Histopathology of Sacral Tumors and Pseudotumors

7

Marilyn M. Bui, Yi Ding, Evita Henderson Jackson, and Angelo Paolo Dei Tos

The sacrum is composed of bone, cartilage, soft mesenchymal tissue, bone marrow, and notochordal remnants, which give rise to tumors or pseudotumors. Tumors of the sacrum include primary and metastatic/systemic origin. The primary tumors consist of malignant and benign entities. Systemic diseases include metastases and hematopoietic malignancies such as lymphoma, multiple myeloma, or plasmacytoma. The incidence of sacral tumors and pseudotumors at the Rizzoli institute is described in the epidemiology chapter of this book. Personal communication with Dr. Xiaohui Niu, Professor and Chair of the Department of Orthopedic Oncology Surgery of the Jishuitan (JST) Hospital in Beijing, China, the largest and a premier Orthopedic Oncology hospital in China, also confirms the most frequently occurring sacral tumors (Table 7.1). This data is retrieved from the JST epidemiology website of musculoskeletal tumors (www.sarcoma-jst.net) based on a collection of 18, 419 cases [1]. In this chapter, the histopathology as well as pertinent ancillary diagnostic, prognostic, and predictive information of these common tumors and pseudotumors will be discussed.

M.M. Bui, M.D., Ph.D. (✉) • E.H. Jackson, M.D.
Department of Anatomic Pathology, Moffitt Cancer Center, Tampa, FL, USA

Department of Sarcoma, Moffitt Cancer Center, Tampa, FL, USA
e-mail: Marilyn.Bui@moffitt.org

Y. Ding, M.D.
Department of Pathology, Jishuitan Hospital, Beijing, China

A.P.D. Tos, M.D.
Department of Medicine, University of Padua School of Medicine, Padua, Italy

P. Ruggieri et al. (eds.), *Tumors of the Sacrum*,
DOI 10.1007/978-3-319-51202-0_7

Table 7.1 Frequency of sacral tumor and pseudotumors (JST data)

Diagnosis	Cases
Primary malignant tumors	
Chordoma	172
Undifferentiated high-grade pleomorphic sarcoma	27
Chondrosarcoma	18
Ewing Sarcoma	12
Small blue round cell tumor	9
Osteosarcoma	11
Malignant peripheral nerve sheath tumor	3
Fibrosarcoma of bone	2
Malignancy in giant cell tumor of bone	2
Angiosarcoma	1
Subtotal	*257*
Benign lesions	
Giant cell tumor of bone	124
Schwannoma/neurofibroma	75
Aneurysmal bone cyst	8
Bone cyst	9
Osteoblastoma	5
Paraganglioma	5
Hemangioma	4
Desmoplastic fibroma of bone	2
Fibrous dysplasia	2
Angiomatosis, Langerhans cell histiocytosis, Lipoma, Myopericytoma, Osteochondroma, Osteoid osteoma	6
Subtotal	*240*
Systemic diseases	
Metastatic disease	84
Plasma cell myeloma	13
Primary non-Hodgkin lymphoma of bone	8
Subtotal	*105*
Total	602

7.1 Malignant Tumors

Malignant tumors include primary sarcoma, primary hematopoietic malignancy, and metastatic diseases. Primary sarcoma may derive from bone or soft tissue. The histological type of a primary bone sarcoma is often indicative of the tumor grade. The most common bone sarcomas are of high-grade malignancy. Soft tissue sarcoma occurring in sacrum is rare. Histological type and grade predict tumor behavior. The Federation Nationale des Cenres de Lutte Contre Le (FNCLCC) grading system is well accepted.

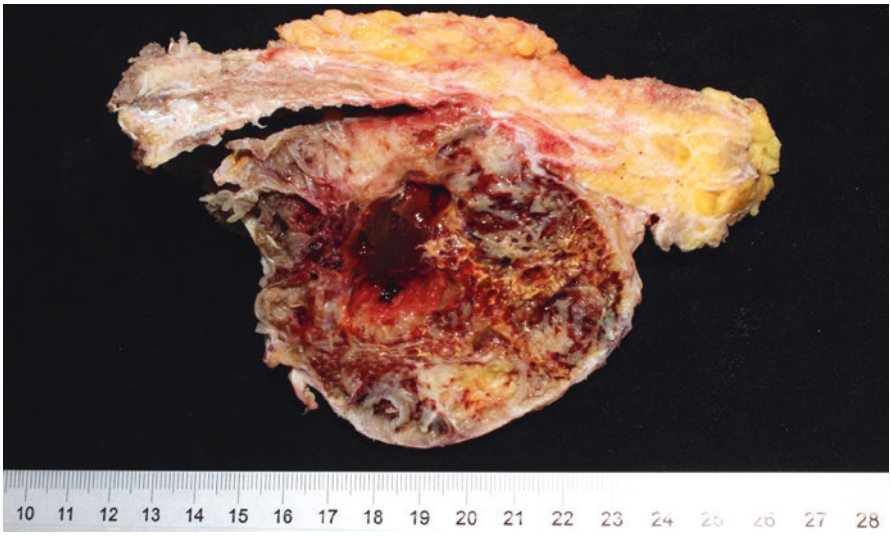


Fig. 7.1 Gross image of a sacral chordoma

7.1.1 Chordoma

Chordoma is the most common primary malignancy occurring in sacrum arising from notochordal rests [2]. Although it is mainly located in the base of the skull, 29.2–60% of chordomas occur in the sacrococcygeal region [3, 4]. It is usually a slow-growing and low-grade tumor, but metastatic disease is seen more frequently in sacral chordomas than in skull base chordomas [5].

Grossly, the tumor has an expansile, lobulated structure with cortical invasion. The cut surface is gelatinous with chondroid texture (Fig. 7.1). By definition, chordoma is a malignant tumor showing notochordal differentiation [3]. Notochordal differentiation is exhibited by epithelioid cells arranged in nests or cords with clear or eosinophilic cytoplasm; some have vacuolated "bubbly" cytoplasm, so called "physaliphorous cells." The tumor cells are separated by fibrous septa, which give rise to the lobulated appearance and are embedded in abundant extracellular myxoid matrix. In a low-grade tumor, the nuclei are small with coarse chromatin. In a high-grade tumor, the nuclei may become larger, pleomorphic and with greater mitotic activity.

Most of the chordomas are designated as chordomas, not otherwise specified (NOS) [3]. Chondroid chordoma is a rare variant which contains hyaline cartilage component. Its behavior is similar to chordoma, NOS, but it may be confused as chondrosarcoma morphologically. Brachyury is a specific immunohistochemical diagnostic marker for chordoma [6]. Nuclear immunoreactivity to Brachyury is seen in chordoma but not in chondrosarcoma, and is therefore extremely helpful in the differential diagnosis. Figure 7.2 shows the histological and immunohistochemical features of a chordoma. In practice, we prefer to use the more specific monoclonal antibody of brachyury than the polyclonal to prevent false positivity; we also

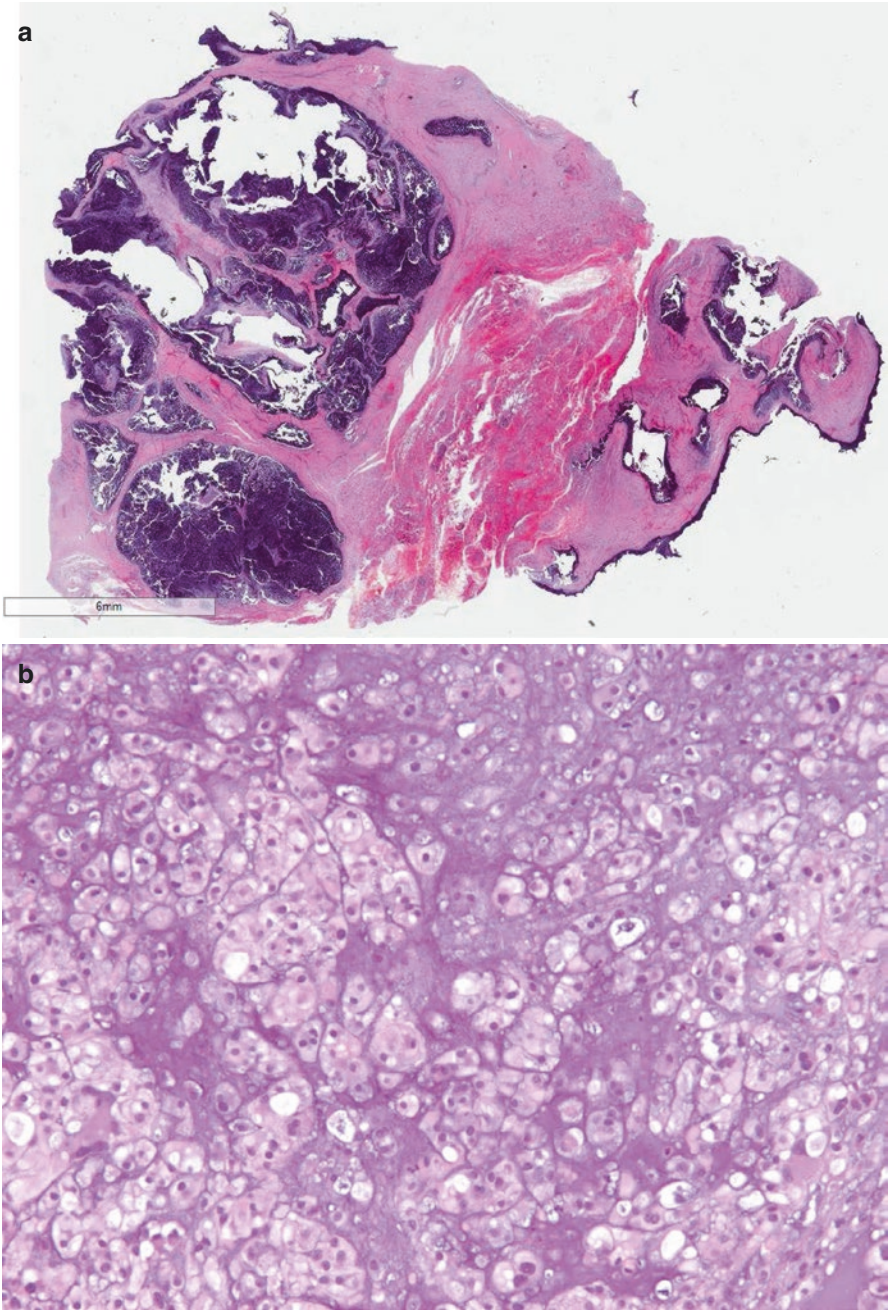


Fig. 7.2 Microscopic images of a chordoma. (**a**) HE digitalized whole slide image. (**b**) HE ×200. (**c**) HE ×600. (**d**) Brachyury stain ×200

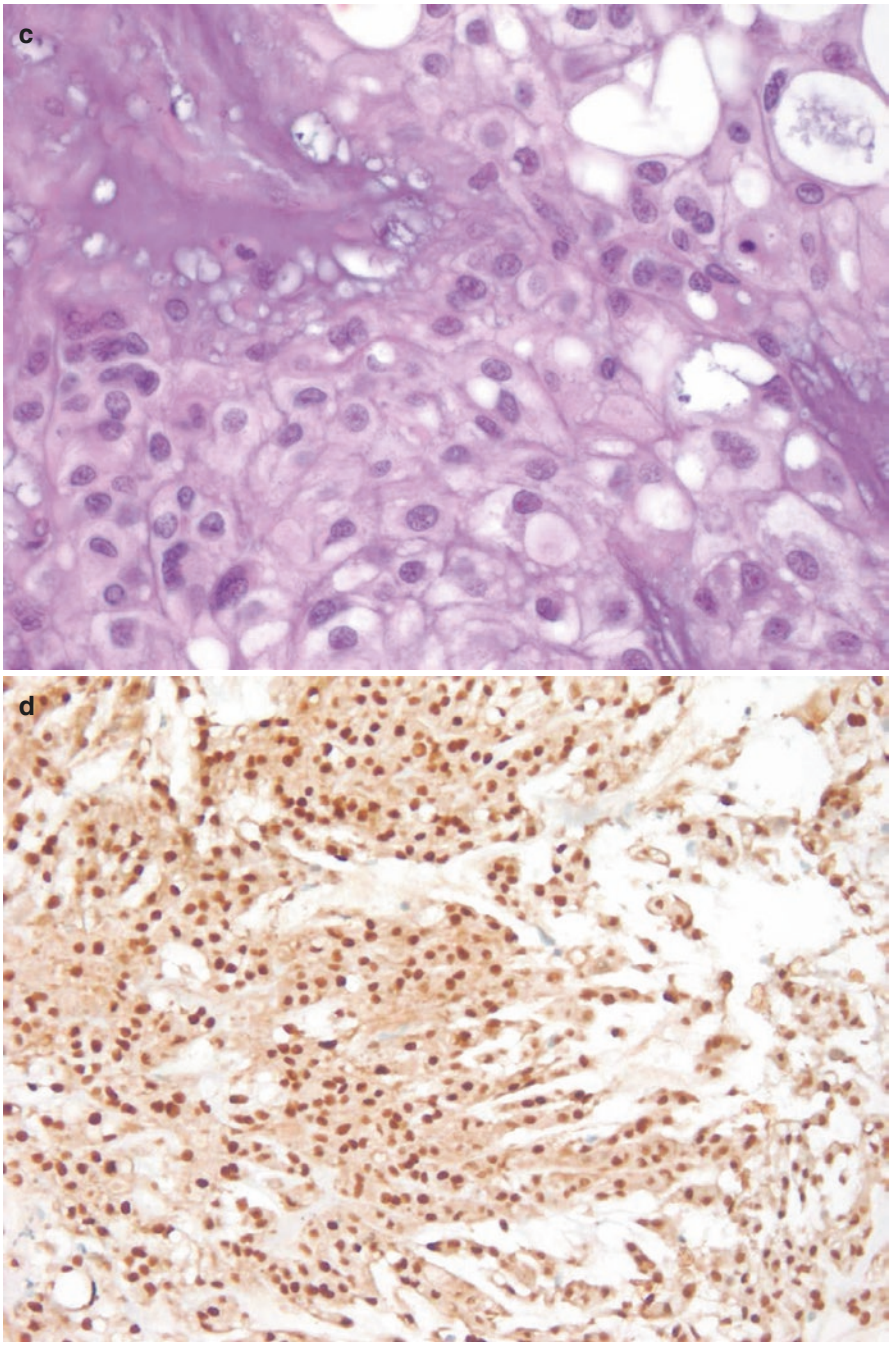


Fig. 7.2 (continued)

prefer to use non-decalcified specimen for brachyury testing to prevent false negativity. Other traditional helpful positive diagnostic immunohistochemical markers for chordoma include keratin, epithelial membrane antigen, and S-100 protein. New markers such as loss of PTEN and loss of INI-1 expression have recently been found in chordoma [7, 8]. Dedifferentiated chordoma is a high-grade and biphasic tumor which consists of a high-grade undifferentiated spindle cell sarcoma or osteosarcoma in association to chordoma, NOS [3]. Recognizing the conventional chordoma component is the key to this diagnosis because the dedifferentiated component does not express the diagnostic markers described here.

7.1.2 Chondrosarcoma

Chondrosarcoma is a locally aggressive malignant tumor that produces cartilaginous matrix [3]. There are four histological variants of chondrosarcoma: conventional, dedifferentiated, mesenchymal, and clear cell (Table 7.2). The histological grade is the single most important prognostic factor of conventional chondrosarcoma. Chondrosarcoma can be classified on the basis of its location in the bone. Central chondrosarcomas are located in the medullary cavity, peripheral chondrosarcomas arise from the surface of the bone, and periosteal (juxtacortical) chondrosarcomas arise from the surface of the bone and the periosteum [3]. According to its origin, a primary chondrosarcoma arises de novo, and secondary chondrosarcoma is a result of malignant transformation of an enchondroma (central) or osteochondroma (peripheral). All types can affect the pelvic bones, including the sacrum; however, peripheral secondary chondrosarcoma is seen more commonly in younger patients than in central primary chondrosarcoma, which predominantly affects patients more than 50 years of age [9]. The majority of the conventional and dedifferentiated chondrosarcomas exhibits somatic mutations of the *isocitrate dehydrogenase genes 1 and 2* (*IDH1 and IDH2*) [10]. However, this finding is absent in mesenchymal and clear cell chondrosarcoma indicating their different pathogenesis. The presence of (*IDH1 and IDH2*) mutation can be used to differentiate a chondroblastic

Table 7.2 Characteristics of histological variants of chondrosarcoma

Tumor type	Component	Prognosis
Conventional	Chondrosarcoma	Depends on grade
	Grade I	
	Grade II	
	Grade III	
Dedifferentiated	Low-grade conventional chondrosarcoma plus high-grade dedifferentiated sarcoma or osteosarcoma	Poor
Mesenchymal	Low-grade conventional chondrosarcoma plus poorly differentiated malignant small round cells	Poor
Clear cell	Clear cells or chondroblastoma-like cells	Depends on grade
	Note: Usually occurs in the ends of long bones; patients younger than conventional	

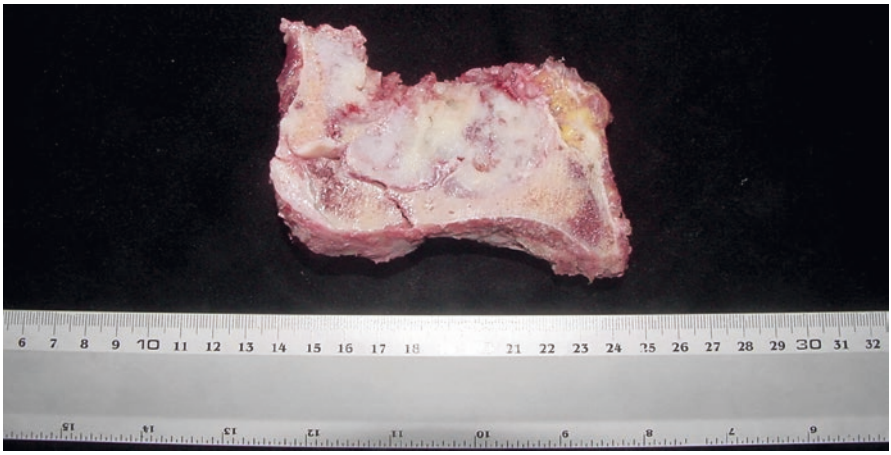


Fig. 7.3 Gross image of a sacral chondrosarcoma

osteosarcoma when it is deemed necessary. These molecular findings also warrant further investigation for their role as potential therapeutic targets [11].

As shown in Fig. 7.3, conventional chondrosarcomas grossly have the cut surface of hyaline cartilage with irregularly lobular appearance. Myxoid, cystic, and calcification changes can be seen. Microscopically, the distinction between enchondroma and grade I chondrosarcoma can be challenging due to overlapping morphological features. A generally accepted minimum diagnostic criteria for chondrosarcoma include hypercellularity, permeation of the host bone, absence of host bone encasement, open chromatin, mucoid matrix, and older patient (age >45 years) [3]. After establishing a diagnosis of chondrosarcoma, the next step is to grade the tumor using the following histological features: cellularity, nuclear size, degree of hyperchromasia, and mitoses. The grade I chondrosarcoma has similar nuclear features of enchondroma, except the architectural changes as described above. Grade III chondrosarcoma exhibits high cellularity, markedly enlarged nuclei, pleomorphic nuclei with nucleoli, and frequent mitoses compared to grade II chondrosarcoma. Tumor grade is the single most important prognostic factor of chondrosarcoma [9, 12]. When a chondrosarcoma has a spectrum of histology from grade I to grade III, it is a good practice to report the percentage of the high-grade component which predicts a worse prognosis. Figure 7.4 is the histological illustration of chondrosarcoma of various grades and dedifferentiated chondrosarcoma.

7.1.3 Ewing Sarcoma

Ewing sarcoma is a high-grade malignancy with small, round tumor cells harboring pathognomonic molecular signatures [3]. Approximately 85% of the Ewing sarcoma harbors a somatic chromosomal translocation t(11;22)(q24;q12) which rearrange *EWSR1* gene to fuse with *FLI1* gene [13]. The fusion protein EWSR1-FLI1 is an oncoprotein and is responsible for the pathogenesis of Ewing sarcoma [14, 15].

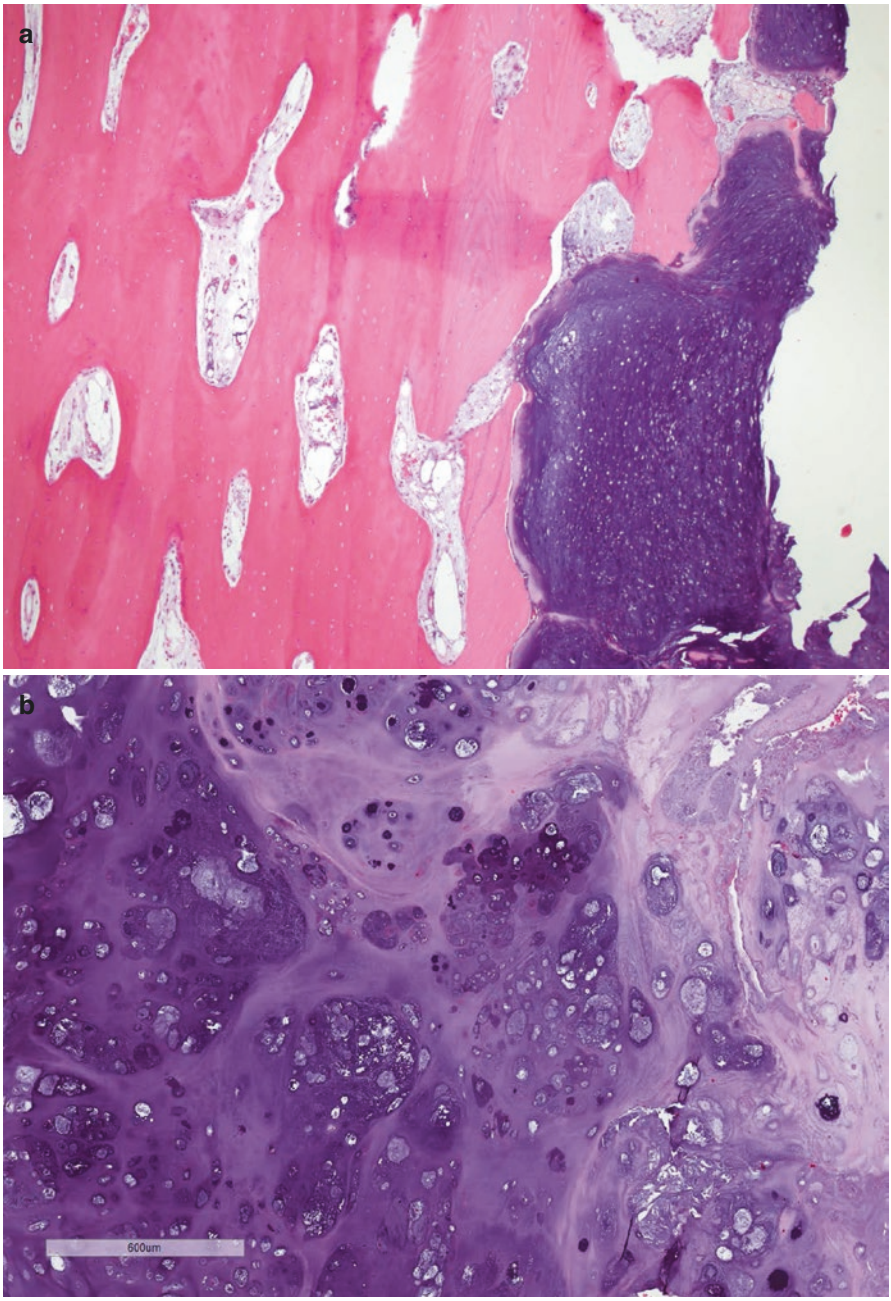


Fig. 7.4 Microscopic images of chondrosarcoma. (**a**) Chondrosarcoma invasion of bone. HE ×40. (**b**) Grade I chondrosarcoma. (**c**) Grade II. HE ×200. (**d**) Grade III. (**e**) Dedifferentiated chondrosarcoma. HE ×400

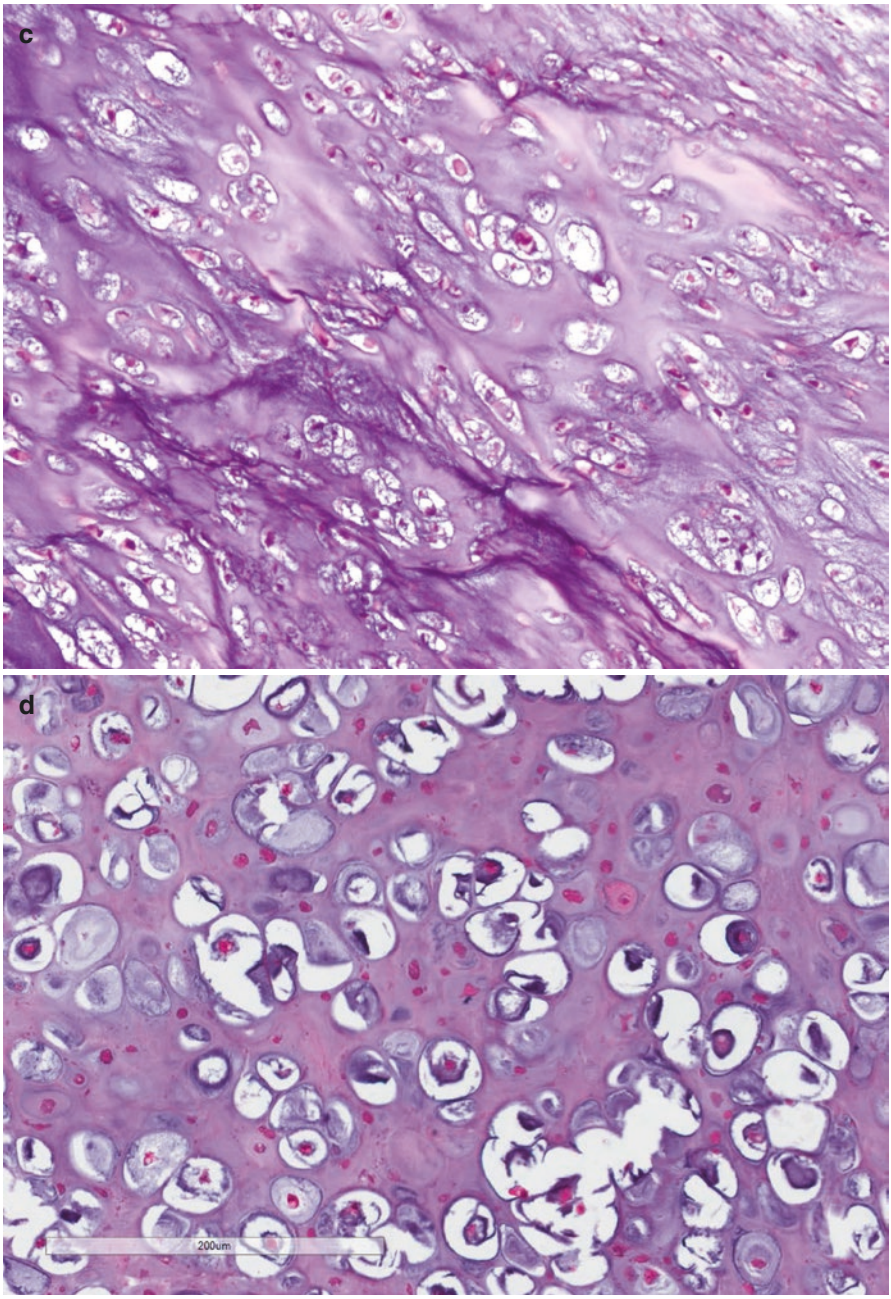


Fig. 7.4 (continued)

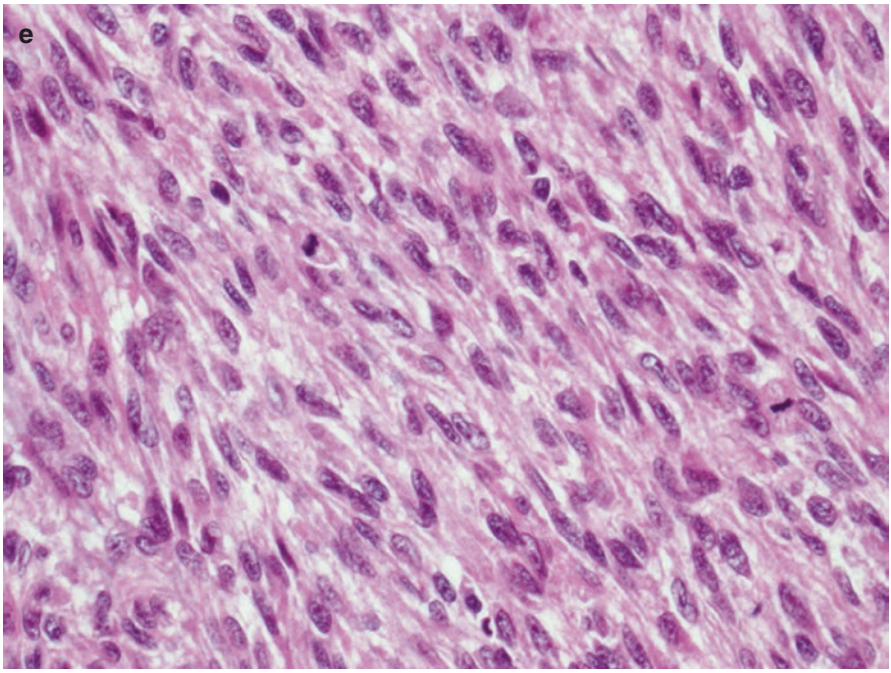


Fig. 7.4 (continued)

The *EWSR1* gene also has many other fusion partners such as the *ERG* gene [13]. Molecular testing for the signature gene and products are useful in confirming the diagnosis [16, 17]. While reverse transcription polymerase chain reaction (RT-PCR) may confirm the presence of *EWSR1-FLI1* or *EWSR1-ERG* fusion products, specific for Ewing sarcoma, the detection of rearrangement of *EWSR1* gene by fluorescence in situ hybridization (FISH) is not specific, because other sarcomas may harbor *EWSR1* gene rearrangements [3].

Primary Ewing sarcoma of the spine including sacrum is uncommon (only 3–10%); while metastatic disease from extraspinal Ewing sarcoma is more frequent. The sacral ala is the most common site for primary Ewing sarcoma of the spine [18, 19]. The prognosis is worse for sacrococcygeal Ewing sarcoma than for extraspinal Ewing sarcoma, usually due to larger tumor size at presentation because of delayed clinical presentation [20].

Grossly, the tumor has tan-grey cut surface with no bone or cartilaginous matrix. Necrosis and hemorrhage can be seen. In a classic Ewing sarcoma, the tumor is composed of small round cells with scant cytoplasm and round nuclei arranged in a vaguely lobular pattern or completely dyscohesive. This latter appearance resembles lymphoma. However, the cytoplasm of Ewing sarcoma appears clear and contains glycogen, which stains positively with periodic acid-Schiff (PAS). Ewing sarcoma also lacks the lymphoglandular bodies which represent cytoplasmic debris of lymphoma cells. In an atypical Ewing sarcoma, the tumor cells are larger with more pleomorphic nuclei and prominent nucleoli [3]. Neuroectodermal differentiation can be

seen with tumor cells forming rosette-like structures. Immunohistochemical stain pattern of Ewing sarcoma includes positive vimentin, CD99 (membranous staining pattern), Keratin (aberrantly expressed in 30% cases), neuroendocrine markers, FLI-1 and, rarely, ERG) [13, 21, 22]. A histological, immunohistochemical and molecular illustration of Ewing sarcoma is in Fig. 7.5.

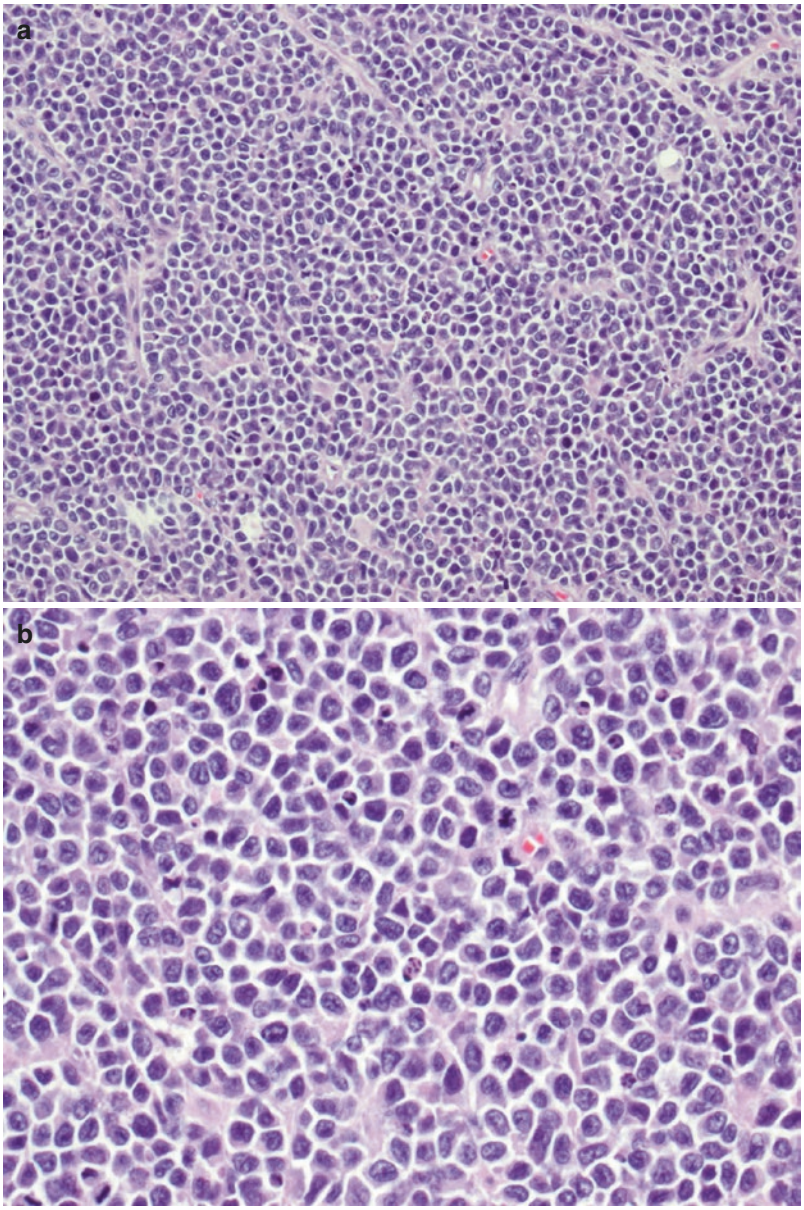


Fig. 7.5 Ewing sarcoma. (**a**) HE ×200. (**b**) HE ×400. (**c**) CD99+ ×400. (**d**) FLI1+ ×400. (**e**) FISH ×1000 showing LSI EWSR1 (22q12) break-apart probe showing EWSR1 rearrangement

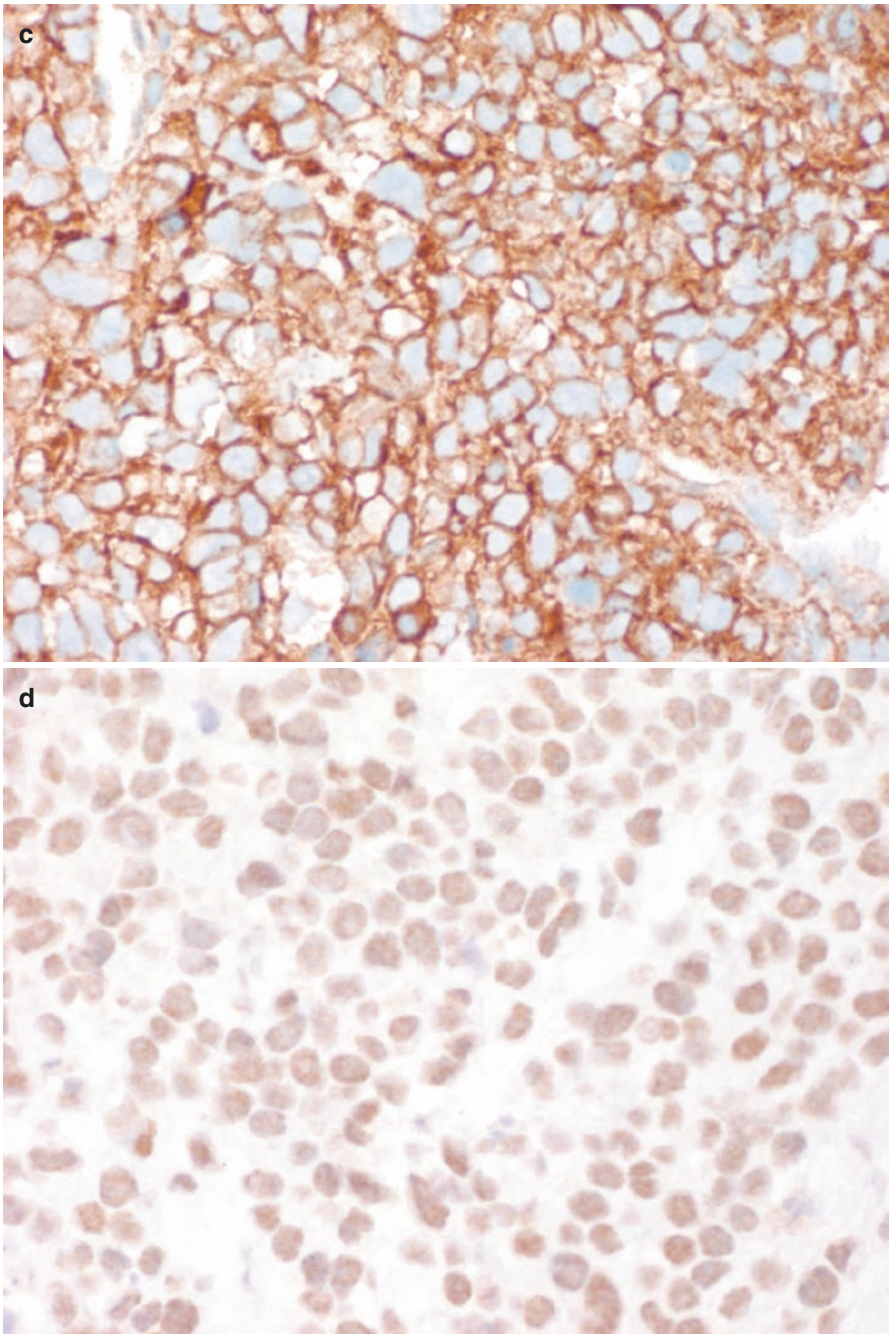


Fig. 7.5 (continued)

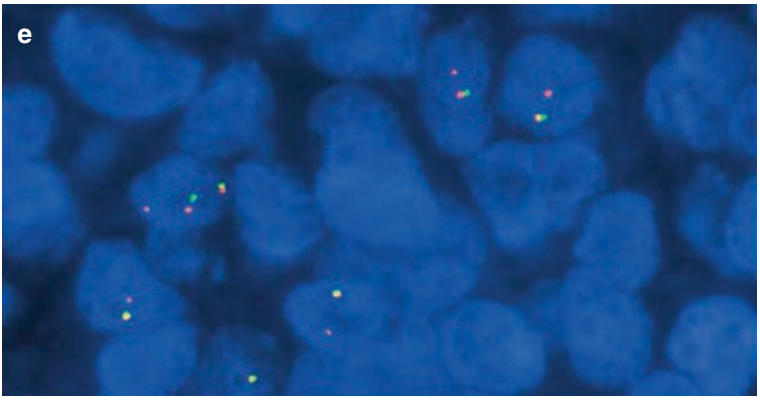


Fig. 7.5 (continued)

Table 7.3 Characteristics of histological variants of primary central osteosarcoma

Tumor type	Component	Prognosis
Conventional	High-grade sarcoma with osteoid formation	High-grade tumor. Subtype does not differ in prognosis and therapy
	Osteoblastic (76–80%) (Fig. 7.6a)	
	Chondroblastic (10–13%) (Fig. 7.6b)	
	Fibroblastic (10%)	
Telangiectatic	High-grade osteosarcoma with characteristic blood lakes and spaces	Similar to conventional type
Giant cell rich	High-grade osteosarcoma with abundant osteoclast-like giant cells (Fig. 7.6c)	Similar to conventional type
Small cell	High-grade osteosarcoma with characteristic small tumor cells (Fig. 7.6d)	Slightly worse prognosis than conventional type
Low-grade central	Low-grade osteosarcoma	Excellent prognosis
	Note: Distinguish from fibrous dysplasia by permeation of the host bone and soft tissue extension; amplification of *MDM2* gene	

7.1.4 Osteosarcoma

Patients with primary lumbosacral osteosarcoma are older at presentation and commonly males [20]. Secondary sacral osteosarcoma occurs in patients with previous radiation treatment or a history of Paget's disease. Elderly patients with polyostotic Paget's disease are most at risk for sarcomatous degeneration [2].

According to its location in the bone, central osteosarcoma is located in the medullary cavity, and peripheral osteosarcoma arises from the surface of the bone [23]. The characteristic of primary central osteosarcoma and surface osteosarcoma are summarized in Tables 7.3 and 7.4. Surface/peripheral osteosarcoma very rarely affects the flat bone.

Table 7.4 Characteristics of histological variants of primary peripheral osteosarcoma

Tumor type	Component	Prognosis
Parosteal (Juxtacortical osteosarcoma)	Low-grade	Excellent
	Spindle cells with mild to moderate atypia, well-formed bone trabeculae arranged in parallel pattern, and associated benign cartilaginous differentiation	
	Note: Amplification of *MDM2* gene	
Periosteal (Juxtacortical chondroblastic osteosarcoma)	Intermediate-grade	Better prognosis than conventional osteosarcoma
	Predominantly atypical cartilage admixed with intermediate-grade osteosarcoma	
High-grade surface osteosarcoma	High-grade osteosarcoma of the surface	Similar to conventional type
	Note: The tumor is predominantly outside the bone; similar variants seen in conventional osteosarcoma	

High-grade osteosarcoma is treated with neoadjuvant chemotherapy. The pathological evaluation of the therapy response is critically important for assessment of prognosis. Osteosarcomas with more than 90% tumor necrosis (less than 10% viable tumor cells) are considered good responders and have better overall and disease-free survival [24]. A generally accepted method of sampling osteosarcoma includes cross-sectioning the central and largest slice of the tumor. The slice is further divided into 1 cm × 1 cm slices and prepared for microscopic examination. Therapy-induced changes include tumor necrosis, pleomorphic changes, cystic changes, fibrosis, etc. However, only the percentage of tumor necrosis characterized by pyknotic, fragmented, or lysed tumor nuclei, which is reversely related to the percentage of viable tumor cells, is accepted as an independent prognostic factor [25].

7.1.5 Undifferentiated Pleomorphic Sarcoma

Undifferentiated pleomorphic sarcoma (UPS) is a group of high-grade tumors that have no identifiable line of differentiation when analyzed by current technologies, and therefore represents a diagnosis of exclusion. Figure 7.7 shows a gross image of a sacral undifferentiated sarcoma. UPS histology is variable and may show several morphologic patterns from storiform areas composed of spindle cells to areas composed of large, pleomorphic neoplastic cells with marked nuclear atypia [3, 26]. Mitotic activity is prominent with atypical mitotic figures.

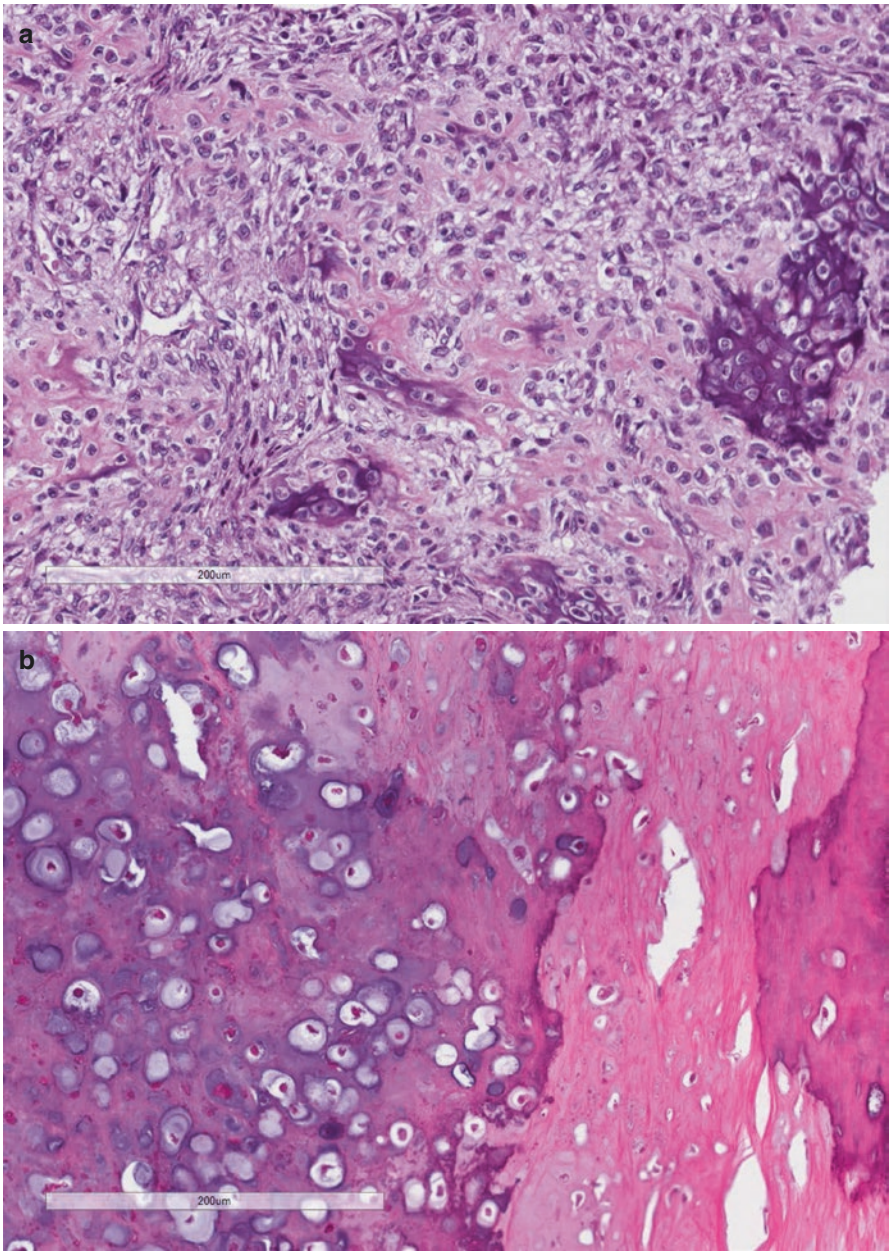


Fig. 7.6 Osteosarcoma. (**a**) Osteoblastic osteosarcoma. (**b**) Chondroblastic osteosarcoma. (**c**) Giant cell rich osteosarcoma. (**d**) Small cell osteosarcoma

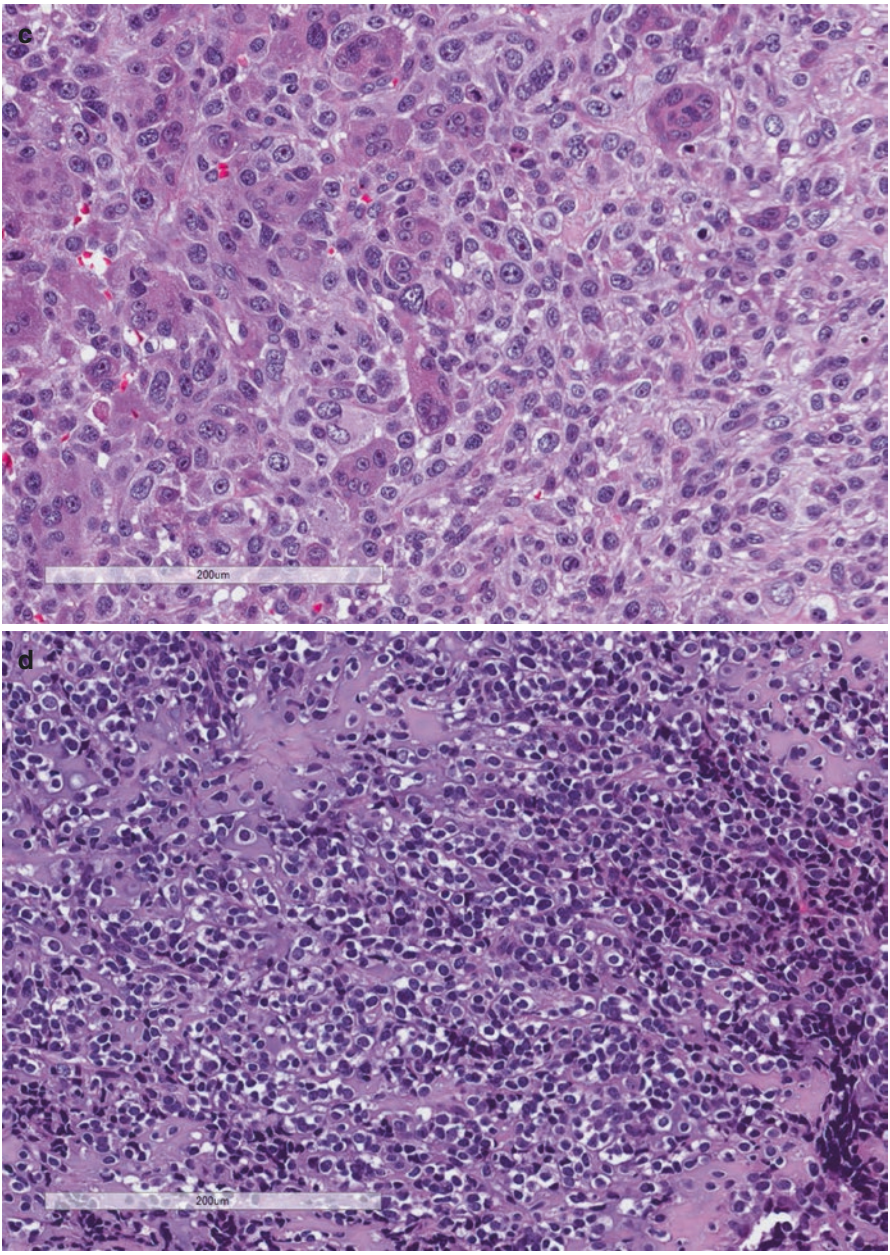


Fig. 7.6 (continued)

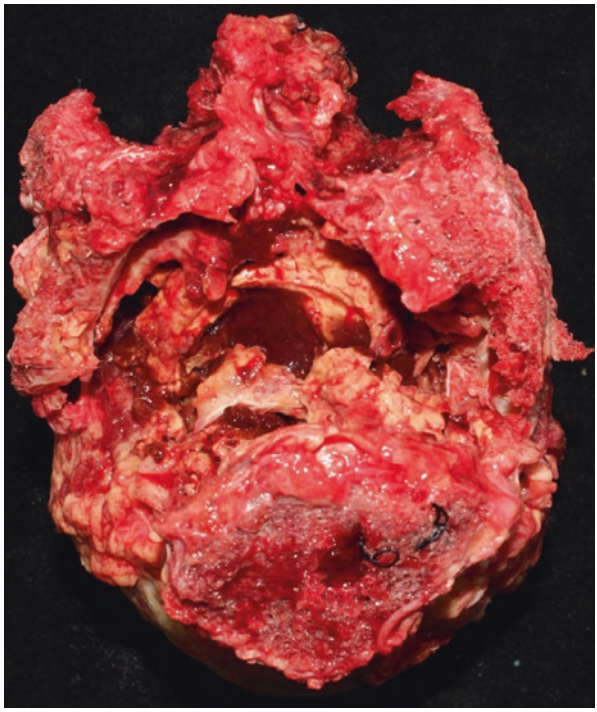


Fig. 7.7 A gross image of undifferentiated sarcoma

7.1.6 Metastatic/Systemic Malignancy

Metastatic disease from epithelial malignancies is the most common secondary malignancy of the sacrum [2]. The primary sites include lung, breast, prostate, kidney, head and neck, and gastrointestinal tract. Melanoma is also a common culprit of metastasis [27]. The most common hematopoietic malignancies of the sacrum are non-Hodgkin lymphoma and multiple myeloma or plasmacytoma. These diseases may be either primary of bone or secondary involvement of the bone in disseminated disease. Our institutional review of primary bone lymphoma (PBL) consisted of 70 patients [28, 29]. PBL cases were included in this cohort using the 2013 WHO criteria for bone/soft tissue tumors [3], as disease was restricted to bone and adjacent soft tissue with or without regional nodes at the time of the diagnosis. Bone lymphoma with distant bone marrow involvement as the only other site of extranodal disease was also included. We found that PBL occurs in sacrum less frequently than extremities, but diffuse large B-cell lymphoma is the most common variant of lymphoma.

When a primary tumor is present, the diagnosis of metastatic disease is achieved by comparing the histology of sacral lesion with the primary disease. However, when a primary site unknown histomorphology in conjunction with pertinent ancillary testing including immunohistochemistry, flow cytometry and molecular testing are used to render a definitive diagnosis.

7.1.7 Rare Primary Sacral Sarcomas

The following malignant tumors have occasionally been reported occurring in sacrum [3, 30–32] (see Table 7.5).

7.2 Benign Tumors

7.2.1 Giant Cell Tumor of Bone

Giant cell tumor of bone (GCTB) is a benign but locally aggressive tumor. The tumor is composed of numerous characteristic giant cells which are large and osteoclast-like. These cells are impressive morphologically; however, they are the background cells reactive to the true neoplastic cells which are primitive mesenchymal stromal cells. The neoplastic cells are mononuclear and express receptor activator for NF-κB ligand (RANKL), the master regulator of osteoclast differentiation. Macrophages and osteoclasts express RANK. The interaction between the

Table 7.5 Rare primary sarcomas of sacrum

Tumor type	Definition	Histology and immunophenotype	Prognosis
Undifferentiated/ unclassified sarcoma	High-grade malignancy showing no identifiable specific lineage of differentiation	Pleomorphic, spindle cell, round cell, epithelial cell	Limited data
		No consistent finding	
Angiosarcoma	Aggressive malignancy with endothelial differentiation	Epithelial, spindle	Poor prognosis associated with high grade, presence of macronucleolus, older age, large size, increased mitoses, and high Ki-67 index
		Express vascular markers (CD34, CD31, ERG, and FLI1)	
Fibrosarcoma	Intermediate- to High-grade fibroblastic spindle cell malignancy	Less pleomorphic than undifferentiated pleomorphic sarcoma	Depend on age, tumor site, grade, and stage
		Rare report of slerosing epithelioid fibrosarcoma	
		No consistent finding	
Malignant solitary fibrous tumor	Malignant variant of solitary fibrous tumor	Large tumor size, infiltrative margin, hypercellularity, nuclear pleomorphism, tumor necrosis, and high mitotic activity (>4/10 HPF)	Depend on age, tumor site, grade, and stage
		Express STAT6 (nuclear), CD34, CD99, and Bcl-2	

neoplastic mononuclear stromal cells and macrophages/osteoclasts by a RANKL-dependent mechanism via the stimulation of macrophage-colony stimulation factor (MCSF) results in neoplastic proliferation and induces osteoclast formation. During this process, tumor-associated macrophage-like osteoclast precursors, which are also mononuclear cells, are recruited by tumoral stromal cells to participate in osteoclast differentiation and activation. Because osteoclast formation is the major consequence of GCTB, inhibition of osteoclast formation and activity is the key therapeutic approach. For example, bisphosphonate inhibits osteoclast-mediated resorption of bone/osteolysis and anti-RANKL antibody targets the RANKL-dependent mechanism of GCTB formation.

Osteoprotegerin (OPG) is a soluble decoy receptor that is produced by osteoblasts to inhibit osteoclast differentiation through its binding to RANKL, which prevents RANK binding. OPG expression reflects a protective mechanism of the skeleton to compensate increased bone resorption. Bone remodeling is mainly controlled by the balance of RANKL/OPG. Osteoprotegerin ligand (OPGL), also named receptor activator of RANKL, is also expressed in the stroma-like tumor cells of GCTB. The ratio of OPGL/OPG by tumor cells may contribute to the degree of osteoclastogenesis and bone resorption [33].

Although giant cell tumors of the bone (GCTB) within the vertebrae are rare (2.7–6.5% of all GCTB), the sacrum may be the most common spinal site for this lesion [34–36]. In a collaborative study with Beijing Jishuitan Hospital, we found that GCTB has significant higher incidences than the Mayo Clinic group [37]. JST group also published an article described two GCTBs of sacrum with pulmonary metastasis [38].

Grossly, the tumor is red-brown with hemorrhage (Fig. 7.8). Yellow areas reflect lipid laden macrophage rich areas. Histologically (Fig. 7.9) the tumor is composed of numerous giant cells with multinucleation and scattered mononuclear cells that are round or spindle. Lipid laden or hemosiderin laden macrophages are also

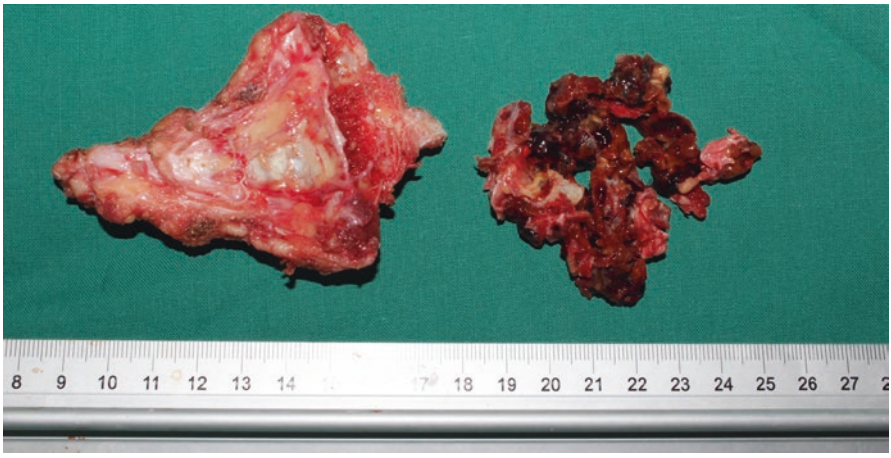


Fig. 7.8 A gross image of a sacral giant cell tumor

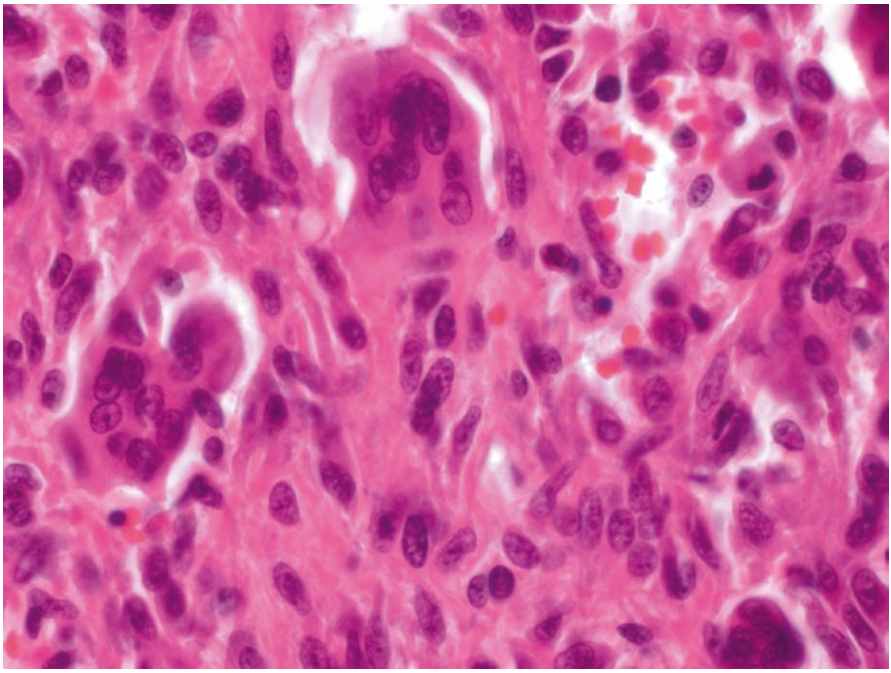


Fig. 7.9 Microscopic images of giant cell tumor

present. The tumor is mainly solid and may contain cystic areas. Secondary aneurysmal bone cyst component is seen in 10% of GCTB. The tumor may be mitotically active; however, a benign giant cell tumor typically does not have atypical mitosis or significant nuclear atypia. The latter is associated with a malignant transformation of GCTB. One diagnostic pitfall is to avoid misdiagnosing an osteosarcoma when a pathological fracture is in association with a malignant giant cell tumor.

7.2.2 Benign Neurogenic Tumor

Benign neurogenic tumors occur in paraspinal or presacral locations. Sacral schwannomas or neurofibromas grow within the sacral canal and only rarely expand through the anterior sacral foramina into the presacral space [39]. Schwannoma (Fig. 7.10) consists of well-differentiated Schwann cells, is usually encapsulated and cut surfaces have a pink, white, or yellow appearance. Classic histology (Fig. 7.11a, b) shows a pattern of alternating Antoni A (cellular areas of spindle cells with occasional palisading) and Antoni B (loose myxoid areas with scattered spindle cells and thick-walled, hyalinized vessels) areas. Degenerative changes such as cyst formation, calcification, hemorrhage, and hyalinization may be present,

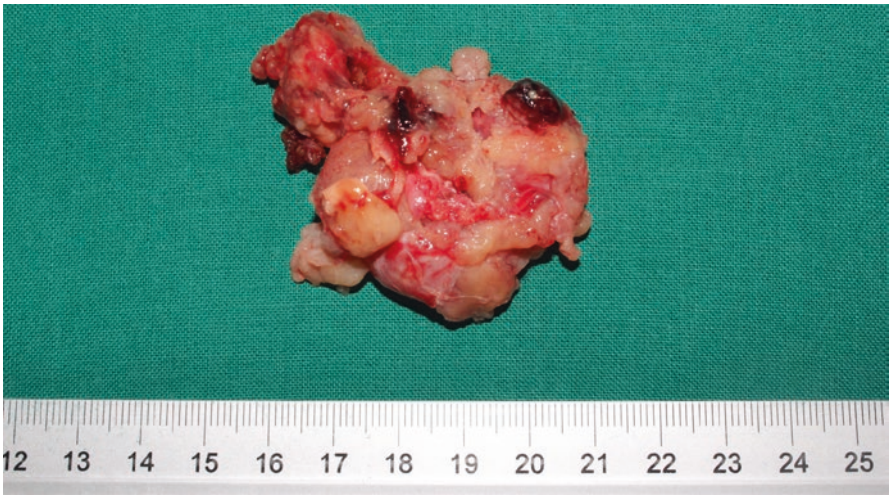


Fig. 7.10 A gross image of a sacral schwannoma

especially if the tumor has been there for a long duration. Ancient schwannoma is characterized by Schwann cells with large and hyperchromatic nuclei, the manifestation of degenerative change. Schwannomas with increased cellularity and occasional mitoses are referred to as cellular schwannomas, a variant of schwannoma. These variants of schwannoma behave similar to conventional schwannomas. Immunohistochemically, schwannomas express strongly and diffusely S-100 protein as well as SOX10, a new marker of neural crest differentiation [40]. Neurofibroma, originating from sacral nerve roots, is composed of Schwann cells, perineurial-like cells, fibroblasts, and axons and are associated with a myxoid or fibrous stroma.

Malignant transformation can occur, often seen in the setting of neurofibromatosis type 1. Differentiation of benign and malignant neoplasms can be difficult, but increased size, rapid growth, infiltrative border, necrosis, increased cellularity, and increased mitotic activity with atypical mitosis favor malignancy. Cellular schwannoma can be misdiagnosed as malignant peripheral nerve sheath tumor (MPNST) (Fig. 7.11c). Morphologic features distinguishing cellular schwannoma from MPNST are the presence of perivascular accentuation of cellularity, tumor herniation into vascular lumens, presence of necrosis, and loss of expression of H3K27me [41].

Other rare neurogenic tumors include sacral ependymomas that arise from ependymal cells of the terminal filum, expand the sacral canal, and are usually of the myxopapillary type. Sacral meningiomas are even more rare than sacral ependymomas and schwannomas and arise within the sacral canal. Neuroblastoma is derived from embryonic neural crest tissue and clinically manifests in infancy. Ganglioneuroma is originated from sympathetic ganglion cells [39]. Ependymomas and meningioma have both benign and malignant variants.

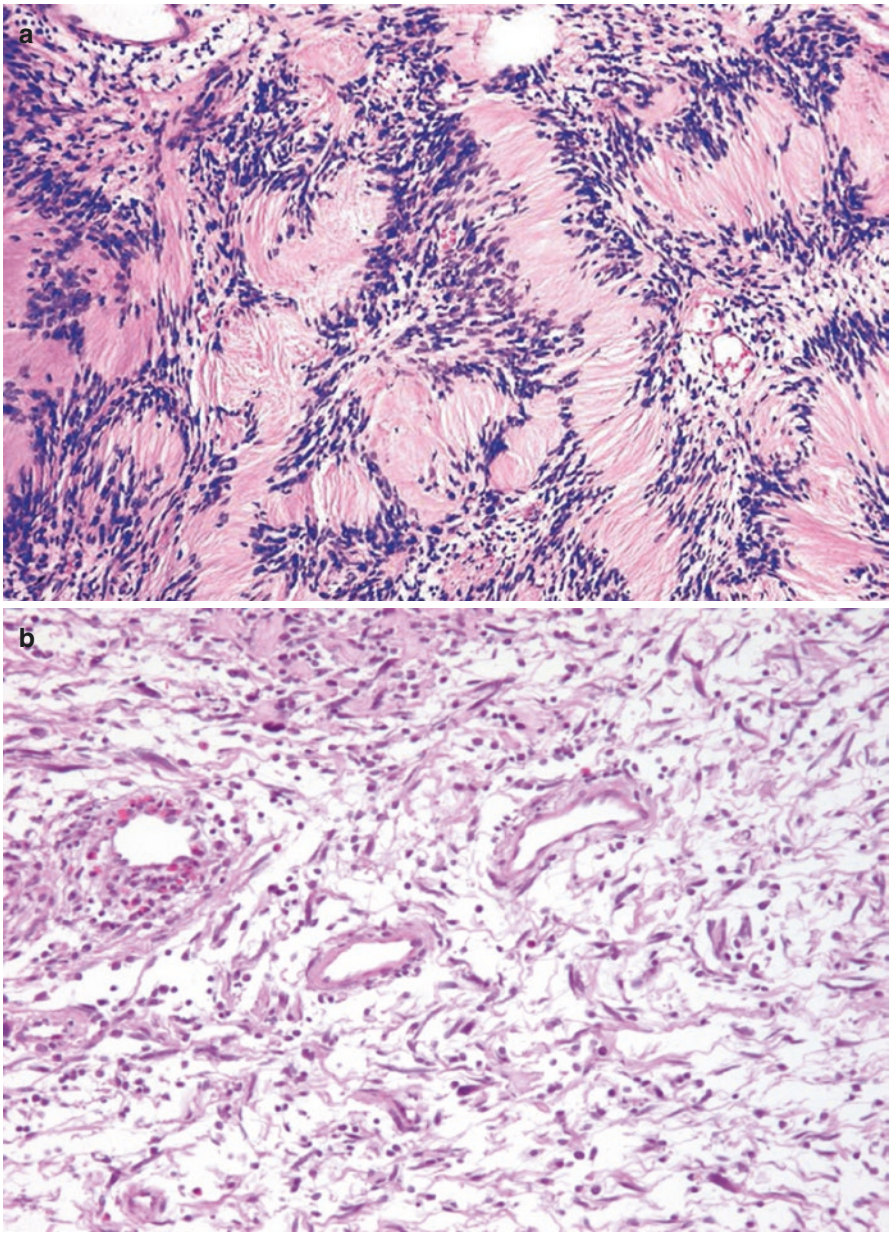
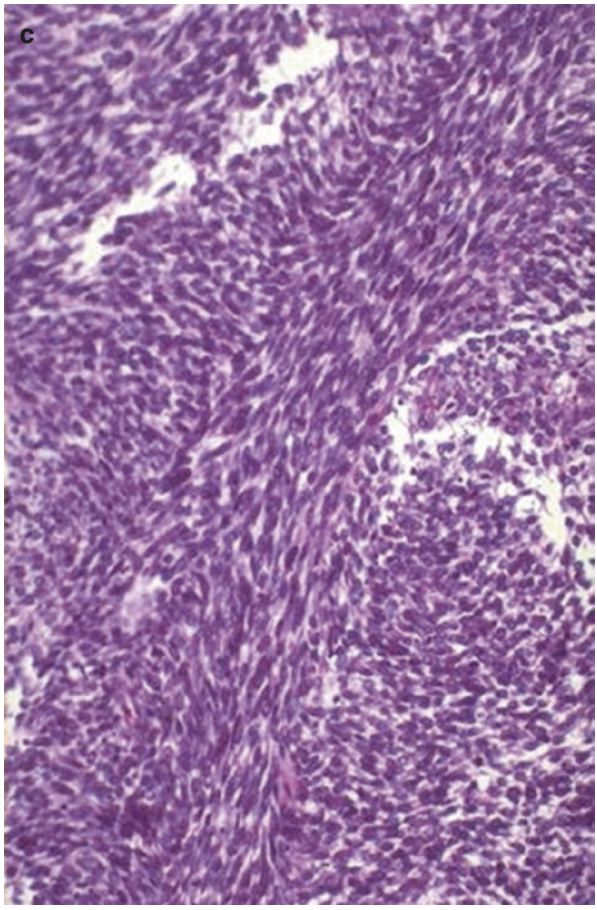


Fig. 7.11 Microscopic images of neurogenic tumors. (**a**) Schwannoma ×200 Antoni A. (**b**) Schwannoma ×200 Antoni B. (**c**) Malignant peripheral nerve sheath tumor

Fig. 7.11 (continued)



7.2.3 Aneurysmal Bone Cyst

Aneurysmal bone cyst (ABC) is a benign tumor. Grossly it is well defined and composed of blood-filled pseudocystic spaces. The cysts lack specific cell-lining and consist of a wall of spindle cells with scattered osteoclast-type multinucleated giant cells. The neoplastic cells are spindle shaped and indistinguishable from reactive fibroblasts and myofibroblasts. However, the tumor cells show *USP6* rearrangement in 70% of ABC [42]. The spindle cells are bland. Mitoses may be frequent without atypical forms. Reactive woven bone may be seen with osteoblastic rimming.

7.2.4 Other Rare Benign Primary Intraosseous Sacral Lesions

Although the true incidence has not been established, the lesions listed here (Table 7.6) rarely occur in sacrum. The diagnosis is mainly based by histologic examination with clinicoradiological correlations. Ancillary testing is not widely used for diagnosis. The ancillary testing described in Table 7.6 are mostly for academic interest except for fibrous dysplasia and Langerhans cell histiocytosis.

7.2.5 Sacrococcygeal Teratoma

Sacrococcygeal teratoma is a germ cell tumor and the most common sacral tumor in neonates, although it is very rare in adults [39]. These tumors are composed of multiple tissues foreign to the tissue in which they arise, which usually include skin, teeth, central nervous system tissue, and respiratory and alimentary mucosa. Mature teratoma (dermoid cyst) is benign and most common. Struma ovarii is a rare form of mature teratoma that contains mostly benign thyroid tissue. Immature teratoma is

Table 7.6 Rare benign primary intraosseous sacral lesions

Name	Nature	Histology	Ancillary testing for diagnosis
Chondroblastoma	Neoplastic	Round to polygonal chondroblasts with round to ovoid nucleus exhibit longitudinal grooves and well-defined cytoplasmic borders. Well. "Chicken wire" calcifications and multinucleated osteoclast-like giant cells are seen	S-100 protein and SOX9 expression by IHC
Chondromyxoid fibroma	Neoplastic	A lobular pattern with cellular stellate or spindle cells at the periphery and less cellular center with myxoid or chondromyxoid matrix. Multinucleated osteoclast-like giant cells, hyaline cartilage and calcification are seen	S-100 protein and SOX9 expression by IHC
Osteochondroma	Neoplastic	Perichondrium, cartilage, and bone	None
Osteoid osteoma	Neoplastic	Nidus consisting of a combination of osteoid and woven bone surrounded by osteoblasts. The nidus is vascular rich with the appearance of granulation tissue. The nidus is surrounded by sclerotic bone	Runx2 and Osterix
Osteoblastoma	Neoplastic	Similar features as seen in osteoid osteoma	None
Fibrous dysplasia	Neoplastic	Bland spindle fibroblastic cells admixed with irregular bony spicules without osteoblastic rimming	*GNAS* mutation

Table 7.6 (continued)

Name	Nature	Histology	Ancillary testing for diagnosis
Langerhans cell histocytosis/ eosinophilic granuloma	Likely neoplastic	Langerhans cells are specialized histiocytes with nuclear grooves (reniform nuclei), which are admixed with inflammatory cells including prominent eosinophilia	CD1a, CD207/ Langerin, and CD45 expression by IHC
Paget disease	Nonneoplastic metabolic disorder of bone remodeling susceptible to deformities and fractures; increased risk to primary bone malignancy	Increase in osteoclastic resorption and secondary bone formation resulting in a disorganized and fragile lamellar bone mosaic pattern	None
	Monostotic or polyostotic		
Simple bone cyst	Nonneoplastic	Unilocular cysts of bone with a fibrous membrane lining. The cyst contains serous or serosanguineous fluid	None

uncommon which differs from mature teratoma by the presence of immature tissue and exhibits malignant clinical behavior.

7.2.6 Developmental Lesions

Sacral meningocele is a cerebrospinal fluid-filled protrusion of the meninges through a defect in the sacrum [39]. Benign sacral meningeal cysts are frequent coincidental findings in the radiological examination of the sacrum, and their pathogenesis is poorly understood.

7.2.7 Intraoperative Pathologic Evaluation of Bone and Soft Tissue Lesions

Intraoperative pathologic diagnosis of bone and soft tissue lesions is an important yet challenging tool in clinical musculoskeletal oncology practice. Indications for frozen section include making a diagnosis, evaluating margin status, determining tumor extent/spread, and obtaining an adequate sample for permanent section and diagnosis. Frozen section pathological evaluation provides real-time guidance to

therapeutic intervention. In our practice, intraoperative cytology is used as an adjunct to frozen section. This approach has proven useful to enhance the accuracy of diagnosing bone and soft tissue lesion [43, 44], including sacral lesions.

References

1. Xu H, Seifert RP, Niu X, Li Y, Bui MM. The establishment and utility of a free online database of primary bone tumors. Pathol Oncol Res. 2016;22(1):129–33. PubMed PMID: 26377426.
2. Thornton E, Krajewski KM, O'Regan KN, Giardino AA, Jagannathan JP, Ramaiya N. Imaging features of primary and secondary malignant tumours of the sacrum. Br J Radiol. 2012;85(1011):279–86. PubMed PMID: 22167504. Pubmed Central PMCID: PMC3473982.
3. Fletcher CDM, World Health Organization, International Agency for Research on Cancer. WHO classification of tumours of soft tissue and bone. 4th ed. Lyon: IARC Press; 2013. p. 468.
4. Diel J, Ortiz O, Losada RA, Price DB, Hayt MW, Katz DS. The sacrum: pathologic spectrum, multimodality imaging, and subspecialty approach. Radiographics. 2001;21(1):83–104. PubMed PMID: 11158646.
5. Ha AS, Chew FS. Imaging of sacral masses: self-assessment module. AJR Am J Roentgenol. 2010;195(3 Suppl):S32–6. PubMed PMID: 20729410.
6. Vujovic S, Henderson S, Presneau N, Odell E, Jacques TS, Tirabosco R, et al. Brachyury, a crucial regulator of notochordal development, is a novel biomarker for chordomas. J Pathol. 2006;209(2):157–65. PubMed PMID: 16538613.
7. Chen K, Mo J, Zhou M, Wang G, Wu G, Chen H, et al. Expression of PTEN and mTOR in sacral chordoma and association with poor prognosis. Med Oncol. 2014;31(4):886. PubMed PMID: 24535608
8. Mobley BC, McKenney JK, Bangs CD, Callahan K, Yeom KW, Schneppenheim R, et al. Loss of SMARCB1/INI1 expression in poorly differentiated chordomas. Acta Neuropathol. 2010;120(6):745–53. PubMed PMID: 21057957.
9. 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. PubMed PMID: 18378543.
10. 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. PubMed PMID: 21598255.
11. 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. PubMed PMID: 21753790. Pubmed Central PMCID: PMC3361898.
12. 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. PubMed PMID: 890662.
13. Henderson-Jackson EB, Bui MM. Molecular pathology of soft-tissue neoplasms and its role in clinical practice. Cancer Control. 2015;22(2):186–92. PubMed PMID: 26068763.
14. Surdez D, Benetkiewicz M, Perrin V, Han ZY, Pierron G, Ballet S, et al. Targeting the EWSR1-FLI1 oncogene-induced protein kinase PKC-beta abolishes Ewing sarcoma growth. Cancer Res. 2012;72(17):4494–503. PubMed PMID: 22930730.
15. Delattre O, Zucman J, Plougastel B, Desmaze C, Melot T, Peter M, et al. Gene fusion with an ETS DNA-binding domain caused by chromosome translocation in human tumours. Nature. 1992;359(6391):162–5. PubMed PMID: 1522903.
16. Coppola D. Mechanisms of oncogenesis: an update on tumorigenesis. Dordrecht: Springer; 2010. xii, 314p.
17. Coppola D. Molecular pathology and diagnostics of cancer. New York: Springer; 2013.

18. Llauger J, Palmer J, Amores S, Bague S, Camins A. Primary tumors of the sacrum: diagnostic imaging. AJR Am J Roentgenol. 2000;174(2):417–24. PubMed PMID: 10658718.
19. Rodallec MH, Feydy A, Larousserie F, Anract P, Campagna R, Babinet A, et al. Diagnostic imaging of solitary tumors of the spine: what to do and say. Radiographics. 2008;28(4):1019–41. PubMed PMID: 18635627.
20. Murphey MD, Andrews CL, Flemming DJ, Temple HT, Smith WS, Smirniotopoulos JG. From the archives of the AFIP. Primary tumors of the spine: radiologic pathologic correlation. Radiographics. 1996;16(5):1131–58. PubMed PMID: 8888395.
21. Olsen SH, Thomas DG, Lucas DR. Cluster analysis of immunohistochemical profiles in synovial sarcoma, malignant peripheral nerve sheath tumor, and Ewing sarcoma. Mod Pathol. 2006;19(5):659–68. PubMed PMID: 16528378.
22. Rossi S, Orvieto E, Furlanetto A, Laurino L, Ninfo V, Dei Tos AP. Utility of the immunohistochemical detection of FLI-1 expression in round cell and vascular neoplasm using a monoclonal antibody. Mod Pathol. 2004;17(5):547–52. PubMed PMID: 15001993.
23. Dodd L, Bui MM. Atlas of soft tissue and bone pathology: with histologic, cytologic, and radiologic correlations. New York: Demos Medical; 2015. viii, 419p.
24. Anninga JK, Gelderblom H, Fiocco M, Kroep JR, Taminiau AH, Hogendoorn PC, et al. Chemotherapeutic adjuvant treatment for osteosarcoma: where do we stand? Eur J Cancer. 2011;47(16):2431–45. PubMed PMID: 21703851.
25. Czerniak B, Dorfman HD. Dorfman and Czerniak's bone tumors. 2nd ed. Philadelphia: Elsevier; 2016.
26. Goldblum JR, Folpe AL, Weiss SW, Enzinger FM, Weiss SW. Enzinger and Weiss's soft tissue tumors. 6th ed. Philadelphia: Saunders/Elsevier; 2014. xiv, 1155p.
27. Disler DG, Miklic D. Imaging findings in tumors of the sacrum. AJR Am J Roentgenol. 1999;173(6):1699–706. PubMed PMID: 10584822.
28. Wu H, Zhang L, Shao H, Sokol L, Sotomayor E, Letson D, et al. Prognostic significance of soft tissue extension, International Prognostic Index, and multifocality in primary bone lymphoma: a single institutional experience. Br J Haematol. 2014;166(1):60–8. PubMed PMID: 24673481.
29. Wu H, Bui MM, Leston DG, Shao H, Sokol L, Sotomayor EM, et al. Clinical characteristics and prognostic factors of bone lymphomas: focus on the clinical significance of multifocal bone involvement by primary bone large B-cell lymphomas. BMC Cancer. 2014;14:900. PubMed PMID: 25465716. Pubmed Central PMCID: PMC4265495.
30. Nakamura M, Tsushima K, Yasuo M, Yamazaki Y, Honda T, Koizumi T, et al. Angiosarcoma with sacral origin metastasizing to the lung. Intern Med. 2006;45(15):923–6. PubMed PMID: 16946576.
31. Chow LT, Lui YH, Kumta SM, Allen PW. Primary sclerosing epithelioid fibrosarcoma of the sacrum: a case report and review of the literature. J Clin Pathol. 2004;57(1):90–4. PubMed PMID: 14693846. Pubmed Central PMCID: PMC1770169.
32. Dv R, Dm K, Vanel D, Campanacci L, Iv B, Ag T, et al. Malignant solitary fibrous tumor of the sacrum: a case report. J Cancer Res Ther. 2015;3(4):52–5. English.
33. Huang L, Xu J, Wood DJ, Zheng MH. Gene expression of osteoprotegerin ligand, osteoprotegerin, and receptor activator of NF-kappaB in giant cell tumor of bone: possible involvement in tumor cell-induced osteoclast-like cell formation. Am J Pathol. 2000;156(3):761–7. PubMed PMID: 10702390. Pubmed Central PMCID: PMC1876848.
34. Shimada Y, Hongo M, Miyakoshi N, Kasukawa Y, Ando S, Itoi E, et al. Giant cell tumor of fifth lumbar vertebrae: two case reports and review of the literature. Spine J. 2007;7(4):499–505. PubMed PMID: 17630149.
35. Bidwell JK, Young JW, Khalluff E. Giant cell tumor of the spine: computed tomography appearance and review of the literature. J Comput Tomogr. 1987;11(3):307–11. PubMed PMID: 3608560.
36. Randall RL. Giant cell tumor of the sacrum. Neurosurg Focus. 2003;15(2):E13. PubMed PMID: 15350044.

37. Niu X, Xu H, Inwards CY, Li Y, Ding Y, Letson GD, et al. Primary bone tumors: epidemiologic comparison of 9200 patients treated at Beijing Ji Shui Tan Hospital, Beijing, China, with 10 165 patients at Mayo Clinic, Rochester, Minnesota. Arch Pathol Lab Med. 2015;139(9):1149–55. PubMed PMID: 25978765.
38. Muheremu A, Huang Z, Niu X. Treatment for giant cell tumor of the spine metastasizing to the lung: A report of two cases and a literature review. Oncol Lett. 2015;9(3):1321–6. PubMed PMID: PMC4315077.
39. Payer M. Neurological manifestation of sacral tumors. Neurosurg Focus. 2003;15(2):E1. PubMed PMID: 15350032.
40. Nonaka D, Chiriboga L, Rubin BP. Sox10: a pan-schwannian and melanocytic marker. Am J Surg Pathol. 2008;32(9):1291–8. PubMed PMID: 18636017.
41. Pekmezci M, Reuss DE, Hirbe AC, Dahiya S, Gutmann DH, von Deimling A, et al. Morphologic and immunohistochemical features of malignant peripheral nerve sheath tumors and cellular schwannomas. Mod Pathol. 2015;28(2):187–200. PubMed PMID: 25189642.
42. Oliveira AM, Perez-Atayde AR, Inwards CY, Medeiros F, Derr V, Hsi BL, et al. USP6 and CDH11 oncogenes identify the neoplastic cell in primary aneurysmal bone cysts and are absent in so-called secondary aneurysmal bone cysts. Am J Pathol. 2004;165(5):1773–80. PubMed PMID: 15509545. Pubmed Central PMCID: PMC3278819.
43. Bui MM, Smith P, Agresta SV, Cheong D, Letson GD. Practical issues of intraoperative frozen section diagnosis of bone and soft tissue lesions. Cancer Control. 2008;15(1):7–12. PubMed PMID: 18094656.
44. Khalbuss WE, Parwani AV. Cytopathology of soft tissue and bone lesions. New York: Springer; 2011.