lab Investig. Oct 2016;96:1128–37.
12. Dong F, et al. Soft tissues: extraskeletal myxoid chondrosarcoma. Atlas Genet Cytogenet Oncol Haematol. 2000;4.
13. Drilon AD, et al. Extraskeletal myxoid chondrosarcoma: A retrospective review from 2 referral centers emphasizing long-term outcomes with surgery and chemotherapy. Cancer. 2008;113(12):3364–71.
14. Enzinger FM, et al. Extraskeletal myxoid chondrosarcoma: an analysis of 34 cases. Hum Pathol. 1972;3:421–35.
15. Folpe AL, et al. Mesenchymal chondrosarcomas showing immunohistochemical evidence of rhabdomyoblastic differentiation: a potential diagnostic pitfall. Hum Pathol. 2018;77:28–34.
16. Frezza AM, et al. Mesenchymal chondrosarcoma: prognostic factors and outcome in 113 patients. A European Musculoskeletal Oncology Society study. Eur J Cancer. 2015;51:374–81.
17. Huvos AG, et al. Mesenchymal chondrosarcoma: a clinicopathologic analysis of 35 patients with emphasis on treatment. Cancer. 1983;51:1230–7.
18. Kapoor N, et al. Clinical and radiologic features of extraskeletal myxoid chondrosarcoma including initial presentation, local recurrence, and metastases. Radiol Oncol. 2014;48:235–42.
19. McGrory JE, et al. Extraskeletal myxoid chondrosarcoma. Clin Orthop Relat Res. 2001;382:185–90.
20. Mendenhall WM, et al. Mesenchymal Chondrosarcoma. Int J Part Ther. 2016;3:300–4.
21. Meis-Kindblom JM, et al. Extraskeletal myxoid chondrosarcoma: a reappraisal of its morphologic spectrum and prognostic factors based on 117 cases. Am J Surg Pathol. 1999;32:636–50.
22. Minami Y, et al. The extracompartmental tumoral invasion of extraskeletal myxoid chondrosarcoma induces distant metastasis. Anticancer Res. 2020;40:1035–9.
23. Morioka H, et al. Results of sub-analysis of phase 2 study on trabectedin treatment for extraskeletal myxoid chondrosarcoma and mesenchymal chondrosarcoma. BMC Cancer. 2016;16:479.
24. Ogura K, et al. Extraskeletal myxoid chondrosarcoma: a review of 23 patients treated at a single referral center with long-term follow-up. Arch Orthop Trauma Surg. 2012;132:1379–186.
25. Patel SR, et al. Extraskeletal myxoid chondrosarcoma: long-term experience with chemotherapy. Am J Clin Oncol. 1995;18:161–3.

26. Raza MU, et al. Mesenchymal chondrosarcoma, clinicopathological characteristics of an uncommon tumor. J Cyto Histol. 2018;9.
27. Schneiderman BA, et al. Survival in mesenchymal chondrosarcoma varies based on age and tumor location: a survival analysis of the SEER database. Clin Orthop Relat Res. 2017;475:799–805.
28. Shao R, et al. Clinicopathologic and radiologic features of extraskeletal myxoid chondrosarcoma: a retrospective study of 40 Chinese cases with literature review. Ann Diagn Pathol. 2016;23:14–20.
29. Shenkar N, et al. "Ascidiacea." *Ascidiacea World Database*. 2020. http://www.marinespecies.org/aphia.php?p=taxdetails&id=1839 on 29 June 2020.
30. Stacchiotti S, et al. Activity of sunitinib in extraskeletal myxoid chondrosarcoma. Eur J Cancer. 2014;50:1657–64.
31. Stacchiotti S, et al. Anthracycline-based chemotherapy in extraskeletal myxoid chondrosarcoma: a retrospective study. Clin Sarcoma Res. 2013;3:16.
32. Stewart FW. "Case 211." Division of laboratories and research. Albany; 1948.
33. Xu J, et al. Mesenchymal chondrosarcoma of bone and soft tissue: a systematic review of 107 patients in the past 20 years. PLoS One. 2015;10:e0122216.

Part III

Management of Chondrosarcoma

6 Chondrosarcoma of the Axial Skeleton

Akash A. Shah, Howard Young Park, Gideon Blumstein, and Don Young Park

Introduction

Chondrosarcomas represent a rare malignant primary bone tumor type that produces cartilage matrix. The estimated incidence of chondrosarcomas in all anatomic locations is 1 in 200,000 per year, with chondrosarcoma of the axial skeleton comprising only 2–10% of these cases [1, 2]. Skull base lesions are relatively rarer than those of the spinal column. Chondrosarcoma of the axial skeleton arises with a mean age in the fifth decade of life, although the distribution of age is broad from 15 to 78 years [3, 4]. Chondrosarcoma of the axial skeleton includes tumors that arise from the skull base and vertebral column. After Ewing sarcoma, chondrosarcomas are the most common primary malignant spinal tumor. Skull base chondrosarcomas may originate near the spinal cord, cranial nerves, and inner ear – and can thus manifest with myelopathy, gait disturbances, and cranial nerve palsies. For skull base tumors, there is an approximate 1.2:1 ratio of females to

A. A. Shah · H. Y. Park · G. Blumstein · D. Y. Park (✉)
UCLA Department of Orthopaedic Surgery, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA
e-mail: AAShah@mednet.ucla.edu; HowardYPark@mednet.ucla.edu; GBlumstein@mednet.ucla.edu; Dypark@mednet.ucla.edu

F. J. Hornicek (ed.), *Chondrosarcoma*,
https://doi.org/10.1007/978-3-030-74572-1_6

males [5, 6]; spinal tumors have a male predilection of nearly 1.7:1 [4, 7]. In a review of 200 skull base chondrosarcomas, all arose about the clivus centered in the sphenoethmoid complex (6%), spheno-occiput (28%), and temporo-occipital junction (66%) [8]. Within the published literature of spinal column chondrosarcoma, anatomic distribution favors the thoracic and lumbar spine, with approximately 40% and 45%, respectively; the cervical and sacral spine proportion of cases are 15% and 1%, respectively [2, 3, 7, 9]. Tumors originating from the spinal column may present with myelopathy, radiculopathy, and pain.

Classification

The Enneking staging system has been primarily described for long bone tumors; however, the system has been applied to spinal tumors by some authors. It divides local malignant tumors into three stages (I, II, and III), each with a subclassification (A, B). This is based on an extensive preoperative workup that includes clinical features, imaging findings, and histologic features [10].

The classification of spinal chondrosarcoma can be based on location within the vertebra using the Weinstein, Boriani, Biagini (WBB) system, as with other primary spinal tumors. This classification system is clinically relevant for surgical planning. The vertebra is divided into 12 radiating zones numbered in a clockwise order as well as into five concentric layers from the paravertebral extraosseous compartments to the dura [11]. This classification system has been shown to have moderate interobserver reliability and excellent intra-observer reliability [12].

Histology

Chondrosarcoma is hypothesized to develop from residual enchondral cartilage nests, which is associated with the three centers of ossification in the vertebra. Unlike other primary malignant spine tumors, chondrosarcoma is seen in the vertebral body (5%), posterior elements (40%), or both (45%) [13]. Histopathologically,

chondrosarcoma is divided into conventional and variant types. Conventional chondrosarcoma accounts for 85% of all chondrosarcoma as well as the overwhelming majority of chondrosarcoma that arise in the spinal column. Conventional chondrosarcoma can be further subdivided into conventional central chondrosarcoma (85%), which arises de novo within the bone. Conventional peripheral chondrosarcoma (15%) usually arises on the surface of the bone due to malignant transformation within a preexisting benign tumor cartilage cap; however, it can also arise within the bone from malignant transformation of enchondroma [14]. Both types extend beyond the cortex and often present with soft tissue components. Due to the higher incidence of osteochondroma in the posterior elements, secondary conventional chondrosarcoma is found more commonly in the posterior elements. Primary conventional chondrosarcoma is found more commonly in the vertebral body, though extension to all columns is common.

Conventional chondrosarcoma – both primary and secondary – are histologically similar and recognized by the same three histopathological grades. Grade I chondrosarcoma demonstrates abundant matrix composed of hyaline cartilage with low cellularity, no pleomorphism, and very low metastatic potential although these may be locally aggressive (Fig. 6.1). Grade II chondrosarcoma demonstrates some pleomorphism and increased cellularity and is metastatic in about 15% of cases [15]. Grade III chondrosarcoma tends to be extremely cellular, with mitotic figures and high pleomorphism; myxoid matrix often replaces hyaline matrix (Fig. 6.2). Metastasis is found in up to 70% of grade III chondrosarcoma. Changes to the World Health Organization Classification of Tumors of Soft Tissue and Bone in 2013 separated chondrosarcoma into two distinct ICD codes based on prognosis; grade I was given the synonym “atypical cartilaginous tumor” and is distinct from grade II and grade III tumors [16].

Within the appendicular skeleton, histopathological grade is the most important factor in predicting chondrosarcoma behavior and prognosis, a feature due in large part to reliance of wide resection for successful treatment given the poor response of all conventional chondrosarcoma types to radiation and chemotherapy. While high-grade tumors also portend worse prognosis

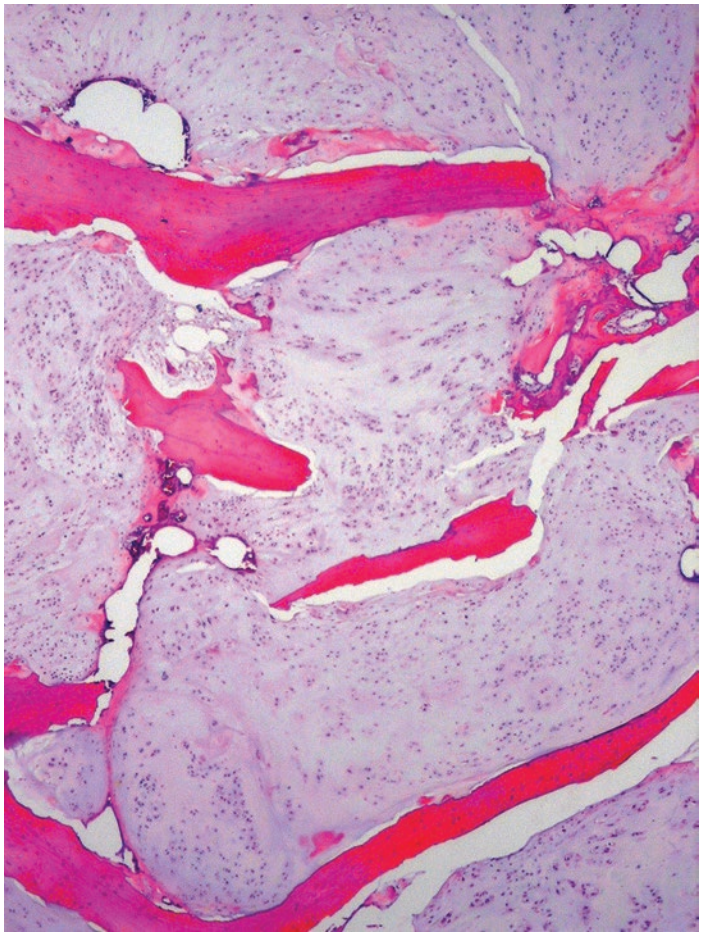

Fig. 6.1 Low magnification of low-grade atypical cartilaginous tumor/chondrosarcoma (grade I). A permeative pattern of invasive tumor is seen with sheets and lobules of malignant cartilage replacing bone marrow. The tumor completely surrounds cancellous lamellar marrow bone fragments (H&E 20×)

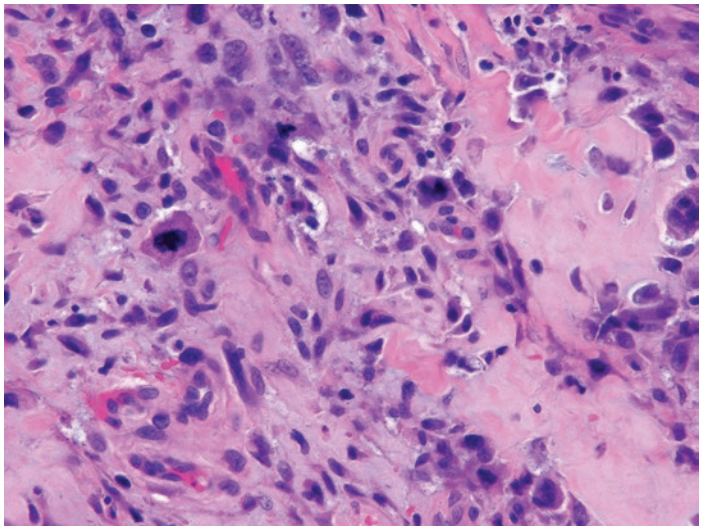

Fig. 6.2 High-grade chondrosarcoma (grade III). Pleomorphic anaplastic chondrocytes are seen with obvious mitotic activity (H&E 400×)

within the axial skeleton, the challenge of attaining wide total resection within the spinal column often leads to dire prognosis even with lower grade tumors [17]. It is also notable that chondrosarcoma often displays a high degree of heterogeneity with grade I and grade III regions coexisting within the same tumor, making surgical planning (wide resection versus marginal resection) based on biopsy results alone challenging [18, 19].

Variant subtypes of chondrosarcoma account for the remaining 15% of chondrosarcomas and include periosteal or juxtacortical, mesenchymal, clear cell, and dedifferentiated chondrosarcomas. These are much rarer than conventional chondrosarcoma. Periosteal or juxtacortical chondrosarcoma does not typically have a precursor lesion and is most commonly found in distal humerus/femur in patients in their fifth decade; despite the high grade in this subtype, prognosis is relatively good. Mesenchymal

chondrosarcoma is found in the axial skeleton most commonly in patients in their 50s and 60s. The mesenchymal subtype is typically high grade and portends a poor prognosis (Fig. 6.3). Clear cell chondrosarcoma is generally lower grade and most often presents in the femoral and humeral epiphyses. Dedifferentiated chondrosarcoma can develop from conventional chondrosarcoma and is most commonly found in the pelvis and femur (Fig. 6.4). These lesions are high grade and carry a poor prognosis. While the clear cell or dedifferentiated variants can occur at any age, peak incidence is between 30 and 60 years [20, 21]. The various characteristics of the chondrosarcoma subtypes are detailed (Table 6.1).

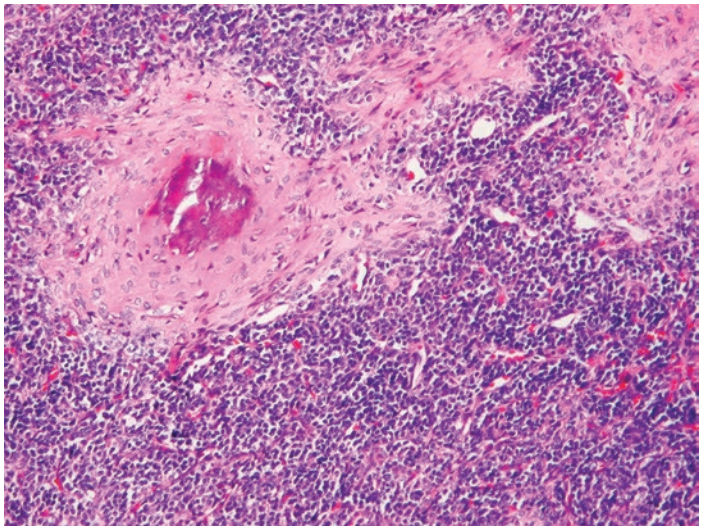

Fig. 6.3 Mesenchymal chondrosarcoma. Nodules of hyaline cartilage are seen juxtaposed with a very cellular small blue round cell component (H&E 100×)

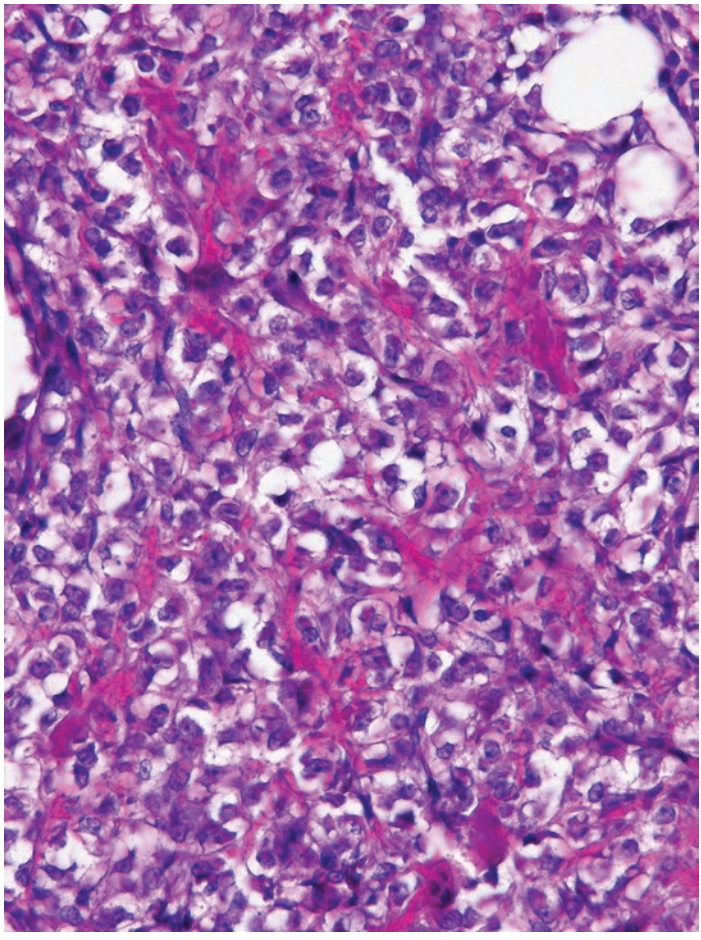

Fig. 6.4 High magnification of the dedifferentiated chondrosarcoma. Sheets of epithelioid cells are seen with mineralized immature woven bone (osteoid) in the manner of osteosarcoma (H&E 200×)

Table 6.1 Characteristics of chondrosarcoma subtypes

	Conventional central chondrosarcoma	Mesenchymal chondrosarcoma	Conventional peripheral chondrosarcoma	Periosteal (juxtacortical) chondrosarcoma	Clear cell chondrosarcoma	Dedifferentiated chondrosarcoma
Percent incidence	75%	2%	10%	1%	2%	10%
Precursor lesion	Enchondroma	None	Osteochondroma	None	None	Conventional chondrosarcoma
Associated syndromes	Ollier disease; Maffucci syndrome	None	Multiple hereditary osteochondromas	None	None	None
Most common age range	50s–60s	50s–60s	40s	40s	Any age, peak 30s–50s	Any age, peak 30s–50s
Common locations	Axial and appendicular skeleton	Axial skeleton, extra-skeletal (meninges)	Shoulder girdle, pelvis	Distal humerus, distal femur	Femoral and humeral epiphyses	Pelvis, femur
Frequent histologic grade	Low grade	High grade	Low grade	High grade	Low grade	High grade
Prognosis	Good if low grade	Poor	Good if low grade	Good	Good	Poor
Chemosensitivity	Low	Sensitive	Low	Low	Low	Low
Radiosensitive	Low	Sensitive	Low	Low	Low	Low

Pathology

The molecular genetics of primary and secondary chondrosarcoma vary despite shared histopathological features. Mutations in the *EXT1* or *EXT2* genes are associated with the formation of both isolated osteochondromas and multiple hereditary exostoses (MHE) [22]. These mutations are also seen secondary peripheral conventional chondrosarcoma; however, the potential for malignant transformation is less than 1% in isolated osteochondromas and 5–10% in patients with MHE [23]. The exact mechanism of transformation is not clear; however, various signaling pathways, which are active under normal development (IHH, PTHLP, Wnt, TGF), are altered in secondary chondrosarcoma. Mutations in p53 and pRb pathways are seen in secondary chondrosarcoma with increased expression associated with tumor grade and are thought to be the source of a secondary alteration responsible for transformation [24, 25].

Mutations in *IDH1* and *IDH2* genes are found in all enchondromas as well as most primary central conventional chondrosarcoma. Malignant transformation in solitary enchondroma is less than 1%, while those associated with the Ollier disease (*IDH1*) and Maffucci syndrome (*IDH2*) reach 50% [26]. Mutations in both genes produce higher levels of D2-hydroxyglutarate, causing multiple epigenetic changes in mesenchymal stem cells and promoting chondrogenic differentiation. As in the mutations associated with secondary chondrosarcoma, mutations in *IDH1* and *IDH2* alone are thought to be insufficient for driving oncogenesis, and other alterations are assumed to be necessary.

Imaging

Chondrosarcoma may appear as lucent, opaque, or heterogeneous on plain radiographs. Soft tissue extension outside of the bone may be visible, especially if calcification is present. Cross-sectional imaging should be obtained in order to differentiate chondrosarcoma from other spinal masses as well as to allow for surgical planning.

Computed tomography (CT) demonstrates a typical pattern of peripheral calcification of matrix lobules, commonly referred to as "rings and arcs" (Fig. 6.5) [27]. On magnetic resonance (MR) images, chondrosarcoma typically shows low intensity on T1 and mixed low and high intensity on T2 and STIR sequences (Figs. 6.6 and 6.7). Peripheral rim enhancement or fluid levels may be seen in gadolinium-enhanced, fat-suppressed T1 images [28]. CT

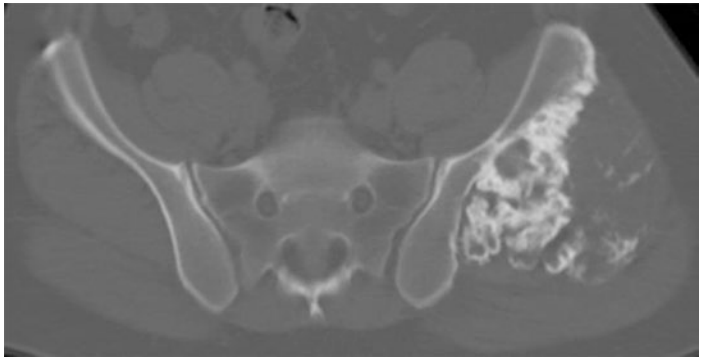

Fig. 6.5 Axial CT of pelvic chondrosarcoma showing mass with typical "rings and arcs"

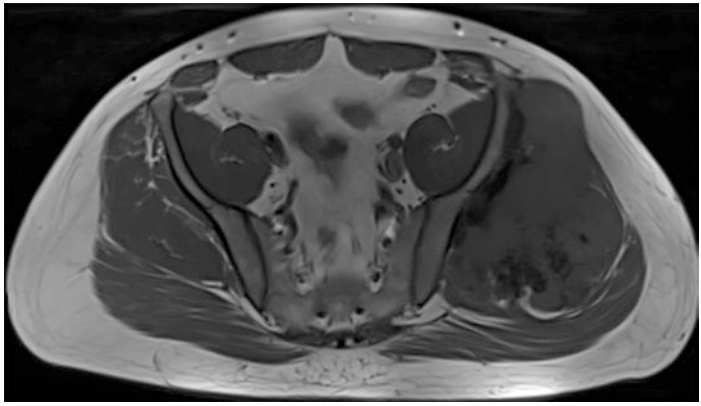

Fig. 6.6 Axial T1-weighted MRI of pelvis showing low-intensity lesion

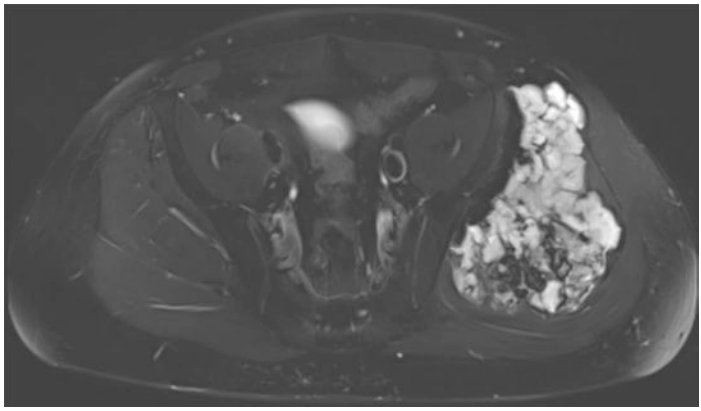

Fig. 6.7 Mixed low and high intensity on T2-weighted, fat-suppressed MRI of pelvis

scans of the abdomen/pelvis and chest may be performed for staging purposes. Whole-body positron emission tomographic (PET) scans may also be obtained to evaluate for metastasis; however, this is not standard.

Treatment

Chemotherapy

The role of chemotherapy for chondrosarcoma is limited. Mesenchymal chondrosarcoma shows sensitivity to doxorubicin and cisplatin combination therapy, and adjuvant chemotherapy may confer a survival benefit in this subtype [29, 30]. Despite this sensitivity, mesenchymal chondrosarcoma carries a poor prognosis. Clinical benefit may be observed with doxorubicin and cisplatin in those with advanced dedifferentiated chondrosarcoma [31]. Periosteal/juxtacortical and clear cell chondrosarcoma are not particularly chemosensitive subtypes.

Chemotherapy is largely ineffective for conventional chondrosarcoma, which comprises the majority of all chondrosarco-

mas. Traditional cytotoxic chemotherapeutic agents that target actively dividing cells may not be effective against slow-growing chondrosarcoma cells with low cell turnover. The poor vascularity and large amount of hyaline extracellular matrix limits the penetration of these agents [32]. Furthermore, chondrosarcoma cells express high levels of the multiple drug resistance (MDR) 1 gene. This gene encodes P-glycoprotein, which is hypothesized to function as an adenosine triphosphate (ATP)-powered efflux pump that actively removes chemotherapeutic agents from tumor cells [33]. Finally, aberrant expression of BCL-2 – an antiapoptotic protein – contributes to therapy resistance of chondrosarcoma [34].

Given the necessity for treatment in widely metastatic disease as well as inoperable tumors, there has been considerable work in animal models in recent years to develop targeted therapeutics for chondrosarcoma. Potential targets include IHH signaling, PTHLH signaling, COX2, SRC pathway, apoptosis pathway, and PD-1 expression [26, 35]. More work is required to realize the promise of targeted therapy and immune checkpoint blockade.

Radiation

As chondrosarcoma is not a highly radiosensitive pathology, the role of radiation therapy is limited and is typically combined with surgical resection. Given the low-grade nature of chondrosarcoma without rapid cell turnover, radiation alone does not offer adequate local control and is only used in unresectable tumors or for palliation. Neoadjuvant radiation for spinal chondrosarcoma is not typically employed, unlike with chordoma. Adjuvant radiation therapy is often employed after resection to lower local recurrence rates and increase overall survival. As is the case with chemosensitivity, mesenchymal chondrosarcoma is a subtype of chondrosarcoma that is particularly radiosensitive [36].

Delivering radiation to the spine is uniquely challenging, given the proximity of the target lesion to sensitive structures such as the spinal cord and traversing/exiting nerve roots. The maximum

tolerance of the spinal cord is approximately 45–50 Gray (Gy); however, chondrosarcomas require doses in excess of this tolerance. Particle therapy – such as proton- or photon-beam therapy – is able to sidestep this issue, as no exit dose is delivered beyond the target lesion with this radiation modality [36, 37]. While data regarding radiation to spinal chondrosarcoma remain limited, local control rates are higher in cohorts of patients with spinal chordoma or chondrosarcoma who undergo proton/photon therapy than control groups [37, 38]. A recent systematic review observed a small benefit with the use of adjuvant radiation therapy in both intralesional and wide resection of spinal chondrosarcomas [39]. Radiation-related complications include sacral insufficiency fractures, sacral neuropathy, pleural effusion, and wound dehiscence [37, 38].

Surgery

Due to the unreliable efficacy of chemotherapy or radiation therapy alone, surgical resection represents the mainstay of therapy for spinal chondrosarcoma. En bloc resection refers to removal of the lesion in one piece, encased by a layer of healthy tissue. Wide en bloc excision with negative margins is considered the gold standard therapy for primary malignant tumors of the vertebral column, including chondrosarcoma. The single most important predictor of local recurrence is positive resection margin [2]. Negative margins are associated with decreased local recurrence rates, which in turn are directly associated with increased survival [40–44].

En bloc resection is more effective at achieving tumor-free margins than marginal excision or intralesional curettage. En bloc resection is associated with decreased rates of local recurrence, thereby improving survival [39, 45]. Long an established principle of appendicular musculoskeletal oncology, en bloc resection in the spinal column is particularly challenging due to the unique anatomic constraints of the spine. In order to obtain a margin of tissue around the tumor, resection of critical structures may be required (e.g., dura, pleura, nerve roots, vessels).

The difficulty of achieving negative margins in the spine had historically limited surgery to curettage and intralesional resection [40, 46].

In a cohort of 22 patients with spinal chondrosarcoma described by Boriani and colleagues, 100% of patients treated with intralesional curettage developed a local recurrence compared; 80% of these patients died within a mean of 36 months. In contrast, 25% of patients treated with en bloc resection developed a local recurrence [2]. Similarly, Shives and colleagues showed that 100% of patients with intralesional excision had disease progression at a mean of 24.8 months [9]. Local recurrence is 12 times more likely in intralesional/marginal resection versus wide excision for spinal chondrosarcoma; notably, death was greater than five times more likely in the intralesional/marginal resection cohort [39].

En bloc resection of spinal chondrosarcoma was first described by Stener in 1971 [47]. Further work by multiple groups described multiple techniques for en bloc resection of spinal tumors through a single posterior approach, combined anterior-posterior approaches, and staged anterior-posterior approaches [46, 48–53]. Modern total en bloc spondylectomy is generally performed with intra-operative confirmation of negative margins by pathology.

There is significant morbidity associated with en bloc techniques. Major risks associated with total en bloc spondylectomy include injury to major vessels, spinal cord/nerve root injury, contamination of tumor cells, spinal instability, excessive bleeding, and death [44, 52–54]. While en bloc resection is superior to intralesional/marginal excision for spinal chondrosarcoma with respect to limiting local recurrence and thereby improving overall survival, the high rate of morbidity associated with en bloc resections and potential functional impairment must be weighed against the survival implications of violating tumor in an intralesional or marginal excision. Extensive preoperative counseling with the patient with a discussion of long-term goals and expectations is recommended [44]. Furthermore, multidisciplinary planning should be regularly performed with vascular surgery, plastic surgery, and/or thoracic surgery as necessary.

Patient Case

The patient is a 28-year-old female presenting with many years of mid-back pain and a few months of a small but noticeable mass over paraspinal thoracic area. She denies fevers, chills, recent weight loss, numbness/weakness, or bowel/bladder dysfunction. She has no pertinent past medical or surgical history. An MRI of the thoracic spine was obtained and showed an 8.8 × 6.3 × 7.4 cm mass extending into the T10 vertebral body and posterior elements, right T10-T11 neural foramen, epidural space, paraspinal musculature, and pleura (Fig. 6.8). This mass causes severe spinal canal stenosis with mass effect on the spinal cord. A biopsy was obtained, which showed a low-grade conventional chondrosarcoma.

The patient underwent T10-T11 en bloc resection of tumor with partial T9 corpectomy, T9-T12 anterior interbody fusion, and T7-L2 posterior spinal instrumented fusion. Postoperative radiographs are shown (Fig. 6.9). The wound was closed with a bilateral paraspinal and left latissimus advancement flap. Estimated blood loss was 2500 mL. Negative margins were obtained. Patient was doing well without evidence of local recurrence at last follow-up.

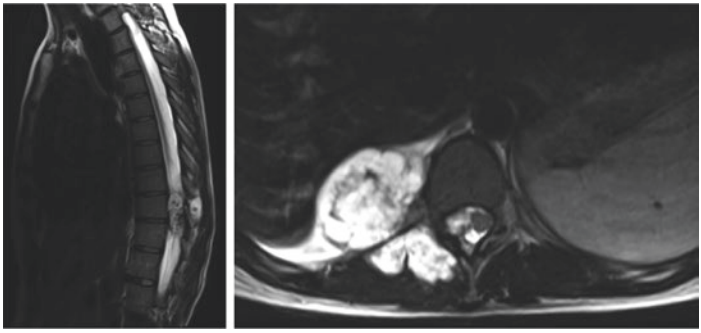

Fig. 6.8 Sagittal and axial T2-weighted MRI showing mass extending into the T10 vertebral body and posterior elements, right T10-T11 neural foramen, epidural space, paraspinal musculature, and pleura

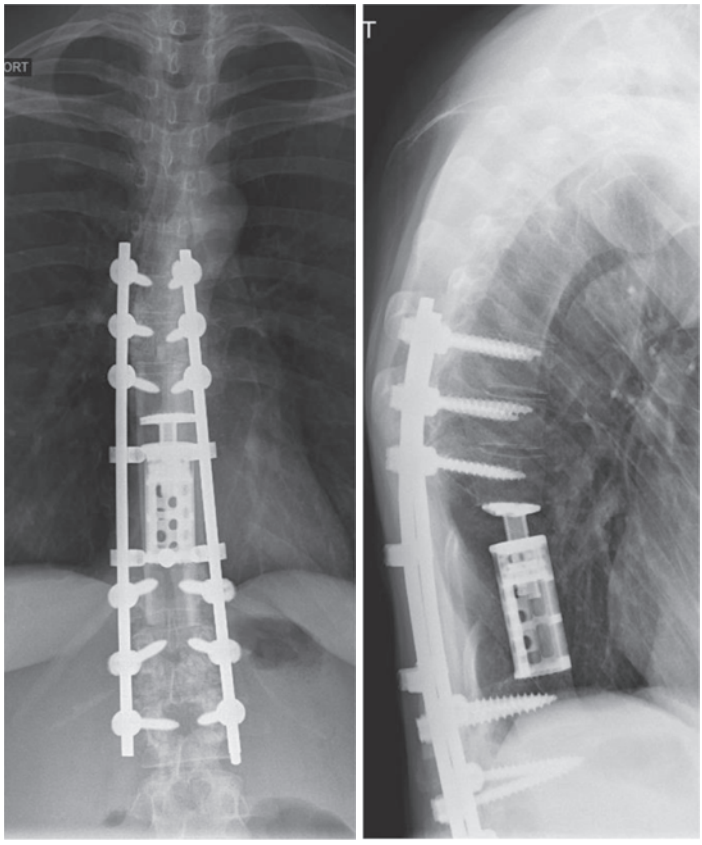

Fig. 6.9 Postoperative radiographs after T10-T11 en bloc resection of tumor with partial T9 corpectomy, T9-T12 anterior interbody fusion, and T7-L2 posterior spinal instrumented fusion

Conclusion

Chondrosarcoma is the second most common primary malignant bone tumor of the axial skeleton. Of these, spinal chondrosarcoma is more common than skull base chondrosarcoma. Spinal chondrosarcoma most commonly occurs in the thoracic and lumbar

spine. These tumors are associated with high morbidity and mortality due to their close proximity to critical neurovascular structures. Due to the limited efficacy of chemotherapy and radiation therapy for the majority of spinal chondrosarcomas, en bloc resection with negative margins is the primary therapeutic modality. Wide resection is associated with high morbidity and should be performed at a high-volume center with a team that has considerable experience in treating these tumors. A multidisciplinary approach with radiation oncology, medical oncology, vascular/thoracic surgery, plastic surgery, and the spinal oncology team is recommended.

References

1. Giuffrida AY, Burgueno JE, Koniaris LG, Guiterrez JC, Duncan R, Scully SP. Chondrosarcoma in the United States (1973 to 2003): an analysis of 2890 cases from the SEER database. J Bone Joint Surg Am. 2009;91:1063–72.
2. Boriani S, De Iure F, Bandiera S, et al. Chondrosarcoma of the mobile spine: report on 22 cases. Spine (Phila Pa 1976). 2000;25(7):804–12.
3. Kerr DA, Rosenberg AE. Pathology of chordoma and chondrosarcoma of the axial skeleton. In: Harsh GR, Vaz-Guimaraes F, editors. Chordomas and chondrosarcomas of the skull base and spine. 2nd ed. London: Academic Press; 2018. p. 11–21.
4. Fisher CG, Versteeg AL, Dea N, et al. Surgical management of spinal chondrosarcomas. Spine (Phila Pa 1976). 2016;41(8):678–85.
5. Korten AG, ter Berg HJ, Spincemaille GH, van der Laan RT, van de Wel AM. Intracranial chondrosarcoma: review of the literature and report of 15 cases. J Neurol Neurosurg Psychiatry. 1998;65(1):88–92.
6. Al-Mefty K, Pravdenkova S, Colli BO, Al-Mefty O, Gokden M. Chordoma and chondrosarcoma: similar, but quite different, skull base tumors. Cancer. 2007;110(11):2457–67.
7. York JE, Berk RH, Fuller GN, et al. Chondrosarcoma of the spine: 1954-1997. J Neurosurg. 1999;90:73–8.
8. Rosenberg AE, Nielsen GP, Keel SB, et al. Chondrosarcoma of the base of the skull: a clinicopathologic study of 200 cases with emphasis on its distinction from chordoma. Am J Surg Pathol. 1999;23(11):1370–8.
9. Shives TC, McLeod RA, Unni KK, Schray MF. Chondrosarcoma of the spine. J Bone Joint Surg Am. 1989;71(8):1158–65.
10. Enneking WF. Staging of musculoskeletal neoplasms. In: Sundaresan N, Schmidek HH, Schiller AL, Rosenthal DI, editors. Tumors of the spine:

diagnosis and clinical management. Philadelphia: W.B. Saunders; 1990. p. 22–33.
11. Boriani S, Weinstein JN, Biagini R. Primary bone tumors of the spine: terminology and surgical staging. Spine (Phila Pa 1976). 1997;22(9):1036–44.
12. Chan P, Boriani S, Fourney DR, et al. An assessment of the reliability of the Enneking and Weinstein-Boriani-Biagini classifications for staging of primary spinal tumors by the Spine Oncology Study Group. Spine (Phila Pa 1976). 2009;34(4):384–91.
13. Hirsh LF, Thanki A, Spector HB. Primary spinal chondrosarcoma with 18-year follow-up: case report and literature review. Neurosurgery. 1984;14(6):747–9.
14. World Health Organization. Cartilage tumors. In: Fletcher CDM, Unni KK, Mertens F, eds. World Health Organization classification of tumors. Pathology and genetics. Tumors of soft tissue and bone. IARC Press; 150 Cours Albert Thomas, 69372 Lyon CEDEX 08, France. 2002: 234–57.
15. Angelini A, Guerra G, Mavrogenis AF, Pala E, Picci P, Ruggieri P. Clinical outcome of central conventional chondrosarcoma. J Surg Oncol. 2012;106(8):929–37.
16. Doyle L. Sarcoma classification: an update based on the 2013 World Health Organization classification of tumors of soft tissue and bone. Cancer. 2014;120(12):1763–74.
17. Katonis P, Alpantaki K, Michail K, et al. Spinal chondrosarcoma: a review. Sarcoma. 2011;2011:378957.
18. Gitelis S, Bertoni F, Picci P, Campanacci M. Chondrosarcoma of bone. The experience of the Istituto Ortopedico Rissoli. J Bone Joint Surg Am. 1981;63(8):1248–57.
19. Zoccali C, Baldi J, Attali D, et al. Intralesional vs. extralesional procedures for low-grade central chondrosarcoma: a systematic review of the literature. Arch Orthop Trauma Surg. 2018;138(7):929–37.
20. Zhou Q, Yang C, Chen M, Li L. Detection of exostosis glycosyltransferase gene mutation in non-hereditary osteochondromas of the mandibular condyle. Mol Clin Oncol. 2016;5(3):295–9.
21. Gelderblom H, Hongendoorn PC, Dijkstra SD, et al. The clinical approach towards chondrosarcoma. Oncologist. 2008;13(3):320–9.
22. Arshi A, Sharim J, Park DY, et al. Chondrosarcoma of the osseous spine: an analysis of epidemiology, patient outcomes, and prognostic factors using the SEER Registry from 1973 to 2012. Spine (Phila Pa 1976). 2017;42(9):644–52.
23. Hallor KH, Staaf J, Bovee JVMG, et al. Genomic profiling of chondrosarcoma: chromosomal patterns in central and peripheral tumors. Clin Cancer Res. 2009;15(8):2685–94.
24. de Andrera CE, Reijnders CM, Kroon HM, et al. Secondary peripheral chondrosarcoma evolving from osteochondroma as a result of outgrowth of cells with functional EXT. Oncogene. 2012;31:1095–104.

25. Schrage YM, Lam S, Jochemsen AG, et al. Central chondrosarcoma progression is associated with pRb pathway alterations: CDK4 downregulation and p16 overexpression inhibit cell growth in vitro. J Cell Mol Med. 2009;13(9A):2843–52.
26. Bovee JV, Hogendoorn PC, Wuner JS, Alman BA. Cartilage tumors and bone development: molecular pathology and possible therapeutic targets. Nat Rev Cancer. 2010;10(7):481–8.
27. Mechri M, Riahi H, Sboui I, Bouaziz M, Vanhoenacker F, Ladeb M. Imaging of malignant primitive tumors of the spine. J Belg Soc Radiol. 2018;102(1):56.
28. Liu G, Wu G, Ghimire P, et al. Primary spinal chondrosarcoma: radiologic manifestations with histopathological correlation in eight patients and literature review. Clin Imaging. 2013;37(1):124–33.
29. Nooij MA, Whelan J, Bramwell VH, et al. Doxorubicin and cisplatin chemotherapy in high-grade spindle cell sarcomas of the bone, other than osteosarcoma or malignant fibrous histiocytoma: a European Osteosarcoma Intergroup study. Eur J Cancer. 2005;41(2):225–30.
30. Frezza AM, Cesari M, Baumhoer D, et al. Mesenchymal chondrosarcoma: prognostic factors and outcome in 113 patients. Eur J Cancer. 2015;51:374–81.
31. Whelan JS, Davis LE. Osteosarcoma, chondrosarcoma, and chordoma. J Clin Oncol. 2017;36(2):188–93.
32. Hsu W, Kosztowski TA, Zaidi HA, et al. Multidisciplinary management of primary tumors of the vertebral column. Curr Treat Options in Oncol. 2009;10:107–25.
33. Trieb K, Sulzbacher I, Kubista B. Recurrence rate and progression of chondrosarcoma is correlated with heat shock protein expression. Oncol Lett. 2016;11(1):521–4.
34. van Oosterwijk JG, Herpers B, Meijer D, et al. Restoration of chemosensitivity for doxorubicin and cisplatin in chondrosarcoma in vitro: BCL-2 family members cause chemoresistance. Ann Oncol. 2012;23(6):1617–26.
35. Thanindratarn P, Dean DC, Nelson SD, Hornicek FJ, Duan Z. Advances in immune checkpoint inhibitors for bone sarcoma therapy. J Bone Oncol. 2019;15:100221.
36. de Amorim Bernstein K, Delaney T. Chordomas and chondrosarcomas – the role of radiation therapy. J Surg Oncol. 2016;114:564–9.
37. Holliday EB, Mitra HS, Somerson JS, et al. Postoperative proton therapy for chordomas and chondrosarcomas of the spine. Spine (Phila Pa 1976). 2015;40(8):544–9.
38. Delaney TF, Liebsch NJ, Pedlow FX, et al. Long-term results of phase II study of high dose photon/proton radiotherapy in the management of spine chordomas, chondrosarcomas, and other sarcomas. J Surg Oncol. 2014;110:115–22.

39. Boriani S, Saravanja D, Yamada Y, Varga PP, Biagini R, Fisher CG. Challenges of local recurrence and cure in low grade malignant tumors of the spine. Spine (Phila Pa 1976). 2009;34(22S):S48–57.
40. Weinstein JN, McLain RF. Primary tumors of the spine. Spine (Phila Pa 1976). 1987;12(9):843–51.
41. Boriani S, Biagini R, De Iure F. En bloc resections of bone tumors of the thoracolumbar spine. A preliminary report on 29 patients. Spine (Phila Pa 1976). 1996;21(16):1927–31.
42. Sundaresan N, Steinberger AA, Moore F, et al. Indications and results of combined anterior-posterior approaches for spine tumor surgery. J Neurosurg. 1996;85(3):438–46.
43. Fisher CG, Keynan O, Boyd MC, Dvorak MF. The surgical management of primary tumors of the spine: initial results of an ongoing prospective cohort study. Spine (Phila Pa 1976). 2005;30(16):1899–908.
44. Cloyd JM, Acosta FL, Polley M, Ames CP. En bloc resection for primary and metastatic tumors of the spine: a systematic review of the literature. Neurosurgery. 2010;67:435–45.
45. Amendola L, Capuccio M, De Iure F, Bandiera S, Gasbarrini A, Boriani S. En bloc resections for primary spinal tumors in 20 years of experience: effectiveness and safety. Spine J. 2014;14(11):2608–17.
46. Sundaresan N, DiGiacinto GV, Krol G, Hughes JE. Spondylectomy for malignant tumors of the spine. J Clin Oncol. 1989;7(10):1485–91.
47. Stener B. Total spondylectomy in chondrosarcoma arising from the seventh thoracic vertebra. J Bone Joint Surg Br. 1971;53(2):288–95.
48. Stener B. Complete removal of vertebrae for extirpation of tumors. A 20-year experience. Clin Orthop Relat Res. 1989;245:72–82.
49. Fidler MW. Radical resection of vertebral body tumors. A surgical technique used in ten cases. J Bone Joint Surg Br. 1994;76(5):765–72.
50. Tomita K, Kawahara N, Baba HH, Tsuchiya H, Fujita T, Toribatake Y. Total en bloc spondylectomy. A new surgical technique for primary malignant vertebral tumors. Spine (Phila Pa 1976). 1997;22(3):324–33.
51. Fourney DR, Abi-Said D, Rhines LD, et al. Simultaneous anterior-posterior approach to the thoracic and lumbar spine for the radical resection of tumors followed by reconstruction and stabilization. J Neurosurg. 2001;94(2 Suppl):232–44.
52. Tomita K, Kawahara N, Murakami H, Demura S. Total en bloc spondylectomy for spinal tumors: improvement of the technique and its associated basic background. J Orthop Sci. 2006;11(1):3–12.
53. Shah AA, Paulino Pereira NR, Pedlow FX, et al. Modified en bloc spondylectomy for tumors of the thoracic and lumbar spine: surgical technique and outcomes. J Bone Joint Surg Am. 2017;99(17):1476–84.
54. Boriani S, Bandiera S, Donthineni R, et al. Morbidity of en bloc resections in the spine. Eur Spine J. 2010;19(2):231–41.

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

F. J. Hornicek (ed.), *Chondrosarcoma*,
https://doi.org/10.1007/978-3-030-74572-1_7

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.

Bibliography

1. Leddy LR, Holmes RE. Chondrosarcoma of bone. Cancer Treat Res. 2014;162:117–30.
2. Jo VY, Doyle LA. Refinements in sarcoma classification in the current 2013 world health organization classification of tumours of soft tissue and bone. Surg Oncol Clin N Am. 2016;25(4):621–43.

3. Fiorenza F, Abudu A, Grimer RJ, Carter SR, Tillman RM, Ayoub K, et al. Risk factors for survival and local control in chondrosarcoma of bone. J Bone Joint Surg. 2002;84(1):93–9.
4. Staals EL, Bacchini P, Bertoni F. Dedifferentiated central chondrosarcoma. Cancer. 2006;106(12):2682–91.
5. Miao R, Choy E, Raskin KA, Schwab JH, Nielsen GP, Deshpande V, et al. Prognostic factors in dedifferentiated chondrosarcoma: a retrospective analysis of a large series treated at a single institution. Sarcoma. 2019;2019:9069272.
6. Mendenhall WM, Reith JD, Scarborough MT, Stechmiller BK, Mendenhall NP. Mesenchymal chondrosarcoma. Int J Part Ther. 2016;3(2):300–4.
7. Cesari M, Bertoni F, Bacchini P, Mercuri M, Palmerini E, Ferrari S. Mesenchymal chondrosarcoma. An analysis of patients treated at a single institution. Tumori. 2007;93(5):423–7.
8. Frezza AM, Cesari M, Baumhoer D, Biau D, Bielack S, Campanacci DA, et al. Mesenchymal chondrosarcoma: prognostic factors and outcome in 113 patients. A European Musculoskeletal Oncology Society study. Eur J Cancer. 2015;51(3):374–81.
9. Kawaguchi S, Weiss I, Lin PP, Huh WW, Lewis VO. Radiation therapy is associated with fewer recurrences in mesenchymal chondrosarcoma. Clin Orthop Relat Res. 2014;472(3):856–64.
10. Xu J, Li D, Xie L, Tang S, Guo W. Mesenchymal chondrosarcoma of bone and soft tissue: a systematic review of 107 patients in the past 20 years. PLoS One. 2015;10(4):e0122216.
11. Lin PP, Moussallem CD, Deavers MT. Secondary chondrosarcoma. J Am Acad Orthop Surg. 2010;18(10):608–15.
12. Klein A, Tauscher F, Birkenmaier C, Baur-Melnyk A, Knösel T, Jansson V, et al. Clear cell chondrosarcoma is an underestimated tumor: report of 7 cases and meta-analysis of the literature. J Bone Oncol. 2019;19:100267.
13. Mavrogenis AF, Angelini A, Vottis C, Palmerini E, Rimondi E, Rossi G, et al. State-of-the-art approach for bone sarcomas. Eur J Orthop Surg Traumatol. 2015;25(1):5–15.
14. Marco RA, Gitelis S, Brebach GT, Healey JH. Cartilage tumors: evaluation and treatment. J Am Acad Orthop Surg. 2000;8(5):292–304.
15. Flemming DJ, Murphey MD. Enchondroma and chondrosarcoma. Semin Musculoskelet Radiol. 2000;4(1):59–71.
16. Murphey MD, Flemming DJ, Boyea SR, Bojescul JA, Sweet DE, Temple HT. Enchondroma versus chondrosarcoma in the appendicular skeleton: differentiating features. Radiographics. 1998;18(5):1213–37; quiz 44-5.
17. Parlier-Cuau C, Bousson V, Ogilvie CM, Lackman RD, Laredo JD. When should we biopsy a solitary central cartilaginous tumor of long bones? Literature review and management proposal. Eur J Radiol. 2011;77(1):6–12.
18. Geirnaerdt MJ, Hogendoorn PC, Bloem JL, Taminiau AH, van der Woude HJ. Cartilaginous tumors: fast contrast-enhanced MR imaging. Radiology. 2000;214(2):539–46.

19. Oliveira I, Chavda A, Rajakulasingam R, Saifuddin A. Chondral tumours: discrepancy rate between needle biopsy and surgical histology. Skelet Radiol. 2020;49(7):1115–25.
20. Saifuddin A, Oliveira I, Singla N, Chavda A, Khoo M, O'Donnell P. The importance of MRI review following the diagnosis of atypical cartilaginous tumour using image-guided needle biopsy. Skeletal Radiol. 2020.
21. Gelderblom H, Hogendoorn PC, Dijkstra SD, van Rijswijk CS, Krol AD, Taminiau AH, et al. The clinical approach towards chondrosarcoma. Oncologist. 2008;13(3):320–9.
22. Enneking WF, Spanier SS, Goodman MA. A system for the surgical staging of musculoskeletal sarcoma. Clin Orthop Relat Res. 1980;153: 106–20.
23. Mohler DG, Chiu R, McCall DA, Avedian RS. Curettage and cryosurgery for low-grade cartilage tumors is associated with low recurrence and high function. Clin Orthop Relat Res. 2010;468(10):2765–73.
24. Aarons C, Potter BK, Adams SC, Pitcher JD Jr, Temple HT. Extended intralesional treatment versus resection of low-grade chondrosarcomas. Clin Orthop Relat Res. 2009;467(8):2105–11.
25. Campanacci DA, Scoccianti G, Franchi A, Roselli G, Beltrami G, Ippolito M, et al. Surgical treatment of central grade 1 chondrosarcoma of the appendicular skeleton. J Orthop Traumatol. 2013;14(2):101–7.
26. Leerapun T, Hugate RR, Inwards CY, Scully SP, Sim FH. Surgical management of conventional grade I chondrosarcoma of long bones. Clin Orthop Relat Res. 2007;463:166–72.
27. Schwab JH, Wenger D, Unni K, Sim FH. Does local recurrence impact survival in low-grade chondrosarcoma of the long bones? Clin Orthop Relat Res. 2007;462:175–80.
28. Shemesh SS, Acevedo-Nieves JD, Pretell-Mazzini J. Treatment strategies for central low-grade chondrosarcoma of long bones: a systematic review of the literature and meta-analysis. Musculoskelet Surg. 2018;102(2): 95–109.
29. Chen X, Yu LJ, Peng HM, Jiang C, Ye CH, Zhu SB, et al. Is intralesional resection suitable for central grade 1 chondrosarcoma: a systematic review and updated meta-analysis. Eur J Surg Oncol. 2017;43(9):1718–26.
30. Dierselhuis EF, Goulding KA, Stevens M, Jutte PC. Intralesional treatment versus wide resection for central low-grade chondrosarcoma of the long bones. Cochrane Database Syst Rev. 2019;3(3):Cd010778.
31. Meader N, King K, Llewellyn A, Norman G, Brown J, Rodgers M, et al. A checklist designed to aid consistency and reproducibility of GRADE assessments: development and pilot validation. Syst Rev. 2014;3:82.
32. Lee FY, Mankin HJ, Fondren G, Gebhardt MC, Springfield DS, Rosenberg AE, et al. Chondrosarcoma of bone: an assessment of outcome. J Bone Joint Surg Am. 1999;81(3):326–38.

33. Grimer RJ, Gosheger G, Taminiau A, Biau D, Matejovsky Z, Kollender Y, et al. Dedifferentiated chondrosarcoma: prognostic factors and outcome from a European group. Eur J Cancer. 2007;43(14):2060–5.
34. de Camargo OP, Baptista AM, Atanásio MJ, Waisberg DR. Chondrosarcoma of bone: lessons from 46 operated cases in a single institution. Clin Orthop Relat Res. 2010;468(11):2969–75.
35. Folkert IW, Devalaraja S, Linette GP, Weber K, Haldar M. Primary bone tumors: challenges and opportunities for CAR-T therapies. J Bone Mineral Res. 2019;34(10):1780–8.
36. Alemany R, Moura DS, Redondo A, Martinez-Trufero J, Calabuig S, Saus C, et al. Nilotinib as coadjuvant treatment with doxorubicin in patients with sarcomas: a phase I trial of the spanish group for research on sarcoma. Clin Cancer Res. 2018;24(21):5239–49.
37. Bilusic M, Heery CR, Collins JM, Donahue RN, Palena C, Madan RA, et al. Phase I trial of HuMax-IL8 (BMS-986253), an anti-IL-8 monoclonal antibody, in patients with metastatic or unresectable solid tumors. J Immunother Cancer. 2019;7(1):240.
38. Morioka H, Takahashi S, Araki N, Sugiura H, Ueda T, Takahashi M, et al. Results of sub-analysis of a phase 2 study on trabectedin treatment for extraskeletal myxoid chondrosarcoma and mesenchymal chondrosarcoma. BMC Cancer. 2016;16:479.
39. Miwa S, Nishida H, Tanzawa Y, Takeuchi A, Hayashi K, Yamamoto N, et al. Phase 1/2 study of immunotherapy with dendritic cells pulsed with autologous tumor lysate in patients with refractory bone and soft tissue sarcoma. Cancer. 2017;123(9):1576–84.
40. Chow W, Frankel P, Ruel C, Araujo DM, Milhem M, Okuno S, et al. Results of a prospective phase 2 study of pazopanib in patients with surgically unresectable or metastatic chondrosarcoma. Cancer. 2020; 126(1):105–11.
41. Laitinen MK, Parry MC, Le Nail LR, Wigley CH, Stevenson JD, Jeys LM. Locally recurrent chondrosarcoma of the pelvis and limbs can only be controlled by wide local excision. Bone Joint J. 2019;101-b(3): 266–71.
42. Streitbuerger A, Ahrens H, Gosheger G, Henrichs M, Balke M, Dieckmann R, et al. The treatment of locally recurrent chondrosarcoma: is extensive further surgery justified? J Bone Joint Surg. 2012;94(1):122–7.
43. Ruggieri P, Mavrogenis AF, Casadei R, Errani C, Angelini A, Calabrò T, et al. Protocol of surgical treatment of long bone pathological fractures. Injury. 2010;41(11):1161–7.
44. Scully SP, Ghert MA, Zurakowski D, Thompson RC, Gebhardt MC. Pathologic fracture in osteosarcoma : prognostic importance and treatment implications. J Bone Joint Surg Am. 2002;84(1):49–57.

45. Albergo JI, Gaston CL, Jeys LM, Khajuria A, Carter SR, Tillman RM, et al. Management and prognostic significance of pathological fractures through chondrosarcoma of the femur. Int Orthop. 2015;39(5):943–6.
46. Chandrasekar CR, Grimer RJ, Carter SR, Tillman RM, Abudu AT, Jeys LM. Outcome of pathologic fractures of the proximal femur in nonosteogenic primary bone sarcoma. Eur J Surg Oncol. 2011;37(6):532–6.
47. Bramer JA, Abudu AA, Grimer RJ, Carter SR, Tillman RM. Do pathological fractures influence survival and local recurrence rate in bony sarcomas? Eur J Cancer. 2007;43(13):1944–51.
48. Omlor GW, Lohnherr V, Hetto P, Gantz S, Fellenberg J, Merle C, et al. Surgical therapy of benign and low-grade malignant intramedullary chondroid lesions of the distal femur: intralesional resection and bone cement filling with or without osteosynthesis. Strategies Trauma Limb Reconstr. 2018;13(3):163–70.
49. Omlor GW, Lohnherr V, Lange J, Gantz S, Merle C, Fellenberg J, et al. Enchondromas and atypical cartilaginous tumors at the proximal humerus treated with intralesional resection and bone cement filling with or without osteosynthesis: retrospective analysis of 42 cases with 6 years mean follow-up. World J Surg Oncol. 2018;16(1):139.
50. Rosen G, Marcove RC, Caparros B, Nirenberg A, Kosloff C, Huvos AG. Primary osteogenic sarcoma: the rationale for preoperative chemotherapy and delayed surgery. Cancer. 1979;43(6):2163–77.
51. Rosen G, Tan C, Sanmaneechai A, Beattie EJ Jr, Marcove R, Murphy ML. The rationale for multiple drug chemotherapy in the treatment of osteogenic sarcoma. Cancer. 1975;35(3 suppl):936–45.
52. Provisor AJ, Ettinger LJ, Nachman JB, Krailo MD, Makley JT, Yunis EJ, et al. Treatment of nonmetastatic osteosarcoma of the extremity with preoperative and postoperative chemotherapy: a report from the Children's Cancer Group. J Clin Oncol. 1997;15(1):76–84.
53. Simon MA, Aschliman MA, Thomas N, Mankin HJ. Limb-salvage treatment versus amputation for osteosarcoma of the distal end of the femur. J Bone Joint Surg Am. 1986;68(9):1331–7.
54. Eilber FR, Mirra JJ, Grant TT, Weisenburger T, Morton DL. Is amputation necessary for sarcomas? A seven-year experience with limb salvage. Ann Surg. 1980;192(4):431–8.
55. Berrey BH Jr, Lord CF, Gebhardt MC, Mankin HJ. Fractures of allografts. Frequency, treatment, and end-results. J Bone Joint Surg Am. 1990;72(6):825–33.
56. Dick HM, Malinin TI, Mnaymneh WA. Massive allograft implantation following radical resection of high-grade tumors requiring adjuvant chemotherapy treatment. Clin Orthop Relat Res. 1985;197:88–95.
57. Mnaymneh W, Malinin TI, Makley JT, Dick HM. Massive osteoarticular allografts in the reconstruction of extremities following resection of tumors not requiring chemotherapy and radiation. Clin Orthop Relat Res. 1985;197:76–87.

58. Hornicek FJ, Gebhardt MC, Tomford WW, Sorger JI, Zavatta M, Menzner JP, et al. Factors affecting nonunion of the allograft-host junction. Clin Orthop Relat Res. 2001;382:87–98.
59. Safran MR, Kody MH, Namba RS, Larson KR, Kabo JM, Dorey FJ, et al. 151 endoprosthetic reconstructions for patients with primary tumors involving bone. Contemp Orthop. 1994;29(1):15–25.
60. Unwin PS, Cannon SR, Grimer RJ, Kemp HB, Sneath RS, Walker PS. Aseptic loosening in cemented custom-made prosthetic replacements for bone tumours of the lower limb. J Bone Joint Surg. 1996;78(1):5–13.
61. Horowitz SM, Glasser DB, Lane JM, Healey JH. Prosthetic and extremity survivorship after limb salvage for sarcoma. How long do the reconstructions last? Clin Orthop Relat Res. 1993;(293):280–6.
62. Fox EJ, Hau MA, Gebhardt MC, Hornicek FJ, Tomford WW, Mankin HJ. Long-term follow-up of proximal femoral allografts. Clin Orthop Relat Res. 2002;397:106–13.
63. Capanna R, Bufalini C, Campanacci M. A new technique for reconstructions of large metadiaphyseal bone defects. Orthop Traumatol. 1993;2(3):159–77.
64. Campanacci DA, Totti F, Puccini S, Beltrami G, Scoccianti G, Delcroix L, et al. Intercalary reconstruction of femur after tumour resection: is a vascularized fibular autograft plus allograft a long-lasting solution? Bone Joint J. 2018;100-b(3):378–86.
65. Houdek MT, Rose PS, Milbrandt TA, Stans AA, Moran SL, Sim FH. Comparison of pediatric intercalary allograft reconstructions with and without a free vascularized fibula. Plast Reconstr Surg. 2018;142(4):1065–71.
66. Hsu RW, Wood MB, Sim FH, Chao EY. Free vascularised fibular grafting for reconstruction after tumour resection. J Bone Joint Surg. 1997;79(1):36–42.
67. Shea KG, Coleman DA, Scott SM, Coleman SS, Christianson M. Microvascularized free fibular grafts for reconstruction of skeletal defects after tumor resection. J Pediatr Orthop. 1997;17(4):424–32.
68. Chen CM, Disa JJ, Lee HY, Mehrara BJ, Hu QY, Nathan S, et al. Reconstruction of extremity long bone defects after sarcoma resection with vascularized fibula flaps: a 10-year review. Plast Reconstr Surg. 2007;119(3):915–24; discussion 25-6.
69. Henderson ER, Groundland JS, Pala E, Dennis JA, Wooten R, Cheong D, et al. Failure mode classification for tumor endoprostheses: retrospective review of five institutions and a literature review. J Bone Joint Surg Am. 2011;93(5):418–29.
70. Grimer RJ, Aydin BK, Wafa H, Carter SR, Jeys L, Abudu A, et al. Very long-term outcomes after endoprosthetic replacement for malignant tumours of bone. Bone Joint J. 2016;98-b(6):857–64.
71. Holm CE, Bardram C, Riecke AF, Horstmann P, Petersen MM. Implant and limb survival after resection of primary bone tumors of the lower

extremities and reconstruction with mega-prostheses fifty patients followed for a mean of fourteen years. Int Orthop. 2018;42(5):1175–81.
72. Asavamongkolkul A, Eckardt JJ, Eilber FR, Dorey FJ, Ward WG, Kelly CM, et al. Endoprosthetic reconstruction for malignant upper extremity tumors. Clin Orthop Relat Res. 1999;360:207–20.
73. Bernthal NM, Schwartz AJ, Oakes DA, Kabo JM, Eckardt JJ. How long do endoprosthetic reconstructions for proximal femoral tumors last? Clin Orthop Relat Res. 2010;468(11):2867–74.
74. Schwartz AJ, Kabo JM, Eilber FC, Eilber FR, Eckardt JJ. Cemented distal femoral endoprostheses for musculoskeletal tumor: improved survival of modular versus custom implants. Clin Orthop Relat Res. 2010;468(8):2198–210.
75. Lesensky J, Prince DE. Distraction osteogenesis reconstruction of large segmental bone defects after primary tumor resection: pitfalls and benefits. Eur J Orthop Surg Traumatol. 2017;27(6):715–27.
76. Tsuchiya H, Tomita K, Minematsu K, Mori Y, Asada N, Kitano S. Limb salvage using distraction osteogenesis. A classification of the technique. J Bone Joint Surg. 1997;79(3):403–11.
77. Watanabe K, Tsuchiya H, Yamamoto N, Shirai T, Nishida H, Hayashi K, et al. Over 10-year follow-up of functional outcome in patients with bone tumors reconstructed using distraction osteogenesis. J Orthop Sci. 2013;18(1):101–9.
78. Hottya GA, Steinbach LS, Johnston JO, van Kuijk C, Genant HK. Chondrosarcoma of the foot: imaging, surgical and pathological correlation of three new cases. Skelet Radiol. 1999;28(3):153–8.
79. Palmieri TJ. Chondrosarcoma of the hand. J Hand Surg Am. 1984;9(3):332–8.
80. Ogose A, Unni KK, Swee RG, May GK, Rowland CM, Sim FH. Chondrosarcoma of small bones of the hands and feet. Cancer. 1997;80(1):50–9.
81. Fayad LM, Ahlawat S, Khan MS, McCarthy E. Chondrosarcomas of the hands and feet: a case series and systematic review of the literature. Eur J Radiol. 2015;84(10):2004–12.
82. González Del Pino J, Lozano Calderón SA, Chebib I, Jupiter JB. Intralesional versus wide resection of low-grade chondrosarcomas of the hand. J Hand Surg Am. 2016;41(4):541–9.e5.
83. Mittermayer F, Dominkus M, Krepler P, Schwameis E, Sluga M, Toma C, et al. Chondrosarcoma of the hand: is a wide surgical resection necessary? Clin Orthop Relat Res. 2004;424:211–5.
84. Patil S, de Silva MV, Crossan J, Reid R. Chondrosarcoma of small bones of the hand. J Hand Surg Br. 2003;28(6):602–8.
85. Bovée JV, van der Heul RO, Taminiau AH, Hogendoorn PC. Chondrosarcoma of the phalanx: a locally aggressive lesion with minimal metastatic potential: a report of 35 cases and a review of the literature. Cancer. 1999;86(9):1724–32.

86. Toepfer A, Harrasser N, Recker M, Lenze U, Pohlig F, Gerdesmeyer L, et al. Distribution patterns of foot and ankle tumors: a university tumor institute experience. BMC Cancer. 2018;18(1):735.
87. Yang P, Evans S, Bali N, Ramasamy A, Evans R, Stevenson J, et al. Malignant bone tumours of the foot. Ann R Coll Surg Engl. 2017;99(7):568–72.
88. Patil S, de Silva MV, Crossan J, Reid R. Chondrosarcoma of the bones of the feet. J Foot Ankle Surg. 2003;42(5):290–5.

8 Chondrosarcoma of the Hand

Karren Takamura and Neil Ford Jones

Introduction

Chondrosarcoma of the hand was first described by Jaffe and Lichtenstein in 1943. Chondrosarcomas are typically found in the pelvis, femur, and humerus [1, 2], but their occurrence in the hand is rare [3–5]. However, chondrosarcoma is the most common primary bony malignancy found in the hand, accounting for 4–10% of all malignant tumors of the hand [5, 6]. In general, chondrosarcomas are slow-growing tumors [7] that behave as locally aggressive lesions in the hand, though metastasis is rare with a late onset [8].

Distinguishing between chondrosarcomas and enchondromas of the hand can be challenging [9, 10] due to the increased cellularity of enchondromas in the hand [8] with similar clinical findings as chondrosarcomas [8, 11]. Enchondromas are the most common primary bone tumor of the hand [12], with up to 54% of all enchondromas being found in the hand and wrist [13]. It is important to distinguish the difference between the two; chondrosarcomas require more prompt and radical treatment as they are locally aggressive [8, 14].

K. Takamura (✉) · N. F. Jones
Department of Orthopaedic Surgery, University of California, Los Angeles, Santa Monica, CA, USA
e-mail: ktakamura@mednet.ucla.edu; nfjones@mednet.ucla.edu

F. J. Hornicek (ed.), *Chondrosarcoma*,
https://doi.org/10.1007/978-3-030-74572-1_8

Clinical Presentation

Pain and progressive swelling are common clinical signs reported in the literature [3, 6, 8, 9, 15, 16]. Fayad et al., in a study of 24 cases of chondrosarcoma in hands and feet, found the presence of a palpable mass to be the most common presenting feature in 73% of patients, and 43% of patients reported pain [15]. Pain cannot be used to differentiate between chondrosarcomas and enchondromas, as patients with enchondromas can also present with pain [17]. In Palmieri's series of 18 patients with chondrosarcoma of the hand, 72% reported pain, with a pathologic fracture causing the pain in 27% of patients [6]. A painful, enlarging osseous swelling should always make the clinician suspicious for chondrosarcoma [6, 18], especially in a patient older than 50 years of age [19]. Additionally, local pain or recurrence of mass after a removal of a benign chondral lesion should alert the clinician to the possibility of a chondrosarcoma [18]. There is no gender predilection for chondrosarcoma [3, 5, 6, 9], and the average age of patients is older compared to patients with enchondroma of the digits [15, 20]. Chondrosarcoma of the hand is typically found in patients between the ages of 60 and 80; however, the age at diagnosis is often a few years after symptoms first appear [6]. Some patients present with long duration of symptoms, with some patients reporting 10–60 years of swelling before presenting for evaluation [5, 19]. Roberts et al. found an average of 19 years of symptoms among older patients in their series, with one patient waiting as long as 72 years before presenting for treatment [19]. Therefore, long duration of symptoms should not preclude clinical suspicion of malignancy.

The proximal phalanx is the most common site for chondrosarcoma found in the short tubular bones of the hand and feet [5, 6, 9, 15, 17], with equal distribution over the five rays [5, 8]. A majority of the lesions originate endosteally near the site of former epiphyseal growth plate [19], and most of the lesions are present centrally [6].

Imaging

Radiographic features are critical in the diagnosis of chondrosarcoma, though radiographic distinction between chondrosarcoma and enchondroma can be challenging [17]. Both chondrosarcoma and enchondroma can display cortical expansion and calcification of cartilaginous matrix; however, cortical destruction and soft tissue extension are features distinctive to chondrosarcoma (Fig. 8.1) [3, 9]. Chondrosarcomas have lytic areas of destruction that most often lack the well-defined margins typically seen in enchondromas [3, 6]. A majority of the chondrosarcoma lesions have mineralized matrix with scattered punctate calcifications within the affected bone or in the related soft tissue tumor [3, 5, 6, 8, 15, 17]. In a review of 111 chondrosarcomas found in the feet and hands, endosteal erosion, cortical destruction, and expansion were observed in over 90%, and soft tissue expansion was present in 80% of cases [17]. Both chondrosarcomas and enchondromas can present with pathologic fractures [3, 15].

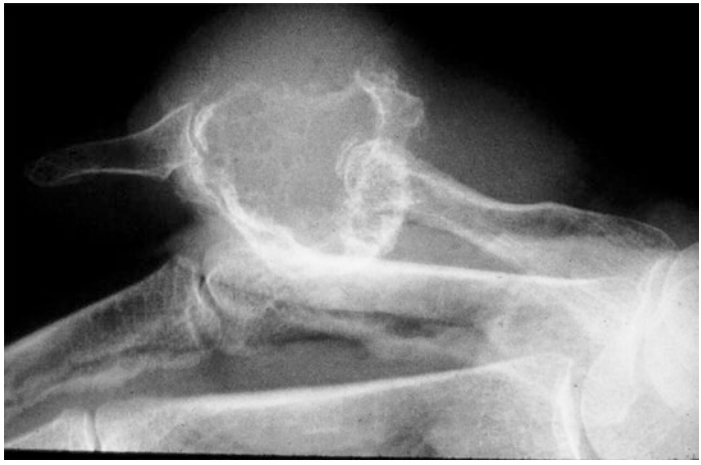

Fig. 8.1 Radiograph demonstrating a lateral view of a chondrosarcoma of the middle phalanx. There is a destructive, lytic lesion with cortical disruption, consistent with chondrosarcoma

Not all chondrosarcomas demonstrate radiographic features of malignancy [9, 21]. Cawte et al. compared 12 cases of chondrosarcomas found in the hands and feet to 12 cases of enchondromas, also in the hands and feet, and found periosteal reaction, cortical destruction, and soft tissue extension to be radiographic features found only in the chondrosarcoma group [9]. It is interesting to note that 3 of the 12 chondrosarcoma cases diagnosed as malignant with histology did not demonstrate any radiographic signs of malignancy. While radiographs can provide helpful information on the malignant nature of the lesion, malignant features are not always present; therefore, close monitoring is indicated in cases where patients have clinical signs of possible malignancy, such as aggressive enlargement of the lesion.

Advanced Imaging

On magnetic resonance image (MRI), chondrosarcomas have homogenous, iso- to low intensity signal on T1-weighted imaging and heterogeneous, high signal intensity with areas of low signal intensity on T2-weighted imaging [22–26]. With gadolinium contrast, the tumor has heterogeneous enhancement [23, 24] and can have enhancement of the peripheral area with high signal intensities in the cortex, suggesting bone permeation [22]. MRI is also useful in determining the presence and extent of associated soft tissue extension. Computed tomography (CT) can also be helpful in observing cortical destruction and cortical thickening, which is rarely seen in enchondromas [22, 23]. Technetium (Tc) bone scans show areas of increased uptake at sites of bone destruction or osteolytic lesions and in the extraskeletal tumor mass [26].

Histology

Histological distinction between chondrosarcomas and enchondromas of the hand can be difficult [10, 17, 20, 27], as enchondromas in the hand demonstrate increased cellularity and more atypia when compared to other locations [10, 13, 26, 28]. Histological features that are indicative of malignancy include a high number

of binucleated cells, nuclear pleomorphism, irregular distribution, high cellularity, absence of encasement, presence of entrapment, cortical destruction, mucoid and myxoid changes, dual occupancy of lacunae, hyperchromasia, mitotic figures, and marrow permeation [3, 8, 9]. Permeation with entrapment of bony trabeculae [11] and penetration of tumor through cortex into adjacent soft tissue [3, 20] are hallmark signs of malignancy. Tumor cell infiltration between bony trabecular is not seen in enchondromas [29].

Grading of chondrosarcomas is done using criteria described by Evans et al., which include cellularity, matrix characteristics, nuclear features, and number of mitoses [30]. However, Eefting et al. found considerable histologic variation in the histologic assessment of cartilaginous tumors among 18 specialized pathologists, with the highest discordancy in the distinction between central Grade I chondrosarcomas and enchondromas [31]. Bovée et al. further argued that the grading by Evans is not useful for prognostic purposes in phalangeal chondrosarcoma because the metastatic rate is very low [8]. A cartilaginous tumor in the hand can demonstrate cellularity and variability that might be considered benign in the hand, but the same histologic appearance may be considered a low-grade chondrosarcoma in another location, such as the femur; therefore, it is important to take into account the overall behavior of the tumor [10]. In Ogose's series of 163 chondrosarcomas of the hands and feet, all Grade III tumors (n = 3) demonstrated mitotic activity, whereas only 2 of 116 Grade I and III of 44 Grade II cases showed any mitotic activity [17]. Ostrowski et al. also only reported mitoses in Grade III lesions and in one recurrent Grade II lesion [20]. Chondrosarcomas can present with benign histology despite malignant radiologic features, which may be attributed to limited biopsy specimens [17]. Therefore, a limited biopsy specimen, such as those obtained from fine needle aspiration (FNA), is of little value.

Treatment and Outcomes

Treatment of low-grade chondrosarcomas in the hand is controversial. In a series of 35 patients with phalangeal chondrosarcomas of the hands and feet, Bovée et al. noted recurrence in 10 out

of 15 tumors that underwent curettage or local resection with a mean interval of 39.3 months [8]. Of this cohort, four developed a second recurrence, and the one patient who did not undergo extensive surgery for a second recurrence developed two more recurrences. In contrast, none of the 13 patients treated by extended therapy (amputation or radical exarticulation) developed a local recurrence. Further analysis by Bovée et al. with cases from their literature review found localization to the proximal phalanx to be associated with local recurrence, and local resection of the first ray was not associated with recurrence. Furthermore, histologic features, immunohistochemical parameters, and histologic grading were not found to be associated with local recurrence. The authors concluded that although local resection and location in the proximal phalanx is associated with recurrence, curettage with adequate follow-up is justified in the first instance given the excellent survival data, especially in those cases where amputation would lead to a significant loss of function.

Ogose et al., in their series of chondrosarcomas of the hands and feet from the Mayo Clinic and consultations from outside institutions, reported recurrence in 10 out of 33 lesions found in the hand [17]. Patients who had curettage had higher rates of recurrence compared to patients who underwent amputation, although the breakdown of patients with lesions in the hand who underwent curettage and amputation was not provided in the paper [17]. The authors concluded that curettage leads to very high rate of recurrence, while amputation leads to a high rate of cure (although there was one patient who developed metastasis despite amputation). Patil et al. reported 23 cases of chondrosarcomas of the hand in the Scottish Bone Tumor Registry from 1954 to 1999; amputation was carried out in 15 cases without recurrence, and 5 out of 8 patients who underwent curettage or excision had local recurrence [5]. The median disease-free interval after curettage was 60 months (range 15–64 months). Given their findings, amputation was their recommended treatment [5]. Figure 8.2 demonstrates a female patient in her 50s who underwent ray amputation for chondrosarcoma of the index finger middle phalanx.

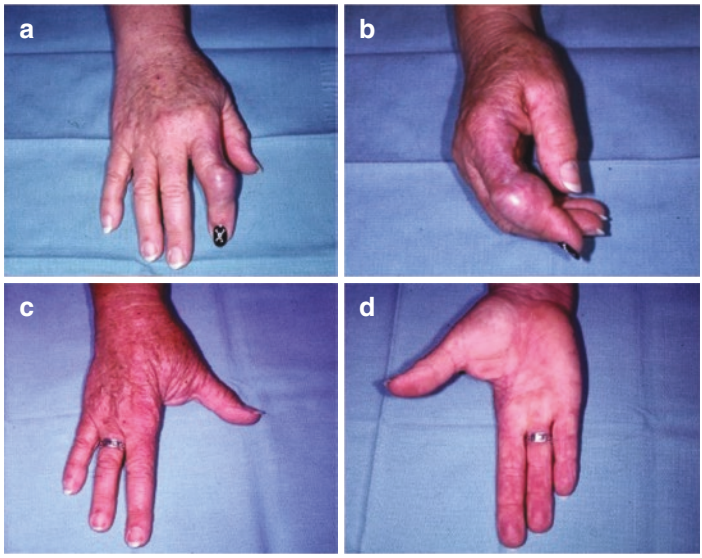

Fig. 8.2 (**a** and **b**) Preoperative clinical photos of a female in her 50s with chondrosarcoma of the index finger middle phalanx. (**c** and **d**) Same patient after index finger ray amputation

Dahlin et al. reported 30 chondrosarcomas in the hands and feet and found curettage or subtotal removal of lesions to be unsuccessful and recommended amputation of the digit, either with a complete ray or part of all of the hand or foot [3]. In cases with recurrence, the interval from treatment to first recurrence was less than 5 years in two-thirds of cases. Palmieri also recommended ray resection, noting that the resulting disability is slight [6]. Furthermore, if there is spread to the adjacent digit, excision of both digital rays is recommended [6]. Palmieri's recurrence rate was 11% in 18 patients with chondrosarcoma of the hand, one in a patient with juxtacortical chondrosarcoma excised without removal of the entire phalanx or digital ray at 6 months, and one in a patient with multiple enchondromas when a second neoplasm occurred in a different enchondroma at 4 years [6].

González del Pino et al. compared intralesional curettage to wide resection in 16 patients with 17 low-grade chondrosarcomas of the hand and found the incidence of recurrence to be the same in both groups [28]. The authors concluded that low-grade chondrosarcomas of the hand are locally aggressive with negligible systemic involvement, and intralesional treatment is adequate if hand function can be preserved and close follow-up can be maintained. Furthermore, wide excision with disarticulation of distal phalanges or digital amputation still plays a role in local control of disease with preserved function, particularly in patients who have marked involvement of the tendons or neurovascular bundles, or severe deformity of adjacent joints [28]. Mittermayer et al. also compared curettage and cancellous bone graft with wide resection of low-grade chondrosarcomas of the hand and had one recurrence out of eight patients in the curettage group and none in the wide resection group [32]. Mittermayer et al. concluded that intralesional resection is the preferred method of treatment in low-grade chondrosarcoma of the hand to avoid major loss of function from amputation, reporting a low relapse rate and no metastatic disease in their series.

Treatment to Preserve Function

Exner et al. reported a chondrosarcoma of the middle phalanx of the index finger in a professional flutist who had two previous curettage procedures and was treated with local excision and reconstruction with an osteocartilaginous allograft [33]. Temporary Kirschner wire fixation was placed through the proximal interphalangeal joint with fixation of the superficial flexor tendon with an anchor, along with reconstruction of the volar plate, collateral ligaments, and extensor hood. The patient was noted to have developed some Charcot-joint like destruction but was free of recurrence 3 years postoperatively.

Amputation can lead to significant functional deficits in chondrosarcomas of the thumb. Calvert et al. reported the case of a 66-year-old woman with a chondrosarcoma at the base of the thumb metacarpal of her dominant hand [34]. Complicating the

situation was that this patient had previously undergone amputation of her index finger, eliminating the possibility of pollicization. She underwent excision of the thumb metacarpal with bone graft from the ipsilateral ulna and Kirschner wire fixation. The patient had satisfactory hand function until her death from metastatic bronchial carcinoma almost 5 years later. Miyake et al. also reported a patient who underwent wide excision of the thumb metacarpal and base of proximal phalanx (due to tumor invasion of the metacarpophalangeal joint) with reconstruction using iliac crest bone grafting and metacarpophalangeal joint fusion with good results [23]. Similar treatment was reported by Wirbel et al. where the thumb metacarpal was excised with reconstruction using iliac crest bone graft and fusion of both the metacarpophalangeal and carpometacarpal joints with good function and opposition of the thumb to all of the fingers [35].

Pathak et al. described a low-grade chondrosarcoma of the dominant thumb metacarpal with soft tissue extension that underwent a function sparing wide local excision with stabilization using a silicone block interposition arthroplasty between the trapezium and proximal phalanx [36]. The silicone was replaced by an iliac crest bone graft with tension band wiring distally and plate fixation proximally a month later, which was complicated by infection requiring multiple debridements and eventual radial artery forearm flap. The patient was noted to be doing well, with an acceptable functional result and no recurrence or metastasis.

Other case reports have described ray amputations of the thumb [21, 37, 38]. A 41-year-old female with Grade II chondrosarcoma of her thumb proximal phalanx underwent disarticulation at the carpometacarpal joint [38]. Almost 6 years later, she developed multiple subcutaneous tumors on the abdominal and chest walls and the frontal scalp and metastatic deposits in both lungs. Biopsies were consistent with Grade III chondrosarcoma, and the patient expired 2 months later. A 67-year-old male with chondrosarcoma of the thumb metacarpal base was treated with radical amputation of the thumb and index finger metacarpals, trapezium, trapezoid, and the distal half of the scaphoid [39]. The patient was noted to be free of recurrence and metastasis at 8 years but died of unrelated causes. An 85-year-old female with

chondrosarcoma of her right thumb metacarpal was treated with a ray amputation but developed a recurrence 3 months later and underwent below-elbow amputation [21]. While it seems reasonable to attempt wide excision with reconstruction in order to preserve function of the thumb, careful surveillance is necessary to detect recurrences, and patients should be appropriately counseled.

Juxtacortical (Periosteal) or Extraosseous Chondrosarcoma

Juxtacortical chondrosarcoma, a rare variant of chondrosarcoma arising from the connective tissue in the periosteum, has been reported in the hand [6, 32, 40, 41]. These lesions present as a large soft tissue mass with distinct calcifications attached to the bone with cortical thickening at the site of origin [32]. Stackhouse et al. described a case of an extraosseous chondrosarcoma between the trapezium and second metacarpal with bony erosion of the radial base of the second metacarpal [42]. The patient was treated with en bloc resection with iliac crest bone graft and Kirschner wire fixation and was noted to be doing well at 12 months post operatively. Wu et al. reported a juxtacortical chondrosarcoma of the proximal phalanx of the thumb, which was treated with curettage but recurred 7 months later and underwent amputation [41].

Metastasis

The reported rate of metastasis in phalangeal chondrosarcoma is extremely low [8]. Reports of pulmonary and cutaneous metastasis from chondrosarcoma of the hand have been described [4, 21, 38, 43–45]. In Bovée et al.'s series of 35 patients with chondrosarcoma of the phalanx in the hands and feet from the Netherlands Committee on Bone Tumors, none of their patients developed metastasis or expired from tumor-related disease. When their data was combined with those from their literature review (n = 112),

only two patients (1.8%) developed metastasis at a median follow-up of 4.5 years. In the series of chondrosarcomas in the hands and feet reported by Ogose et al., 3 patients out of 33 chondrosarcomas of the hand developed metastasis [17]. Their study found Grade II chondrosarcomas to have a higher incidence of metastasis compared to Grade I chondrosarcomas, and grading may provide some information of prognosis. Palmieri did not report any metastasis in 18 chondrosarcomas of the hand [6], and similarly Patil et al. did not report any metastasis in 23 chondrosarcomas from the Scottish Bone Tumor Registry [5]. Mankin argued that chondrosarcoma of the hand is a different entity compared to chondrosarcomas in other locations, given its infrequency of metastasis and death, speculating that it may be due to difference in genetics, influence of size or mechanism of metastasis being deficient, or the lower temperature of extremities [14].

Maffucci's and Ollier's Disease

Ollier's disease was first described by Ollier in 1899 and is characterized by multiple enchondromas with asymmetric distribution that are variable in size, location, and number (Fig. 8.3) [46]. Maffucci's syndrome is characterized by multiple enchondromas associated with cutaneous, soft tissue, or visceral hemangiomas [47]. There are a few case reports of malignant transformation of multiple enchondromas in the hand in association with Ollier's disease (or multiple enchondromatosis) [3, 9, 17, 21, 24, 26, 48] and Maffucci's syndrome [17, 49], although it is thought to be very rare in the hands and feet [3]. In an international multicenter study of 144 patients with Ollier's disease and 17 patients with Maffucci's syndrome, 40% of Ollier's patients and 53% of Maffucci's patients developed chondrosarcoma [49]. In 18% of cases, only the hands and feet were affected; of these, 4 of 27 patients with Ollier's disease (15%) but none of 2 patients with Maffucci's developed chondrosarcomas. In contrast, patients with multiple enchondromas found only in the long tubular bones and flat bones had a higher incidence of developing chondrosar-

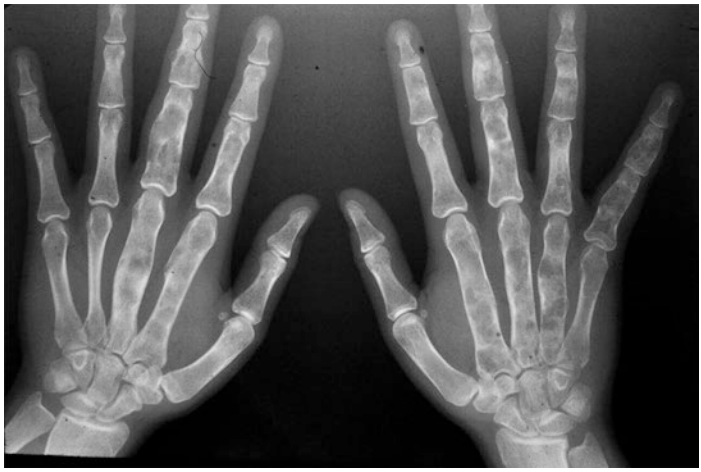

Fig. 8.3 Bilateral AP hand radiographs of a patient with Ollier's disease, demonstrating multiple enchondromas

coma (28 out of 62 Ollier's and 1 out of 2 Maffucci's). Muramatsu et al. reported a 78-year-old male with chondrosarcoma of the ring and small fingers with painless increase in size [24]. The tumors were large, approximately 10 cm in diameter for the ring finger and 8 cm for the small finger, resulting in significant deformities, and imaging demonstrated multiple osteolytic lesions in the phalanges of the other fingers. The patient underwent ray amputations of the ring and small fingers, and the final pathology report demonstrated areas of focally benign enchondroma, suggestive of malignant transformation from Ollier's disease to chondrosarcoma. Goto et al. reported on two patients with multiple enchondromatosis who developed chondrosarcomas in their hands; both patients had multiple osteolytic lesions in the hand and were treated with ray amputations [26]. There has been one unusual case of a chondrosarcoma arising from a solitary osteochondroma in the hand [50] and one case report of a 21-year-old male with multiple hereditary exostosis who developed chondrosarcoma [25].

Differential Diagnosis

Differential diagnosis includes chondromyxoid fibroma, benign chondroblastoma, enchondroma, synovial chondromatosis, subungual exostosis, and chondroblastic osteosarcoma.

Chondromyxoid fibroma is a rare, benign tumor of chondral origin and rarely occurs in the hand [51, 52]. This can also destroy the cortex and expand to soft tissue and can demonstrate cytologic pleomorphism [13]. The histologic characteristics were first described by Lichtenstein in 1948 and distinguish it from low-grade chondrosarcoma and enchondroma [53]. An essential histological feature is increased concentration of nuclei at the periphery of a well-defined lobule [51].

Benign chondroblastoma is a rare, benign bone tumor that is cartilaginous in origin and is commonly found in the knee and proximal humerus but uncommon in the hands and feet. It typically presents as a lytic lesion with sclerotic margins on imaging which can be associated with aneurysmal bone cysts [54].

Enchondroma usually presents in younger patients, typically in the third and fourth decades of life, and radiographically does not have cortical destruction or associated soft tissue mass [55]. While it can be difficult to distinguish between low-grade chondrosarcoma and enchondroma in the hand, clinical, radiographic, and histological features are critical in making the distinction. While it is thought to be extremely rare, there are reports of malignant transformation of solitary enchondroma to chondrosarcoma [11, 37, 56]. In a retrospective study of 113 patients with enchondromas of the hand, two were reported to have malignant transformation [57]. Signs of malignant transformation include increase in size of lesion, onset of pain, and cortical destruction with soft tissue mass on imaging [58].

Synovial chondromatosis and periosteal chondroma can mimic sarcoma with nuclear pleomorphism [13] and arise in the soft tissue without direct bony involvement [6]. Synovial chondromatosis is a rare, benign, proliferative cartilaginous lesion arising from synovial tissue [59]. There have been reports of malignant transformation to chondrosarcoma [60], with one case report of acral

synovial chondrosarcoma involving the thumb metacarpophalangeal joint in a 69-year-old man [61].

Subungual exostosis is an uncommon benign tumor of the distal phalanx that can cause nail deformity and pain [62]. Radiographs demonstrate a bony mass projecting from the distal tuft of the distal phalanx [63]. On histology, there is a base or stalk of normal-appearing trabecular bone with a fibrocartilaginous cap [1].

Chondroblastic osteosarcoma can also occur in the hand with extremely hyperchromatic and pleomorphic tumor cells with malignant osteoid cells [64].

Discussion

Chondrosarcoma of the hand is rare, although it is the most common malignant bony tumor of the hand. Diagnosis can be difficult, and careful scrutiny of clinical presentation, radiologic appearance, and histological analysis is critical. A painful, enlarging osseous swelling, especially in the older patient, should make the clinician suspicious for a malignant process. On radiographs, lytic areas with lack of well-defined margins and cortical destruction with soft tissue extension on radiographs are characteristic of chondrosarcomas. Histologic features suggestive of malignancy include high number of binucleated cells, nuclear pleomorphism, mitotic figures, and permeation with entrapment of bony trabeculae. Chondrosarcomas in the hand behave more locally aggressive but rarely metastasize. It is very rare for malignant transformation of enchondromas to chondrosarcomas. Treatment is controversial, and it is reasonable to attempt function-sparing reconstruction with close monitoring.

References

1. Lee FY, Mankin HJ, Fondren G, et al. Chondrosarcoma of bone: an assessment of outcome. J Bone Joint Surg Am. 1999;81(3):326–38.
2. Eyre-Brook AL. A bone tumour registry--chondrosarcoma and fibrosarcoma of bone. Proc R Soc Med. 1961;54(7):595–610.

3. Dahlin DC, Salvador AH. Chondrosarcomas of bones of the hands and feet--a study of 30 cases. Cancer. 1974;34(3):755–60.
4. Justis EJ Jr, Dart RC. Chondrosarcoma of the hand with metastasis: a review of the literature and case report. J Hand Surg Am. 1983;8(3): 320–4.
5. Patil S, de Silva MV, Crossan J, Reid R. Chondrosarcoma of small bones of the hand. J Hand Surg Br. 2003;28(6):602–8.
6. Palmieri TJ. Chondrosarcoma of the hand. J Hand Surg Am. 1984;9(3):332–8.
7. Habal MB, Snyder HH Jr, Murray JE. Chondrosarcoma of the hand. Am J Surg. 1973;125(6):775–6.
8. Bovée JV, van der Heul RO, Taminiau AH, Hogendoorn PC. Chondrosarcoma of the phalanx: a locally aggressive lesion with minimal metastatic potential: a report of 35 cases and a review of the literature. Cancer. 1999;86(9):1724–32.
9. Cawte TG, Steiner GC, Beltran J, Dorfman HD. Chondrosarcoma of the short tubular bones of the hands and feet. Skeletal Radiol. 1998;27(11):625–32.
10. Kocher MS, Jupiter JB. Enchondroma versus chondrosarcoma of the phalanx. Orthopedics. 2000;23(5):493–4.
11. Demireli P. econdary chondrosarcoma arising from a solitary enchondroma at the index finger of the right hand-a case report. Turkish Journal of Pathology. 2006;22(1):53–6.
12. O'Connor MI, Bancroft LW. Benign and malignant cartilage tumors of the hand. Hand Clin. 2004;20(3):317–23. vi
13. Unni K, Dahlin D. *Dahlin's bone tumors: general aspects and data on 11,087 cases*. 5th ed. *Philadelphia*: *Lippincott-Raven*; *1996*.
14. Mankin HJ. Chondrosarcomas of digits: are they really malignant? Cancer. 1999;86:1635–7.
15. Fayad LM, Ahlawat S, Khan MS, McCarthy E. Chondrosarcomas of the hands and feet: A case series and systematic review of the literature. Eur J Radiol. 2015;84(10):2004–12.
16. Stomeo D, Tulli A, Ziranu A, Mariotti F, Maccauro G. Chondrosarcoma of the Hand: A Literature Review. Journal of Cancer Therapy. 2014;5:403–9.
17. Ogose A, Unni KK, Swee RG, May GK, Rowland CM, Sim FH. Chondrosarcoma of small bones of the hands and feet. Cancer. 1997;80(1):50–9.
18. Hernàndez-Vaquero D, Cima-Suarez M, Garcia-Pravia C. Chondrosarcoma of the bones of the hand. Report of two cases. Arch Orthop Trauma Surg. 1991;110(5):265–8.
19. Roberts PH, Price CH. Chondrosarcoma of the bones of the hand. J Bone Joint Surg Br. 1977;59(2):213–21.
20. Ostrowski ML, Spjut HJ. Lesions of the bones of the hands and feet. Am J Surg Pathol. 1997;21(6):676–90.

21. García-Jiménez A, Chanes-Puiggrós C, Trullols-Tarragó L, Pulido-García MC. Chondrosarcoma of the Hand Bones: A Report of 6 Cases and Review of the Literature. J Hand Surg Asian Pac Vol. 2019;24(1):45–9.
22. Hatori M, Watanabe M, Kotake H, Kokubun S. Chondrosarcoma of the ring finger: a case report and review of the literature. Tohoku J Exp Med. 2006;208(3):275–81.
23. Miyake A, Morioka H, Yabe H, et al. A case of metacarpal chondrosarcoma of the thumb. Arch Orthop Trauma Surg. 2006;126(6):406–10.
24. Muramatsu K, Kawakami Y, Tani Y, Taguchi T. Malignant transformation of multiple enchondromas in the hand: case report. J Hand Surg Am. 2011;36(2):304–7.
25. Saunders C, Szabo RM, Mora S. Chondrosarcoma of the hand arising in a young patient with multiple hereditary exostoses. J Hand Surg Br. 1997;22(2):237–42.
26. Goto T, Motoi T, Komiya K, et al. Chondrosarcoma of the hand secondary to multiple enchondromatosis; report of two cases. Arch Orthop Trauma Surg. 2003;123(1):42–7.
27. Jakobson E, Spjut HJ. Chondrosarcoma of the bones of the hand; report of 3 cases. Acta radiol. 1960;54:426–32.
28. González Del Pino J, Lozano Calderón SA, Chebib I, Jupiter JB. Intralesional Versus Wide Resection of Low-Grade Chondrosarcomas of the Hand. J Hand Surg Am. 2016;41(4):541–549.e545.
29. Mirra JM, Gold R, Downs J, Eckardt JJ. A new histologic approach to the differentiation of enchondroma and chondrosarcoma of the bones. A clinicopathologic analysis of 51 cases. Clin Orthop Relat Res. 1985;201:214–37.
30. Evans HL, Ayala AG, Romsdahl MM. Prognostic factors in chondrosarcoma of bone: a clinicopathologic analysis with emphasis on histologic grading. Cancer. 1977;40(2):818–31.
31. Eefting D, Schrage YM, Geirnaerdt MJ, et al. Assessment of interobserver variability and histologic parameters to improve reliability in classification and grading of central cartilaginous tumors. Am J Surg Pathol. 2009;33(1):50–7.
32. Mittermayer F, Dominkus M, Krepler P, et al. Chondrosarcoma of the hand: is a wide surgical resection necessary? Clin Orthop Relat Res. 2004;424:211–5.
33. Exner GU, Dumont CE, Malinin TI, von Hochstetter AR. Recurrent aggressive chondrosarcoma of the middle phalanx of the index finger: excision and reconstruction with an osteocartilaginous allograft. Arch Orthop Trauma Surg. 2003;123(8):425–8.
34. Calvert PT, MacLellan GE, Sullivan MF. Chondrosarcoma of the thumb. A case report of treatment with preservation of function. J Hand Surg Br. 1985;10(3):415–7.

35. Wirbel RJ, Remberger K. Conservative surgery for chondrosarcoma of the first metacarpal bone. Acta Orthop Belg. 1999;65(2):226–9.
36. Pathak G, Conolly WB, McCarthy SW. Chondrosarcoma of thumb metacarpal--a case report with literature review. Hand Surg. 2001;6(1):81–7.
37. Peiper M, Zornig C. Chondrosarcoma of the thumb arising from a solitary enchondroma. Arch Orthop Trauma Surg. 1997;116(4):246–8.
38. Karabela-Bouropoulou V, Patra-Malli F, Agnantis N. Chondrosarcoma of the thumb: an unusual case with lung and cutaneous metastases and death of the patient 6 years after treatment. J Cancer Res Clin Oncol. 1986;112(1):71–4.
39. Barnes R, Catto M. Chondrosarcoma of bone. J Bone Joint Surg Br. 1966;48(4):729–64.
40. Jokl P, Albright JA, Goodman AH. Juxtacortical chondrosarcoma of the hand. J Bone Joint Surg Am. 1971;53(7):1370–6.
41. Wu KK, Kelly AP. Periosteal (juxtacortical) chondrosarcoma: report of a case occurring in the hand. J Hand Surg Am. 1977;2(4):314–5.
42. Stackhouse TG, Weiland AJ. Extraosseous chondrosarcoma of the wrist: a case report. J Hand Surg Am. 1984;9(3):338–42.
43. Cruickshank AH. Chondrosarcoma of a phalanx with cutaneous metastases. J Hand Surg [Am]. 1990;15:655–9.
44. Lalam RK, Cassar-Pullicino VN, Kumar N, Cool WP, Cribb GL, Mangham DC. Subcutaneous and lung metastases from chondrosarcoma of the thumb. BJR Case Rep. 2015;1(3):20150129.
45. Damron TA, Rock MG, Unni KK. Subcutaneous involvement after a metacarpal chondrosarcoma. Case report and review of literature. Clin Orthop Relat Res. 1995;316:189–94.
46. Silve C, Jüppner H. Ollier disease. Orphanet J Rare Dis. 2006;1:37.
47. Elmore SM, Cantrell WC. Maffucci's syndrome. Case report with a normal karyotype. J Bone Joint Surg Am. 1966;48(8):1607–13.
48. Martínez Villén G, Hernández Rossi A, Martínez Tello A, Herrera RA. Deforming chondrosarcoma of the fingers secondary to a long-term enchondromatosis of 28 years. Chir Main. 2004;23(4):196–200.
49. Verdegaal SH, Bovée JV, Pansuriya TC, et al. Incidence, predictive factors, and prognosis of chondrosarcoma in patients with Ollier disease and Maffucci syndrome: an international multicenter study of 161 patients. Oncologist. 2011;16(12):1771–9.
50. Cash SL, Habermann ET. Chondrosarcoma of the small bones of the hand: case report and review of the literature. Orthop Rev. 1988;17(4):365–9.
51. Anderson WJ, Bowers WH. Chondromyxoid fibroma of the proximal phalanx. A tumour that may be confused with chondrosarcoma. J Hand Surg Br. 1986;11(1):144–6.
52. Hau MA, Fox EJ, Rosenberg AE, Mankin HJ. Chondromyxoid fibroma of the metacarpal. Skeletal Radiol. 2001;30(12):719–21.

53. Jaffe HL, Lichtenstein L. Chondromyxoid fibroma of bone; a distinctive benign tumor likely to be mistaken especially for chondrosarcoma. Arch Pathol (Chic). 1948;45(4):541–51.
54. Davila JA, Amrami KK, Sundaram M, Adkins MC, Unni KK. Chondroblastoma of the hands and feet. Skeletal Radiol. 2004;33(10):582–7.
55. Lubahn JD, Bachoura A. Enchondroma of the Hand: Evaluation and Management. J Am Acad Orthop Surg. 2016;24(9):625–33.
56. Wu KK, Frost HM, Guise EE. A chondrosarcoma of the hand arising from an asymptomatic benign solitary enchondroma of 40 years' duration. J Hand Surg Am. 1983;8(3):317–9.
57. Rieger H, Neuber M, Joosten U, Grünert J, Brug E, Strobel M. Therapy and prognosis of enchondroma of the hand. Chirurg. 2000;71(9):1152–5.
58. Block RS, Burton RI. Multiple chondrosarcomas in a hand: a case report. J Hand Surg Am. 1977;2(4):310–3.
59. Ho YY, Choueka J. Synovial chondromatosis of the upper extremity. J Hand Surg Am. 2013;38(4):804–10.
60. Hamilton A, Davis RI, Hayes D, Mollan RA. Chondrosarcoma developing in synovial chondromatosis. A case report. J Bone Joint Surg Br. 1987;69(1):137–40.
61. Wenger DE, Sundaram M, Unni KK, Janney CG, Merkel K. Acral synovial chondrosarcoma. Skeletal Radiol. 2002;31(2):125–9.
62. Lee SK, Jung MS, Lee YH, Gong HS, Kim JK, Baek GH. Two distinctive subungual pathologies: subungual exostosis and subungual osteochondroma. Foot Ankle Int. 2007;28(5):595–601.
63. Carroll RE, Chance JT, Inan Y. Subungual exostosis in the hand. J Hand Surg Br. 1992;17(5):569–74.
64. Okada K, Wold LE, Beabout JW, Shives TC. Osteosarcoma of the hand. A clinicopathologic study of 12 cases. Cancer. 1993;72(3):719–25.

9 Chondrosarcoma of the Clavicle

Tang Liu, Chao Tu, and Zhihong Li

Introduction

In contrast to other tubular bones, the clavicle exists on a horizontal axis and is first formed through intramembranous ossification [1] before undergoing endochondral ossification at the acromial and sternal ends. It contains scanty red marrow in a medullary cavity with sparse vascularization surrounded by thick cortices of compact bone [2]. Interestingly, the clavicle has characteristics of both long and flat bones [3]. It is a rare site of primary tumor formation, as the incidence of primary clavicular tumors is reported between 0.45% and 1.01% [3], perhaps due to its unique development [4]. The distribution of tumors in the clavicle is similar to those reported in long bones, where the distal ends (mainly the acromion) are favored over the clavicular shaft [2].

Chondrosarcomas are malignancies developed from cartilage and produce a significant amount of hyaline cartilaginous extracellular matrix [5]. It is a relatively slow-growing malignancy that rarely metastasizes [6, 7]. Primary chondrosarcomas arise de novo, whereas those developed from preexisting enchondromas or osteochondromas are referred to as secondary [8]. In terms of

T. Liu · C. Tu · Z. Li (✉)
Department of Orthopaedics, The Second Xiangya Hospital of Central South University, Changsha, Hunan Province, China
e-mail: liutang1204@csu.edu.cn; tuchao@csu.edu.cn; lizhihong@csu.edu.cn

F. J. Hornicek (ed.), *Chondrosarcoma*,
https://doi.org/10.1007/978-3-030-74572-1_9

prevalence, chondrosarcoma is the second most common primary malignancy of the bone (about two to three cases per million in the adult population), second only to osteosarcoma. It more often affects adults, especially those between 40 and 60 years of age [9]. Males are more commonly affected than females. Secondary chondrosarcomas affect 0.5–1% of all solitary osteochondroma patients [10].

Chondrosarcomas most often arise from appendicular bones of the pelvis, femur, humerus, and scapula, with the clavicle being less common [11, 12]. Of the approximately 20% of chondrosarcomas which occur in the shoulder girdle, the clavicular chondrosarcomas account for a relatively small proportion [13]. Unni and Inwards summarized 1073 cases of chondrosarcoma in which five were clavicular [14]. In contrast, chondrosarcomas account for nearly one-third of all primary chest wall tumors, making it the most common primary chest wall malignancy [15]. When considering all the cancer types affecting the clavicle, chondrosarcomas are quite rare. In a review of 206 cases in East Asia, the major clavicular neoplasms were eosinophilic granuloma (18.5%), plasmacytoma (10.2%), Ewing sarcoma (7.8%), osteosarcoma (8.7%), osteochondroma (8.7%), and chondrosarcoma (5.3%) [4].

Clinical Manifestation

Similar to chondrosarcoma at other sites, clavicular chondrosarcoma may present as a palpable elastic-hard mass, with possible skin ulceration, swelling, and dysphagia [16]. Generally, the most prominent initial symptom of chest wall chondrosarcoma is a palpable lump, with a reported incidence of 69% at the first visit [11, 17]. However, since the clavicle is not weight-bearing, patients with clavicular chondrosarcoma may have an absence of pain and ultimately a delayed diagnosis [11].

Interestingly, Horner's syndrome secondary to a clavicular chondrosarcoma has also been reported [18]. Mechanistically, the second-order neuron that passes from the ciliospinal center of Budge to the superior cervical ganglion in neck can become compressed or damaged by swelling, mass, or surgery. Therefore,

the supraclavicular fossa must be carefully examined in patients with Horner's syndrome.

Another rarely reported symptom of clavicular chondrosarcoma is thoracic outlet syndrome, which is caused by compression of the neurovascular structures within the retroclavicular space [10]. Hiroshi Kobayashi et al. described a 26-year-old man with secondary chondrosarcoma arising from osteochondroma of the left midshaft of the clavicle. Because the tumor protruded in a posteroinferior direction, it resulted in thoracic outlet syndrome. Compression of the subclavian artery and brachial plexus was confirmed by angiography and intraoperatively, respectively [10]. Radiating arm or hand pain can accompany the presentation [10].

In addition, patients may also suffer from a progressive restriction of motion, pain, and dysesthesia. A fixed and hard mass in the infraclavicular space may support the diagnosis of the syndrome. Moreover, frozen shoulder syndrome has been described in shoulder girdle neoplasms [19] and considered in a clinical workup.

Imaging

On plain radiographs, clavicular chondrosarcoma is a bony lesion with a characteristic chondroid calcification (Fig. 9.1a). Periosteal reaction and pathological fracture are infrequent. Although conventional radiography is a poor modality for distinguishing enchondromas from Grade 1 central chondrosarcomas [20], a larger tumor size (more than 5cm) can help predict malignancy [21]. Of note, chondrosarcomas in elderly patients with degenerative joint disease are especially challenging to interpret on conventional radiographs [6].

Computed tomography (CT) scan and magnetic resonance imaging (MRI) have comparatively superior diagnostic specificity compared to plain radiographs [22]. On CT, the density of chondrosarcoma is comparable to that of muscle and appears as a bulky soft tissue mass with a punctate or "ring-and-arc" pattern of prominent calcification that is shaped from mineralized chondroid matrix lobules [23] (Fig. 9.1b, c). MRI is more sensitive for clavicular chondrosarcomas and is especially useful for defining

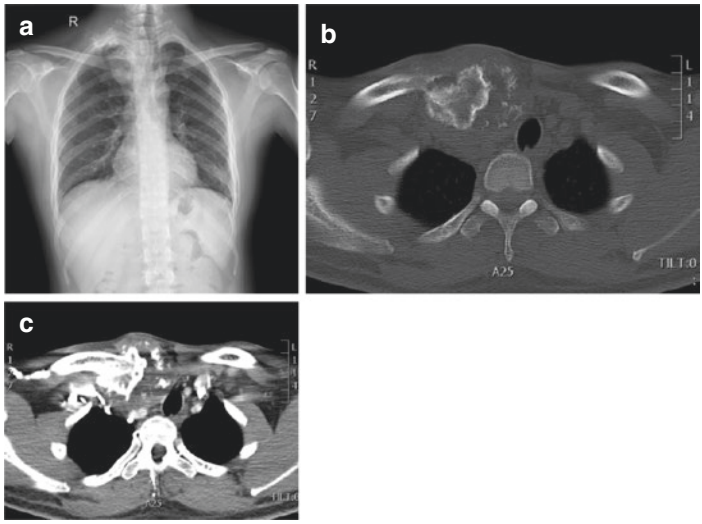

Fig. 9.1 A 30-year-old male with secondary chondrosarcoma arising from an osteochondroma of the right supraclavicular fossa. (**a**) Anteroposterior radiograph of the right clavicle showing a poorly demarcated lesion containing cauliflower-like calcification in the right supraclavicular fossa. Axial CT scan with bone windowing (**b**) and soft tissue windowing (**c**) displaying a periosteal-based, isodense, lobulated mass arising from the diaphysis of the clavicle, with flocculent calcification and a coarse periphery

the extent of intraosseous and soft tissue involvement for preoperative planning. Typically, a low-signal-intensity lobulated lesion on T1-weighted images combined with a mixed low- and high-intensity lesion on T2-weighted images is indicative of chondrosarcoma. Of the various imaging signs that aid in diagnosis, deep endosteal scalloping is regarded as the most sensitive sign for Grade 1 chondrosarcomas [24]. However, it is challenging to distinguish endogenous chondromas from low-grade chondrosarcomas by MRI. Even dynamic contrast-enhanced MRI can fail to discriminate between enchondromas and low-grade chondrosarcomas [24].

Whole-body fluorodeoxyglucose positron-emission tomography/CT (FDG PET-CT) or bone scans are not typically needed

for a chondrosarcoma diagnosis but can be useful for identifying metastatic spread. They are therefore used for clinical staging [25].

Chondrosarcoma variants can show a diversity of characteristic radiographic appearances. For instance, a less extensive area of matrix mineralization can exist in aggressive chondrosarcoma subtypes such as dedifferentiated and mesenchymal chondrosarcomas (MSC). They may demonstrate intraosseous lytic areas and aggressive cortical erosions accompanied by large soft tissue masses. In contrast, matrix mineralization is less frequent in clear cell chondrosarcoma compared to conventional chondrosarcoma.

Biopsy and Histology

A core needle biopsy is critical during the initial diagnosis and to ascertain the tumor grade [25]. Since chondrosarcoma is rare, cases are generally referred to a multidisciplinary team at specialized treatment centers for diagnosis and definitive care. Data supports this important step, as fine-needle aspiration cytology (FNAC) can reach a diagnostic accuracy of 94% in specialized sarcoma centers and only 26% in nonspecialized centers. A repeat needle biopsy or conversion to an open biopsy should be conducted if the initial findings are benign or inconclusive [17]. Some argue that FNAC can be less commonly performed for clavicular chondrosarcomas due to associated risks to neighboring neurovascular structures [4]. However, CT or ultrasound-guided techniques may increase procedural safety and accuracy [26]. Ultimately, patients should be referred to a specialized sarcoma center for treatment for the diagnostic decision-making.

The WHO classifies chondrosarcomas into Grade 1, 2, or 3 based on their abundance of chondrocytes, atypia (shown in Fig. 9.4.), chondrocyte cellularity, proportion of binucleate cells and mitotic figures, and mucoid and myxoid changes within the cartilage matrix. Specifically, Grade 1 chondrosarcoma has low cellularity in a chondroid matrix and absent mitoses. As it is clinically indolent and has low metastatic potential, it does not

require any staging investigation [8]. In Grade 2 and 3 chondrosarcoma, there is high cellularity, mucomyxoid matrix change, cytonuclear atypia, and mitoses, which contribute to its aggressiveness [6].

The conventional chondrosarcoma subtype comprises more than 90% of all chondrosarcomas [23], of which 90% are low to intermediate grade [23]. The conventional subtype can be further categorized into central, peripheral, and juxtacortical according to its location in the bone [20]. Other chondrosarcoma variants, including dedifferentiated chondrosarcoma, MCS, clear cell chondrosarcoma, and extraskeletal myxoid chondrosarcoma, are much less common. Dedifferentiated chondrosarcoma may arise from the transformation of low-grade conventional chondrosarcoma and exhibits characteristics of fibrosarcoma, osteosarcoma, or undifferentiated pleomorphic sarcoma (UPS). MCS is a high-grade chondrosarcoma displaying a dimorphic histological pattern with a highly undifferentiated small round cell component mixed with cartilage islands [23]. Clear cell chondrosarcoma contains prominent glycogen in tumor cells. It is relatively slow-growing and usually involves the epiphyses of long bones [23]. Extraskeletal myxoid chondrosarcoma is genetically distinct and considered a low-grade malignancy with prominent myxoid degeneration [23, 27]. On histologic appearance, extraskeletal myxoid chondrosarcoma is characterized by lobular growth of oval- or spindle-shaped acidophilic cells [28]. The lobules are arranged in cords or strands in a prominent myxoid stroma [28].

Metastasis

Compared to osteosarcoma and Ewing sarcoma, chondrosarcoma has a much lower tendency toward distant metastasis [6]. If metastasis does occur, it most often reaches the lung. Other metastatic sites, including the bone, regional lymph nodes, liver, kidney, skin, ovary, and heart, are extremely rare [6]. Douis et al. reported an incidence of 5.3% (10 in 188 patients) for lung metastasis in chondrosarcoma [29]. In a retrospective study, Gulia A et al. reviewed patients with conventional chondrosarcoma of the

extremity including the clavicle. Among them, 35 of 427 patients (8.2%) were identified with isolated pulmonary metastasis. All histologically proven patients were graded and staged by a PET/CT or bone scan with non-contrast CT [6]. Of the Grade 2 chondrosarcoma patients, only three had pure bony metastasis, and two had combined lung and skeletal metastasis. Interestingly, no skeletal metastasis occurred in patients with Grade 1 or 3 chondrosarcoma [6]. This may have resulted from potential areas of bias, including a loss of numbers in the final analysis from inadequate biopsy validation of the bony metastatic sites and inconsistent results in the Grade 3 chondrosarcoma patients [6].

Treatment and Outcomes

Due to its robust resistance to all tested chemotherapies, no effective induction or adjuvant therapies for conventional chondrosarcoma currently exist. Initial results in chondrosarcoma patients treated with a combination of doxorubicin and cisplatin showed them to have a longer progression-free survival (PFS) than those receiving doxorubicin monotherapy [30, 31]. However, further analysis showed the chondrosarcoma patients receiving chemotherapy to have no overall survival benefit compared with those who did not receive chemotherapy [32]. Mechanistically, the chemoresistance of chondrosarcoma may result from the heightened expression of chemoresistance genes such as multidrug resistance 1 and P-glycoprotein, a slow division rate, and significant barriers of antineoplastic drugs to cells due to poor vascularity and robust extracellular matrix [15, 23, 33].

As chondrosarcomas are relatively resistant to radiotherapy as well, there is no consensus regarding their use in treatment. A recent study showed that irradiation with protons or other charged particles may benefit chondrosarcoma patients [20]. Another in vitro study showed that olaparib, a PARP inhibitor, is able to sensitize mutated Grade 3 chondrosarcoma cells to conventional photon and proton and carbon ion irradiation, indicating a promising treatment avenue [5].

Novel targeted therapies (pazopanib, abemaciclib, and dasatinib) and immunotherapies (pembrolizumab, nivolumab) are under investigation for use in chondrosarcoma but need further validation for clinical application [34–36]. Currently, given the rarity of clavicular chondrosarcoma, there are no reported randomized clinical trials evaluating the efficacy of chemotherapy, radiotherapy, or targeted therapy for these tumors. Thus, more therapeutic targets and subsequent trials are needed to improve outcomes in chondrosarcoma of the clavicle and reach clinic readiness.

Given its resistance to chemotherapy and radiotherapy, the primary treatment for chondrosarcoma remains surgical resection [15]. Therefore, any evaluation should consider the tumor's resectability [25]. Generally, for low-grade chondrosarcoma confined to the bone, extensive intralesional curettage followed by local adjuvant therapy with bone grafting may achieve local control and good long-term outcomes [20]. In contrast, intermediate- to high-grade chondrosarcoma should undergo wide en bloc excision [20].

Since chondrosarcoma of the clavicle is anatomically close to vital neurovascular structures, a multidisciplinary team consisting of orthopedic, thoracic, and vascular surgeons and oncologists may be required for evaluation and surgical decision-making. Radical en bloc resection with negative margins is considered the "gold standard" of care for aggressive clavicular chondrosarcoma. To achieve definitive treatment, a proximal, distal, or total claviculectomy may be required based on lesion location [13]. As shown in Figs. 9.2 and 9.3., a 30-year-old male with secondary chondrosarcoma arising from an osteochondroma of the right clavicle was treated by partial claviculectomy. With respect to resection margins, most consider a minimum of 3–5 cm around the macroscopic tumor is necessary to achieve a histologically disease-free margin R0 with significantly reduced recurrence [37, 38]. However, unlike chondrosarcoma located in long bones, clear surgical margins for tumors of the clavicle may be challenging. Extended chest wall resection, including the sternum and parietal pleura, may be required in certain cases [39]. Ali Ghorbani Abdehgah et al. reported a case of a 22-year-old woman with cla-

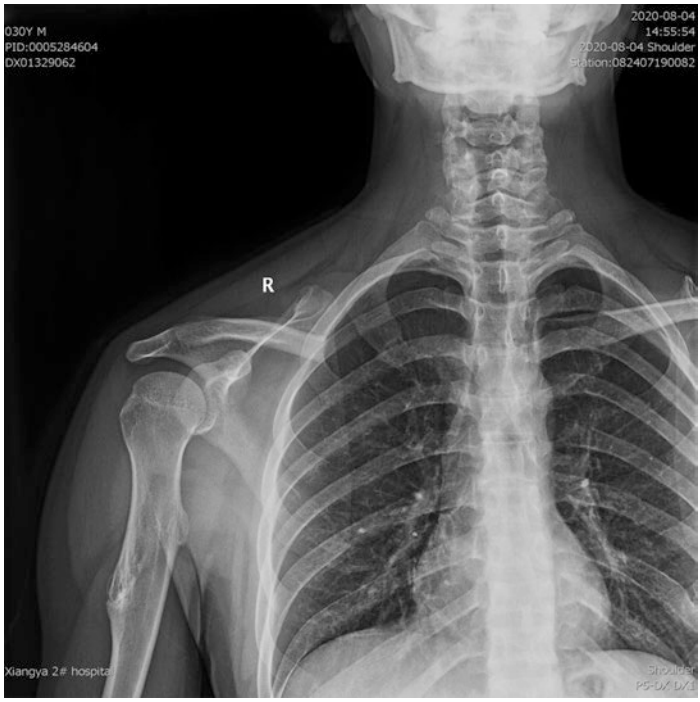

Fig. 9.2 Postoperative X-ray after wide en bloc resection (partial claviculectomy) of the clavicular chondrosarcoma

vicular chondrosarcoma. During the total claviculectomy, a quarter of her sternum was surgically removed alongside the tumor to achieve negative margins [11]. Postoperatively, the shoulder is usually immobilized with a sling for 3 weeks followed by rehabilitation for improved recovery [10].

Given the rarity of clavicular chondrosarcoma, few publications detail the long-term patient outcomes following surgery [25]. According to available evidence, however, the tumor grade, stage, local recurrence, resection margins, and metastasis are predictive for clavicular chondrosarcoma outcomes [13].

Grade 1 chondrosarcoma is comparatively less malignant than Grade 2 and Grade 3. Accordingly, the 5-year survival rate in

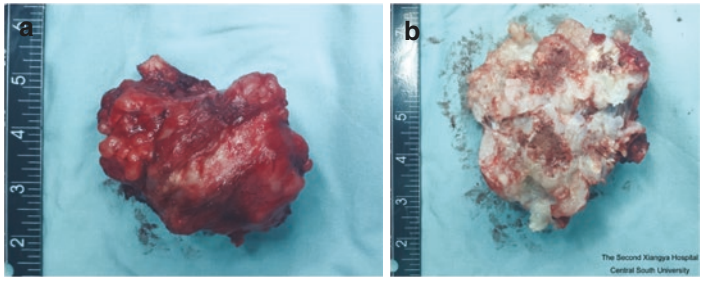

Fig. 9.3. (**a**) Macroscopic views and (**b**) cross-sectional view of the lobular clavicular mass after resection

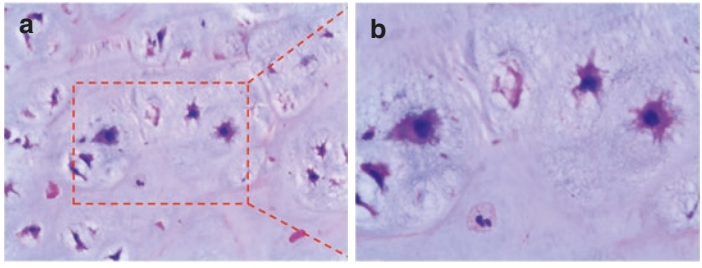

Fig. 9.4. (**a**) Histology of the resected tumor with hematoxylin and eosin (H&E) staining. (**b**) On higher magnification (square area in **A**), hyaline cartilage with mild nuclear atypia of the neoplastic chondrocytes is noted

Grade 1 patients is 90% and decreases dramatically to 60% for those with Grade 2 and 3 chondrosarcoma [11]. When chondrosarcoma recurrence occurs, it generally presents within the first 5 years following surgical treatment. Similarly, recurrence is also closely related to histological grade. In a single-center retrospective cohort of 20 patients with primary chondrosarcoma of the scapula or clavicle, all recurrences occurred in the higher-grade tumors, while none occurred in Grade 1 tumors [13].

Radical en bloc resection is critical for improved long-term outcomes. In a study from the Mayo Clinic, the 10-year disease-free survival rate for chondrosarcoma patients with wide or local excision was 95.4% and 65.4%, respectively [40]. In a single-institution study evaluating the surgical treatment of primary chest wall sarcoma including chondrosarcoma (5 in 23)

[39], R0 margins were achieved in 83% with a 5-year overall survival of 35%. The investigators found that R0 resection closely correlated with overall survival, while tumor histological grade and extended resection were associated with recurrence [39]. Consistent with this study, another work confirmed wide resection significantly decreased recurrence [13].

Reconstruction

The clavicle functions as struts to prevent the upper limb and scapula from depression via the acromioclavicular joint and coracoclavicular ligament [4]. Currently, reconstruction following removal of clavicular neoplasms is controversial. Some studies have shown that mobility and most functions of the upper limb after partial or total claviculectomy could be preserved without clavicular reconstruction [3, 4]. Others have argued that excision of the medial clavicle, costoclavicular ligament, and subclavius disrupts the ligamentous attachments of the clavicle to the chest wall and may result in chronic pain, instability, and reduced shoulder strength and mobility [41]. Therefore, reconstruction is typically recommended, especially for the elderly or adolescents with less growth potential; this protects the surrounding neurovascular structures, restores symmetry, and preserves a more cosmetic appearance [4].

Several materials have been incorporated to improve reconstruction of chest wall defects, such as polytetrafluorethylene patches, titanium plates, stainless steel mesh, resin plates, cryopreserved sternochondral allograft [42], methyl methacrylate cement sandwiched in Marlex mesh, and mesh-bone cement sandwiches [40, 43]. Necati Çitak et al. reported a 63-year-old woman with a giant anterior chest wall chondrosarcoma (15 x 15 cm) situated between the anterior mediastinum, proximal ends of both clavicles, and bilateral costochondral joints [37]. The patient underwent a wide resection, and the large chest wall defect was reconstructed by polypropylene mesh and a pedicled latissimus dorsi muscular flap [37]. Generally, in order to achieve good upper extremity function, preservation of the glenoid and rotator cuff is needed [13].

However, it should be noted that if only soft tissue reconstruction is performed, the patient may still suffer from respiratory and circulatory disorders. Therefore, reconstruction of the bony thorax may be necessary for fast postoperative recovery, stability, adequate pulmonary function, and protection of internal organs by providing a rigid thoracic scaffold [40]. Wei Guo et al. reported a massive clavicular chondrosarcoma with invasion of the subclavian artery, vein, and brachiocephalic trunk, which was treated through a scapular girdle amputation and sectioning of tumors of the clavicle and upper chest wall. After radical resection, the large thoracic wall defect (15 x 10cm) was further reconstructed by implantation of an autograft scapula [44].

Joint stability is dependent on ligamentous supports [41]. The sternoclavicular joint is a major construct and serves as the only articulation between the axial skeleton and upper limb [41]. Costoclavicular and infraclavicular portions are pivotal for stability of the sternoclavicular joint [40]. Clinically, however, reconstruction of the sternoclavicular joint is challenging due to the associated risks [41]. Charlotte L Bendon et al. reported on a 26-year-old woman with clavicular chondrosarcoma who was treated by excision of the left sternoclavicular joint and medial clavicle. A vascularized and innervated second toe metatarsophalangeal (MTP) joint and a subsequent extensor tendon graft were applied for reconstruction of the sternoclavicular joint [41]. No intraoperative complications were noted, and clavicle-to-metatarsal union and proximal phalanx-to-manubrium union were shown on radiographs 10 months postoperatively [41]. Reconstruction with the vascularized MTP joint was more resistant to infection and osteonecrosis and allowed motion in three planes, thus providing elevation/depression, protraction/retraction, and rotational movement [41].

Conclusions and Perspective

Chondrosarcoma of the clavicle is extremely rare and, as a result, poorly studied. It typically presents as a supraclavicular mass that is tender to palpation but otherwise painless. Needle biopsy is a

valuable diagnostic tool and should be performed in specialist centers where results are considerably more accurate. Benign or indefinite results of a needle biopsy should be interpreted with caution, and a repeat test or open biopsy is suggested. Primary clavicular chondrosarcoma is therapeutically challenging. It is strongly resistant to radiotherapy and chemotherapy, making wide resection, such as claviculectomy, the mainstay treatment for attempted cure. If there is a large chest wall defect following radical en bloc resection, reconstruction is required to maintain chest wall stability and range of motion of the upper arms and neck [40]. Prognostically, the most important factors for long-term survival and function include tumor histologic grading, wide radical resection, and metastasis [25]. It should be noted that since most studies are single-centered retrospective with limited sample sizes and heterogeneous indications, few concrete conclusions have been drawn, and results may not be applicable between treatment centers. Definitive conclusions should therefore be interpreted with caution and take into account all unique patient characteristics [13].

References

1. Cho CH, Kim BS, Kim DH, Jung GH. Posterior Displacement and Angulation of Displaced Lateral Clavicle Fractures: A 3-Dimensional Analysis. Orthop J Sports Med. 2020;8(11):2325967120964485.
2. Smith J, Yuppa F, Watson RC. Primary tumors and tumor-like lesions of the clavicle. Skeletal Radiol. 1988;17(4):235–46.
3. Rossi B, Fabbriciani C, Chalidis BE, Visci F, Maccauro G. Primary malignant clavicular tumours: a clinicopathological analysis of six cases and evaluation of surgical management. Arch Orthop Trauma Surg. 2011;131(7):935–9.
4. Ren K, Wu S, Shi X, Zhao J, Liu X. Primary clavicle tumors and tumorous lesions: a review of 206 cases in East Asia. Arch Orthop Trauma Surg. 2012;132(6):883–9.
5. Cesaire M, Ghosh U, Austry JB, Muller E, Cammarata FP, Guillamin M, et al. Sensitization of chondrosarcoma cells with PARP inhibitor and high-LET radiation. J Bone Oncol. 2019;17:100246.

6. Gulia A, Kurisunkal V, Puri A, Purandare N, Gupta S, Rangarajan DV. Is Skeletal Imaging Essential in the Staging Workup for Conventional Chondrosarcoma? Clin Orthop Relat Res. 2020;478(11):2480–4.
7. Aprin H, Calandra J, Mir R, Lee JY. Radiation-induced chondrosarcoma of the clavicle complicating Hodgkin's disease. A case report. Clin Orthop Relat Res. 1986;209:189–93.
8. Efremidou EI, Oikonomou A, Pavlidou E, Drosos G, Koutsopoulos A, Liratzopoulos N. Juxtacortical clavicular chondrosarcoma: diagnostic dilemmas: case report and review of literature. Clin Med Insights Oncol. 2013;7:13–9.
9. Puri A, Gulia A, Kurisunkal VJ, Sukumar V, Rekhi B. Chondrosarcomas in adolescents: are they different? J Pediatr Orthop B. 2020;29(5):505–9.
10. Kobayashi H, Ikegami M, Ushiku T, Anraku M, Ohki T, Shinoda Y, et al. Secondary Chondrosarcoma Presenting with Symptoms Similar to Thoracic Outlet Syndrome. Case Rep Orthop. 2018;2018:9347145.
11. Ghorbani Abdehgah A, Molavi B, Mehrpour SR, Radmard AR, Mahjori M, Kamalian N, et al. Clavicular Chondrosarcoma: A Case Report and Brief Review of the Literature. Int J Hematol Oncol Stem Cell Res. 2016;10(3):191–4.
12. Amalourde A, Vinayaga P, Naveed N, Jamal A, Looi LM, Sengupta S. A rare case of chondrosarcoma of the clavicle. Med J Malaysia. 2004;59(Suppl F):60–2.
13. Nota SP, Russchen MJ, Raskin KA, Mankin HJ, Hornicek FJ, Schwab JH. Functional and oncological outcome after surgical resection of the scapula and clavicle for primary chondrosarcoma. Musculoskelet Surg. 2017;101(1):67–73.
14. Damron T. Dahlin's bone tumors: general aspects and data on 10,165 cases. 6th ed. Jbjs. Philadelphia: Wolters Kluwer; 2010. p. 92.
15. Marulli G, Duranti L, Cardillo G, Luzzi L, Carbone L, Gotti G, et al. Primary chest wall chondrosarcomas: results of surgical resection and analysis of prognostic factors. Eur J Cardio-Thoracic Surg. 2014;45(6):e194–201.
16. Huang J, Zhang HZ, Zheng L, Zhou J, Jiang ZM. Clinicopathologic diagnosis of de-differentiated chondrosarcoma. Chinese J Pathol. 2009;38(12):820–3.
17. Widhe B, Bauer HC. Diagnostic difficulties and delays with chest wall chondrosarcoma: a Swedish population based Scandinavian Sarcoma Group study of 106 patients. Acta Oncol 2011;50(3):435-440.
18. Kapoor V, Sudheer V, Waseem M, Cole AS, Weeden DF. An Unusual Presentation of Chondrosarcoma of the Clavicle With Horner's Syndrome. Sarcoma. 2004;8(2-3):87–9.
19. Robinson D, Halperin N, Agar G, Alk D, Rami K. Shoulder girdle neoplasms mimicking frozen shoulder syndrome. J Shoulder Elbow Surg. 2003;12(5):451–5.

20. Gelderblom H, Hogendoorn PC, Dijkstra SD, van Rijswijk CS, Krol AD, Taminiau AH, et al. The clinical approach towards chondrosarcoma. Oncologist. 2008;13(3):320–9.
21. Geirnaerdt MJ, Hermans J, Bloem JL, Kroon HM, Pope TL, Taminiau AH, et al. Usefulness of radiography in differentiating enchondroma from central grade 1 chondrosarcoma. AJR Am J Roentgenol. 1997;169(4):1097–104.
22. Littrell LA, Wenger DE, Wold LE, Bertoni F, Unni KK, White LM, et al. Radiographic, CT, and MR imaging features of dedifferentiated chondrosarcomas: a retrospective review of 174 de novo cases. Radiographics. 2004;24(5):1397–409.
23. Chow WA. Chondrosarcoma: biology, genetics, and epigenetics. F1000Research. 2018;7.
24. Douis H, Parry M, Vaiyapuri S, Davies AM. What are the differentiating clinical and MRI-features of enchondromas from low-grade chondrosarcomas? Eur Radiol. 2018;28(1):398–409.
25. Wald O, Islam I, Amit K, Ehud R, Eldad E, Omer O, et al. 11-year experience with Chest Wall resection and reconstruction for primary Chest Wall sarcomas. J Cardiothorac Surg. 2020;15(1):29.
26. Marulli G, Dell'amore A, Calabrese F, Schiavon M, Daddi N, Dolci G, et al. Safety and Effectiveness of Cadaveric Allograft Sternochondral Replacement After Sternectomy: A New Tool for the Reconstruction of Anterior Chest Wall. Ann Thorac Surg. 2017;103(3):898–905.
27. Drilon AD, Popat S, Bhuchar G, D'Adamo DR, Keohan ML, Fisher C, et al. Extraskeletal myxoid chondrosarcoma: a retrospective review from 2 referral centers emphasizing long-term outcomes with surgery and chemotherapy. Cancer. 2008;113(12):3364–71.
28. Nakazora S, Kusuzaki K, Matsubara T, Shintani K, Matsumine A, Fukutome K, et al. Extraskeletal myxoid chondrosarcoma arising from the clavicle. Oncol Rep. 2006;16(1):115–8.
29. Douis H, James SL, Grimer RJ, Davies MA. Is bone scintigraphy necessary in the initial surgical staging of chondrosarcoma of bone? Skeletal Radiol. 2012;41(4):429–36.
30. Dickey ID, Rose PS, Fuchs B, Wold LE, Okuno SH, Sim FH, et al. Dedifferentiated chondrosarcoma: the role of chemotherapy with updated outcomes. J Bone Joint Surg Am. 2004;86(11):2412–8.
31. van Maldegem A, Conley AP, Rutkowski P, Patel SR, Lugowska I, Desar IME, et al. Outcome of First-Line Systemic Treatment for Unresectable Conventional, Dedifferentiated, Mesenchymal, and Clear Cell Chondrosarcoma. Oncologist. 2019;24(1):110–6.
32. Monga V, Mani H, Hirbe A, Milhem M. Non-Conventional Treatments for Conventional Chondrosarcoma. Cancer. 2020;12(7):1962.
33. Wyman JJ, Hornstein AM, Meitner PA, Mak S, Verdier P, Block JA, et al. Multidrug resistance-1 and p-glycoprotein in human chondrosarcoma

cell lines: expression correlates with decreased intracellular doxorubicin and in vitro chemoresistance. J Orthop Res. 1999;17(6):935–40.
34. Schuetze SM, Bolejack V, Choy E, Ganjoo KN, Staddon AP, Chow WA, et al. Phase 2 study of dasatinib in patients with alveolar soft part sarcoma, chondrosarcoma, chordoma, epithelioid sarcoma, or solitary fibrous tumor. Cancer. 2017;123(1):90–7.
35. Stacchiotti S, Ferrari S, Redondo A, Hindi N, Palmerini E, Vaz Salgado MA, et al. Pazopanib for treatment of advanced extraskeletal myxoid chondrosarcoma: a multicentre, single-arm, phase 2 trial. Lancet Oncol. 2019;20(9):1252–62.
36. van Oosterwijk JG, van Ruler MA, Briaire-de Bruijn IH, Herpers B, Gelderblom H, van de Water B, et al. Src kinases in chondrosarcoma chemoresistance and migration: dasatinib sensitises to doxorubicin in TP53 mutant cells. Br J Cancer. 2013;109(5):1214–22.
37. Citak N, Celikten A, Metin M, Pekcolaklar A, Gurses A. Radical resection of a giant recurrent chondrosarcoma of the anterior chest wall. Gen Thorac Cardiovasc Surg. 2011;59(7):512–4.
38. King RM, Pairolero PC, Trastek VF, Piehler JM, Payne WS, Bernatz PE. Primary chest wall tumors: factors affecting survival. Ann Thorac Surg. 1986;41(6):597–601.
39. Collaud S, Stork T, Dirksen U, Pottgen C, Hegedus B, Schildhaus HU, et al. Surgical Treatment for Primary Chest Wall Sarcoma: A Single-Institution Study. J Surg Res. 2020;260:149–54.
40. Chaudhry I, Alhajji Z, Aldulaijan F, Mutairi H, Amr SS. Manubrioclavicular and Manubriosternal Reconstruction After Radical Resection for Chondrosarcoma of Manubriosternum: A Modified Surgical Technique. Ann Thorac Surg. 2015;99(6):e137–9.
41. Bendon CL, Giele HP. Second toe metatarsophalangeal joint transfer for sternoclavicular joint reconstruction. J Hand Surg Am. 2014;39(7):1327–32.
42. Chapelier A. Resection and reconstruction for primary sternal tumors. Thorac Surg Clin. 2010;20(4):529–34.
43. Collaud S, Pfofe D, Decurtins M, Gelpke H. Mesh-bone cement sandwich for sternal and sternoclavicular joint reconstruction. Eur J Cardiothorac Surg. 2013;43(3):643–5.
44. Wei Guo XT, Guo Y, et al. Repair of chest wall defect with scapula autogaft after resection of a giant clavicular chondrosarcoma: a case report. Chinese J Orthop. 2003;23(9):535.

10 Radiation Therapy for Chondrosarcoma

Ting Martin Ma, Thomas DeLaney, and Anusha Kalbasi

Introduction

Chondrosarcoma is the most common primary malignant bone tumor in adults and is heterogeneous with respect to anatomic location, histologic subtype, and histologic grade. Each of these factors impacts the approach to treatment, and radiation therapy is no exception. In this chapter, we will consider chondrosarcoma from the perspective of the radiation oncologist, whose primary concern is to assess whether radiation can provide a clinically meaningful improvement in local disease control without introducing excess toxicity. We will then explore the technical aspects of radiation

T. M. Ma · A. Kalbasi (✉)
Department of Radiation Oncology, Jonsson Comprehensive Cancer Center, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, CA, USA
e-mail: anushakalbasi@mednet.ucla.edu

T. DeLaney
Department of Radiation Oncology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

F. J. Hornicek (ed.), *Chondrosarcoma*,
https://doi.org/10.1007/978-3-030-74572-1_10

therapy, including the choice of modality, treatment volume, and dose while in parallel exploring available data on therapeutic and safety outcomes. We will focus primarily on chondrosarcoma arising from two special anatomic locations – the skull base and spine, where radiation therapy is most often utilized – and finish the chapter with a brief discussion of pelvic chondrosarcoma.

Role of Radiation Therapy (RT): An Overview

It is estimated that 13% of patients with a histological diagnosis of chondrosarcoma received a form of RT [1]. The primary goal of RT is to improve local control (LC), and it should be noted that in general RT is not associated with improved survival [1]. Common indications for RT are as follows:

- *Adjuvant RT to maximize local control after incomplete resection.* RT is a valuable adjuvant treatment modality where wide excision cannot be accomplished [2]. In a study of 5427 patients with a histologic diagnosis of chondrosarcoma in the National Cancer Database (NCDB), in patients with positive surgical margins, there was a trend toward improved survival for those treated with RT (HR 0.81, 95% CI 0.58–1.13) [1]. It should be noted that adjuvant radiation is not a substitute to achieving maximal resection whenever possible as R1 and R2 resections have worse LC despite adjuvant radiation therapy (95% and 40% for R1 and R2, respectively, compared to 100% for R0 at 10 years) [2]. According to National Comprehensive Cancer Network (NCCN) guideline, doses ~70 Gy are needed in attempts to achieve LC after R1 resection and >70 Gy for R2 resection using specialized techniques [3]. RT is not routinely recommended as an adjuvant modality after successful margin-negative wide excision of chondrosarcoma [3], though selective use of adjuvant RT for high-risk lesions even after complete resection is reasonable.
- *Definitive treatment modality when resection is not feasible or would cause unacceptable morbidity, especially in the skull*

base and the spine. Definitive RT can be considered for borderline resectable and unresectable disease [3]. In some cases where an uncontrolled primary tumor can be the cause of death, RT can prolong survival. In another NCDB study of 863 chondrosarcoma patients receiving definitive radiation therapy, a higher dose (>70 Gy, 40.6% vs. 16.9%; $p = 0.006$) and the use of proton therapy (75.0% vs. 19.1%; $p = 0.046$) were associated with improved OS at 5 years on multivariable analysis [4].

- *Salvage after tumor recurrence.* When chondrosarcomas demonstrate progression after initial treatment, they often exhibit a slow but relentless local growth. If wide excision of a local recurrence can be achieved, RT is not always indicated [5], though some consider local recurrence as an *a priori* indication for salvage radiation therapy. If wide excision cannot be achieved at recurrence, revision resections can be performed with the goal of debulking tumor and decompressing organs at risk, with RT playing a role as an adjunct or alternative treatment [6, 7]. Patients treated for recurrent tumors with salvage radiation typically have worse LC compared to these treated for a primary tumor (50% vs. 11%, $p = 0.002$), based on data from a phase 2 prospective study [8].
- *Palliation for metastatic disease.* Although there is a paucity of data of RT in this setting and there are no prospective studies, the role of palliative RT is well described as a means to address or prevent symptoms including pain, obstruction, and bleeding from advanced malignancies independent of histology [9]. In one study of the SEER database with 200 patients with upfront metastatic chondrosarcoma, resection of the primary tumor was associated with improved OS (hazard ratio 0.481, $p < 0.001$). Although RT was not associated with either improved OS or DFS [10], this does suggest a value to controlling the primary tumor, for which RT can play a role especially if surgery is not possible.
- *Treatment of oligometastatic disease.* Pulmonary metastasectomy is a commonly performed operation for sarcoma patients with pulmonary metastasis with or without extrapul-

monary metastasis. Although there have been no large prospective studies of metastasectomy for patients with sarcoma, the effectiveness of metastasectomy is inferred from retrospective surgical series and registry data given favorable survival data when this approach is employed [11–13]. Long-term results indicate resection may prolong survival following complete resection [14]. For bone sarcoma, about 34% of patients were alive at 5 years after a first metastasectomy [11]. The absence of effective systemic therapy is another motive for an aggressive local therapy approach in patients with oligometastatic disease. Radiation therapy, and in particular, stereotactic body radiotherapy (SBRT), offers an effective alternative to metastasectomy for patients with oligometastatic disease. This approach has been well studied across a wide range of malignancies [15] and even in patients with oligometastatic sarcoma of different histological subtypes, including chondrosarcoma [16–18]. SBRT is especially valuable when treating bilateral disease, multiple synchronous lesions, or in patients with contraindications to surgery. Multiple studies have demonstrated that SBRT is an effective and safe method for treating pulmonary metastasis from sarcoma, with LC around 86%~96% [19–21]. In one study, the actuarial 5-year LC was 96%, and no severe toxicity events were recorded [17]. Long-term data is lacking, but studies have shown a 5-year overall survival (OS) from 50% to 60.5% [16, 17].

Doses of radiation at or above 70 Gy are advised in the adjuvant and definitive setting for the treatment of chondrosarcoma [3]. However, application of this dose with conventional RT is often impossible in the vicinity of critical neurologic structures, especially in chondrosarcomas arising in the skull base and axial skeleton (recall that spinal cord tolerance is about 45–54 Gy with conventionally fractionated RT and brainstem tolerance is approximately 54–60 Gy). Paradoxically, postoperative RT is often needed the most given these tumors are less accessible for radical resection than lesions in the appendicular skeleton. In light of this,

advanced radiation modalities, such as intensity-modulated radiation therapy (IMRT), proton-beam therapy, carbon ion radiotherapy, stereotactic radiosurgery (SRS), or fractionated stereotactic radiotherapy (FSRT), are essential to maximize the therapeutic window. For example, in a phase II study of high-dose mixed photon/proton radiotherapy in the management of spine sarcoma, patients with unresectable or gross residual disease received a total dose of 77.4 Gy (relative biological effectiveness, RBE) [8]. In a study of the NCDB comparing advanced and conventional RT modalities, advanced RT was associated with significantly decreased mortality (HR 0.55, 95% CI 0.38–0.80) [1], with data suggesting that this association with improved outcome may be related to the ability to deliver higher doses of RT. These advanced modalities are discussed in more detail below. In summary, RT is an essential tool in selected cases of chondrosarcomas but must be considered on a case-by-case basis, and a multidisciplinary approach is paramount to optimal patient management.

Radiotherapy Considerations

Surgical Approach and Tumor Location

All grades and subtypes of nonmetastatic chondrosarcoma require surgery for curative potential [22, 23]. Wide, *en bloc* excision is the preferred surgical treatment of almost all chondrosarcomas [22]. Anatomic location is a critical consideration because it influences surgical resection, which in turn has an impact on local disease control and the need for adjuvant radiation therapy. Anatomic location also defines proximity to nearby critical normal structures that may influence the feasibility and toxicity of radiotherapy.

Chondrosarcomas occur predominantly in the trunk and limb girdles (acral or appendicular skeleton lesions), with approximately one-third occurring in the pelvis, sacrum, and mobile spine (axial lesions, although pelvis is part of the appendicular skeleton by strict definition) [24]. Acral lesions rarely metastasize, regardless of grade, whereas axial lesions are much more likely to metastasize than tumors found in the distal extremities

with equivalent histology [23] and portend poorer oncologic outcomes [25]. Studies have shown that for the conventional-type chondrosarcoma, anatomic location was one of the two most significant factors (the other being grade) that predicted different oncologic end points, namely disease-specific death, metastasis, and local recurrence [25–27]. For example, in one study, 10-year local recurrence-free survival was 88% for appendicular vs. 53% for axial/pelvis lesions [26]. Because of the effective LC with surgery alone, radiotherapy has had limited utilization for patients with appendicular lesions, with the exception of scenarios at highest risk for local recurrence, such as tumor with pathologic fracture at diagnosis and/or evidence of malignant contamination of soft tissue at surgery. Thus not surprisingly, radiotherapy was more commonly utilized for axial lesions than appendicular lesion (constitutes 78% vs. 22% of patients undergoing RT in an analysis of the NCDB [1]).

For skull base locations involving the clivus, cranial nerves or carotid artery, and spine, wide excision can lead to considerable morbidity and a demanding reconstruction, despite advanced endoscopic approaches. In these locations, resection in a piecemeal fashion may be the only feasible approach [28]. Surgeries at these sites can even be limited to debulking and facilitating good geometry for radiation (i.e., addressing brainstem compression) [29]. Adjuvant radiation therapy is often necessary to ensure adequate disease control. RT is also used as an alternative to surgery as the definitive treatment when surgical resection is not feasible [30–32].

One notable exception to the rule for wide, *en bloc* resection is the treatment of low-grade acral chondrosarcomas and low-grade intracompartmental chondrosarcomas arising centrally within the medullary cavity, which remains controversial [23]. Many surgeons choose extensive intralesional excision and curettage [27, 28, 33]. While low-grade chondrosarcomas rarely metastasize, they do have the potential to recur locally after intralesional excision and curettage. Still, despite the higher likelihood for local recurrence, radiation therapy is not utilized after a limited surgery. In these cases, patients are observed and local recurrences may be managed with wide excision [3].

Histologic Grade and Subtype

Grade is another important factor dictating oncologic outcomes [25–27], and it is cited as the best predictor of clinical behavior at present [2]. Chondrosarcomas are characterized as grades I–III (certain sources classify as I–IV), with higher grades having a greater tendency to metastasize. Grade I chondrosarcomas rarely metastasize [34]. In contrast, grade III chondrosarcomas have metastases developing in 70% of patients [35]. About 90% of all chondrosarcomas are conventional chondrosarcomas, and 10% are one of the following subtypes: dedifferentiated, clear-cell, mesenchymal, and myxoid [36]. The NCCN guidelines suggest that radiation should be considered only for unresectable diseases in the low-grade setting but can be considered for both borderline resectable and clearly unresectable diseases for high-grade and clear-cell chondrosarcoma [3]. In addition, a study from MD Anderson Cancer Center (MDACC) demonstrated that none of the patients with conventional grade I chondrosarcomas developed local recurrence after surgical resection despite several having residual disease after their index operation. The authors stated they typically reserve radiation for salvage treatment of recurrent, progressive grade I chondrosarcoma while delivering radiation therapy uniformly postresection in higher grade conventional chondrosarcomas. On the other hand, some practitioners employ adjuvant radiation therapy if the tumor is of high grade even when R0 resection is achieved, especially for tumors in anatomic locations that pose surgical challenges [2]. It should be noted that these practices are under investigation and not widely adopted. More evidence is needed to support histologic grade-specific radiation treatment protocols [37].

Biological Considerations

Chondrosarcoma is generally considered a radioresistant tumor that requires high doses of RT for adequate disease control. The radioresistant nature of chondrosarcoma may be related to the following features: (1) it is slow growing with a relatively low fraction of dividing cells, and RT acts on dividing cells; (2) it can be

relatively acellular with a prominent extracellular cartilage matrix that does not respond to RT, and (3) its poor vascularity and hypoxic microenvironment limits the generation of reactive oxygen species (ROS) by RT [38]. On a molecular level, alteration in tumor suppressor p16, p21, and Rb and increased expression of antiapoptotic proteins such as Bcl-2, Bcl-xL, and XIAP contribute to its radioresistance as well [38–40]. Investigations to address the radioresistance include approaches such as p16-restoring oncolytic viruses, siRNA-based downregulation of antiapoptotic proteins, or acridine orange to enhance generation of ROS [38].

Pre-radiotherapy Evaluation

Radiation planning for patients with chondrosarcoma requires advanced axial imaging including both magnetic resonance imaging (MRI) and computed tomography (CT). MRI helps differentiate chondrosarcoma from benign entities like osteochondroma, and it is necessary to delineate the extent of the intraosseous and soft tissue involvement, including neurovascular structures. Classically they appear hyperintense on T2-weighted MRI due to high water content [28]. However, there do not appear to be any imaging hallmarks to differentiate low-grade from high-grade chondrosarcomas [28]. Computed tomography is especially recommended in the pelvis and other flat bones where it may be difficult to discern the pattern of bone destruction and the presence of matrix mineralization. It typically is of low attenuation on CT due to high water content. For staging, chondrosarcoma patients should undergo chest CT (especially for high-grade lesions as lungs are the main site of metastatic disease); a bone scan can be considered [23, 29]. The role of PET/CT in distinguishing benign from malignant chondroid lesions, and to identify metastatic disease, is uncertain.

Chondrosarcoma can result in extensive destruction of key weight-bearing osseous structures. RT, although treating the causative agent, does not restore the integrity of the bone (and, in fact, can weaken the remaining normal bone). Thus, prior to any radiation, an orthopedic oncology evaluation is necessary to assess structural integrity of the bone in weight-bearing areas. In addi-

tion, for tumors near critical neurologic structures, a neurosurgery evaluation to assess neurological compromise and need for immediate surgery in the setting of spine and skull base chondrosarcomas should be carried out before radiation planning.

Skull Base Chondrosarcoma

Only 1% of chondrosarcomas arise in the skull base and account for 6% of all skull base tumors [41]. The vast majority of lesions occur along the spheno-petro-clival junction involving the bone of the clivus and extending anteriorly into the parasellar sinuses, nasopharynx, orbits, or middle cranial fossa including the sella (30–50%) or posteriorly into the posterior fossa (50%) [42]. The majority of patients present with symptoms of cranial nerve compression [30]. Most common presenting symptoms include diplopia, decreased visual acuity, and headaches [43]. About half of the skull base chondrosarcomas are low grade (grade I), and 40% are intermediate grade (grade II), and the remaining 10% are high grade [30]. Skull base chondrosarcoma has a gradual, slow progression resulting in a relatively asymptomatic growth which can lead to late diagnosis. This unfortunately results in extensive locoregional infiltration at the time of diagnosis [44].

Role of Surgery and Radiation

The current standard for initial treatment of cranial chondrosarcoma is surgical resection to obtain a definitive tissue diagnosis and maximally cytoreduce the tumor [30]. The appropriate surgical approach depends largely on the size and location of the tumor. Local bony destruction and invasion can make oncologic excision challenging with significant potential morbidity and mortality. In retrospective series, 25–41% of patients developed new cranial nerve deficits, and more than half of patients had no improvement of their preoperative cranial neuropathy [45, 46]. In addition, modern surgical series also report an approximately 10–15% rate of vascular injury, 10% rate of cerebrospinal fluid leak, and up to

5% perioperative mortality [30, 42]. In fact, it is estimated that 60–80% of skull base chondrosarcomas cannot be safely removed [44]. In one series, less than half of the surgeries result in total resection [42].

Given the high morbidity associated with aggressive surgery, many surgeons now advocate maximal safe tumor debulking followed by adjuvant radiation to improve local control. There is no direct evidence to suggest that extent of resection at the initial operation offers any recurrence or survival benefit when adjuvant radiation is given [30]. Bloch et al. showed that adjuvant irradiation after surgery significantly reduced 5-year rate of disease recurrence from 44% after surgery alone to 9% after radiation [30, 31]. The same group showed that 5-year mortality was decreased from 25% to 9% with the addition of any form of radiation for skull base chondrosarcoma for majority of patients [30, 31]. In a SEER database analysis of 269 patients with skull base chondrosarcoma, postoperative adjuvant RT significantly improved 10-year OS rate (62% vs. 41%, $p = 0.04$) [47]. This is echoed in another SEER database analysis in which surgery followed by radiation offers the longest survival [48]. Therefore, the current standard approach is maximally safe resection followed by adjuvant radiation. Definitive radiation alone when surgery is not feasible offers good local control and may even afford a favorable 5-year recurrence rate compared to patients who received surgery as their only treatment modality (19% vs. 44%, $p = 0.036$) [31], though retrospective comparisons are difficult given inherent selection bias for each treatment. Regarding the optimal timing of RT after surgery, it has been reported that early primary adjuvant radiation therapy after surgery had higher rates of disease control than those referred for salvage treatment of recurrent disease (2-year LC 80% vs. 45.5%; $p = 0.024$) [32, 49].

Cumulative data from all published series of skull base chondrosarcoma demonstrate 5-year LC and OS between 70–100% and 65–95%, respectively. In general, positive prognostic factors include younger age, conventional subtype (vs. mesenchymal type), gross total resection, and smaller lesion size [30, 31, 37, 47, 50–53].

Radiation Delivery Modalities

Radiation for chondrosarcoma may be delivered in one of a number of advanced treatment modalities. These include photon-based treatments, in particular IMRT, SRS, and FSRT, as well as particle-based (proton, carbon ion) radiotherapy. These techniques differ primarily in the type of radiation therapy (photon-based vs. particle-based), the precision and accuracy of patient setup and treatment delivery, and the dose delivered per fraction of treatment.

Radiation therapy is most commonly administered using photon-based techniques (also referred to as gamma rays or X-rays). Radiation can also be delivered using particles, such as protons or carbon ions, which result in a unique distribution of dose within the patient compared to photon-based techniques. Specifically, whereas each beam of photon therapy results in "exit dose" on the contralateral side of the target, proton and carbon ion therapy deposit the vast majority of their dose at particular depth within the patient, resulting in minimal "exit dose" on the contralateral side of the target. This property is advantageous for tumors in some anatomic locations. In addition, proton therapy and in particular carbon ion therapy have slightly higher biological effectiveness at similar dose levels.

With respect to the dose per fraction, radiation therapy has historically been given in small increments of 1.8–2.0 Gy per treatment to allow for maximal sparing of normal tissue in the radiation field. Modern image guidance (IG) and radiation planning techniques (e.g., IMRT) have allowed improved sparing of normal tissue, allowing for an escalation of radiation dose per fraction, up to as high as ~20 Gy per fraction. Higher dose per fraction treatments, such as SRS, typically employ photon-based radiation, although particle-based approaches with higher dose per fraction are actively under investigation.

Advanced radiation techniques appear to yield better outcome than conventional fractionated photon RT, but currently there is no direct head-to-head comparison of various advanced modalities suggesting that one is superior to another. In general, to

achieve adequate local control, doses approaching 70 Gy and higher (or 60 Gy and higher for carbon ion therapy) are necessary due to the relatively high radioresistance of chondrosarcoma with conventional techniques [54]. An overview of different advanced radiation therapy modalities for skull base chondrosarcoma is shown in Table 10.1. A discussion of conventionally fractionated 2D or 3D conformal RT is not included here, as this is an outdated approach for the definitive treatment of chondrosarcoma. Tumor control is unsatisfactory with this approach given the inability to deliver a sufficient dose of RT to the primary tumor without damaging surrounding normal tissue [55, 56].

Image-Guided IMRT (Conventional Fractionation) This refers to the use of advanced imaging to guide the setup of the patient for each fraction of radiotherapy (image guidance), combined with an advanced radiation planning and delivery system (IMRT) that maximizes dose to the tumor while minimizing dose to normal structures. IMRT is by convention considered a photon-based modality, unless explicitly noted otherwise (e.g., intensity-modulated proton therapy). Image guidance (IG) and IMRT are now standard in the treatment of spine and skull base tumors when attempting to achieve doses approaching 70 Gy. An example IG-IMRT plan for a skull base chondrosarcoma is shown in Fig. 10.1. Sahgal et al. reported their experience with IG-IMRT for treating 18 patients with skull base chondrosarcoma with a median follow-up of 67 months [57]. Patients received a median dose of 70 Gy using conventional fractionation (2 Gy per fraction) with cone-beam CT-based daily image guidance. With these techniques, the 5-year LC was 88.1% and 5-year OS was 65.3%. Around 14% of patients developed radiation-associated toxicities, including one patient who developed a radiation-associated secondary malignancy occurring 6.7 years later. Both cases of local failures were in patients with higher-grade tumors (grades II and III). Age but not extent of surgical resection was a predictor of local control.

Of note, FSRT is a type of radiation modality that delivers conventionally fractionated radiation under stereotactic guidance

Table 10.1 Comparison of advanced radiation therapy modalities in skull base chondrosarcomas

Modality	Best suited	Dosing	Pros	Cons	Oncological control
IG-IMRT (conventional fractionation)	n/a	70 Gy in 2 Gy/fraction	• Wide infrastructure availability • Relatively low treatment cost	• Limited tumor control	5-yr LC: 88.1%, 5-yr OS: 65.3%
SRS	Small-volume tumors in brain locations that are high risk for resection-related complications	Marginal dose should be >16–24 Gy (single fraction)	• Shorter treatment duration, convenient • Precise targeting • Better toxicity profile than conventional fractionated RT	• Limited to smaller tumors (10–20 mL) • Radiation-related complications may be relatively high, especially when combined with fractionated radiation therapy • Less effective at managing recurrent disease and ineffective at managing CNS metastasis	5-yr LC: ~70–80%; PFS 80–85% at 5 years and 70% at 10 years

(continued)

Table 10.1 (continued)

Modality	Best suited	Dosing	Pros	Cons	Oncological control
Proton (including combination with photon)	Well suited for residual lesions of ≥20 mL where a generous treatment volume is recommended to reduce the risk of recurrence	68–72 Gy (RBE) delivered in 1.8–2.0 Gy (RBE) per fraction. Doses ≥66–70 Gy (RBE) is needed for adequate tumor control	• Minimal exit dose after energy deposition (Bragg peak) • Sharper dose falloff, better sparing of surrounding critical structure • Greater biological effective dose	• High treatment cost • Not widely available	5-yr LC: 94–100%; 5-yr PFS in the same range; 5-yr OS >90–95%
Carbon ion	n/a	60 Gy (RBE) at 3 Gy (RBE) per fraction	• Higher relative biological effectiveness (RBE) • Increased linear energy transfer (LET) • Good toxicity profile	• Very limited availability (Heidelberg, Germany, and a few centers in Asia) • Highest treatment cost	5-yr LC: ~88%, 5-yr OS: 95–96%

IG-IMRT image-guided intensity-modulated radiation therapy, *SRS* stereotactic radiosurgery, *LC* local control, *PFS* progression-free survival, *OS* overall survival, *yr* year

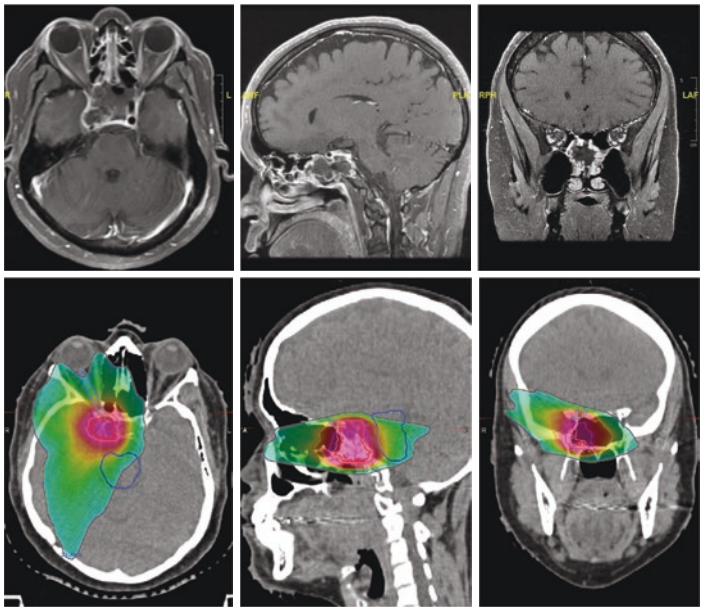

Fig. 10.1 Example plan of a skull base chondrosarcoma treated with conventionally fractionated IMRT. A 46-year-old female with low-grade chondrosarcoma of the right sphenoid and cavernous sinus with locally osseous destruction s/p subtotal resection followed by conventionally fractioned IMRT to the residual disease. Upper panels: postoperative MRI showed persistent disease at the inferolateral aspect of the resection cavity, measuring approximately 2.3 cm. Lower panels: radiation plan of conventionally fractionated IMRT, 70 Gy in 35 fractions. GTV in red and PTV in tomato. Isodose lines (95%: magenta, 50% yellow, and 20% cyan) with dose wash are shown. Optic nerve is contoured in light blue and brainstem in dark blue. Note that PTV coverage has to be reduced anteriorly due to its proximity to the optic nerve. Case contributed by Tania Kaprealian, MD, MBA, Department of Radiation Oncology, UCLA Medical Center

(though this term has also been used to refer to hypofractionated stereotactic radiotherapy; see Sect. "SRS"). It combines the precision of stereotactic positioning with the radiobiological advantage of fractionation for large tumors. In a study by Debus et al. delivering a median dose of 64.9 Gy in 1.8 Gy fractions, all eight chondrosarcoma patients achieved and maintained local control and recurrence-free status at follow-up of 5 years [58].

SRS SRS refers to treatments that are delivered in a single fraction of high-dose radiation. SRS can be delivered either from a cobalt-60 source (Gamma Knife® surgery, GKS) or a linear accelerator [59, 60]. It is an effective adjuvant RT option following incomplete resection especially suited for patients who have small-volume tumors in brain locations that are high risk for resection-related complications. Table 10.2 summarizes major studies utilizing SRS in skull base chondrosarcomas. Overall, 5-year LC of GKS for skull base chondrosarcomas has been reported to be ~70–80% [7, 32, 61]. SRS has progression-free survival (PFS) rates around 80–85% at 5 years and 70% at 10 years [7, 61, 62]. The caveat is that there are currently a small number of studies in the literature with more than ten patients. Factors associated with longer survival after SRS included patient age >40 years, a shorter interval (<6 months) between diagnosis and SRS, and either no or a single prior resection [32].

Regarding the optimal dose, it has been shown that patients receiving <16–24 Gy marginal dose have inferior outcomes [7, 62, 63]. In a study by Koga et al., 5-year PFS for patients who underwent SRS with higher marginal doses (mean 18 Gy, range, 16–20 Gy) was 80%, significantly higher than 14% for those with lower marginal doses (mean 12 Gy, range, 10–12.5 Gy) [63]. The authors concluded that sufficient marginal doses of at least 16 Gy appeared crucial, although those who received lower doses tended to be patients who had fractionated radiation therapy before and underwent SRS in the recurrent setting.

Radiation-related complications are reported to be fewer than that of fractionated RT [6] but can still be relatively high, especially when used for larger lesions or when radiosurgery is combined with fractionated radiation therapy. In a study by Forander et al. including nine patients with skull base chondrosarcoma treated with GKS [64], one patient had radiation necrosis, which required microsurgery, and two patients had new cranial nerve palsies. In another study by Krishnan et al. [65] including 29 patients with skull base chondrosarcoma or chordoma, ten patients (34%) had radiation-related complications. Complications included cranial nerve deficits ($n = 6$), radiation necrosis ($n = 5$), and pituitary dysfunction ($n = 3$). Median tumor volume was

Table 10.2 Major studies utilizing SRS in skull base chondrosarcomas

First author, year	No. of patients	Follow-up (months)	RT modality	Mean tumor volume	Dosing	Local control	PFS	OS	Toxicity
Feigl, 2005 [105]	10	17	Adjuvant GKS	9.7 cm^3 (range 1.4–20.3 cm^3)	Mean marginal dose of 17 Gy and the at mean isodose line of 52%	100% final follow-up	100% final follow-up		Cranial nerve function after GKS improved in seven patients (53.8%)
Martin, 2007 [61]	10	76	Adjuvant GKS	9.8 cm^3	Mean marginal dose of 16.5 Gy (10.5–25 Gy); Mean Maximum tumor doses of 33 Gy (21–50 Gy)	5-yr: 80 +/– 10.1%	5-yr: 80%	5-yr: 70%	None had acute toxicity due to radiation. No new cranial nerve, motor, or sensory deficits were detected during follow-up.

(continued)

Table 10.2 (continued)

First author, year	No. of patients	Follow-up (months)	RT modality	Mean tumor volume	Dosing	Local control	PFS	OS	Toxicity
Iyer, 2012 [32]	22	75.4	GKS	8.0 cm^3 (range 0.9–28.2 cm^3)	Median margin dose of 15.0 Gy (range, 10.5–20 Gy)	1-yr: 91% 3-yr: 72% 5-yr: 72% 10-yr: 54%		1-yr: 95% 3-yr: 76% 5-yr: 70% 10-yr: 56%	Symptomatic adverse radiation effects occurred in two patients (10%)
Jiang, 2013 [62]	12	33	Cyberknife SRS	35.1 cm^3 (median 11.0 cm^3)	Median marginal dose of 22, 24, 26, 27, and 30 Gy for 1–5 fractionations	58% at final follow-up		1-yr: 81% 3-yr: 67% 5-yr: 55%	One patient had radiation injury as severe headache and progressive vertigo with radiographic evidence of radiation-induced inflammation in the brainstem
Kano, 2015 [7]	46	75	GKS (78% post-op)	8.0 cm^3 (range 0.9–28.2 cm^3)	Median marginal dose of 15 Gy (range 10.5–20 Gy)	78.2% at final follow-up	Overall: 3-yr: 88% 5-yr: 85% 10-yr: 70% No prior RT: 3-yr: 92% 5-yr: 88% 10-yr: 81%	3-yr: 89% 5-yr: 86% 10-yr: 76%	Six patients (13%) had deterioration in cranial nerve function after SRS in the absence of tumor progression

PFS progression-free survival, *OS* overall survival, *yr* year

14.4 cm^3 (range, 0.6–65.1 cm^3). The exposure of the optic apparatus, pituitary stalk, and brainstem must be considered during planning to minimize complications. If the optic apparatus is included in the 80% isodose line, it might be best to fractionate therapy. Exposure of the pituitary stalk should be kept to <30 Gy to minimize endocrine dysfunction. Brainstem exposure should be limited to <12 Gy in SRS [59].

The most prominent limitation for SRS is tumor size. The treatment was usually addressed to small residual lesions (10–20 mL) after maximal tumor resection [7, 44, 64, 66], and volume >20 mL was associated with poor local control [66]. In most published series, the mean tumor volume was <10 mL although a range of tumor sizes were included. In fact, a large proportion of chondrosarcoma exceed the size suitable for SRS or have irregular configurations making the use of SRS not widely applicable.

Of note, hypofractionated stereotactic radiation therapy (also known as FSRT although this term may also refer to conventionally fractionated radiotherapy under stereotactic positioning; see above) has also been reported in the literature to treat skull base or upper cervical spine chondrosarcoma. This approach utilizes the advantages of stereotactic positioning and delivery accuracy and delivers 21–43.6 Gy in 3–5 fractions [60, 67]. Early reports support this modality as a safe and effective option although longer term data is lacking.

Proton Therapy As described above, compared to photon therapy, proton therapy results in minimal exit dose after energy deposition (Bragg peak) at the target location. When using advanced treatment planning and delivery, such as pencil beam scanning or intensity-modulated proton therapy (IMPT), proton therapy results in a sharp dose falloff to spare surrounding critical structures while delivering a slightly greater biological effective dose. Published series of proton radiotherapy in the treatment of skull base chondrosarcoma are summarized in Table 10.3. When treating with proton therapy, conventional fractionation (1.8–2.0 Gy (RBE) per fraction) is employed, and the most common dosing regimen has been 68–72 Gy (RBE) delivered in 1.8–2.0 Gy (RBE) per fraction.

A retrospective comparative study of surgery alone vs. surgery followed by adjuvant proton therapy showed that adjuvant proton therapy was associated with a significantly lower rate of relapse (34% vs. 11%; $p = 0.01$). No difference in 10-year disease-specific survival (DSS) between patients initially treated with or without proton was observed [68]. In a recent analysis of NCDB including 863 patients with chondrosarcoma, proton therapy was associated with improved 5-year OS in the definitive RT setting (75.0% vs. 19.1%; $p = 0.007$) and in the perioperative setting (97.1% vs. 69.4%; $p = 0.005$) [4]. However, this survival advantage may be attributed in part to a selection bias wherein tumors treated with proton therapy are most likely to have favorable anatomy allowing delivery of higher doses of radiation. Indeed, a subgroup analysis limited to patients receiving high-dose radiation showed no significant difference in OS between proton and photon-based RT in chondrosarcoma. There have been no prospective trials comparing proton radiation to other radiation modalities [44]. An example proton plan for a skull base chondrosarcoma is shown in Fig. 10.2.

Retrospective studies have reported LC at 5 years with adjuvant proton therapy between 94% and 99% [53, 69–71] with PFS in the same range [68–70] as local recurrence is the most common type of failure (95%, [71]). The 5-year OS has been reported to be higher than 90% [70, 71]. In addition, proton therapy appears to be well suited for patients with residual lesions ≥20 mL after surgery that may not be suitable for SRS or hypofractionated approaches [44]. However, it should be noted that one series reported that a GTV >25 mL is associated with lower LC rates [70].

Based on these retrospective studies, the rate of adverse radiation effects of proton beam RT appears to be low. Acute toxicity is considered negligible [44], and the rate of severe late effects is limited (<10% incidence of RTOG grade 3 toxicity) [33]. In a large series by Munzenrider et al. [71], optic neuropathy developed in 12 of 274 patients (4.4%) who received prescribed tumor doses ranging from 63.4 to 79.4 Gy (RBE). Median dose to the optic structures in injured patients was 62.1 Gy (RBE). In a study by Austin-Seymour et al., 4% had visual complications [72].

Table 10.3 Major studies utilizing proton-only radiotherapy in skull base chondrosarcomas

First author, year	No. of patients	Follow-up (months)	RT modality	Dosing	Local control	PFS	OS	Toxicity
Austin-Seymour, 1989 [72]	28	34	Fractionated proton (160-MeV)	Median tumor dose 69 Gy (RBE)	5-yr: 82%	82% at 5 years		4% had visual complications; pituitary insufficiency
Simon, 2018 [68]	23	91	Adjuvant proton	Mean total dose 70 Gy (RBE), 1.8 Gy (RBE)/day	89%	100%		39% had sensorineural hearing loss
Munzenrider, 1999 [71]	229	42.5	Adjuvant proton RT	63.0–79.2 Gy (RBE) (mean 67.8 Gy [RBE]) in 1.92 Gy (RBE) fractions	5-yr: 98% 10-yr: 94%		5-yr: 91% 10-yr: 88%	Three patients died of brainstem injury. Median dose to the optic structures in injured patients was 62.1 Gy (RBE). Audiographically significant hearing loss occurred 2–5 years after irradiation in 15 of 33 patients prospectively evaluated after treatment. The estimated probability of neuropathy rose from 1% at 62 Gy (RBE) (0.5–3%) to 5% at 73.2 Gy (RBE) (64–81 Gy [RBE])

(continued)

Table 10.3 (continued)

First author, year	No. of patients	Follow-up (months)	RT modality	Dosing	Local control	PFS	OS	Toxicity
Rosenberg, 1999 [69]	200	63	Adjuvant conformal proton RT	64.2–79.6 Gy (RBE) (median, 72.1 Gy [RBE]), given in 38 fractions, 1.8–1.92 Gy (RBE)/fx	5-yr: 99% 10-yr: 98%	5-yr: 99% 10-yr: 99%		
Mattke, 2018 [53]	22	40	Adjuvant protons via a raster scan technique	Median total dose 70 Gy (RBE) at 2 Gy (RBE) per fx	1-yr: 100% 2-yr: 100% 4-yr: 100%		1-yr: 100% 2-yr: 100% 4-yr: 100%	No toxicity worse than Common Toxicity Criteria grade 3 was observed after treatment. No significant difference in rate of double vision in proton vs. carbon ion group
Ares, 2009 [70]	22	38	Spot-scanning-based proton radiotherapy	Median total dose 68.4 Gy (RBE) at 1.8–2.0 Gy (RBE)/fx	5-yr: 94%	5-yr: 100%	5-yr: 91%	Actuarial 5-year freedom from high-grade toxicity was 94%: unilateral optic neuropathy, CNS necrosis. No brainstem toxicity

PFS progression-free survival, *OS* overall survival, *yr* year, *fx* fraction

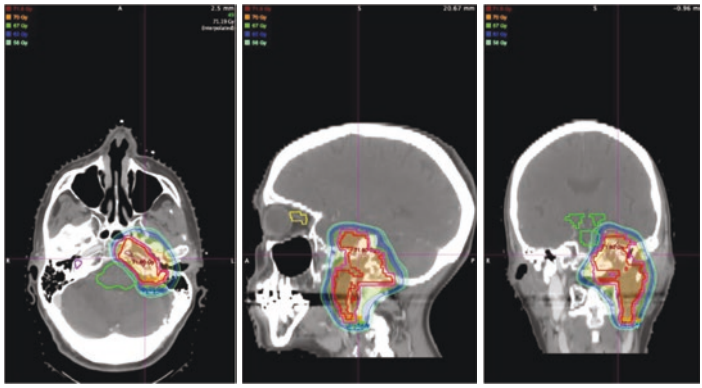

Fig. 10.2 Example plan of a chondrosarcoma involving the skull base treated with proton therapy. Isodose lines: 71.8 Gy: maroon, 70 Gy: orange, 67 Gy: green, 62 Gy: blue, and 56 Gy: cyan. Case contributed by Shannon MacDonald, MD, Department of Radiation Oncology, Massachusetts General Hospital, Harvard Medical School

Audiographically significant hearing loss occurred 2–5 years after irradiation in 15 of 33 (45%) patients prospectively evaluated after treatment. The estimated probability of neuropathy rose from 1% at 62 Gy (RBE) (0.5–3%) to 5% at 73.2 Gy (RBE) (64–81 Gy (RBE)) [71]. Similarly, in another study by Simon et al., 39% of patients had sensorineural hearing loss [68]. Ares et al. report that high-grade toxicity developed in 6% of patients in 5 years, in the form of unilateral optic neuropathy and CNS necrosis [70]. While a newer study by Mattke et al. in 2018 reports no toxicity worse than CTCAE grade 3 after treatment [53], some consider toxicity from proton therapy to be higher than that of SRS [7], though any comparison is confounded by the fact that proton beam RT tends to be used for larger tumors.

Mixed Proton/Photon Therapy When combined with photons, proton therapy could be delivered either before or after the photon therapy. The most common dosing regimen has been 67–70 Gy (RBE) delivered in 1.8–2.0 Gy (RBE) per fraction. Total doses up to 80 Gy (RBE) can be safely applied to the skull base using pro-

tons or a proton-photon combination [71]. LC between 75% and 96% at 5 years have been reported [53, 69–71], along with 5-year OS of 95% or higher [73–76]. From retrospective series, there does not appear to be an obvious difference in the reported PFS and OS between proton-only therapy and combined photon/proton treatments [75]. A summary of major studies utilizing mixed proton/photon therapy in skull base chondrosarcomas is shown in Table 10.4.

Local failure appears to be the major mode of failure. In one study, relapses were located in the GTV in two-thirds of the cases, highlighting the radioresistant nature of this tumor [77]. GTV <25–28 mL [75, 77], maximum diameter <45 mm [77], younger age [74, 77], and primary versus recurrent disease status [74] are prognostic indicators of better local control, PFS, and OS. Tumor directly adjacent to critical structures is also more difficult to control due to limitations of RT dose. For example, optic pathway compression was significantly associated with the risk of treatment failure ($p = 0.027$) [75]. Brainstem involvement was also associated with worse recurrence [76] and the volume of the brainstem receiving 60 Gy (RBE) is an independent negative prognostic factor [73].

Late grade ≥3 toxicities were observed in 6–15% of patients in reported case series [73–77], including oculomotor impairment, severe hearing loss, loss of vision, temporal lobe damage, and focal seizure. Interestingly, in the largest study of patients treated with mixed protons and photons ($n = 135$) or protons alone ($n = 116$), there was no difference in toxicity rates between the two groups [75]. Feuvret et al. compared these two modalities for skull base tumors and demonstrated that proton planning [78] decreased the distribution of low-intermediate dose to organs at risk (OARs), but this differential dose deposition may not be large enough to translate into an increased therapeutic window.

Carbon Ion Therapy Carbon ion therapy has proven to be an effective and safe treatment for skull base chondrosarcoma. From a radiobiology standpoint, carbon ion has advantages compared to photon or proton therapy, including higher RBE and increased linear energy transfer (LET) which may help overcome the inherent radioresistance of chondrosarcoma. In a recent meta-analysis

Table 10.4 Major studies utilizing combined proton and photon radiotherapy in skull base chondrosarcomas

First author, year	No. of patients	Follow-up (months)	RT modality	Dosing	Local control	PFS	OS	Toxicity
Noel, 2003 [77]	18	29	Combined high-energy photon (2/3) and protons (1/3)	Median total dose 67 Gy (RBE) (60–70 Gy [RBE])	3-yr: 85%		3-yr: 94% 4-yr: 75%	49% developed late adverse effects. All required hormone replacement. 6% had grade 3+ side effect: oculomotor impairment, severe hearing loss, and loss of vision
Debus, 1997 [73]	172	42.5	Combined photon and proton RT	Mean dose 67.8 Gy (RBE) (63 Gy [RBE] to 79.2 Gy [RBE]), 1.8 Gy (RBE) per fraction	82% (including chordoma)		5-yr: 94% 10-yr: 85% (including chordoma pts)	4.6% had brainstem toxicity and 3 pts. died. Actuarial rates of 5 and 10-yr high-grade toxicity-free survival were 94 and 88%, respectively

(continued)

Table 10.4 (continued)

First author, year	No. of patients	Follow-up (months)	RT modality	Dosing	Local control	PFS	OS	Toxicity
Feuvret, 2015 [74]	159	77	Post-op adjuvant protons alone or in combination with photons	Median dose 70.2 Gy (RBE) (range 67–71 Gy [RBE])	5-yr: 96.4% 10-yr: 93.5%		5-yr: 95% 10-yr: 87%	The 5- and 10-yr grade 3 to 5 toxicity rates were 10% and 10%, respectively
Weber, 2019 [75]	251	88	Protons alone (46%) or in combination with photons (54%)	Median dose 70.2 Gy (RBE)	7-yr: 95.6%	7-yr: 93.1%	7-yr: 93.6%	Late grade ≥ 3 radiation-induced toxicities were observed in 15.1% of patients
Hug, 1999 [76]	25	33	Protons alone (88%) or in combination with photons (12%)	Mean dose 69.3 Gy (RBE) (range 64.8–72.0 Gy [RBE]), 1.8 Gy (RBE) per fraction	3-yr: 94% 5-yr: 75%		5-yr: 100%	Grade 3 and 4 late toxicities were observed in 7% and were symptomatic in 5%: temporal lobe damage, hearing loss, focal seizure, bilateral loss of vision; 14% had grade 1–2 toxicity

PFS progression-free survival, *OS* overall survival, *yr* year

of carbon ion radiotherapy from the Mayo Clinic that included 243 patients with skull base chondrosarcomas, the estimated 1-, 5-, and 10-year LC were 99%, 89%, and 88%, respectively. OS at 1, 5, and 10 years were 99%, 95%, and 79%, respectively [79]. Across published series, 5-year LC has been ~88%, while OS at 5 years has been 95–96% [53, 54, 79, 80]. A summary of major studies utilizing carbon ion therapy in skull base chondrosarcomas is shown in Table 10.5.

There are also a few series on the performance of carbon ions in the re-irradiation setting. Combs et al. reported local tumor control after re-irradiation as 92% at 24 months and 64% at 36 months for skull base tumors [81]. One major caveat is that this therapy is only offered in a few centers around the world, including Heidelberg, Germany, and a few centers in Asia (China and Japan) [54, 79, 82].

Despite the theoretical advantage of carbon ion therapy, comparisons between carbon ion and other radiation types are challenging. A study by Mattke et al. [53] included 101 patients with skull base chondrosarcoma treated by either proton or carbon-ion-beam treatment at the Heidelberg Ion Beam Therapy Center. This study found no significant difference in survival outcomes among patients with skull base chondrosarcomas treated with carbon ions versus protons. Regarding prognostic factors, similar to proton therapy, younger age (≤44–45 years old [53, 54]) and a boost volume ≤55 mL [53] were associated with significantly better local control rates with carbon ion therapy.

The toxicity profile of carbon ion treatment appears to likewise be very favorable. The incidence of early and late toxicity (grade ≥ 3) is low (0–4%) across studies [79]. Radiographic changes in the brain have been observed after carbon-ion therapy, though these have also been reported following proton therapy in approximately 6% of patients. However, there is no indication that such changes altered the postradiation treatment course or resulted in worse survival outcomes [79]. The occurrence of visual loss seems to be correlated with a delivery of >60 Gy (RBE) to 20% of the volume of the optic nerve [83]. V_{50} >4.6 mL of the brain is associated with grade 2 or higher brain injury [84]. And although carbon ions have a theoretical sharper radiation

Table 10.5 Major studies utilizing carbon ion radiotherapy in skull base chondrosarcomas

First author, year	No. of patients	Follow-up (months)	RT modality	Dosing	Local control	OS	Toxicity
Uhl, 2014 [54]	79	91	Adjuvant carbon ion (12 biopsy and 67 with R2 resection)	60 Gy (RBE) at 3 Gy (RBE) per fraction	3-yr: 95.9% 5-yr: 88% 10-yr: 88%	3-yr: 96.1% 5-yr: 96.1% 10-yr: 78.9%	CN deficits 73% at baseline, decreases over time, from 53% at year 1 to 45% at year 10
Schulz-Ertner, 2007 [80]	54	33	Carbon ions	60 Gy (RBE) (57–70) at 3 Gy (RBE) per fraction, 7 fx/week; BED: 76 Gy (RBE) (PTV2)	3-yr: 96.2% 4-yr: 89.8%	3-yr: 98.2% 4-yr: 98.2%	Only one patient developed a mucositis CTCAE Grade 3; the remaining patients did not develop any acute toxicities >CTCAE Grade 2
Mattke, 2018 [53]	79	40	Adjuvant carbon ions with Intensity-Modulated Active Raster Scanning	60 Gy (RBE) at 3 Gy (RBE) per fraction	1-yr: 98.6% 2-yr: 97.2% 4-yr: 90.5%	1-yr: 100% 2-yr: 98.5% 4-yr: 92.9%	No toxicity worse than CTC grade 3 was observed after treatment. Symptom of double vision decreased from 42% in the carbon-ion group to 21%. No significant difference in rate of double vision in proton vs. carbon ion group

PFS progression-free survival, *OS* overall survival, *yr* year, *fx* fraction

dose falloff, which may result in lower post-RT complication rates, this has not been substantiated in the clinic. It is intriguing in a study by Shulz-Ertner et al. with 54 patients treated with carbon ions [80], only one patient developed a Common Terminology Criteria for Adverse Events (CTCAE) grade 3 mucositis; the remaining patients did not develop any acute CTCAE grade >2 toxicities. The authors suggest that late toxicities after carbon ions may be reduced, though this claim requires further investigation. It should be noted that the cost per treatment of carbon ion therapy is significantly more expensive than the cost of proton (in a proton-only facility) or photon therapy [85].

Currently, there is an ongoing phase III single institution clinical trial at Heidelberger Ionenstrahl-Therapiezentrum (HIT) center in Germany, which randomizes patients with skull base chondrosarcomas to either proton (70 Gy (RBE) ± 5%) or carbon ion radiation therapy (60 Gy (RBE) ± 5%) with 5-year local-PFS rate as the primary end point [86] (ClinicalTrials.gov identifier: NCT01182753).

Radiation Field Design

Designing the radiation target volume for the treatment of skull base chondrosarcoma is similar across various modalities, with minor differences. Gross tumor volume (GTV) captures the gross disease visible on advanced axial imaging and is delineated based on the planning CT scan in combination with pre- and/or postoperative MRI scans. The clinical target volume (CTV) captures the GTV plus an additional margin to capture regions of suspected microscopic spread. The CTV typically encompasses a 5–10 mm margin around the GTV and is adjusted manually to account for natural anatomic barriers to tumor spread and to ensure the volume captures presurgical disease extent. The surgical pathway is not typically covered. The planning target volume (PTV) encompasses the CTV plus an expansion to account for daily variability in the patient setup and uncertainty in treatment accuracy. This expansion depends on the modality of imaging guidance, patient immobilization, and the treatment setup (thermoplastic mask,

presence or absence of a bite block) but is typically around 3 mm (2–6 mm).

In some studies, a separate PTV1 and PTV2 were defined when treating with proton or carbon ion therapy. For example, Schulz-Ertner et al. [80] defined PTV1 as the GTV plus suspected subclinical disease with a safety margin of 1–2 mm for possible patient misalignment. A smaller boost planning target volume of PTV2 was defined to include GTV plus a 1–2 mm margin. PTV1 was treated to a target dose between 45 and 52.5 Gy (RBE) within 15 fractions, and a boost dose of 12–17.5 Gy (RBE) was delivered to the PTV2; the total target dose within PTV2 was therefore 57–70 Gy (RBE). Similarly, Ares et al. defined PTV1 = CTV+5 mm and PTV2 = GTV+5 mm when delivering proton RT [70]. For stereotactic radiosurgery, the target volume is often the GTV without an additional expansion [87]. A summary of suggested dose and target volumes is shown in Table 10.6.

Table 10.6 Suggested dose and target volumes for radiation therapy for skull base chondrosarcoma

Volume	Description	Dose
GTV	Gross tumor delineated on planning CT and preoperative MRI	
CTV1	CTV1 = GTV + 5 ~ 10 mm. Includes preoperative tumor extension and suspected microscopic spread. Volumes should be adjusted to account for the anatomy, natural barriers, etc.	
PTV1	PTV1 = CTV1 + 3 mm (2–6 mm, depending on daily imaging setup)	45–52.5 Gy (RBE)[a] [80]
PTV2	PTV2 = GTV + 1 ~ 2 mm	Consider boost 15–17.5 Gy (RBE) to a total dose of 60–70 Gy (RBE)[a] [80]

Note: for SRS, often only the GTV is targeted in radiosurgery [87]
GTV gross tumor volume, *CTV* clinical target volume, *PTV* planning target volume
[a]Example dosing regimen. See main text for discussion of commonly used dosing regimen under each radiation delivery modality

Spine Chondrosarcoma

Role of Surgery and Radiation

Although less than 12% of chondrosarcomas occur in the spine [88], they represent a unique challenge for local disease control due to their sensitive anatomic location. As a result, radiotherapy plays a prominent role in the treatment of chondrosarcoma of the spine, relative to tumors of the extremities. Up to 60% of tumors arise in the thoracic region, with the remaining lesions divided between the lumbar (20–39%) and cervical spine (19–20%) [89].

A complete *en bloc* resection (vertebrectomy/spondylectomy) is the ideal surgical technique for resecting chondrosarcomas, which has been shown to be associated with increased LC and recurrence rates of 20% or less [89]. However, gross-total resection is often not achievable in spine chondrosarcomas due to proximity to critical structures, and the presence of gross disease after surgery appears to portend worse clinical outcome. In a study by Murray et al., fewer than half (45.1%) of the surgeries were GTRs prior to adjuvant proton therapy [90].

Local curettage of a chondrosarcoma is an alternative surgical technique, but it almost always results in recurrence [91, 92]. Patients treated with *en bloc* resection appear to have significantly better OS (mean 198 months) than those who underwent intralesional curettage (mean 77 months, $p = 0.05$) even when adjuvant radiation therapy is given [88]. In one study, *en bloc* resection and curettage did not result in a significant difference in oncologic outcome as long as GTR is achieved [90]. Maximal safe resection followed by appropriate adjuvant therapy remains the standard of care. In a small report of 21 patients from MDACC with chondrosarcoma of the spine, half of whom received adjuvant radiation, GTR was associated with prolonged disease-free interval [93].

The appropriate timing of radiation therapy (preoperative vs. postoperative) has not been determined, though the majority of retrospective studies have used an adjuvant rather than a neoadjuvant approach. Still, the neoadjuvant approach deserves consider-

ation. In a large single center study from Massachusetts General Hospital (MGH) spinal chondrosarcoma in 80% of patients [94], 44 of 95 patients were treated with a combination pre- and postoperative proton-based radiotherapy approach (the remaining patients were treated with surgery and postoperative radiation). Patients received between 19.8 and 50.4 Gy (RBE) preoperatively, depending on the concern for perioperative wound complications. Postoperatively, patients received a dose such that the initial larger target volume received a total of 50.4 Gy (RBE) (thus, patients receiving 50.4 Gy (RBE) preoperatively did not receive any additional dose to this larger volume, whereas patients who did not receive preoperative treatment received 50.4 Gy (RBE) postoperatively to this volume). Then, patients received a postoperative boost to a total of 70.2 Gy (RBE) to the tumor bed with a 5 mm margin. Patients with gross residual disease were treated to a final dose of 77.4 Gy (RBE) targeting residual tumor. The 5-year LC and OS were 57% and 68%, respectively. In another Canadian study, 40% of patients with extracranial chondrosarcoma underwent preoperative RT in situations where it was anticipated that there was a high probability of a positive resection margin, particularly where more extensive surgery would result in excess morbidity [2]. In this study, the median dose was 50 Gy for preoperative radiation and 60 Gy for postoperative radiation. There are several technical advantages of preoperative radiation. These include the opportunity to sterilize tumor cells prior to surgery, which can reduce the risk of tumor autotransplantation at surgery which can result in unsalvageable failures in these patients, such as pleural failures in patients with thoracic spine chondrosarcomas. A component of preoperative radiation allows for smaller fields (i.e., will not need to treat spine stabilization hardware) and allows radiation planning and delivery without any metallic spine hardware, which degrades imaging and treatment planning algorithms.

Regarding the delivery modality of RT, most series in the literature employ high-dose photon/proton combination or proton-only RT. Major studies utilizing radiotherapy in treating spine chondrosarcomas are summarized in Table 10.7. With good positioning (3 mm positioning accuracy), proton beam therapy per-

mits higher doses to significantly more of the tumor in these sites than photons [95] and yields lower mean doses for all OARs (spinal cord, esophagus, heart, and both lungs) [96]. An example plan of a sacral chondrosarcoma treated with proton therapy is shown in Fig. 10.3. Note the area of low-dose spillage (20% isodose line) is smaller compared to a conventionally fractionated IMRT plan (Fig. 10.1). In a retrospective dosimetric study reviewing thoracic spine treatment plans, proton therapy plans were compared to various photon-based plans, including tomotherapy, intensity-modulated radiation therapy, and dynamic arc photon therapy. The conclusion was that tomotherapy plans produce superior results compared with other photon modalities and are comparable to proton plans, which makes tomotherapy an attractive alternative to proton therapy when the latter is not available [96].

While these results are encouraging for potential benefits or proton and/or photon-based tomotherapy, it should be noted that these *in silico* dosimetric studies provide no evidence that either modality outperforms conventional photon-based intensity-modulated radiation therapy (IMRT) in the clinic [97], and there has been no direct comparison of short- or long-term clinical between these delivery modalities in patients. Of note, SBRT/SRS, as a commonly used technique for treating smaller chondrosarcoma of the skull base, has not been widely studied in the setting of chondrosarcoma in the spine [60, 62]. In one study utilizing CyberKnife SRS, tumor control was poor at 38% for spinal lesions compared to 58% for cranial lesions in the same series [62]. Carbon ion therapy has also been reported to treat chondrosarcomas involving the spine, and LC and OS are significantly lower in larger tumors (volume $\geq$ 470 mL) [98].

Dosing and Field Design

Typically 70–77.4 Gy (RBE) is delivered to the gross disease [8, 49, 56, 90, 97], using conventional fractionation of 1.8–2.0 Gy (RBE) per fraction. As described above, up to 50.4 Gy (RBE) of this dose may be administered preoperatively. Local control varies between studies but in general appears to reach approximately

Table 10.7 Major studies utilizing radiotherapy in treating spine chondrosarcomas

First author, year	No. of patients	Follow-up (months)	RT modality	Dosing	Local control	PFS	OS	Toxicity
Delaney, 2009 [8]	14	Median 48	High-dose photon/proton RT	50.4 Gy (RBE) to subclinical disease, 70.2 Gy (RBE) to microscopic disease in the tumor bed, and 77.4 Gy (RBE) to gross disease at 1.8 Gy (RBE) per daily fraction	2/9 primary chondrosarcoma pt. recurred, 4/5 recurrent chondrosarcoma pt. (at time of start of study) recurred	n/a	n/a	10% developed late radiation-associated complications (including other spine sarcomas) Sacral nerves receiving 77.12–77.4 Gy (RBE) are at risk for late toxicity
Murray, 2020 [90]	39	Median 64.7 (12.2–204.8)	Adjuvant pencil-beam scanning proton therapy	Median dose 74 Gy (RBE) (range 48.6–77 Gy [RBE])	5-yr: 55.9%	5-yr: 51.7%	5-yr: 67.3%	Long-term radiation-induced toxicities in 33.5% of all patients; 7.7% with high-grade toxicities (≥ grade 3)

Indelicato, 2016 [97]	17	Mean 44 (4–92)	Proton alone or proton + photon	Median dose of 70.2 Gy (RBE) (range, 64.2–75.6 Gy [RBE])	4-yr: 39%	4-yr: 57%[a]	4-yr: 72%[a]	Sacral soft tissue necrosis requiring surgery ($n = 2$), T1 vertebral fracture requiring fusion surgery ($n = 1$), chronic urinary tract infections ($n = 1$), surgery for necrotic bone cyst ($n = 1$), and grade 2 bilateral radiation nephritis ($n = 1$). Secondary cancers developed in two patients

(continued)

Table 10.7 (continued)

First author, year	No. of patients	Follow-up (months)	RT modality	Dosing	Local control	PFS	OS	Toxicity
Holliday, 2015 [49]	6	Median 34.5	Proton (adjuvant or salvage)	70 Gy (RBE) (range: 56–78 Gy [RBE]) in 2 Gy (RBE) per daily fraction	66.6% (chondrosarcoma only, end of follow-up); 2-yr LC: 58%[a]	2-yr: 51.9%[a]	2-yr: 93.3%[a]	None developed grade 3 to 5 toxicity or required a treatment break
Schoenfeld, 2012 [88]	20	All ≥24	10 pts, preoperative RT; 9 pts, IORT; 16 pts, photon + proton; 4 pts, proton alone	Mean dose of 71 Gy (RBE) (range 53–83 Gy [RBE])	100% in the *en bloc* group and 62% in the curettage group	n/a	1-yr: 90% 5-yr: 61% Mean: 120.5 months	RT-induced complications occurred in 33% pts.: pharyngitis, neuritis, wound breakdown, ulnar nerve neuropathy, postradiation hypothyroidism, and hearing loss

PFS progression-free survival, *OS* overall survival, *yr* year, *fx* fraction

[a]Combined chordoma and chondrosarcoma

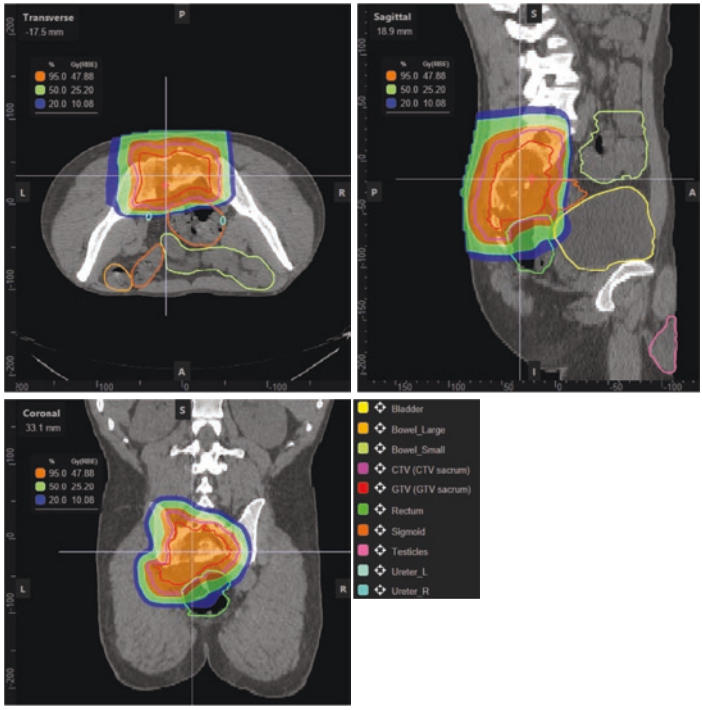

Fig. 10.3 Example plan of a sacral chondrosarcoma treated with preoperative proton therapy. A 29-year-old male with chondrosarcoma centered in the left hemisacrum with extraosseous soft tissue component protruding through the anterior left S2 and S3 neural foramina. There is perineural spread along these nerves, and invasion into the left piriformis muscle. He underwent preoperative radiation 50.4 Gy in 28 fractions with scanned protons (illustrated here), followed by surgical resection and postoperative proton therapy. Isodose lines: 95%: orange, 50%: green, and 20%: blue. GTV is shown in red and CTV is shown in pink. Case contributed by Thomas DeLaney, MD, Department of Radiation Oncology, Massachusetts General Hospital, Harvard Medical School. Note the smaller area of low dose spillage (20% isodose line) compared to a conventionally fractionated IMRT plan (Fig. 10.1)

50% (range 39–58%) after 2–5 years of follow-up. Though these rates are lower than those observed with skull base chondrosarcoma, one confounding factor is that spinal chondrosarcomas are often larger [99]. It is important to note that local control beyond 5 years is very relevant for these patients with spinal chondrosarcomas, as the majority of patients survive beyond 5 years. OS is approximately 90% at 1–2 years, 70% at 4 years, and 60–70% after 5 years [49, 56, 90, 97].

There is no consensus regarding the RT field design, and dosing and practice vary between institutions. For preoperative radiation of the spine, in a report from MGH, CTV1 was defined as GTV + ≥1 cm of soft tissue margin on extraosseous tumor, as well as grossly involved vertebrae plus one vertebra above and below. In this study, volumes were cropped at facial barriers (i.e., pleura or periosteum), and biopsy sites were included in CTV1. For sacral chordoma, more generous margins of ≥1.5 cm on areas of extraosseous tumor were employed [8]. For tumors located in the thoracolumbar area, the authors prescribed 50.4 Gy (RBE) to CTV1. Resection was performed 4–5 weeks after completion of RT. For sacral lesions, due to inherently higher risk of wound complications, only 19.8 Gy (RBE) was delivered preoperatively, with the remaining 30.6 Gy (RBE) to CTV1 delivered postoperatively without including surgically manipulated tissues or stabilization hardware [8].

For postoperative adjuvant radiation, patients are most often treated with a two-phase technique delivering 50.4–54 Gy (RBE) to a larger volume to address subclinical disease, followed by a boost to a total of 70–77.4 Gy (RBE) to the tumor bed (consisting of the preoperative tumor volume plus a small 0.5 cm margin) and any gross residual disease [90]. In the study by Delaney et al. [8], CTV1 encompassed surgically manipulated tissues including scars, drain sites, and stabilization hardware and received 50.4 Gy (RBE) in 28 fractions, and as described above, the dose to this volume may be administered preoperatively. CTV2 (consisting of the tumor bed and including all of the preoperative gross diseases) received an additional 19.8 Gy (RBE) (in 11 fractions) to a total of 70.2 Gy (RBE). For patients whose tumor was unresectable or who had gross residual disease postoperatively, the gross or gross

residual disease was boosted with another 7.2 Gy (RBE) (in four fractions) to a total of 77.4 Gy (RBE).

In another study, CTV1 has been defined as the GTV (preoperative tumor volume and postoperative bed) with a 1–2 cm expansion, encompassing tissue at high risk of microscopic disease restricted based on anatomic barriers of tumor spread [97]. The PTV1 has been defined as the CTV1 plus an additional 5 mm to account for daily setup variation and dose uncertainty and has been prescribed a dose of 45 Gy (RBE) or 54 Gy (RBE) [90, 97]. This is followed by a cone down to PTV2, which is defined as GTV plus an additional 5 mm [97] to a total dose of 70–74 Gy (RBE) [90, 97]. Notably, Murray et al. found that treatment volumes (PTV1 and PTV2) have grown over two decades (increase in median volume by 40% and 18%, respectively) [90]. A summary of suggested dose and target volumes is shown in Table 10.8.

Radiation Toxicity and Dose Constraints

The tabulation of radiation-associated toxicities in patients with chondrosarcoma is primarily based on retrospective studies, which may often fail to completely capture the nature and extent of treatment-related toxicities. Still, these studies provide a framework for which clinical decisions can be made in the absence of higher level evidence. Late radiation-related treatment toxicities occurred in 10–33% of patients with spinal chondrosarcomas [8, 88, 90], with grade 3 or higher toxicity ranging from 0% to 7.7% [49, 90]. More serious adverse effects include myelitis, esophageal strictures which may require dilatation, insufficiency fractures, soft tissue necrosis, subcutaneous fistula formation, neuropathic pain, femoral insufficiency which may require hip replacement, and ureteral stenosis [90]. Although tumor site (sacrum vs. spine, cervical spine vs. other) does not appear to have an impact on oncologic control [97], sacral chondrosarcomas are more challenging to plan given their proximity of the tumor to the bladder, bowel, perineum, and sacral plexus and the higher risk of wound complications.

Table 10.8 Suggested dose and target volumes for proton/photon radiation therapy for spine chondrosarcoma

Setting	Volume	Description	Dose
Preoperative	GTV	Gross tumor delineated on preoperative imaging	
	CTV1 [8]	GTV + ≥1 cm of soft tissue margin on extraosseous tumor, as well as grossly involved vertebrae plus one vertebra above and below. For sacral tumor, consider margins of ≥1.5 cm on areas of extraosseous tumor. Volumes should be cropped at facial barriers (i.e., pleura or periosteum)	
	PTV [8]	For photon: PTV = CTV1 + 5 mm For protons: apertures were designed to allow for 3 mm of lateral target expansion secondary to intrafraction motion	Thoracolumbar spine: 50.4 Gy (RBE) followed by resection 4–5 weeks later; sacral spine: 19.8 Gy (RBE) immediately prior to resection, followed by 30.6 Gy (RBE) adjuvant RT without including surgically manipulated tissues or stabilization hardware
Postoperative	GTV	Gross disease prior to surgery	
	CTV1 [8, 97]	Encompassed surgically manipulated tissues including scars, drain sites, and stabilization hardware. Alternatively, use GTV (preoperative tumor volume and postoperative bed) with a 1–2 cm expansion. Encompassing tissue at high risk of microscopic disease restricted based on anatomic barriers of tumor spread	
	PTV1 [8, 97]	PTV1 = CTV1 + 5 mm	50.4 Gy (RBE) in 1.8 Gy (RBE)/ fraction
	PTV2 [8, 97]	PTV2 = GTV+ 5 mm	70–74 Gy (RBE) in 1.8 Gy (RBE)/ fraction

Note: Consider boost to gross residual disease after resection to a total dose of 77.4 Gy (RBE) in the case of R2 resection. *GTV* gross tumor volume, *CTV* clinical target volume, *PTV* planning target volume

With regard to normal tissue dose constraints, Delaney et al. limited spinal cord center dose to 54 Gy (RBE) and cord surface dose to 63 Gy (RBE) over a length ≤5 cm. The cauda equina was constrained to 70.2 Gy (RBE), except areas in direct contact with tumor where the dose limit was 77.4 Gy (RBE). No specific sacral nerve constraints were used, other than trying to spare contralateral sacral nerves for lateralized lesions. Small bowel dose was ≤50.4 Gy (RBE). Omentum was placed posterior to the rectum during surgery to create anatomic separation and minimize rectal dose when possible. Sacral nerves receiving 77.12–77.4 Gy (RBE) are at risk for late toxicity [8].

Pattern of Failure and Prognosis

Not surprisingly, local control is superior in cases where adjuvant radiation is delivered at initial presentation versus at recurrence (19%) [97]. Holliday et al. reported similar findings wherein patients with spinal chordomas and chondrosarcomas given radiation at initial presentation had LC of 80%, compared with 46% in those who were treated at the time of recurrence [49]. RT also does not "make up for" suboptimal surgery, such has intralesional curettage [88]; it is most effective as an adjuvant for patients who have undergone *en bloc* resection. In addition, additional prognostic factors associated with poor local control include the presence of metastasis and high-grade tumor [88, 97]. Similar to the skull base, recurrent chondrosarcoma of the spine appears to be refractory to radiation therapy with very high recurrence rate [8, 97]. In a study by Delaney et al., four out of five patients with recurrent spine chondrosarcoma experienced another recurrence after treating with high-dose photon/proton RT [8].

Interestingly, the presence of surgical stabilization hardware is also found to be associated with worse outcome when treated with pencil-beam proton therapy [90]. It has been postulated that this is due to the inability of current treatment planning systems to accurately calculate proton dose distribution near these

implants due to the presence of CT imaging artifacts, inaccurate estimates of metal geometric dimensions, and uncertainties in the calculation of laterally scattered protons and other particles [97]. One approach is to utilize combined photon/proton RT when treating patients with hardware, which was described above [97]. In addition, pencil-beam proton therapy is also generally avoided in this scenario [97]. When these adjustments are made, patients with hardware experienced a similar (or perhaps even lower) local recurrence rate compared with patients without hardware [97]. As noted above, this problem can be mitigated to a substantial degree by delivering a significant proportion of the RT prior to surgery.

In an early experience from MGH, in which 41 patients with chordoma and chondrosarcoma of the base of skull and cervical spine were treated with proton and photon irradiation between 1980 and 1989, 23% of the cases failed in the prescribed dose region, 58% failed in regions where tumor dose was limited by normal tissue constraints, 10% of the patients recurred in the surgical pathway, and 10% were judged to be marginal misses [99]. The prescribed doses in this study ranged from 67 Gy to 72 Gy (RBE) (mean 69 Gy [RBE]). Overall, 75% of the patients failed in regions receiving less than the prescribed dose. All tumors which failed in the high-dose region had volume greater than 75 cm^3.

Pelvic Chondrosarcoma

Although pelvis is part of the appendicular skeleton, this anatomic location poses unique challenges. Traditionally, pelvic chondrosarcomas were treated with external hemipelvectomy (also known as hindquarter amputation), which is associated with poor functional and cosmetic outcomes. But nowadays more often than not patients are treated with limb-salvaging resection [100]. Nevertheless, it is still a challenging procedure given complex pelvic anatomy, the proximity to major neurovascular structures, often large tumor size at the time of diagnosis, and challenges

associated with reconstruction. Wide local excision with good margins is adequate for excellent tumor control. In a recent large single center study involving resection of 262 pelvic chondrosarcomas, overall 26% patients had local recurrence. However, no patients with a surgical margin ≥1 mm had local recurrence, metastasis, or disease-related death, irrespective of tumor grade [101].

The role of RT in the definitive setting is largely undefined, while some publications describe a possible role of RT in the adjuvant setting for inadequate margins or local recurrence [100]. RT has been described as not reliably effective in the adjuvant setting for pelvic chondrosarcoma, as some advocate that adequacy of surgical resection is the primary driver of patient outcome [102]. In a SEER database analysis of 262 pelvic chondrosarcoma patients treated between 2004 and 2016, 93.1% patients underwent surgery and only 6.9% received any type of radiotherapy [103]. The infrequent use of RT in this setting compared to the spine or skull base may be related to the ability to perform more aggressive resections to achieve negative margins. Furthermore, patients with recurrent tumors may still have surgical options. In an early report from MDACC on 21 patients with recurrent pelvic chondrosarcoma, with aggressive surgical intervention, approximately 50% of patients achieved long-term survival [102]. Thus, the use of adjuvant radiation remains infrequent and for cases in which complete resections are not possible. Of note, a combination of short-course preoperative radiation, surgical resection, and reduced-field high-dose postoperative radiation, developed at MGH, appears to be an effective way of treating pelvic (and spine) chondrosarcomas. In a study by Wagner et al. including 15 chondrosarcomas with the majority involving pelvis/sacrum, a median preoperative dose of 20 Gy radiation was delivered to a preoperative volume (CTV1 = GTV + 1 ~ 1.5 cm). Postoperative radiation included multiple phases with progressively shrinking volumes: a total dose of 50.4 Gy (including the preoperative dose) was delivered to the preoperative treatment volume, followed by 19.8 Gy boost to the GTV plus 5–10 mm margin, followed by an additional

boost of 7.2 Gy to residual gross disease to a total dose of 77.4 Gy in cases of subtotal resection. This approach affords a 5-year LC of 88.9% and 5-year DFS of 71.5% in the primary disease setting [104].

Concluding Remarks

Chondrosarcoma is a unique malignancy because of its local disease morbidity. Even in patients with limited metastatic disease, or even without metastatic disease, local disease control is paramount because patients can often have extended survival beyond 5 years. Surgery is the mainstay of local control, but tumors in the skull base and spine are often challenging to resect with widely negative margins, resulting in inferior local control.

Radiotherapy is an important adjunct for chondrosarcoma of the skull base and spine. However, treatment of these tumors with radiotherapy is challenging because effective treatment requires high cumulative doses (~70 Gy or higher), and the treatment target is often near critical structures (e.g., brain, brainstem, spinal cord, optic and other cranial nerves). Advanced treatment modalities are critical to be able to achieve the appropriate dose and to spare nearby critical structures. Patients should be considered for particle-based therapies (proton or carbon ion) when possible. Photon-based therapies should be delivered using advanced image guidance and intensity-modulated radiotherapy. For smaller tumors in the skull base, stereotactic radiosurgery should be considered. Most often, radiation therapy is administered postoperatively, though combined preoperative and postoperative therapies can be effective in the spine or the pelvis.

And, finally, chondrosarcomas are rare tumors requiring specialized expertise. Thus, we recommend patients position themselves for the best local disease control by seeking treatment from a radiation oncologist at a high-volume sarcoma center with expertise in bone and soft tissue tumors and access to advanced treatment modalities and a multidisciplinary team of surgeons, pathologists, radiologists, and medical oncologists.

References

1. Catanzano AA, et al. Revisiting the role of radiation therapy in chondrosarcoma: a National Cancer Database Study. Sarcoma. 2019;2019:4878512.
2. Goda JS, et al. High-risk extracranial chondrosarcoma: long-term results of surgery and radiation therapy. Cancer. 2011;117(11):2513–9.
3. Network, N.C.C. NCCN clinical practice guidelines in oncology: bone cancer. Version 1.2020. August 12, 2019 ed. 2019: NCCN.
4. Palm RF, et al. The role of dose escalation and proton therapy in perioperative or definitive treatment of chondrosarcoma and chordoma: an analysis of the National Cancer Data Base. Cancer. 2019;125(4):642–51.
5. Holtzman AL, et al. Proton therapy for skull-base chondrosarcoma, a single-institution outcomes study. J Neuro-Oncol. 2019;142(3):557–63.
6. Kano H, Iyer A, Lunsford LD. Skull base chondrosarcoma radiosurgery: a literature review. Neurosurgery. 2014;61 Suppl 1:155–8.
7. Kano H, et al. Skull base chondrosarcoma radiosurgery: report of the North American Gamma Knife Consortium. J Neurosurg. 2015;123(5):1268–75.
8. DeLaney TF, et al. Phase II study of high-dose photon/proton radiotherapy in the management of spine sarcomas. Int J Radiat Oncol Biol Phys. 2009;74(3):732–9.
9. Butala AA, Lo SS, Jones JA. Advanced radiotherapy for metastatic disease-a major stride or a futile effort? Ann Palliat Med. 2019;8(3):337–51.
10. Song K, et al. Does resection of the primary tumor improve survival in patients with metastatic chondrosarcoma? Clin Orthop Relat Res. 2019;477(3):573–83.
11. Treasure T, et al. Pulmonary metastasectomy: what is the practice and where is the evidence for effectiveness? Thorax. 2014;69(10):946–9.
12. Marulli G, et al. Survival and prognostic factors following pulmonary metastasectomy for sarcoma. J Thorac Dis. 2017;9(Suppl 12):S1305–15.
13. Kim S, et al. Pulmonary resection of metastatic sarcoma: prognostic factors associated with improved outcomes. Ann Thorac Surg. 2011;92(5):1780–6; discussion 1786–7.
14. Digesu CS, et al. Management of sarcoma metastases to the lung. Surg Oncol Clin N Am. 2016;25(4):721–33.
15. Palma DA, et al. Stereotactic ablative radiotherapy versus standard of care palliative treatment in patients with oligometastatic cancers (SABR-COMET): a randomised, phase 2, open-label trial. Lancet. 2019;393(10185):2051–8.
16. Soyfer V, et al. Single-institution experience of SBRT for lung metastases in sarcoma patients. Am J Clin Oncol. 2017;40(1):83–5.

17. Navarria P, et al. Stereotactic body radiation therapy for lung metastases from soft tissue sarcoma. Eur J Cancer. 2015;51(5):668–74.
18. Frakulli R, et al. Stereotactic radiotherapy in the treatment of lung metastases from bone and soft-tissue sarcomas. Anticancer Res. 2015;35(10):5581–6.
19. Mehta N, et al. Safety and efficacy of stereotactic body radiation therapy in the treatment of pulmonary metastases from high grade sarcoma. Sarcoma. 2013;2013:360214.
20. Lindsay AD, et al. Treatment of sarcoma lung metastases with stereotactic body radiotherapy. Sarcoma. 2018;2018:9132359.
21. Baumann BC, et al. Efficacy and safety of stereotactic body radiation therapy for the treatment of pulmonary metastases from sarcoma: a potential alternative to resection. J Surg Oncol. 2016;114(1):65–9.
22. Fiorenza F, et al. Risk factors for survival and local control in chondrosarcoma of bone. J Bone Joint Surg Br. 2002;84(1):93–9.
23. Leddy LR, Holmes RE. Chondrosarcoma of bone. Cancer Treat Res. 2014;162:117–30.
24. Bergh P, et al. Prognostic factors and outcome of pelvic, sacral, and spinal chondrosarcomas: a center-based study of 69 cases. Cancer. 2001;91(7):1201–12.
25. Giuffrida AY, et al. Chondrosarcoma in the United States (1973 to 2003): an analysis of 2890 cases from the SEER database. J Bone Joint Surg Am. 2009;91(5):1063–72.
26. Bindiganavile S, et al. Long-term outcome of chondrosarcoma: a single institutional experience. Cancer Res Treat. 2015;47(4):897–903.
27. Donati D, et al. Surgical treatment and outcome of conventional pelvic chondrosarcoma. J Bone Joint Surg Br. 2005;87(11):1527–30.
28. Van Gompel JJ, Janus JR. Chordoma and chondrosarcoma. Otolaryngol Clin N Am. 2015;48(3):501–14.
29. De Amorim Bernstein K, DeLaney T. Chordomas and chondrosarcomas-The role of radiation therapy. J Surg Oncol. 2016;114(5):564–9.
30. Bloch O, Parsa AT. Skull base chondrosarcoma: evidence-based treatment paradigms. Neurosurg Clin N Am. 2013;24(1):89–96.
31. Bloch OG, et al. Cranial chondrosarcoma and recurrence. Skull Base. 2010;20(3):149–56.
32. Iyer A, et al. Stereotactic radiosurgery for intracranial chondrosarcoma. J Neuro-Oncol. 2012;108(3):535–42.
33. Gelderblom H, et al. The clinical approach towards chondrosarcoma. Oncologist. 2008;13(3):320–9.
34. Kitamura Y, Sasaki H, Yoshida K. Genetic aberrations and molecular biology of skull base chordoma and chondrosarcoma. Brain Tumor Pathol. 2017;34(2):78–90.
35. Boehme KA, et al. Chondrosarcoma: a rare misfortune in aging human cartilage? The role of stem and progenitor cells in proliferation, malignant degeneration and therapeutic resistance. Int J Mol Sci. 2018;19(1):311.

36. Javad Parvizi GKK. Chapter 49 - Chondrosarcoma. In: High yield orthopaedics. Philadelphia, PA: Saunders/Elsevier; 2010. https://www.worldcat.org/title/high-yield-orthopaedics/oclc/698080054.
37. Raza SM, et al. Multimodality treatment of skull base chondrosarcomas: the role of histology specific treatment protocols. Neurosurgery. 2017;81(3):520–30.
38. Onishi AC, Hincker AM, Lee FY. Surmounting chemotherapy and radioresistance in chondrosarcoma: molecular mechanisms and therapeutic targets. Sarcoma. 2011;2011:381564.
39. de Jong Y, et al. Radiotherapy resistance in chondrosarcoma cells; a possible correlation with alterations in cell cycle related genes. Clin Sarcoma Res. 2019;9:9.
40. Girard N, et al. Heterogeneity of chondrosarcomas response to irradiations with X-rays and carbon ions: a comparative study on five cell lines. J Bone Oncol. 2020;22:100283.
41. Richardson MS. Pathology of skull base tumors. Otolaryngol Clin N Am. 2001;34(6):1025–42, vii.
42. Samii A, et al. Surgical treatment of skull base chondrosarcomas. Neurosurg Rev. 2009;32(1):67–75; discussion 75.
43. Lustig LR, Sciubba J, Holliday MJ. Chondrosarcomas of the skull base and temporal bone. J Laryngol Otol. 2007;121(8):725–35.
44. Amichetti M, et al. A systematic review of proton therapy in the treatment of chondrosarcoma of the skull base. Neurosurg Rev. 2010;33(2):155–65.
45. Wanebo JE, et al. Management of cranial base chondrosarcomas. Neurosurgery. 2006;58(2):249–55; discussion 249–55.
46. Sekhar LN, et al. Chordomas and chondrosarcomas of the skull base: results and complications of surgical management. Neurosurg Focus. 2001;10(3):E2.
47. Bohman LE, et al. Skull base chordoma and chondrosarcoma: influence of clinical and demographic factors on prognosis: a SEER analysis. World Neurosurg. 2014;82(5):806–14.
48. Jones PS, et al. Outcomes and patterns of care in adult skull base chondrosarcomas from the SEER database. J Clin Neurosci. 2014;21(9):1497–502.
49. Holliday EB, et al. Postoperative proton therapy for chordomas and chondrosarcomas of the spine: adjuvant versus salvage radiation therapy. Spine (Phila Pa 1976). 2015;40(8):544–9.
50. Oghalai JS, et al. Skull base chondrosarcoma originating from the petroclival junction. Otol Neurotol. 2005;26(5):1052–60.
51. Li D, et al. Proposed treatment paradigm for intracranial chondrosarcomas based on multidisciplinary coordination. World Neurosurg. 2018;109:e517–30.
52. Carlson ML, et al. Petroclival chondrosarcoma: a multicenter review of 55 cases and new staging system. Otol Neurotol. 2016;37(7):940–50.
53. Mattke M, et al. High control rates of proton- and carbon-ion-beam treatment with intensity-modulated active raster scanning in 101 patients

with skull base chondrosarcoma at the Heidelberg Ion Beam Therapy Center. Cancer. 2018;124(9):2036–44.
54. Uhl M, et al. High control rate in patients with chondrosarcoma of the skull base after carbon ion therapy: first report of long-term results. Cancer. 2014;120(10):1579–85.
55. McNaney D, et al. Fifteen year radiotherapy experience with chondrosarcoma of bone. Int J Radiat Oncol Biol Phys. 1982;8(2):187–90.
56. Krochak R, et al. Results of radical radiation for chondrosarcoma of bone. Radiother Oncol. 1983;1(2):109–15.
57. Sahgal A, et al. Image-guided, intensity-modulated radiation therapy (IG-IMRT) for skull base chordoma and chondrosarcoma: preliminary outcomes. Neuro-Oncology. 2015;17(6):889–94.
58. Debus J, et al. Stereotactic fractionated radiotherapy for chordomas and chondrosarcomas of the skull base. Int J Radiat Oncol Biol Phys. 2000;47(3):591–6.
59. Hauptman JS, et al. Challenges in linear accelerator radiotherapy for chordomas and chondrosarcomas of the skull base: focus on complications. Int J Radiat Oncol Biol Phys. 2012;83(2):542–51.
60. Gwak HS, et al. Hypofractionated stereotactic radiation therapy for skull base and upper cervical chordoma and chondrosarcoma: preliminary results. Stereotact Funct Neurosurg. 2005;83(5–6):233–43.
61. Martin JJ, et al. Radiosurgery for chordomas and chondrosarcomas of the skull base. J Neurosurg. 2007;107(4):758–64.
62. Jiang B, et al. CyberKnife radiosurgery for the management of skull base and spinal chondrosarcomas. J Neuro-Oncol. 2013;114(2):209–18.
63. Koga T, Shin M, Saito N. Treatment with high marginal dose is mandatory to achieve long-term control of skull base chordomas and chondrosarcomas by means of stereotactic radiosurgery. J Neuro-Oncol. 2010;98(2):233–8.
64. Förander P, et al. Combination of microsurgery and Gamma Knife surgery for the treatment of intracranial chondrosarcomas. J Neurosurg. 2006;105 Suppl:18–25.
65. Krishnan S, et al. Radiosurgery for cranial base chordomas and chondrosarcomas. Neurosurgery. 2005;56(4):777–84; discussion 777–84.
66. Hasegawa T, et al. Gamma Knife surgery for skull base chordomas and chondrosarcomas. J Neurosurg. 2007;107(4):752–7.
67. Vasudevan HN, et al. Management of chordoma and chondrosarcoma with fractionated stereotactic radiotherapy. Front Surg. 2017;4:35.
68. Simon F, et al. Surgery and protontherapy in Grade I and II skull base chondrosarcoma: a comparative retrospective study. PLoS One. 2018;13(12):e0208786.
69. Rosenberg AE, et al. Chondrosarcoma of the base of the skull: a clinicopathologic study of 200 cases with emphasis on its distinction from chordoma. Am J Surg Pathol. 1999;23(11):1370–8.

70. Ares C, et al. Effectiveness and safety of spot scanning proton radiation therapy for chordomas and chondrosarcomas of the skull base: first long-term report. Int J Radiat Oncol Biol Phys. 2009;75(4):1111–8.
71. Munzenrider JE, Liebsch NJ. Proton therapy for tumors of the skull base. Strahlenther Onkol. 1999;175 Suppl 2:57–63.
72. Austin-Seymour M, et al. Fractionated proton radiation therapy of chordoma and low-grade chondrosarcoma of the base of the skull. J Neurosurg. 1989;70(1):13–7.
73. Debus J, et al. Brainstem tolerance to conformal radiotherapy of skull base tumors. Int J Radiat Oncol Biol Phys. 1997;39(5):967–75.
74. Feuvret L, et al. Efficacy and safety of adjuvant proton therapy combined with surgery for chondrosarcoma of the skull base: a retrospective, population-based study. Int J Radiat Oncol Biol Phys. 2016;95(1):312–21.
75. Weber DC, et al. Long term outcome of skull-base chondrosarcoma patients treated with high-dose proton therapy with or without conventional radiation therapy. Radiother Oncol. 2018;129(3):520–6.
76. Hug EB, et al. Proton radiation therapy for chordomas and chondrosarcomas of the skull base. J Neurosurg. 1999;91(3):432–9.
77. Noël G, et al. Radiation therapy for chordoma and chondrosarcoma of the skull base and the cervical spine. Prognostic factors and patterns of failure. Strahlenther Onkol. 2003;179(4):241–8.
78. Feuvret L, et al. A treatment planning comparison of combined photon-proton beams versus proton beams-only for the treatment of skull base tumors. Int J Radiat Oncol Biol Phys. 2007;69(3):944–54.
79. Lu VM, et al. Carbon ion radiotherapy for skull base chordomas and chondrosarcomas: a systematic review and meta-analysis of local control, survival, and toxicity outcomes. J Neuro-Oncol. 2020;147(3):503–13.
80. Schulz-Ertner D, et al. Carbon ion radiotherapy of skull base chondrosarcomas. Int J Radiat Oncol Biol Phys. 2007;67(1):171–7.
81. Combs SE, et al. Carbon ion radiotherapy performed as re-irradiation using active beam delivery in patients with tumors of the brain, skull base and sacral region. Radiother Oncol. 2011;98(1):63–7.
82. Guan X, et al. The preliminary results of proton and carbon ion therapy for chordoma and chondrosarcoma of the skull base and cervical spine. Radiat Oncol. 2019;14(1):206.
83. Hasegawa A, et al. Outcomes of visual acuity in carbon ion radiotherapy: analysis of dose-volume histograms and prognostic factors. Int J Radiat Oncol Biol Phys. 2006;64(2):396–401.
84. Koto M, et al. Risk factors for brain injury after carbon ion radiotherapy for skull base tumors. Radiother Oncol. 2014;111(1):25–9.
85. Peeters A, et al. How costly is particle therapy? Cost analysis of external beam radiotherapy with carbon-ions, protons and photons. Radiother Oncol. 2010;95(1):45–53.

86. Nikoghosyan AV, et al. Randomised trial of proton vs. carbon ion radiation therapy in patients with low and intermediate grade chondrosarcoma of the skull base, clinical phase III study. BMC Cancer. 2010;10:606.
87. Hug EB, Slater JD. Proton radiation therapy for chordomas and chondrosarcomas of the skull base. Neurosurg Clin N Am. 2000;11(4):627–38.
88. Schoenfeld AJ, et al. Chondrosarcoma of the mobile spine: a review of 21 cases treated at a single center. Spine (Phila Pa 1976). 2012;37(2):119–26.
89. McLoughlin GS, Sciubba DM, Wolinsky JP. Chondroma/chondrosarcoma of the spine. Neurosurg Clin N Am. 2008;19(1):57–63.
90. Murray FR, et al. Prognostic factors for spinal chordomas and chondrosarcomas treated with postoperative pencil-beam scanning proton therapy: a large, single-institution experience. J Neurosurg Spine. 2020:1–10.
91. Dickman CA, Fehlings M, Gokaslan ZL. Spinal cord and spinal column tumors: principles and practice. Stuttgart, Germany: Georg Thieme Verlag; 2006. https://www.worldcat.org/title/spinal-cord-and-spinal-column-tumors-principles-and-practice/oclc/1170993163&referer=brief_results.
92. Boriani S, et al. Chondrosarcoma of the mobile spine: report on 22 cases. Spine (Phila Pa 1976). 2000;25(7):804–12.
93. York JE, et al. Chondrosarcoma of the spine: 1954 to 1997. J Neurosurg. 1999;90(1 Suppl):73–8.
94. Bhatt AD, et al. High-dose proton beam-based radiation therapy in the management of extracranial chondrosarcomas. Int J Part Ther. 2017;3(3):373–81.
95. Tatsuzaki H, Urie MM. Importance of precise positioning for proton beam therapy in the base of skull and cervical spine. Int J Radiat Oncol Biol Phys. 1991;21(3):757–65.
96. Yadav P, Paliwal BR, Kozak K. Dosimetric comparison of photon and proton treatment techniques for chondrosarcoma of thoracic spine. Med Dosim. 2013;38(3):233–7.
97. Indelicato DJ, et al. A prospective outcomes study of proton therapy for chordomas and chondrosarcomas of the spine. Int J Radiat Oncol Biol Phys. 2016;95(1):297–303.
98. Imai R, Kamada T, Araki N. Clinical efficacy of carbon ion radiotherapy for unresectable chondrosarcomas. Anticancer Res. 2017;37(12):6959–64.
99. Austin JP, et al. Probable causes of recurrence in patients with chordoma and chondrosarcoma of the base of skull and cervical spine. Int J Radiat Oncol Biol Phys. 1993;25(3):439–44.
100. Bus MPA, et al. Conventional primary central chondrosarcoma of the pelvis: prognostic factors and outcome of surgical treatment in 162 patients. J Bone Joint Surg Am. 2018;100(4):316–25.

101. Tsuda Y, et al. Is the width of a surgical margin associated with the outcome of disease in patients with peripheral chondrosarcoma of the pelvis? A multicenter study. Clin Orthop Relat Res. 2019;477(11):2432–40.
102. Weber KL, Pring ME, Sim FH. Treatment and outcome of recurrent pelvic chondrosarcoma. Clin Orthop Relat Res. 2002;397:19–28.
103. Chen L, et al. Prognostic nomograms to predict overall survival and cancer-specific survival in patients with pelvic chondrosarcoma. Cancer Med. 2019;8(12):5438–49.
104. Wagner TD, et al. Combination short-course preoperative irradiation, surgical resection, and reduced-field high-dose postoperative irradiation in the treatment of tumors involving the bone. Int J Radiat Oncol Biol Phys. 2009;73(1):259–66.
105. Feigl GC, et al. Evaluation of a new concept for the management of skull base chordomas and chondrosarcomas. J Neurosurg. 2005;102 Suppl:165–70.

11 Systemic Therapy for Chondrosarcoma

Arun S. Singh, Jomjit Chantharasamee, and Francis J. Hornicek

Introduction

Chondrosarcomas are a heterogeneous group of bone tumors with an estimated incidence of 1 in 200,000 cases per year [1]. The extremities are the most common primary location, followed by the axial skeleton. The median age is typically in the fourth to fifth decade with equal sexual distribution [1]. The 10-year overall survival in patients with localized disease ranges from 64% to 95% for low- and intermediate-grade chondrosarcoma and 25% to 58% for high-grade chondrosarcoma and less than 10% for metastatic

A. S. Singh (✉)
Division of Hematology and Oncology, Department of Medicine, University of California Los Angeles, Los Angeles, CA, USA
e-mail: Asingh@mednet.ucla.edu

J. Chantharasamee
Division of Hematology and Oncology, Department of Medicine, University of California Los Angeles, Los Angeles, CA, USA

Division of Medical Oncology, Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand
e-mail: jomjit.cha@mahidol.ac.th

F. J. Hornicek
Department of Orthopaedic Surgery, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA
e-mail: FHornicek@mednet.ucla.edu

F. J. Hornicek (ed.), *Chondrosarcoma*,
https://doi.org/10.1007/978-3-030-74572-1_11

disease [2–5]. Tumor grading and surgical stage are considered to be significant prognostic factors. Negative prognostic factors include pelvic location, older age, and tumor size [5–10]. The 2013 WHO Classification of Bone and Soft Tissue Tumors characterized four chondrosarcoma subtypes, conventional, mesenchymal, clear cell, and dedifferentiated chondrosarcoma, and also classified the origin of tumor into primary chondrosarcoma and secondary chondrosarcoma arising from a preexisting benign bone tumor [4]. The clinical course of low-grade chondrosarcoma is typically indolent with a low metastatic rate. In contrast, mesenchymal and high-grade tumors usually behave aggressively and have a higher metastatic rate [2, 7, 11, 12].

The molecular pathogenesis of chondrosarcoma is associated with abnormal chondrocyte proliferation and differentiation of growth plate precursors. Various mutations have been implicated in the growth of chondrosarcomas including mutations of IDH1 and IDH2 (isocitrate dehydrogenases 1 and 2), abnormal regulation of the Indian hedgehog (IHH)/parathyroid hormone-related protein (PTHRP) signaling pathway, HEY-NCOA2 translocations in mesenchymal chondrosarcoma, and CDKN2A, COL2A1, and TP53 mutations [7, 13–16].

For the treatment of metastatic/unresectable chondrosarcoma, conventional chemotherapy is often ineffective. However, the clinical benefit from chemotherapy was demonstrated in mesenchymal and dedifferentiated chondrosarcoma [7, 17]. Translating the knowledge of molecular alterations into clinical approach is recently in progress.

Molecular Pathogenesis

1. *Isocitrate dehydrogenase (IDH1 and IDH2) gene mutation*

   Alterations in IDH1 and IDH2 gene linked to the oncogenesis of chondrosarcoma.

   IDH1 and IDH2 catalyze the decarboxylation of isocitrate into 2-KG and carbon dioxide in the Krebs cycle. Mutations of these IDH genes result in the conversion of α-KG to the oncometabolite D-2KG, and the accumulation of D-2KG leads to

HIF-1α degradation, which in turn is thought to deregulate epigenetic homeostasis and mesenchymal differentiation [18–20].

Mutant IDH was detected in approximately 52% of central chondrosarcomas, 52–59% of central intermediate, high-grade and dedifferentiated chondrosarcoma, and 71% of periosteal chondrosarcoma [21]. Molecular studies of cartilaginous tumor in patients with Ollier disease and Maffucci syndrome, a nonhereditary enchondromatosis, demonstrated an association between enchondromas and somatic mosaicism of IDH1 and IDH2 mutations [15].

2. *Exostosin (EXT1 and EXT2) gene alterations*

Sporadic osteochondromas and multiple osteochondromatosis have been linked to genetic mutations in the EXT1 and EXT2 genes. Homozygous EXT1/EXT2 mutations or inactivated EXT1/EXT2 genes were detected in the majority of these tumors [14, 22]. Although osteochondromas and secondary peripheral chondrosarcomas are associated, several studies reported that only 15% of secondary peripheral chondrosarcomas harbored homozygous mutations or inactivation of EXT genes [23]. Andrea et al. reported the presence of functional EXT genes within secondary periosteal chondrosarcomas in contrast to the dysfunctional EXT gene within osteochondromas, indicating that the oncogenesis of secondary chondrosarcomas requires an EXT-independent pathway [14]. In a mouse model, disruption of cell cycle regulators such as TP53 and CDKN2A promoted the progression of osteochondromas into secondary peripheral chondrosarcomas [24].

3. *Indian Hedgehog homolog (IHH)/parathyroid-related protein(PTHRP) signaling pathway*

The IHH/PTHRP signaling pathway is involved in chondrocyte proliferation.

PTHRP expression has been found to be significantly elevated in grade 1 peripheral and central chondrosarcomas. The absence of elevated IHH concurrent with the upregulation of PTHRP is thought to be an important facet of the malignant transformation of osteochondroma; it is also associated with increased histologic grade in chondrosarcoma [25, 26].

4. *Vascular endothelial growth factor (VEGFR)*
   VEGF-A expression was positively correlated with the tumor type. Higher VEGF-A expression levels were detected in grade 2 and 3 conventional chondrosarcomas compared to dedifferentiated chondrosarcomas [27]. Also, in preclinical mouse models, the inhibition of endothelial cell attachment to collagen I prevents tumor angiogenesis and chondrosarcoma growth. While this preclinical data supports a role for antiangiogenic therapy for chondrosarcoma, this has not been shown to be clinically translatable [28].
5. *Src pathway*
   The Src pathway is active in chondrosarcoma, and inhibition of Src in vitro by dasatinib has led to reduced CS viability, reduced cell motility, and induced apoptosis in cell lines [29]. Oosterwijk et al. reported Src family kinase inhibition was found to overcome chemoresistance, to induce apoptosis, and to inhibit migration in chondrosarcoma cell lines with TP53 mutations [30].

Adjuvant Chemotherapy

Most low-grade and clear-cell chondrosarcomas are considered to be chemoresistant. The low mitotic rates of these tumors theoretically would make them both chemo- and radiation resistant. Moreover, it is felt that the abundant hyaline cartilaginous matrix can prevent the penetration of chemotherapy into the cellular niche. Expression of the drug resistance gene P-glycoprotein and high expression of anti-apoptotic, bcl-2 family members, are putative causes of resistance to systemic therapy. There is no evidence to suggest a benefit of adjuvant systemic therapy in low-grade chondrosarcoma [31, 32].

Some small retrospective studies have shown a trend toward better outcomes for the use of adjuvant chemotherapy in patients with dedifferentiated chondrosarcoma and chondrosarcoma that arises within an osteochondroma [33, 34]. However, a large retrospective study showed no significant difference on the rate of

disease-free survival in patients receiving adjuvant chemotherapy [9].

Adjuvant or neoadjuvant chemotherapy seems to be useful in mesenchymal chondrosarcoma, a variant that contains amount of small round cell and less cartilage content. Huvos et al. reported a pathological response from neoadjuvant cisplatin and doxorubicin or T10 regimen as in osteosarcoma [35]. Moreover, a retrospective study showed that the administration of chemotherapy in patients with localized mesenchymal chondrosarcoma significantly reduced the risk of recurrence and prolong 5-year and 10-year overall survival; however, no details of the chemotherapy regimens used are presented in this study [7].

Treatment of Metastatic Disease

Chemotherapy

The majority of metastatic chondrosarcoma has a modest or no response to conventional chemotherapy. However, anthracycline-based chemotherapy may lead to objective responses in dedifferentiated and mesenchymal variants. The median progression-free survival for these subtypes with anthracycline-based therapy ranges from 3.7 to 7 months [7, 17, 36, 37]. The most effective regimen is still unclear (Table 11.1). A study by Italiano et al. showed that combination chemotherapy including doxorubicin/ifosfamide, doxorubicin/ifosfamide/cisplatin, and cisplatin/doxorubicin is associated with a longer progression-free survival compared to single agent regardless of subtype [37]. In contrast, the report by Annemiek et al. revealed no differences in progression-free survival benefit in dedifferentiated chondrosarcoma treated with combined chemotherapy or single agent [17]. Most patients with mesenchymal chondrosarcoma in the historical studies received anthracycline-containing multi-agent regimens [7, 11, 17, 36, 37]. The benefit of palliative chemotherapy on PFS and OS is inconsistent.

Table 11.1 Efficacy data of chemotherapy in patients with locally advanced/metastatic chondrosarcoma

Study	Subtype	Chemotherapy	RR	PFS
Frezza et al. [7]	Mesenchymal, $n = 2$	Epirubicin, ifosfamide High-dose chemotherapy with stem cell rescue	N/A	1 and 8 years
Cesari et al. [38]	Mesenchymal, $n = 3$	Anthracycline-based	N/A	PFS N/A OS 13–43.5 months
Nooji et al. [36]	Non-osteosarcoma, non-MFH bone tumor, $n = 37$	Cisplatin/doxorubicin 6 cycles	25%	0–18 months (median PFS 10 months)
Italiano et al. [37]	Dedifferentiated, $n = 42$	Anthracycline-based	20.5%	3 months for single agent, 6.8 months for combination
	Mesenchymal, $n = 17$		31%	
Annemiek et al. [17]	Conventional, $n = 15$	Various anthracycline-based	PR = 4%	2–3.6 months
	Mesenchymal, $n = 25$	Multi-agent: cisplatin/doxorubicin; cisplatin/ifosfamide	PR = 16%	mPFS 3.7 months mPFS 7.7 months
	Dedifferentiated, $n = 19$	Doxorubicin-based	PR = 10%	
		Doxorubicin single agent		mPFS 5.5 months
		Cisplatin/doxorubicin		mPFS 2.9 months

Abbreviation: *mPFS* median progression-free survival, *N/A* not available data, *OS* overall survival, *PFS* progression-free survival, *PR* partial response, *RR* response rate

Novel Therapy

The efficacy of current systemic agents for chondrosarcoma is limited. More detailed molecular studies to identify the oncogenic drivers are needed for development of targeted therapy in these diseases. A few signaling cascades have been reported to date including the VEGFR, IDH1/2, hedgehog signaling pathway, and Src pathways [39].

VEGFR Inhibitor

Angiogenesis is the most common oncogenic pathway in various cancers. A phase II study by Chow et al. demonstrated the activity of pazopanib 800 mg daily against all grade of metastatic conventional chondrosarcoma. The disease-control rate at 16 week was 43%, and the median overall survival was 17.6 months (11.3–25 months) [40].

Src Inhibitor

The Src pathway has been linked in sarcomas to promoting cell proliferation, migration, and angiogenesis [29, 41]. Src dysregulation has been found in many types of sarcoma tissue including osteosarcoma, leiomyosarcoma, Ewing sarcoma, and chondrosarcoma [29, 42].

Dasatinib is a small molecule inhibitor of the Src family of kinases, platelet-derived growth factor receptors α and β, c-KIT, BCR-ABL, and ephrin receptor kinases. SARC 009, a single-arm phase II trial, showed 6-month PFS in patients with metastatic chondrosarcoma treated with dasatinib 70 mg twice daily was 47%, and 2-year and 5-year overall survival was 56% and 9%, respectively [43].

IDH1/2 Inhibitor

IDH plays an important role in the regulation and tumorigenesis of chondrosarcoma. Treatment with AGI-5198, a specific inhibitor of mutant IDH1, has been shown to reduce production of 2-HG by up to 90% across a number of chondrosarcoma cell lines harboring endogenous IDH1 mutation [44]. Preliminary data from phase 1 clinical trials enrolling patients with cancers harboring an IDH1 mutation indicate that AG-120 has an acceptable safety profile and clinical activity in patients with relapsed/refractory mutant IDH1 tumor including acute myeloid leukemia, gliomas, and cholangiocarcinoma [45–48]. A recent phase I study by Trent et al. showed a median progression-free survival of 5.6 months in patients with metastatic IDH-1-mutant chondrosarcoma and with 56% with stable disease as best response [49].

Histone Deacetylase Inhibitor

Dysregulation of histone modification is commonly found across a broad range of cancer types and has emerged to be the novel therapeutic target. Preclinical study showed the effects of histone deacetylase inhibitors on the induction of differentiation in chondrosarcoma cells [50].

Immunotherapy

Preclinical evidences suggested that higher grade and dedifferentiated chondrosarcomas are associated with the presence of predictive biomarkers for response to immunotherapy [51, 52]. Studies of PD-L1 expression demonstrated that 41% of dedifferentiated chondrosarcoma expressed PD-L1 by IHC and correlated with high number of TILs. On the contrary, conventional, mesenchymal, and clear-cell subtype did not express PD-L1 [51]. Moreover, expression of PD-L1 was also associated with younger age, larger tumor, and early recurrence in which combined PD-L1/PD-L2 expression was analyzed [52]. The findings hint at the

potential for immune checkpoint blockade for treatment of dedifferentiated chondrosarcoma. However, there is a paucity of evidence to support the clinical benefit of this approach. SARC 028, a single-arm phase II trial, demonstrated that only one patient with a dedifferentiated chondrosarcoma had partial response with pembrolizumab [53]. Similarly, a retrospective study by Paoluzzi et al. reported a partial response in a patient with dedifferentiated chondrosarcoma treated with nivolumab [54]. However, the phase II prospective, randomized controlled trial (Alliance 091401) revealed no clinical benefit of either nivolumab alone or the nivolumab/ipilimumab combination in chondrosarcoma [55]. For other chondrosarcoma subtypes, only case reports are available about the activity of immune checkpoint inhibitors. Wagner et al. reported near complete response in a patient with a PD-1-negative conventional chondrosarcoma treated with nivolumab [56]. Several studies for combination immunotherapy in bone sarcoma including chondrosarcoma are ongoing (Table 11.2).

Table 11.2 Clinical studies of immunotherapy for chondrosarcoma

Trial	Subtype and treatment	Outcome
Alliance 091401, phase II, randomized controlled trial [55]	Nivolumab arm: dedifferentiated ($n = 1$), extraskeletal myxoid chondrosarcoma ($n = 1$) Nivolumab+ipilimumab arm: dedifferentiated ($n = 1$), Extraskeletal myxoid chondrosarcoma ($n = 1$)	No clinical benefit
SARC 028 [53]	Pembrolizumab: dedifferentiated ($n = 5$)	Partial response one of five patients (20%)
Wagner et al. [56]	Nivolumab: conventional ($n = 1$)	Partial response
NCT03190174, phase I/II	Nivolumab+ ABI-009 (nab-rapamycin)	Ongoing
NCT02636725, phase II	Pembrolizumab+axitinib	Ongoing
NCT02982486, phase I,II	Nivolumab+ipilimumab	Ongoing

Conclusion

Chondrosarcoma subtypes differ in their biology, clinical appearance and behavior, prognosis, and response to therapy. Due to their rarity and diversity, chondrosarcomas should be managed by multidisciplinary teams in high volume centers consisting of orthopedic oncologists, radiologists, radiation oncologists, pathologists, and medical oncologists. Treatment of advanced stage chondrosarcoma remains challenging as no known effective systemic therapy is currently well established. Novel targeted drugs and immunotherapy remain under investigation in the preclinical and clinical studies.

References

1. Giuffrida AY, Burgueno JE, Koniaris LG, Gutierrez JC, Duncan R, Scully SP. Chondrosarcoma in the United States (1973 to 2003): an analysis of 2890 cases from the SEER database. JBJS. 2009;91(5):1063–72.
2. Angelini A, Guerra G, Mavrogenis AF, Pala E, Picci P, Ruggieri P. Clinical outcome of central conventional chondrosarcoma. J Surg Oncol. 2012;106(8):929–37.
3. Björnsson J, McLeod RA, Unni KK, Ilstrup DM, Pritchard DJ. Primary chondrosarcoma of long bones and limb girdles. Cancer. 1998;83(10):2105–19.
4. Hogendoorn P, Bovée J, Nielsen G. Chondrosarcoma (grades I-III), including primary and secondary variants and periosteal chondrosarcoma. In: WHO classification of tumours of soft tissue and bone. Lyon: IARC; 2013;264(8).
5. Evans HL, Ayala AG, Romsdahl MM. Prognostic factors in chondrosarcoma of bone. A clinicopathologic analysis with emphasis on histologic grading. Cancer. 1977;40(2):818–31.
6. Lee FY, Mankin HJ, Fondren G, et al. Chondrosarcoma of bone: an assessment of outcome. JBJS. 1999;81(3):326–38.
7. Frezza AM, Cesari M, Baumhoer D, et al. Mesenchymal chondrosarcoma: prognostic factors and outcome in 113 patients. A European Musculoskeletal Oncology Society study. Eur J Cancer. 2015;51(3):374–81.
8. Fromm J, Klein A, Baur-Melnyk A, et al. Survival and prognostic factors in conventional central chondrosarcoma. BMC Cancer. 2018;18(1):1–10.
9. Grimer RJ, Gosheger G, Taminiau A, et al. Dedifferentiated chondrosarcoma: prognostic factors and outcome from a European group. Eur J Cancer. 2007;43(14):2060–5.

10. Nie Z, Lu Q, Peng H. Prognostic factors for patients with chondrosarcoma: a survival analysis based on the Surveillance, Epidemiology, and End Results (SEER) database (1973–2012). J Bone Oncol. 2018;13:55–61.
11. Xu J, Li D, Xie L, Tang S, Guo W. Mesenchymal chondrosarcoma of bone and soft tissue: a systematic review of 107 patients in the past 20 years. PLoS One. 2015;10(4):e0122216.
12. Strotman PK, Reif TJ, Kliethermes SA, Sandhu JK, Nystrom LM. Dedifferentiated chondrosarcoma: a survival analysis of 159 cases from the SEER database (2001-2011). J Surg Oncol. 2017;116(2):252–7.
13. Bovée JV, Hogendoorn PC, Wunder JS, Alman BA. Cartilage tumours and bone development: molecular pathology and possible therapeutic targets. Nat Rev Cancer. 2010;10(7):481–8.
14. de Andrea CE, Reijnders CM, Kroon HM, et al. Secondary peripheral chondrosarcoma evolving from osteochondroma as a result of outgrowth of cells with functional EXT. Oncogene. 2012;31(9):1095–104.
15. Pansuriya TC, Van Eijk R, d'Adamo P, et al. Somatic mosaic IDH1 and IDH2 mutations are associated with enchondroma and spindle cell hemangioma in Ollier disease and Maffucci syndrome. Nat Genet. 2011;43(12):1256.
16. Tarpey PS, Behjati S, Cooke SL, et al. Frequent mutation of the major cartilage collagen gene COL2A1 in chondrosarcoma. Nat Genet. 2013;45(8):923–6.
17. van Maldegem A, Conley AP, Rutkowski P, et al. Outcome of first-line systemic treatment for unresectable conventional, dedifferentiated, mesenchymal, and clear cell chondrosarcoma. Oncologist. 2019;24(1):110–6.
18. Molenaar RJ, Radivoyevitch T, Maciejewski JP, van Noorden CJ, Bleeker FE. The driver and passenger effects of isocitrate dehydrogenase 1 and 2 mutations in oncogenesis and survival prolongation. Biochim Biophys Acta. 2014;1846(2):326–41.
19. Schaap FG, French PJ, Bovée JV. Mutations in the isocitrate dehydrogenase genes IDH1 and IDH2 in tumors. Adv Anat Pathol. 2013;20(1):32–8.
20. Amary MF, Damato S, Halai D, et al. Ollier disease and Maffucci syndrome are caused by somatic mosaic mutations of IDH1 and IDH2. Nat Genet. 2011;43(12):1262–5.
21. Amary MF, Bacsi K, Maggiani F, et al. IDH1 and IDH2 mutations are frequent events in central chondrosarcoma and central and periosteal chondromas but not in other mesenchymal tumours. J Pathol. 2011;224(3):334–43.
22. Hameetman L, Szuhai K, Yavas A, et al. The role of EXT1 in nonhereditary osteochondroma: identification of homozygous deletions. J Natl Cancer Inst. 2007;99(5):396–406.
23. Hecht JT, Hogue D, Strong LC, Hansen MF, Blanton SH, Wagner M. Hereditary multiple exostosis and chondrosarcoma: linkage to chro-

mosome II and loss of heterozygosity for EXT-linked markers on chromosomes II and 8. Am J Hum Genet. 1995;56(5):1125.
24. de Andrea CE, Zhu JF, Jin H, Bovée JV, Jones KB. Cell cycle deregulation and mosaic loss of Ext1 drive peripheral chondrosarcomagenesis in the mouse and reveal an intrinsic cilia deficiency. J Pathol. 2015;236(2):210–8.
25. Bovée JV, van den Broek LJ, Cleton-Jansen A-M, Hogendoorn PC. Up-regulation of PTHrP and Bcl-2 expression characterizes the progression of osteochondroma towards peripheral chondrosarcoma and is a late event in central chondrosarcoma. Lab Investig. 2000;80(12):1925–33.
26. Rozeman LB, Hameetman L, Cleton-Jansen AM, Taminiau AH, Hogendoorn PC, Bovée JV. Absence of IHH and retention of PTHrP signalling in enchondromas and central chondrosarcomas. J Pathol. 2005;205(4):476–82.
27. Kalinski T, Krueger S, Sel S, Werner K, Ropke M, Roessner A. Differential expression of VEGF-A and angiopoietins in cartilage tumors and regulation by interleukin-1β. Cancer. 2006;106(9):2028–38.
28. Furumatsu T, Yamaguchi N, Nishida K, et al. Endostatin inhibits adhesion of endothelial cells to collagen I via α2β1 integrin, a possible cause of prevention of chondrosarcoma growth. J Biochem. 2002;131(4):619–26.
29. Schrage YM, Briaire-de Bruijn IH, de Miranda NF, et al. Kinome profiling of chondrosarcoma reveals SRC-pathway activity and dasatinib as option for treatment. Cancer Res. 2009;69(15):6216–22.
30. Van Oosterwijk J, Van Ruler M, Briaire-de Bruijn I, et al. Src kinases in chondrosarcoma chemoresistance and migration: dasatinib sensitises to doxorubicin in TP53 mutant cells. Br J Cancer. 2013;109(5):1214–22.
31. Wyman JJ, Hornstein AM, Meitner PA, et al. Multidrug resistance-1 and p-glycoprotein in human chondrosarcoma cell lines: expression correlates with decreased intracellular doxorubicin and in vitro chemoresistance. J Orthop Res. 1999;17(6):935–40.
32. van Oosterwijk JV, Herpers B, Meijer D, et al. Restoration of chemosensitivity for doxorubicin and cisplatin in chondrosarcoma in vitro: BCL-2 family members cause chemoresistance. Ann Oncol. 2012;23(6):1617–26.
33. Mitchell A, Ayoub K, Mangham D, Grimer R, Carter S, Tillman R. Experience in the treatment of dedifferentiated chondrosarcoma. J Bone Joint Surg. 2000;82(1):55–61.
34. Staals EL, Bacchini P, Mercuri M, Bertoni F. Dedifferentiated chondrosarcomas arising in preexisting osteochondromas. JBJS. 2007;89(5):987–93.
35. Huvos AG, Rosen G, Dabska M, Marcove RC. Mesenchymal chondrosarcoma a clinicopathologic analysis of 35 patients with emphasis on treatment. Cancer. 1983;51(7):1230–7.
36. Nooij M, Whelan J, Bramwell V, et al. Doxorubicin and cisplatin chemotherapy in high-grade spindle cell sarcomas of the bone, other than osteo-

sarcoma or malignant fibrous histiocytoma: a European Osteosarcoma Intergroup Study. Eur J Cancer. 2005;41(2):225–30.
37. Italiano A, Mir O, Cioffi A, et al. Advanced chondrosarcomas: role of chemotherapy and survival. Ann Oncol. 2013;24(11):2916–22.
38. Cesari M, Bertoni F, Bacchini P, Mercuri M, Palmerini E, Ferrari S. Mesenchymal chondrosarcoma. An analysis of patients treated at a single institution. Tumori. 2007;93(5):423–7.
39. Polychronidou G, Karavasilis V, Pollack SM, Huang PH, Lee A, Jones RL. Novel therapeutic approaches in chondrosarcoma. Future Oncol. 2017;13(7):637–48.
40. Chow W, Frankel P, Ruel C, et al. Results of a prospective phase 2 study of pazopanib in patients with surgically unresectable or metastatic chondrosarcoma. Cancer. 2020;126(1):105–11.
41. Wheeler DL, Iida M, Dunn EF. The role of Src in solid tumors. Oncologist. 2009;14(7):667.
42. Bai Y, Li J, Fang B, et al. Phosphoproteomics identifies driver tyrosine kinases in sarcoma cell lines and tumors. Cancer Res. 2012;72(10):2501–11.
43. Schuetze SM, Bolejack V, Choy E, et al. Phase 2 study of dasatinib in patients with alveolar soft part sarcoma, chondrosarcoma, chordoma, epithelioid sarcoma, or solitary fibrous tumor. Cancer. 2017;123(1):90–7.
44. Li L, Paz AC, Wilky BA, et al. Treatment with a small molecule mutant IDH1 inhibitor suppresses tumorigenic activity and decreases production of the oncometabolite 2-hydroxyglutarate in human chondrosarcoma cells. PLoS One. 2015;10(9):e0133813.
45. Popovici-Muller J, Lemieux RM, Artin E, et al. Discovery of AG-120 (Ivosidenib): a first-in-class mutant IDH1 inhibitor for the treatment of IDH1 mutant cancers. ACS Med Chem Lett. 2018;9(4):300–5.
46. DiNardo CD, De Botton S, Stein EM, et al. Ivosidenib (AG-120) in mutant IDH1 AML and advanced hematologic malignancies: results of a phase 1 dose escalation and expansion study. Blood. 2017;130 (Supplement 1):725.
47. Lowery MA, Abou-Alfa GK, Burris HA, et al. Phase 1 study of AG-120, an IDH1 mutant enzyme inhibitor: results from the cholangiocarcinoma dose escalation and expansion cohorts. Safety. 2017;132(2):3.
48. Mellinghoff IK, Touat M, Maher E, et al. ACTR-46. AG-120, a first-in-class mutant IDH1 inhibitor in patients with recurrent or progressive IDH1 mutant glioma: updated results from the phase 1 non-enhancing glioma population. Neuro-Oncology. 2017;19(suppl_6):vi10–1.
49. Tap WD, Villalobos VM, Cote GM, et al. Phase I study of the mutant IDH1 inhibitor ivosidenib: safety and clinical activity in patients with advanced chondrosarcoma. J Clin Oncol. 2020;38(15):1693–701.
50. Sakimura R, Tanaka K, Yamamoto S, et al. The effects of histone deacetylase inhibitors on the induction of differentiation in chondrosarcoma cells. Clin Cancer Res. 2007;13(1):275–82.

51. Kostine M, Cleven AH, de Miranda NF, Italiano A, Cleton-Jansen A-M, Bovée JV. Analysis of PD-L1, T-cell infiltrate and HLA expression in chondrosarcoma indicates potential for response to immunotherapy specifically in the dedifferentiated subtype. Mod Pathol. 2016;29(9):1028–37.
52. Yang X, Zhu G, Yang Z, Zeng K, Liu F, Sun J. Expression of PD-L1/PD-L2 is associated with high proliferation index of Ki-67 but not with TP53 overexpression in chondrosarcoma. Int J Biol Markers. 2018;33(4):507–13.
53. Tawbi HA, Burgess M, Bolejack V, et al. Pembrolizumab in advanced soft-tissue sarcoma and bone sarcoma (SARC028): a multicentre, two-cohort, single-arm, open-label, phase 2 trial. Lancet Oncol. 2017;18(11):1493–501.
54. Paoluzzi L, Cacavio A, Ghesani M, et al. Response to anti-PD1 therapy with nivolumab in metastatic sarcomas. Clin Sarcoma Res. 2016;6(1):24.
55. D'Angelo SP, Mahoney MR, Van Tine BA, et al. Nivolumab with or without ipilimumab treatment for metastatic sarcoma (Alliance A091401): two open-label, non-comparative, randomised, phase 2 trials. Lancet Oncol. 2018;19(3):416–26.
56. Wagner MJ, Ricciotti RW, Mantilla J, Loggers ET, Pollack SM, Cranmer LD. Response to PD1 inhibition in conventional chondrosarcoma. J Immunother Cancer. 2018;6(1):1–4.

12 Vascular Issues in Complex Surgical Resection of Chondrosarcoma

Rhusheet Patel and Donald T. Baril

Introduction

In cases requiring anterior or lateral resection of central pelvic and lumbar spine chondrosarcomas, careful evaluation by orthopedic, vascular, and general surgery teams is critical to optimizing surgical outcomes. Appropriate preoperative imaging and multidisciplinary planning contribute to a well-informed operative strategy and optimal outcomes in this younger patient population.

Imaging

In addition to plain radiographs or magnetic resonance imaging (MRI) obtained for diagnosis and staging, computed tomography

R. Patel
Division of Vascular Surgery, UCLA Medical Center, Los Angeles, CA, USA
e-mail: RhusheetPatel@mednet.ucla.edu

D. T. Baril (✉)
Division of Vascular Surgery, Cedars-Sinai, Los Angeles, CA, USA
e-mail: Donald.Baril@cshs.org

F. J. Hornicek (ed.), *Chondrosarcoma*,
https://doi.org/10.1007/978-3-030-74572-1_12

(CT) imaging of the abdomen and pelvis with arterial and venous phases should be performed in cases requiring lumbar spine or pelvic resection. The pelvic venous vasculature should be evaluated for patency, abnormal collateralization, and any anatomic involvement with tumor. Any congenital anatomic abnormalities, including duplicated inferior vena cava (IVC), left-sided IVC, or May-Thurner iliac vein compression, should also be assessed and noted. If there is a concern for deep venous thrombosis (DVT) due to tumor compression or invasion, duplex ultrasound of the pelvis and lower extremities will provide additional information to help guide the use of preoperative anticoagulation, inferior vena cava filters, and consideration of venous ligation intraoperatively. The arterial anatomy should be similarly evaluated for any stenosis, aneurysmal disease, or intimate involvement with tumor. CT angiography will delineate the aortic anatomy with precise detail to determine whether arterial reconstruction will be necessary and to what extent. As with the venous system, noninvasive evaluation of the arterial system with duplex ultrasound imaging and ankle-brachial indices may also be beneficial to determine a baseline level of perfusion to the lower extremity, particularly in a patient who has any degree of atherosclerotic disease. Additionally, the aortic bifurcation and iliac arteries should be carefully evaluated for calcification, as this may limit the ability to mobilize and manipulate these vessels safely intraoperatively (Fig. 12.1). In cases of pelvic resections and planned internal iliac artery ligation, the internal iliac anatomy should be evaluated for the level of bifurcation and branching. Similarly, the contralateral side should be evaluated for patency to maintain cross pelvic perfusion. For patients with prior abdominal surgery, the presence or absence of anatomic tissue planes may be evaluated, as well as the presence of any abdominal mesh.

In cases with planned Tomita saw placement via a posterior approach, contrast CT imaging should always be done preoperatively to identify any lumbar arteries or veins that may otherwise be inadvertently caught during saw placement. When saw placement between the vessels and spine is done with direct visualization from an anterior approach, interval contrast CT imaging is

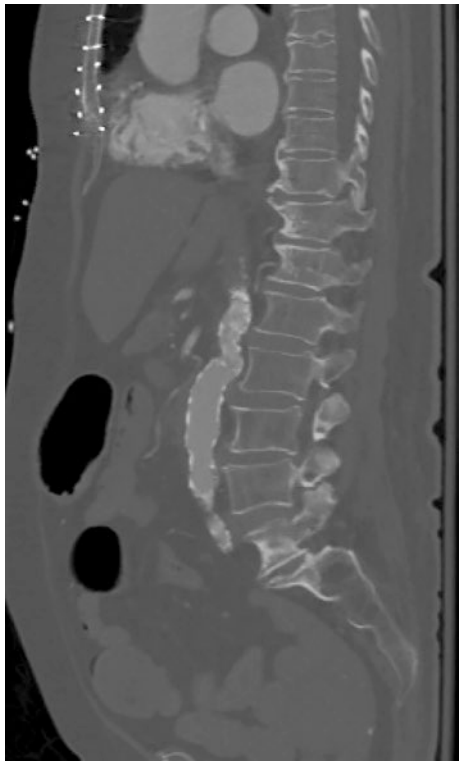

Fig. 12.1 Sagittal preoperative CT scan. Hyperenhancement along the aortic wall represents significant calcification. This can make the vessel wall friable and less mobile during exposure as well as difficult to control with vascular clamps. Care should be taken prior to manipulating calcified vessels to avoid dislodging plaque and tearing the vessel wall

still necessary prior to the posterior portion stage to ensure no saw migration has occurred (Fig. 12.2).

For those patients unable to tolerate intravenous contrast due to increased risk of contrast-induced nephropathy in the setting of chronic kidney disease, a magnetic resonance angiogram (MRA) with gadolinium or MRA with Feraheme may be considered, depending on the patient's level of kidney dysfunction.

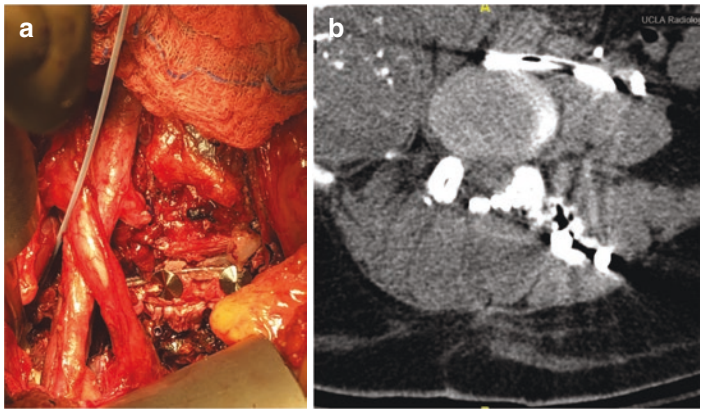

Fig. 12.2 (**a**) Intra-op placement of Tomita saws from an anterior approach. In this case, the saws are placed under direct visualization posterior to the ureter and iliac vessels and anterior to the spine. The saws are held in place by two surgical tacks, as shown. The free end of the saws, seen in a protective silicone sleeve here, is retrieved posteriorly during the second stage of the corpectomy with patient prone. (**b**) Axial images from interval CT scan. An interval CT scan between the anterior and posterior stages confirms that the saws lie between the spine and vessels. This is essential to avoiding catastrophic hemorrhage from accidental vascular injury in the prone position

Preoperative Considerations

A clear understanding of the extent of dissection and involved anatomic structures will inform any consideration for preoperative intervention and assist in eventual tumor resection. Physical examination remains a fundamental aspect of the preoperative evaluation. A lower extremity pulse exam should be well documented and can alert the provider to any existing peripheral or central arterial occlusive disease. Unilateral leg swelling can suggest existing acute or chronic venous changes and may warrant further ultrasound evaluation. Thorough and complete physical examination along with careful review of the axial imaging will assist with multiple preoperative considerations, including the use of IVC filters, periprocedural ureteral stenting, and arterial or venous stenting, as well as assess the probability of intraoperative vessel ligation.

Preoperative IVC filter placement should be considered in all cases of patients with existing iliofemoral DVT or caval thrombus. Filters should ideally be placed in a patent portion of the infrarenal IVC, although there may be instances where they are placed in a suprarenal position due to thrombus burden. Filter placement should also be considered in patients with planned acetabular resection and prolonged immobilization. Given the extensive raw surface dissection involved in most resections, a majority of patients are not able to receive prophylactic or therapeutic anticoagulation, and all of these patients by definition are high risk for DVT and thromboembolism. Temporary filters should be removed as soon as patients are able to tolerate anticoagulation to avoid potential thrombus propagation and any long-term sequela of indwelling IVC filters.

In cases of prior retroperitoneal surgery or possible fibrosis/scar development secondary to prior radiation, preoperative ureteral stenting should be considered. Although prior studies have not shown reduced rates of transection, preoperative stenting may assist with locating the ureter as well as identification of injuries intraoperatively.

Finally, in cases of obvious tumor invasion into the arterial vasculature or evidence of obliteration of the peri-adventitial plane, placement of covered stents in the arterial or venous system may be considered to help avoid uncontrolled blood loss during resection. If preoperative stenting is not done, access to bilateral femoral arteries should be considered during positioning and prepping to allow for possible endovascular balloon control of the iliac vessels. Temporary balloon control can be utilized in instances where proximal and distal dissection and clamping is not possible due to tumor mass. However, this requires a hybrid operating room or fluoroscopy to safely pass and position the intra-arterial support wires and balloon.

Operative Exposures

The surgical incision is based on the extent of tumor and planned resection. When possible, a retroperitoneal exposure is preferred to a transperitoneal approach to lessen the incidence of postopera-

tive ileus. However, the extent of the tumor and the possible involvement of the intra-abdominal contents may necessitate a transabdominal approach to safely remove the tumor en bloc. A midline or paramedian retroperitoneal exposure may be sufficient for exposure of the L2–5 lumbar spine and sacrum. Resections requiring access to the sacrum and pelvis may require a lateral flank incision, and in the most extensive cases, a thoracoabdominal incision in the lateral position may be necessary for complete vascular control and tumor resection. Regardless of exposure, preoperative pulse exam and placement of toe pulse oximetry are essential to assure perfusion to the lower extremities throughout the operation.

Our practice is to use the Gadelius Omni-Tract retractor to assist with surgical approach. Appropriate clearance and rail placement on the operating room table should be verified prior to prepping and draping to allow for the retractor post to be optimally secured intraoperatively. Also, consideration to the use of intraoperative imaging with either fluoroscopy or navigation must be made as the retractor may interfere with the imaging device itself or the quality of the imaging. Our experience has found the adjustable configuration and blade selection most conducive to deep pelvis retroperitoneal dissections compared to the retractor systems which are designed primarily for anterior lumbar fusion surgery.

Midline/Paramedian Incision

The midline incision is ideal for tumors isolated to the lumbar spine and sacrum. Patients are positioned supine with both arms out. The abdomen and bilateral groins are included in the surgical field. The anterior fascia is divided longitudinally off of the midline, and the retro-rectus space is entered at the midline. The retroperitoneal space can be entered on the right or left, depending on the location of tumor. This retroperitoneal plane is developed first laterally and inferiorly, allowing the peritoneal sac to be mobilized to the contralateral side. Using a combination of manual dissection and gentle traction, the parietal peritoneum is dissected free from the periaortic fat and rolled medially to expose the iliac bifurcation and lower lumbar spine. As the dissection is

carried cephalad, the peritoneum must be dissected from the posterior sheath and the posterior sheath divided to allow complete exposure.

The ureter should be identified and protected. The ipsilateral iliac artery will be most anterior, with the vein underneath. Prior to complete mobilization of the aortic bifurcation and the caval confluence, the middle sacral artery and iliolumbar vein should be identified and ligated at the L5 level. For dissections extending into the pelvis, the internal iliac artery and vein may be ligated to allow for further mobilization and complete tumor resection. If there is a planned sacral or pelvic resection, we routinely ligate the internal iliac artery and vein on the side of the tumor from an anterior approach to minimize blood loss during the second stage posterior, prone approach when the tumor is removed.

Iliofemoral/Rutherford Morrison Incision

A lateral "hockey-stick" incision is most appropriate in cases with lateral tumor invasion necessitating access to the spine as well as iliac crest and acetabulum. The patient is positioned in a lateral position, again dependent on the side of tumor involvement. The ipsilateral arm is placed in an airplane above the head, and a shoulder roll is placed under the chest. The operating table may be hyperextended to open the space between the costal margin and iliac crest. The lower body is kept in a supine position as able, to allow access to both femoral vessels. The dissection is carried down through the subcutaneous tissues and oblique muscles to identify the transversalis fascia. This fascia is carefully divided and separated from the peritoneum, which is then swept medially away from the abdominal wall.

The retroperitoneal space is developed as previously described. This dissection can be extended caudally to the pelvis across the inguinal ligament into the thigh and cephalad along the lumbar spine (Fig. 12.3). If necessary, the lumbar vessels should be ligated close to the aorta prior to more cephalad mobilization.

Thoracoabdominal Incision

In cases requiring resection of tumor from the thoracic and lumbar spine, a thoracoabdominal incision and retroperitoneal expo-

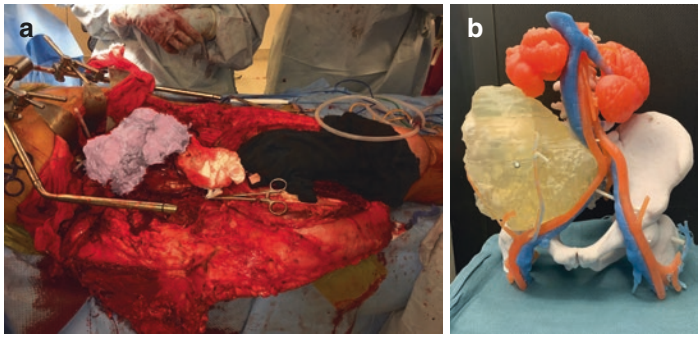

Fig. 12.3 (**a**) Resection of large pelvic tumor. A flank incision was extended across the inguinal ligament into the thigh to facilitate retroperitoneal exposure and resection of a pelvic chondrosarcoma. The patient is positioned in lateral decubitus with head to the left. The tumor has been lightly shaded for clarity. (**b**) Shown is a 3D reconstruction of the tumor removed above. Control of the IVC, bilateral internal iliac artery and veins and right external iliac were required during this resection

sure is required. The patient is positioned in a lateral decubitus position with the shoulder 60° to the table, as detailed above. Based on the necessary level of exposure, the incision is started in the intercostal space between ribs five and 11 and extended caudally and medially (Fig. 12.4). This incision can be limited to the thoracic cavity if appropriate.

The thoracic dissection is carried through the latissimus dorsi, anterior serratus, and intercostal muscles to enter the pleural space after switching to single lung ventilation. The anterior portion of the inferior rib may be resected for greater exposure. The abdominal dissection is continued down through the anterior fascia, external and internal oblique, and transversalis muscles to identify the peritoneum.

Once the peritoneum is identified, it is separated from the abdominal wall using a combination of manual dissection and gentle traction. The peritoneum and the abdominal viscera, including Gerota's fascia and the kidney, are retracted medially to reveal the retroperitoneal fat. The plane between the retroperitoneal fat and the psoas muscle is then created bluntly and traced superiorly to the diaphragm. The ureter should again be identified and protected as it crosses the iliac bifurcation caudally. The dia-

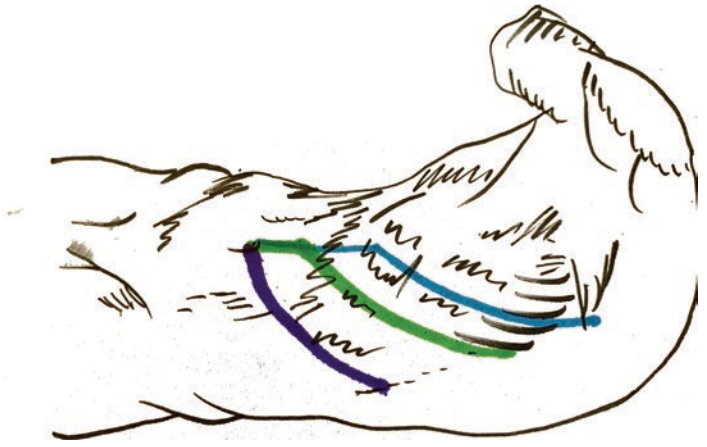

Fig. 12.4 Thoracoabdominal exposures. With patient in a lateral decubitus position, the thoracic and retroperitoneal cavities can be entered separately or as one to access the lumbar and thoracic spine. Shown are skin incisions at the 11th (purple), 9th (green), and 7th (blue) intercostal spaces used to reach the spine and overlying vascular structures

phragm is divided circumferentially, allowing greater mobility of the aorta and exposure of the anterolateral spine between the thoracic and abdominal compartments. Careful, circumferential dissection and mobilization of the aorta if on the left, and cava if on the right, is then done in preparation for tumor resection.

During closure, the diaphragm is first reapproximated and closed posteriorly and laterally. The bed is unflexed and the chest wall is then brought together prior to completion to facilitate a tension-free repair. The posterior sheath is closed if possible, followed by closure of the anterior fascia. The intercostals and latissimus fascia are then reapproximated prior to subcutaneous and skin closure.

Vascular Reconstruction

In instances of vessel involvement or injury during resection, restoring both arterial and venous anatomies should be done whenever possible. However, location, extent of vascular injury,

available conduit, and patient hemodynamics must all be considered prior to undertaking any reconstruction. In the case of venous injury or tumor involvement, ligation of bilateral internal iliac veins is well tolerated. Ligation of the external or common iliac veins may be necessary in the case of complete transection; however, repair should be attempted to avoid significant lower extremity venous congestion and swelling.

Arterial ligation is less well tolerated, and while unilateral internal iliac artery ligation can be done routinely, bilateral ligation carries the risk of buttock ischemia. In cases of prior colonic surgery (and interruption of the collateral system), bilateral internal iliac artery ligation should be not be performed in order to avoid pelvic ischemia. In-line flow through the iliofemoral arterial system must be maintained to avoid limb ischemia in these patients. Small, transverse arteriotomies may be repaired with interrupted prolene sutures, while larger, longitudinal injuries may require patch repair with bovine pericardium or vein. Transection or resection due to tumor involvement requires healthy artery both proximally and distally for a tension-free interposition bypass graft. Dacron graft, as the most expedient conduit with good long-term patency in this population, may be used in a noninfected field. Cryo-artery can be considered in cases with a concern for infection, although this comes at a significant financial cost and time necessary for graft preparation. If arterial tumor involvement is suspected, perioperative stenting or endovascular control should be considered, as detailed above.

Postoperative Care

The initial postoperative care of these patients is again best managed by a collaborative effort, involving both the orthopedic and vascular surgery teams. In patients without peritoneal violation, a diet can be started postoperative day one and advanced as tolerated. In patients with significant bowel or peritoneal sac manipulation, return of bowel function should be confirmed prior to oral intake. Retroperitoneal exposure largely results in faster recovery times; however, any concern for bowel obstruction warrants a CT

scan to rule out intraperitoneal hematoma or, rarely, bowel incarceration in cases of unidentified peritoneal violation.

All patients should be closely monitored for unilateral leg swelling suggestive of DVT. Bilateral SCDs should be placed in all cases, and early mobilization as allowed may help mitigate the risk of DVT in this high-risk population. Prophylactic anticoagulation should be started as soon as deemed appropriate by both surgical teams.

Given the extensive nature of many of these surgical resections, patients are also at risk of hernia formation during recovery. Larger thoracoabdominal incisions with potential denervation of the subcostal nerves are especially high risk. An abdominal binder is recommended during initial mobilization and the early postoperative period. Lifting and abdominal straining should be restricted for at least four weeks following surgery.

Conclusion

Despite a variety of advances in other modalities of treatment, surgical resection of pelvic and lumbar spine chondrosarcomas remains the mainstay of definitive therapy. As we have outlined here, with appropriate planning and multidisciplinary approaches to such tumors, optimal outcomes may be obtained even in the most complex of cases.

Bibliography

1. Harsh GR, Vaz-Guimaraes F, Gardner PA, Snyderman CH. Chordomas and chondrosarcomas of the skull base and spine. London: Academic Press; 2018.
2. Sidawy AN, Perler BA, Rutherford RB. Rutherford's vascular surgery and endovascular therapy. Philadelphia: Elsevier; 2019.
3. Skinner H. Current diagnosis and treatment in orthopedics. New York: McGraw-Hill Professional Publishing; 2013.
4. Wind G, Valentine J. Anatomic exposures in vascular surgery. Philadelphia: Lippincott, Williams & Wilkins; 2013.

Part IV

The Future of Chondrosarcoma Research and Treatment

13

The Future of Chondrosarcoma Research and Treatment

Pichaya Thanindratarn, Dylan C. Dean, Francis J. Hornicek, and Zhenfeng Duan

Introduction

Chondrosarcoma (CS) is a malignant cartilage-producing tumor with an estimated incidence of 0.5/100,000 per year, which accounts for 20–30% of all primary bone malignancies [1]. The majority of cases occur in patients over 50 years of age, and there is a slight male predominance [2]. CS arising de novo are termed primary CS, and those developing in preexisting benign cartilaginous lesions such as osteochondroma or enchondroma are called secondary CS. The primary conventional type accounts for 85–90% of all CS and is subdivided into central, periosteal, and peripheral subgroups according to its bony tissue origin [1]. The most commonly affected sites are the pelvis, followed by the metaphysis or diaphysis of the proximal femur and humerus, distal femur, and ribs. Less than 1% of all CS arise in

P. Thanindratarn · D. C. Dean · F. J. Hornicek · Z. Duan (✉)
Department of Orthopaedic Surgery, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA
e-mail: fhornicek@mednet.ucla.edu; zduan@mednet.ucla.edu

F. J. Hornicek (ed.), *Chondrosarcoma*,
https://doi.org/10.1007/978-3-030-74572-1_13

the small bones of the hands and feet. Nonconventional variants of CS include clear cell CS, mesenchymal CS, and dedifferentiated CS [1].

CS is characterized by its diverse histopathology, clinical behavior, and therapeutic sensitivities. Complete surgical resection with uninvolved margins, with or without adjuvant treatment, remains the mainstay treatment for patients with localized chondrosarcoma [3, 4]. To date, no chemotherapeutics have proven effective in the treatment of conventional or clear cell CS, while adjuvant anthracycline-based combination chemotherapy has modest efficacy in mesenchymal CS [5, 6]. In dedifferentiated CS, adjuvant chemotherapy markedly improves disease-free survival compared to resection alone [7]. Chemotherapeutic protocols for advanced CS are controversial and rely on data extrapolated from osteosarcoma treatment regimens of cisplatin and doxorubicin. Specifically, previous studies have shown that patients with conventional CS treated with doxorubicin monotherapy had a mean progression-free survival (PFS) of 2.5 months, while those who received a combination treatment of cisplatin and doxorubicin had PFS of 3.6 months [8, 9]. Interestingly, antihormonal treatment, such as aromatase inhibitors, demonstrated a better mean PFS of 6.7 months [8]. In a recent study of 865 CS patients in the national cancer database, no survival benefit was observed with chemotherapy [10]. Additionally, there was no statistically significant 5-year overall survival benefit for stage III CS patients treated with chemotherapy, which was 60.6% compared to 58.6% without chemotherapy ($p = 0.709$). Similar results were reported for patients with stage IV CS treated with chemotherapy compared to those without chemotherapy (5-year overall survival at 28.2% and 31.2%, respectively ($p = 0.366$)). These findings highlight the urgent need for novel and potentially more effective therapeutic strategies. In this chapter, we discuss the current research surrounding molecular targets in CS and comprehensively describe the ongoing clinical trials evaluating novel approaches for CS treatment, as shown in Table 13.1.

Table 13.1 Ongoing clinical trials for chondrosarcoma treatment

Trial identifier	Phase	Agent	Mechanism of action	Study population	Status
IDH inhibitors					
NCT03684811	I/II	FT-2102 or FT-2102 + azacitidine	Oral IDH1 inhibitor in combination with hypomethylating agent	Advanced solid tumors and gliomas including chondrosarcoma with IDH1 mutation	Recruiting
NCT04278781	II	AG-120	Oral IDH1 inhibitor	IDH1 mutant chondrosarcoma	Recruiting
Angiogenesis inhibitors					
NCT02389244	II	Regorafenib	Multi-kinase inhibitor	Metastatic bone sarcoma, chondrosarcoma	Recruiting
Cyclin-dependent kinase (CDK) inhibitors					
NCT04040205	II	Abemaciclib	CDK 4/6 inhibitor	Advanced bone sarcoma including chondrosarcoma	Recruiting

(continued)

Table 13.1 (continued)

Trial identifier	Phase	Agent	Mechanism of action	Study population	Status
P13k-Akt-mTOR pathway					
NCT02821507	II	Combination sirolimus + cyclophosphamide	mTOR inhibition with cyclophosphamide	Metastatic or unresectable myxoid liposarcoma, chondrosarcoma	Recruiting
Osteoclast inhibitors					
NCT03173976	Ib	Zoledronic acid	Bisphosphonate therapy affecting osteoclast activity	Resectable chondrosarcoma	Recruiting
Epigenetic therapy					
NCT02959164	Ib	Combination gemcitabine + decitabine	Demethylation and inhibition of DNA synthesis	Advanced malignancies, bone sarcomas	Active, not recruiting
NCT04340843	II	Combination belinostat + guadecitabine	HDAC inhibitor together with demethylation	Conventional chondrosarcoma	Not recruiting

Immune checkpoint inhibitors					
NCT03190174	I/II	Combination nivolumab + nab-rapamycin (ABI-009)	Anti-PD-1 antibody with CTLA-4 antibody	Advanced malignancies including sarcomas with deficient mismatch repair	Recruiting
NCT03474640	I	Toripalimab	Anti-PD-1 antibody	Advanced malignancies including chondrosarcoma	Recruiting
NCT02982486	II	Combination nivolumab + ipilimumab	Anti-PD-1 antibody with CTLA-4 antibody	Unresectable sarcomas including chondrosarcoma	Not yet recruiting
NCT02888665	I/I	Combination pembrolizumab + doxorubicin	Anti-PD-1 antibody with chemotherapy	Advanced sarcomas	Active, not recruiting
NCT03277924	I/II	Combination nivolumab + sunitinib	Anti-PD-1 antibody with tyrosine kinase inhibitor	Advanced bone sarcomas	Recruiting

Abbreviations: CTLA-4 cytotoxic T-lymphocyte-associated protein 4, *HDAC* histone deacetylase, *IDH* isocitrate dehydrogenase, *mTOR* mammalian target of rapamycin, *PD-1* programmed cell death receptor 1

Targeted Therapies

IDH Inhibitors

Isocitrate dehydrogenase (IDH) is an NADP+-dependent enzyme that collateralizes the oxidative decarboxylation of isocitrate to α-ketoglutarate in the Krebs cycle. In one previous study, somatic mutations of IDH1 and IDH2 were identified in approximately 50% of patients with CS and cartilaginous tumors [11]. These mutations resulted in the accumulation of a putative oncometabolite, 2-hydroxyglutarate (2-HG) [12]. Widespread DNA hypermethylation and impaired cell differentiation was observed in an IDH2 mutant-expressing mouse model of mesenchymal progenitor cells. These progenitor cells eventually led to the formation of undifferentiated sarcomas [13]. In a retrospective study of 80 CS patients, activating IDH1/2 mutations were found in 34% of patients and correlated to a shorter 5-year overall survival rate of 64% compared to 93% in those without such mutations [14]. These mutations were found in 21% of grade 1 CS patients, 39% of grade 2 CS patients, and 44% of grade 3 CS patients [14]. Theoretically, inhibition of mutated IDH1 in CS cells should decrease 2-HG production, therefore restoring normal cell differentiation and anticancer effects.

Ivosidenib or AG-120 is an oral inhibitor of mutant IDH1 that has been studied in a phase I trial of patients with IDH1 mutant chondrosarcomas. The drug was well tolerated and showed promising clinical activity in 21 enrolled patients with advanced chondrosarcoma, with 52% showing disease-stabilizing effects and a median PFS of 5.6 months [15]. The 6-month PFS rate was 39.5%. Since 62% of the patients did not have dedifferentiated histology, the authors suggested ivosidenib may in fact be more effective in conventional CS. Additionally, no dose-limiting toxicities occurred, and common adverse events were grade 1 or 2. Of the escalating doses evaluated, the 500 mg oral once-daily dose was the most efficacious and achieved maximum inhibition of plasma 2-HG levels in the first 28 days. Up to 98.6% reduction in plasma 2-HG levels was reported in tumor specimens compared to their baseline values. Another phase I trial using another oral IDH1

inhibitor, FT 2102, has shown efficacy in patients with relapsed and refractory acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) and has garnered interest in other IDH1 mutated solid tumors including CS (NCT03684811).

The R140-IDH2 mutation has also been described in three very high-grade conventional CS [14]. Enasidenib, a specific IDH2-R140 inhibitor, was recently approved by the FDA for refractory and relapsed AML. Accordingly, this new targeted drug gained interest for its potential use in CS patients with the IDH2-R140 mutation. There is an ongoing phase I/II study in advanced solid tumors such as CS currently underway (NCT01915498).

Angiogenesis Inhibitors

Neovascularization in cartilaginous tumors is associated with clinical aggressiveness and metastasis [16, 17]. Multiple antiangiogenic drugs such as tyrosine kinase inhibitors and monoclonal antibodies targeting vascular endothelial growth factor (VEGF) have been approved for clinical use in various cancers. For instance, pazopanib is an oral tyrosine kinase inhibitor that suppresses the VEGF pathway in murine CS xenografts [18]. One retrospective study with ten advanced CS patients including seven with conventional CS published results on pazopanib and ramucirumab as antiangiogenic therapy [19]. Seven patients achieved stable disease over 6 months. One patient with conventional CS who received ramucirumab had stable disease for 23 months. The median PFS was 22.6 months [19]. The most common adverse effects were hypertension and fatigue [19]. Another study evaluated pazopanib as a single agent in 47 patients with unresectable and metastatic conventional CS [20]. In this study, 43% of the patients met the disease control rate at 16 weeks. The median overall survival was 17.6 months, and one patient had a partial response [20]. Median PFS was 7.9 months. Hypertension and increase alanine aminotransferase were the most common grade 3 adverse reactions [20].

Regorafenib is another oral multi-kinase antiangiogenic drug that has been approved for patients with refractory colorectal cancers and gastrointestinal stromal tumors. Recently, a phase II ran-

domized, double-blinded, controlled trial including four parallel independent cohorts described the efficacy of regorafenib as a single agent in patients with osteosarcoma, Ewing sarcoma, CS, and chordoma [21]. The osteosarcoma treatment cohort showed 65% of the patients to have stable disease at 8 weeks compared to none in the placebo group [21]. Serious adverse events were reported in 13 patients including chest pain, hypertension, hand-foot skin reaction, fatigue, and hypophosphatemia. However, the results of CS cohort are not yet available [21].

Cyclin-Dependent Kinase Inhibitors

Cyclin-dependent kinase (CDK) inhibitors are widely used in the treatment of advanced breast cancer and have shown benefit in liposarcoma [22]. A previous study evaluated CDK4 expression in CS tissue samples and reported that heightened CDK4 expression was associated with greater rates of metastasis and recurrence [23]. Treatment with the CDK4/6 inhibitor, palbociclib, attenuated CDK4 and inhibited CS cell viability via regulation of the CDK4/RB signaling pathway. These findings suggest CDK is a promising therapeutic target for future clinical trials. Abemaciclib is currently being studied in a phase II clinical trial in advanced soft tissue and bone sarcomas including CS (NCT04040205). Previously, abemaciclib was studied as a monotherapy for patients with advanced breast cancer in the MONARCH-3 trial [24]. Treatment-related adverse events were mostly grade 1 or 2, with diarrhea being the most commonly reported side effect.

Tyrosine Kinase Inhibitors and the Mammalian Target of Rapamycin (mTOR) Pathway

A phase II trial of imatinib, a PDGFR/C-KIT tyrosine kinase inhibitor, and dasatinib, a tyrosine kinase inhibitor, could not demonstrate clinically meaningful activity in CS despite promising preclinical results [25, 26]. Another recent study reported that treatment with dasatinib resulted in sensitization for doxorubicin

treatment in TP53 mutant CS cell lines, therefore suggesting its potential roles in combination therapy regimens [27].

Phosphorylated S6, a downstream marker in the mTOR pathway, has increased activity in up to 69% of conventional CS and 44% of dedifferentiated CS [28]. In addition, the dual PI3K/mTOR inhibitor BEZ235 has been shown to inhibit the CS cell line JJ012 in vitro and in an in vivo murine xenograft, suggesting the crucial role of the mTOR pathway in CS treatment [28]. In another study, everolimus monotherapy showed a suppressive effect on CS; however, it had no synergistic effects when combined with doxorubicin [29]. In a study of ten unresectable CS, a combination treatment of sirolimus with cyclophosphamide demonstrated a median PFS of 13.4 months [30]. One patient achieved an objective response, and six patients had stable disease for six or more months. Grade 3 to 4 treatment-related adverse events were observed in four patients in the form of lymphopenia. Other common side effects included asthenia, anemia, nausea, stomatitis, and skin rash. These studies indicate that mTOR inhibition alongside other chemotherapies may stabilize the disease; however, careful consideration of the side effects is required prior to administration.

Osteoclast Inhibitors

Several components of the tumor microenvironment, such as osteoclasts, have shown to influence the growth of CS in preclinical studies [31, 32]. In a murine CS model, zoledronic acid prevented cortical bone destruction, inhibited trabecular bone resorption, and resulted in decreased tumor volume in the bone [32]. To evaluate zoledronic acid as a therapeutic option in human CS, there is an ongoing phase IIB trial in patients with any grade CS with or without metastasis for whom surgical resection is indicated (NCT03173976). Patients with dedifferentiated CS in the trial are permitted if they opt out of the standard doxorubicin-based regimen. The standard dose of zoledronic acid is delivered 3 weeks preoperatively and again postoperatively. The primary outcome measure is a comparison of osteoclast density in pre-

treated biopsy specimens and post-treated resected tumors. Overall survival and relapse-free survival are secondary outcomes. The results are not yet published.

Epigenetic Inhibitors

Hypomethylating Agents

As previously described, IDH mutations may impair histone demethylation and create a hypermethylated phenotype in CS cell lines, resulting in a block to cell differentiation [33]. Inhibition of DNA-methyltransferase by decitabine in the CS cell line H-HEMC-SS led to restoration of heparin sulfate 3-0-sulfotranferase gene expression, thereby decreasing CS cell proliferation and tumor invasiveness [34]. Interestingly, however, loss of DNA methylation in murine CS cells treated with decitabine showed increased tumor growth and invasiveness [35]. It is clear that more preclinical research is required to reveal the complex epigenetic mechanisms of this pathway.

Recently, a phase IB/II clinical trial evaluated a combination of hypomethylating agent decitabine, 5-azacitidine, and gemcitabine chemotherapy in patients with bone and soft tissue sarcomas, including relapsed refractory CS (NCT02959164) [36]. A partial response was observed in a patient with IDH1 mutant CS, but they discontinued the study after 7 months due to treatment toxicity. Another patient with wild-type IDH CS had progressive disease without clinical response after two treatment cycles. These results support a combination therapy consisting of a hypomethylating agent and chemotherapy for patients with IDH mutant CS. Results are ongoing and pending.

Histone Deacetylase (HDAC) Inhibitor

Preclinical studies have demonstrated several antitumor effects of HDAC inhibitors on CS [37]. Histone acetylation is a key epigenetic mechanism for regulating gene expression and, when dys-

regulated, can promote cancer growth. Accordingly, HDAC inhibitors suppress cell growth and induce apoptosis in CS cells [37]. Of note, four HDAC inhibitors have been approved for refractory T cell lymphoma and multiple myeloma treatment. A phase II clinical trial of the HDAC inhibitor romidepsin was recently completed for treatment of extra-skeletal chondrosarcoma, with results pending (NCT00112463).

The combination therapy of the HDAC inhibitor suberoylanilide hydroxamic acid (SAHA) and the DNA hypomethylating agent decitabine was examined in IDH wild type, IDH1 mutant, and IDH2 mutant CS cell lines both in vitro and in vivo [38]. All three of the CS cell lines showed decreased cell viability and increased expression of the apoptotic marker poly-ADP ribose polymerase (PARP). Another combination regimen of the HDAC inhibitor belinostat with the long-acting hypomethylating agent guadecitabine is currently in a phase II clinical trial (NCT04340843).

Immunotherapy

Cancer immunotherapy is rapidly growing subspecialty of oncology treatment that artificially stimulates the immune system. It is divided into three main categories: tumor vaccinations, adoptive T cell transfer, and immune checkpoint blockade. Immune checkpoint blockade has shown remarkable clinical outcomes in several malignancies. PD-1 is a cell surface protein receptor expressed on activated CD8+ T lymphocytes, B cells, and natural killer (NK) cells. It has roles in dampening the immune response to deter autoimmune disease but can also diminish the cancer immune response and therefore a robust therapeutic target. Blockade of the PD-1 pathway has proven effective in malignant melanoma, non-small cell lung cancer, renal cell carcinoma, breast cancer, and various other malignancies [39]. Early phase clinical trials are ongoing in bone and soft tissue sarcomas [39].

PD-L1 overexpression was observed in approximately 41% of dedifferentiated CS [40]. Despite favorable preclinical results, clinical studies of immune checkpoint blockade in CS remain

sparse. In the SARC028 trial, one of five dedifferentiated CS patients treated with pembrolizumab achieved an objective response [41]. A phase I/II clinical trial investigating a combination of pembrolizumab and doxorubicin in metastatic sarcomas is currently underway (NCT02888665).

In a phase II study evaluating the anti-PD-1 antibody nivolumab, one patient with dedifferentiated CS showed a partial response [42]. Another study reported a favorable response in one patient with metastatic conventional CS treated with nivolumab [43]. There are several clinical trials currently investigating anti-PD-1 antibodies in sarcomas including CS. A phase IB dose escalation trial of nivolumab combined with ABI-009 (nab-sirolimus) is ongoing in patients with bone and soft tissue sarcomas (NCT03190174). Initial phase I evidence reports that among nine treated patients, two achieved stable disease, and of the seven that discontinued treatment, five had progressive disease and two sustained grade 2 adverse effects (acneiform rash and pruritus). Phase II is currently ongoing.

Another phase II trial of nivolumab combined with the CTLA-4 inhibitor ipilimumab is ongoing in patients with unresectable sarcomas including CS (NCT02982486). A recombinant humanized PD-1 monoclonal antibody, toripalimab, is also being evaluated in a phase 1 trial across various tumor subtypes including CS (NCT03474640).

Conclusion

The limited therapeutic options in CS make its clinical management particularly challenging and prognosis dismal. This is due to its resistance to conventional chemotherapies and many of the targeted therapies to date. Future studies are needed to reveal the underlying molecular pathways and immunology in CS to inform therapeutic regimens. Future clinical management will likely benefit by an improved understanding of differences between CS subtypes and personalized medicine. Ongoing and prospective clinical trials will provide the basis for improved treatment regimens for patients with CS and serve as adjuvants to wide-margin surgical resection.

Acknowledgment This work was supported, in part, by the Department of Orthopaedic Surgery at UCLA.

References

1. Jo VY, Fletcher CD. WHO classification of soft tissue tumours: an update based on the 2013 (4th) edition. Pathology. 2014;46(2):95–104.
2. van Praag Veroniek VM, Rueten-Budde AJ, Ho V, Dijkstra PDS, Study group B, Soft tissue t, et al. Incidence, outcomes and prognostic factors during 25 years of treatment of chondrosarcomas. Surg Oncol. 2018;27(3):402–8.
3. Angelini A, Guerra G, Mavrogenis AF, Pala E, Picci P, Ruggieri P. Clinical outcome of central conventional chondrosarcoma. J Surg Oncol. 2012;106(8):929–37.
4. Fromm J, Klein A, Baur-Melnyk A, Knosel T, Lindner L, Birkenmaier C, et al. Survival and prognostic factors in conventional central chondrosarcoma. BMC Cancer. 2018;18(1):849.
5. Gelderblom H, Hogendoorn PC, Dijkstra SD, van Rijswijk CS, Krol AD, Taminiau AH, et al. The clinical approach towards chondrosarcoma. Oncologist. 2008;13(3):320–9.
6. Frezza AM, Cesari M, Baumhoer D, Biau D, Bielack S, Campanacci DA, et al. Mesenchymal chondrosarcoma: prognostic factors and outcome in 113 patients. A European Musculoskeletal Oncology Society study. Eur J Cancer. 2015;51(3):374–81.
7. van Maldegem AM, Bovee JV, Gelderblom H. Comprehensive analysis of published studies involving systemic treatment for chondrosarcoma of bone between 2000 and 2013. Clin Sarcoma Res. 2014;4:11.
8. van Maldegem A, Conley AP, Rutkowski P, Patel SR, Lugowska I, Desar IME, et al. Outcome of first-line systemic treatment for unresectable conventional, dedifferentiated, mesenchymal, and clear cell chondrosarcoma. Oncologist. 2019;24(1):110–6.
9. Nooij MA, Whelan J, Bramwell VH, Taminiau AT, Cannon S, Hogendoorn PC, et al. Doxorubicin and cisplatin chemotherapy in high-grade spindle cell sarcomas of the bone, other than osteosarcoma or malignant fibrous histiocytoma: a European Osteosarcoma Intergroup Study. Eur J Cancer. 2005;41(2):225–30.
10. Xu KM, Switchenko JM, Tian S, Escott CE, Pfister NT, Gillespie TW, et al. More effective systemic therapies are needed for chondrosarcoma: A National Cancer Data Base (NCDB) analysis. J Clin Oncol. 2018;36(15_suppl):e23508-e.
11. Amary MF, Bacsi K, Maggiani F, Damato S, Halai D, Berisha F, et al. IDH1 and IDH2 mutations are frequent events in central chondrosarcoma and central and periosteal chondromas but not in other mesenchymal tumours. J Pathol. 2011;224(3):334–43.

12. Dang L, White DW, Gross S, Bennett BD, Bittinger MA, Driggers EM, et al. Cancer-associated IDH1 mutations produce 2-hydroxyglutarate. Nature. 2009;462(7274):739–44.
13. Lu C, Venneti S, Akalin A, Fang F, Ward PS, Dematteo RG, et al. Induction of sarcomas by mutant IDH2. Genes Dev. 2013;27(18):1986–98.
14. Lugowska I, Teterycz P, Mikula M, Kulecka M, Kluska A, Balabas A, et al. IDH1/2 mutations predict shorter survival in chondrosarcoma. J Cancer. 2018;9(6):998–1005.
15. Tap WD, Villalobos VM, Cote GM, Burris H, Janku F, Mir O, et al. Phase I study of the mutant IDH1 inhibitor ivosidenib: safety and clinical activity in patients with advanced chondrosarcoma. J Clin Oncol. 2020;38(15):1693–701.
16. Ayala G, Liu C, Nicosia R, Horowitz S, Lackman R. Microvasculature and VEGF expression in cartilaginous tumors. Hum Pathol. 2000;31(3):341–6.
17. McGough RL, Aswad BI, Terek RM. Pathologic neovascularization in cartilage tumors. Clin Orthop Relat Res. 2002;397:76–82.
18. Klenke FM, Abdollahi A, Bertl E, Gebhard MM, Ewerbeck V, Huber PE, et al. Tyrosine kinase inhibitor SU6668 represses chondrosarcoma growth via antiangiogenesis in vivo. BMC Cancer. 2007;7:49.
19. Jones RL, Katz D, Loggers ET, Davidson D, Rodler ET, Pollack SM. Clinical benefit of antiangiogenic therapy in advanced and metastatic chondrosarcoma. Med Oncol. 2017;34(10):167.
20. Chow W, Frankel P, Ruel C, Araujo DM, Milhem M, Okuno S, et al. Results of a prospective phase 2 study of pazopanib in patients with surgically unresectable or metastatic chondrosarcoma. Cancer. 2020;126(1):105–11.
21. Duffaud F, Mir O, Boudou-Rouquette P, Piperno-Neumann S, Penel N, Bompas E, et al. Efficacy and safety of regorafenib in adult patients with metastatic osteosarcoma: a non-comparative, randomised, double-blind, placebo-controlled, phase 2 study. Lancet Oncol. 2019;20(1):120–33.
22. Dickson MA, Tap WD, Keohan ML, D'Angelo SP, Gounder MM, Antonescu CR, et al. Phase II trial of the CDK4 inhibitor PD0332991 in patients with advanced CDK4-amplified well-differentiated or dedifferentiated liposarcoma. J Clin Oncol. 2013;31(16):2024–8.
23. Ouyang Z, Wang S, Zeng M, Li Z, Zhang Q, Wang W, et al. Therapeutic effect of palbociclib in chondrosarcoma: implication of cyclin-dependent kinase 4 as a potential target. Cell Commun Signal. 2019;17(1):17.
24. Johnston S, Martin M, Di Leo A, Im SA, Awada A, Forrester T, et al. MONARCH 3 final PFS: a randomized study of abemaciclib as initial therapy for advanced breast cancer. NPJ Breast Cancer. 2019;5:5.
25. Grignani G, Palmerini E, Stacchiotti S, Boglione A, Ferraresi V, Frustaci S, et al. A phase 2 trial of imatinib mesylate in patients with recurrent nonresectable chondrosarcomas expressing platelet-derived growth fac-

tor receptor-alpha or -beta: an Italian Sarcoma Group study. Cancer. 2011;117(4):826–31.
26. Schuetze SM, Bolejack V, Choy E, Ganjoo KN, Staddon AP, Chow WA, et al. Phase 2 study of dasatinib in patients with alveolar soft part sarcoma, chondrosarcoma, chordoma, epithelioid sarcoma, or solitary fibrous tumor. Cancer. 2017;123(1):90–7.
27. van Oosterwijk JG, van Ruler MA, Briaire-de Bruijn IH, Herpers B, Gelderblom H, van de Water B, et al. Src kinases in chondrosarcoma chemoresistance and migration: dasatinib sensitises to doxorubicin in TP53 mutant cells. Br J Cancer. 2013;109(5):1214–22.
28. Zhang YX, van Oosterwijk JG, Sicinska E, Moss S, Remillard SP, van Wezel T, et al. Functional profiling of receptor tyrosine kinases and downstream signaling in human chondrosarcomas identifies pathways for rational targeted therapy. Clin Cancer Res. 2013;19(14):3796–807.
29. Perez J, Decouvelaere AV, Pointecouteau T, Pissaloux D, Michot JP, Besse A, et al. Inhibition of chondrosarcoma growth by mTOR inhibitor in an in vivo syngeneic rat model. PLoS One. 2012;7(6):e32458.
30. Bernstein-Molho R, Kollender Y, Issakov J, Bickels J, Dadia S, Flusser G, et al. Clinical activity of mTOR inhibition in combination with cyclophosphamide in the treatment of recurrent unresectable chondrosarcomas. Cancer Chemother Pharmacol. 2012;70(6):855–60.
31. David E, Blanchard F, Heymann MF, De Pinieux G, Gouin F, Redini F, et al. The bone niche of chondrosarcoma: a sanctuary for drug resistance, tumour growth and also a source of new therapeutic targets. Sarcoma. 2011;2011:932451.
32. Otero JE, Stevens JW, Malandra AE, Fredericks DC, Odgren PR, Buckwalter JA, et al. Osteoclast inhibition impairs chondrosarcoma growth and bone destruction. J Orthop Res. 2014;32(12):1562–71.
33. Lu C, Ward PS, Kapoor GS, Rohle D, Turcan S, Abdel-Wahab O, et al. IDH mutation impairs histone demethylation and results in a block to cell differentiation. Nature. 2012;483(7390):474–8.
34. Bui C, Ouzzine M, Talhaoui I, Sharp S, Prydz K, Coughtrie MW, et al. Epigenetics: methylation-associated repression of heparan sulfate 3-O-sulfotransferase gene expression contributes to the invasive phenotype of H-EMC-SS chondrosarcoma cells. FASEB J. 2010;24(2):436–50.
35. Hamm CA, Xie H, Costa FF, Vanin EF, Seftor EA, Sredni ST, et al. Global demethylation of rat chondrosarcoma cells after treatment with 5-aza-2'-deoxycytidine results in increased tumorigenicity. PLoS One. 2009;4(12):e8340.
36. Monga V, Dodd R, Scherer A, Gutierrez WR, Tanas M, Mott SL, et al. Phase Ib study of decitabine in combination with gemcitabine in treatment of advanced soft tissue and bone sarcomas. J Clin Oncol. 2020;38(15_suppl):11550.
37. Sakimura R, Tanaka K, Yamamoto S, Matsunobu T, Li X, Hanada M, et al. The effects of histone deacetylase inhibitors on the induction of

differentiation in chondrosarcoma cells. Clin Cancer Res. 2007;13(1):275–82.
38. Sheikh T, Patwardhan P, Schwartz GK. Abstract 5066: Combination treatment with SAHA and 5-Azacytidine (Decitabine) induces apoptosis and suppresses tumor growth in preclinical models of chondrosarcoma. Cancer Res. 2017;77(13 Supplement):5066.
39. Thanindratarn P, Dean DC, Nelson SD, Hornicek FJ, Duan Z. Advances in immune checkpoint inhibitors for bone sarcoma therapy. J Bone Oncol. 2019;15:100221.
40. Kostine M, Cleven AH, de Miranda NF, Italiano A, Cleton-Jansen AM, Bovee JV. Analysis of PD-L1, T-cell infiltrate and HLA expression in chondrosarcoma indicates potential for response to immunotherapy specifically in the dedifferentiated subtype. Mod Pathol. 2016;29(9):1028–37.
41. Tawbi HA, Burgess M, Bolejack V, Van Tine BA, Schuetze SM, Hu J, et al. Pembrolizumab in advanced soft-tissue sarcoma and bone sarcoma (SARC028): a multicentre, two-cohort, single-arm, open-label, phase 2 trial. Lancet Oncol. 2017;18(11):1493–501.
42. Paoluzzi L, Cacavio A, Ghesani M, Karambelkar A, Rapkiewicz A, Weber J, et al. Response to anti-PD1 therapy with nivolumab in metastatic sarcomas. Clin Sarcoma Res. 2016;6:24.
43. Wagner MJ, Ricciotti RW, Mantilla J, Loggers ET, Pollack SM, Cranmer LD. Response to PD1 inhibition in conventional chondrosarcoma. J Immunother Cancer. 2018;6(1):94.

Index

A
Adjuvant chemotherapy, 258, 259, 284
Appendicular skeleton
  allograft and allograft-prosthetic composite, 150–152
  anatomic distribution, 133
  biopsy sampling errors, 140
  bone transport, 156, 157
  distraction osteogenesis, 156, 157
  endoprosthetic reconstruction, 153–156
  free fibular grafts, 152, 153
  histologic grade, 139, 140
  histologic subtypes, 134–136
  imaging, 137–139
  initial examination, 136, 137
  intralesional procedure, 140
  limb amputation, 150
  marginal excision, 140
  prognosis, 134
  radical resection, 141
  reconstruction options, 149, 150
  treatment
    dedifferentiated chondrosarcoma, 145, 146
    grade 1 chondrosarcoma, 141–144
    high-grade chondrosarcoma, 144–146
    pathologic fracture, 147–149
    recurrent chondrosarcoma, 146, 147
  wide resection, 140
Atypical cartilaginous tumor, 28, 115, 117

B
Benign chondroblastoma, 181
Bone tumors, 114

C
Cancer mouse models, 40
Carbon ion therapy, 226, 229–231
Central chondrosarcoma, 54
  aggressive features, 56, 58
  appendicular skeleton, 54
  bone scintigraphy, 56
  cartilaginous features, 56
  classification, 54
  FDG-PET imaging, 56, 57
  matrix mineralization, 56
  mild peripheral and septal enhancement, 56, 57
  mixed lytic and sclerotic lesion, 54, 55
  pathologic fractures, 54, 56

F. J. Hornicek (ed.), *Chondrosarcoma*,
https://doi.org/10.1007/978-3-030-74572-1

Chemotherapy, 259, 260, 284
Chondroblastic osteosarcoma, 182
Chondromyxoid fibroma, 181
Clavicle
  biopsy, 191, 192
  clinical manifestation, 188, 189
  histology, 191, 192, 196
  imaging, 189–191
  metastasis, 192, 193
  reconstruction, 197, 198
  recurrence, 194–197
  treatment, 193, 194
Clear cell chondrosarcoma, 86, 87
  hemorrhagic cystic change, 12, 16
  imaging, 61–63
  immunohistochemistry, 13
  non-neoplastic osteoblasts and occasional osteoclasts, 13, 17–19
Comparative genomic hybridization (CGH), 30
Conventional chondrosarcoma
  atypical cartilaginous tumor/grade 1 chondrosarcoma, 5, 8
  central chondrosarcoma, 5
  clinical presentation, 79
  grade 2 chondrosarcoma, 7–9
  grade 3 chondrosarcoma, 7, 8, 10
  hyaline matrix, 5–7
  imaging characteristics, 79, 80
  overview, 78
  pathology, 79, 81, 82
  prognosis, 79, 81, 82
  treatment, 80
Cyclin-dependent kinase (CDK) inhibitors, 290
Cyclin-dependent kinase 4 (CDK4) gene, 31

D
Dedifferentiated chondrosarcoma, 9, 11, 14, 15, 86, 119
  imaging, 68, 70–72
  treatment, 145, 146
Desert hedgehog (DHH), 36
DNA methylation, 37, 38

E
Enchondroma, 57–61, 79, 82, 181
Exostosin (EXT1 and EXT2), 257
Exostosin glycosyltransferase genes (EXT1 and EXT2), 30
Extracellular matrix (ECM), 35
Extraosseous chondrosarcoma, 178
Extraskeletal myxoid chondrosarcoma
  epidemiology, 101
  history, 100, 101
  outcomes, 107
  presentation and diagnosis, 101–103
  radiation therapy, 105, 106
  staging, 103, 104
  surgical therapy, 106
  systemic therapy, 104, 105

F
[^{18}F] fluoro-2-deoxy-D-glucose positron emission tomography (^{18}FDG-PET) imaging, 56, 57
Foot chondrosarcoma, 158–160
Fusion genes, 37

G
Gene amplification/deletions, 30, 31
Gene mutations
  COL2A1, 34, 35
  hedgehog-related genes, 36, 37
  IDH1 and IDH2, 32–34
  p53 and Rb1, 35, 36
Genetic targets
  alterations, 41
  hedgehog pathway, 42, 43
  IDH protein, 41, 42

Rb and CDK4, 43
Sox2 and Sox9 transcriptional factors, 43, 44
Grade 1 chondrosarcoma treatment, 141–144
Gross tumor volume (GTV), 231, 232

H
Hand chondrosarcoma, phalangeal, 157, 158
clinical presentation, 170
computed tomography, 172
differential diagnosis, 181, 182
extraosseous chondrosarcoma, 178
histological features, 172, 173
juxtacortical chondrosarcoma, 178
Maffucci's syndrome, 179, 180
magnetic resonance image, 172
metastasis, 178, 179
Ollier's disease, 179, 180
radiographic features, 171, 172
reconstruction, 176–178
recurrence, 176
treatment, 173–176
HEY1–NCOA2 gene fusion, 4
High-grade chondrosarcoma treatment, 144–146
Histone deacetylase (HDAC) inhibitor, 292, 293

I
Immunotherapy, 44, 45, 262, 263, 293, 294
Indian hedgehog (IHH), 36
Indian hedgehog homolog (IHH) signaling pathway, 257
Intensity-modulated radiation therapy (IMRT), 214, 217
Intramedullary chondrosarcoma, *see* Central chondrosarcoma
Isocitrate dehydrogenase (IDH), 41, 42, 262, 288, 289
Isocitrate dehydrogenase (IDH1 and IDH2), 32–34, 256, 257
Ivosidenib, 288, 289

J
Juxtacortical chondrosarcoma, 87, 88, 178

L
Loss of heterozygosity (LOH), 31

M
Maffucci's syndrome, 121, 179, 180
Mammalian target of rapamycin (mTOR) pathway, 291
Mesenchymal chondrosarcoma, 14, 15, 17, 20, 21, 87, 118
aggressive radiographic features, 65
epidemiology, 94
history, 93, 94
internal calcifications, 66–68
outcomes, 99, 100
overview, 65
presentation and diagnosis, 94–97
radiation therapy, 98, 99
septal and peripheral enhancement pattern, 66
staging, 97
surgical therapy, 99
systemic therapy, 97, 98
Mesenchymal stem cells (MSCs), 29
Molecular targets, 284–287
Multiple hereditary exostoses (MHE), 121
Myxoid chondrosarcoma imaging, 68–70

N
Noncoding RNAs (ncRNAs), 38, 39
Novel therapy
histone deacetylase inhibitor, 262
IDH1/2 inhibitor, 262
Src pathway, 261
VEGFR inhibitor, 261

O
Ollier's disease, 121, 179, 180
Osteochondroma, 57–61

P
Parathyroid Related Protein(PTHRP) signaling pathway, 257
Pelvic chondrosarcoma, 244–246
Periosteal chondroma, 181
Periosteal chondrosarcoma, 87, 88
imaging, 63, 64
Primary chondrosarcoma, 3
Programmed cell death receptor-1 (PD-1), 44, 45
Proton therapy, 221–225

R
Radiation therapy (RT)
advanced radiation modalities, 207
definitive RT, 205
doses, 206
grading, 209
local control, 204
oligometastatic disease, 205, 206
palliation, 205
pelvic chondrosarcoma, 244–246
pre-radiotherapy evaluation, 210, 211
radioresistant tumor, 209, 210
salvage, 205
skull base chondrosarcoma (*see* Skull base chondrosarcoma)
spine chondrosarcoma (*see* Spine chondrosarcoma)
surgical approach, 207, 208
tumor location, 207, 208
Recurrent chondrosarcoma treatment, 146, 147

S
Secondary chondrosarcoma, 8, 9, 11–13
clinical presentation, 83
enchondroma, 57–61
genetics, 84, 85
imaging characteristics, 83, 84
mutations, 85
osteochondroma, 57–61
overview, 81, 82
pathology, 84
prognosis, 86
surveillance protocols, 85, 86
treatment, 86
Single-strand conformation polymorphism (SSCP) analysis, 31
Skull base chondrosarcoma
advanced therapy modalities, 213–216
carbon ion therapy, 226, 229–231
image-guided IMRT, 214, 217
mixed proton/photon therapy, 225–228
proton therapy, 221–225
radiation field design, 231, 232
SRS, 218–221
surgical role, 211, 212
symptoms, 211
Soft tissue chondrosarcoma
extraskeletal myxoid chondrosarcoma
epidemiology, 101
history, 100, 101
outcomes, 107
presentation and diagnosis, 101–103

radiation therapy, 105, 106
staging, 103, 104
surgical therapy, 106
systemic therapy, 104, 105
mesenchymal chondrosarcoma
epidemiology, 94
history, 93, 94
outcomes, 99, 100
presentation and diagnosis, 94–97
radiation therapy, 98, 99
staging, 97
surgical therapy, 99
systemic therapy, 97, 98
Sonic hedgehog (SHH), 36
Spinal tumors
chemotherapy, 123, 124
classification system, 114
en bloc resection, 125, 126
histology, 114–120
imaging, 121–123
pathology, 121
patient history, 127, 128
radiation therapy, 124, 125
Spine chondrosarcoma
dose constraints, 243
dosing and field design, 235, 240–242
failure pattern and prognosis, 243, 244
radiation-associated toxicities, 241
surgical role, 233–238
Stereotactic radiosurgery (SRS), 218–221
Subungual exostosis, 182
Synovial chondromatosis, 181
Systemic therapy
adjuvant chemotherapy, 258, 259
chemotherapy, 259, 260
immunotherapy, 262, 263
metastatic chondrosarcoma novel therapy, 262
molecular pathogenesis
EXT1 and EXT2 gene alteration, 257
IDH1 and IDH2 gene mutation, 256, 257
IHH/PTHRP signaling pathway, 257
Src pathway, 258
VEGFR, 258
novel therapy, 261, 262

T

Targeted therapy
angiogenesis inhibitors, 289, 290
CDK inhibitors, 290
HDAC inhibitors, 292, 293
hypomethylating agent, 292
IDH, 288, 289
immunotherapy, 293, 294
mTOR pathway, 291
osteoclast inhibitors, 291, 292
tyrosine kinase inhibitor, 290
Total en bloc spondylectomy, 126
Tumor resection
aortic bifurcation, 270, 271
arterial anatomy, 270
clearance and rail placement, 274
computed tomography (CT) imaging, 269–270, 272
iliac arteries, 270, 271
iliofemoral/Rutherford Morrison incision, 275, 276
inferior vena cava (IVC), 270
magnetic resonance angiogram (MRA), 271
midline/paramedian incision, 274, 275
post-operative care, 278, 279
pre-operative intervention, 272, 273
retroperitoneal exposure, 273, 274
thoracoabdominal incision, 275–277
vascular reconstruction, 277, 278
Tyrosine kinase inhibitor, 290

V
Vascular endothelial growth factor (VEGF), 258, 289
Vascularized fibular graft (VFG), 151, 152
VEGFR inhibitor, 261

W
Weinstein, Boriani, Biagini (WBB) system, 114
Wnt inhibitory factor 1 (WIF1), 38