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The clincoradiologic spectrum of notochordal derived masses

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ABSTRACT

The notochord is an essential part of human development that regresses with age. Masses derived from notochordal tissue may be encountered during imaging of the neuroaxis. Fortunately, the majority of these are benign and can usually be differentiated by radiological and clinical findings. In this manuscript, we discuss the clinical and radiologic presentation of the four notochordal derived masses and present a brief overview of their management.

1. Introduction

The notochord is a transient embryonic structure that induces chondrification of ossification centers and regulates the development of the spine and surrounding tissues [1]. By ten years of age, the notochord has usually regressed [1–3]. However, heterotopic notochordal rests outside the nucleus pulposus, primarily within the clival or sacrococcygeal spine, are occasionally encountered during diagnostic imaging [4]. These notochordal derived masses include the tornwaldt cyst, ecchordosis physaliphora (EP), benign notochordal cell tumor (BNCTs), and malignant chordoma. Pathologically, these masses are composed of univacuolated physaliferous cells and stain for brachyury, cytokeratin, EMA, NSE and S-100 protein and focally for vimentin [5–8]. Fortunately, the majority of these are benign and can usually be differentiated from each other in addition to other types of masses by a combination of clinical and radiological data (Table 1 and Fig. 1).

2. Clinicopathological features

2.1. Tornwaldt cyst

The Tornwaldt bursa, also known as the Luschka bursa [9], was first recognized by Tornwaldt in 1885 [10,11]. During embryogenesis, focal contact between notochordal tissue and pharyngeal ectoderm occurs and persistent attachment of pharyngeal notochord to the endoderm during tissue migration results in the creation of a nasopharyngeal cyst [9,11]. Cyst occlusion as a consequence of inflammation or mechanical blockage results in Tornwaldt disease [9–11]. There is up to a 3% prevalence of this cyst in healthy individuals most frequently detected between the ages of 15 to 30 years [9]. Most cysts measure < 1 cm in diameter and are asymptomatic [9]. However, some may be associated with localized inflammation and pain, muscle pain and spasm [9,12].

2.2. Ecchordosis physaliphora

Extraosseous notochordal remnants of the skull base were identified in the mid-nineteenth century but the term “ecchordosis physaliphora” (EP) was first coined by Luschka in 1856 [3,13]. Autopsy studies estimate the prevalence of EP to be between 0.4% and 2.0% [3,6] while imaging studies report a prevalence range from 0.8 to 8% [14]. Classically midline intradural lesions [15] and usually associated with the clivus, EPs have been reported at the dorsal sella [14]. Low mitotic activity as measured by Ki-67 < 1% (a cellular marker for proliferation), the absence of tumor necrosis, and a lack of pleomorphism favor the diagnosis of EP over chordoma [6]. Due to EPs' slow growth rate, the majority remain asymptomatic unless tumor compresses surrounding structures in the skull base and posterior fossa [5,6,16].

2.3. Benign notochordal cell tumor

In 2013, the World Health Organization (WHO) classification of bone and soft tissue tumors recognized the benign notochordal cell

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Table 1
Summary table of notochord derived tumors.

	Tornwaldt cyst	Ecchordosis physalifora	Benign notochordal cell tumor	Chordoma
Location	– Midline – nasopharyngeal wall – Between longus coli	– Clival region – Projects dorsally	– Intraosseous – Tends to be midline – May be multiple	– Midline – Clivus – Vertebral bodies – Sacrum
CT	– Circumscribed – Round – Density varies depending on content	– Small mass – May see geographic lytic lesion with sclerotic rim in clivus – May not see at all due to artifact	– Mild osteosclerosis – No osteolysis – No soft tissue mass	– Osteolysis – Soft tissue mass
MRI	T1: variable depending on cyst content T2: variable depending on cyst content, often hyperintense Post-contrast: peripheral enhancement	T1:hypointense T2: hyperintense Post-contrast: no enhancement Atypical features include: calcification, absence of pedicle, basilar artery encasement, clival bone changes, T2 hypointense center and/or rim, and post-contrast enhancement	T1: hypointense T2: hyperintense Post-contrast: minimal to no enhancement	T1: hypointense T2: hyperintense; Post-contrast: Extensive solid enhancement
Histology	– Univacuolated physaliferous cells – Stain (+) for brachyury, cytokeratin			

tumor (BNCT) [17]. BNCTs were first described by Darby et al. as an "intraosseous chordoma" [8,18] and later referred to as "benign notochordal cell tumor" by Yamaguchi et al. in 2004 [8]. Post mortem studies describe a prevalence of 20% with highest frequency in the sacral and clival spine [19]. On pathology, BNCTs are un-encapsulated and unlike chordomas, BNCTs are well-defined masses that lack an intercellular myxoid matrix and cellular atypia [8,13,17]. Furthermore, involved bone is usually sclerotic [8,13]. BNCTs are usually asymptomatic [8,19]. BNCTs are characterized with a slow rate of growth with previous studies reporting a lack of intraosseous disease progression after an average follow-up of up to 120 months [20–22].

2.4. Chordoma

While Virchow initially described a clival chordoma in 1856, Ribbert was the first to refer to the malignant notochordal tumor as "chordoma" in 1894 [23]. Chordomas are the second most common tumors of the spine [24], accounting for 1.4% and 4% of all primary malignant bone tumors and all primary bone tumors, respectively [25]. Classically, chordomas were described to arise most frequently from the sacral region (55%) [26], however, recent analyses have shown a more equal distribution along the spine [24,26–28]. A male predominance has been reported and skull base chordomas are detected in younger patients when compared to chordomas of the vertebral column [28–30]. Chordomas may remain asymptomatic for long periods of time until symptoms arise as a result of mass effect on neighboring structures and organs [12,26,31].

2.4.1. Extra-axial chordoma

Extra-axial chordomas (EAC) are morphologically similar to their axial counterpart [32] but that they arise in the extra-axial skeleton and soft tissue [33,34]. EACs are rare tumors with a review of literature by Tsukamato et al. reporting 20 cases of brachury-positive EACs (14 osseous and 6 soft tissues EACs) [33]. It has been suggested that EAC are derived from ectopic or migratory notochordal remnants [31,35]. Another theory is that EAC are not notochordal in origin, but that genomic mutations cause malignant cells to express brachyury and other genes normally expressed in notochordal tissue [36].

3. Imaging features

3.1. Tornwaldt cyst

Computed tomography (CT) scans show a well-circumscribed midline low-density cyst on the superior posterior nasopharyngeal wall between the longus coli muscles although increased density may be seen when proteinaceous material is present [9]. Tornwaldt cysts demonstrate peripheral enhancement following contrast administration [9]. On magnetic resonance imaging (MRI), these lesions are typically hyperintense on T2-weighted images with variable T1 signal depending on the cyst contents (Fig. 2) [9,11].

3.2. Ecchordosis physaliphora

Given the potential for artifact with CT, MRI is the ideal imaging modality to detect and fully characterize these lesions [14]. Park et al. described a "typical EP" as an extradural or intradural well-circumscribed T2 hyperintense, non-enhancing, non-septated mass of up to 2 cm that projects from the clivus via a T2-hypointense pedicle (Fig. 3) [14]. Atypical features may include calcifications, a lack of a pedicle, basilar artery encasement, clivus bone changes and T2 hypointense center and/or rim, as well as post-contrast administration enhancement [14]. Chihara et al. proposed an MRI classification scheme describing classical EPs as lesions with hyperintense cyst-like components on the dorsal side of the clivus with or without a hyperintense lesion within the clivus. "Possible EPs" were subdivided into "incomplete EPs or EP buds" characterized by T2 hypointense clival projections and "EP variants" as hyperintense lesions only within the clivus [37].

The differential diagnosis is narrow in the setting of a classic appearance. However, when the diagnosis is less clear, such as a lesion only located within the clivus, a differential should be entertained that includes fibrous dysplasia, arachnoid cysts, chondrosarcoma, pneumatized clivus and giant cell tumor of bone. Fibrous dysplasia appears radiographically as a geographic intraosseous lesion with a ground glass matrix, bone expansion, possible endosteal thinning and a heterogeneous appearance on MRI. Arachnoid cysts are cystic masses with high T2, low T1 signal and peripheral enhancement that may slowly remodel bone due to chronic mass effect [14]. Chondrosarcomas often appear as a destructive mass with high T2 signal, thin peripheral and septal enhancement, and chondroid matrix seen radiographically. Giant cell tumors appear as geographic lytic lesions without a complete sclerotic rim and generally do not contain a tumor matrix. At MRI, GCT

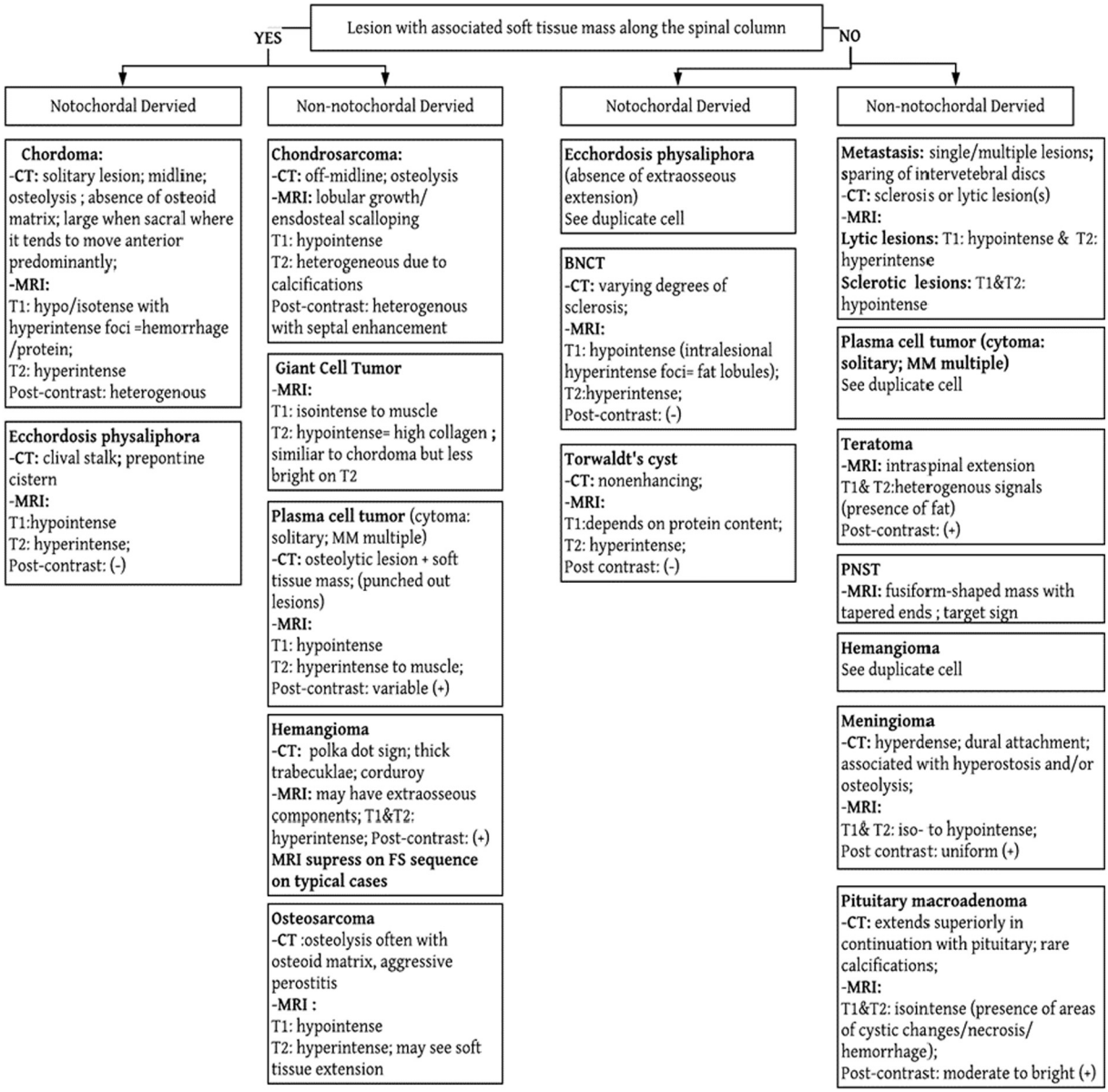

Fig. 1. Differential diagnosis algorithm by imaging features.

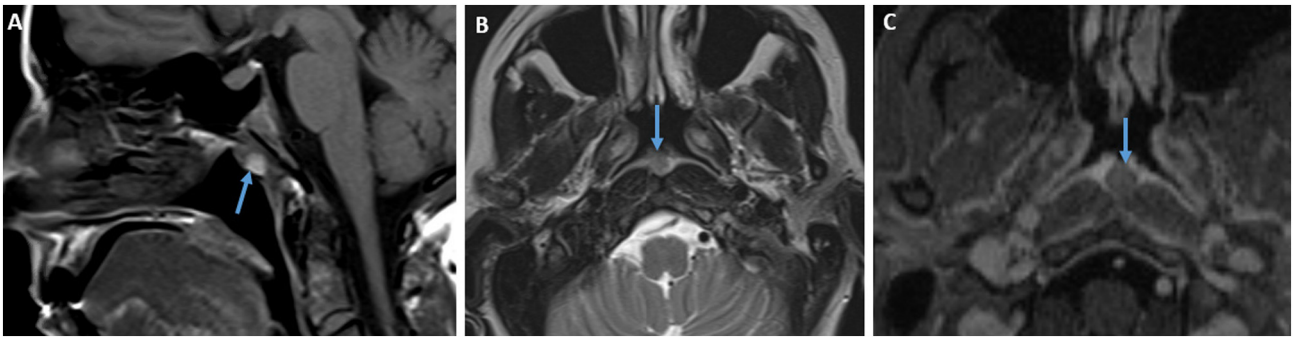

Fig. 2. A–C: Tornwaldt cyst. 48-year-old female with incidental finding of a midline T1 hyperintense T1 iso to hypointense non-enhancing mass centered in the nasopharynx (blue arrows). The high T1 and lower T2 signal suggests proteinaceous material in the cyst. There is no association with bone. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

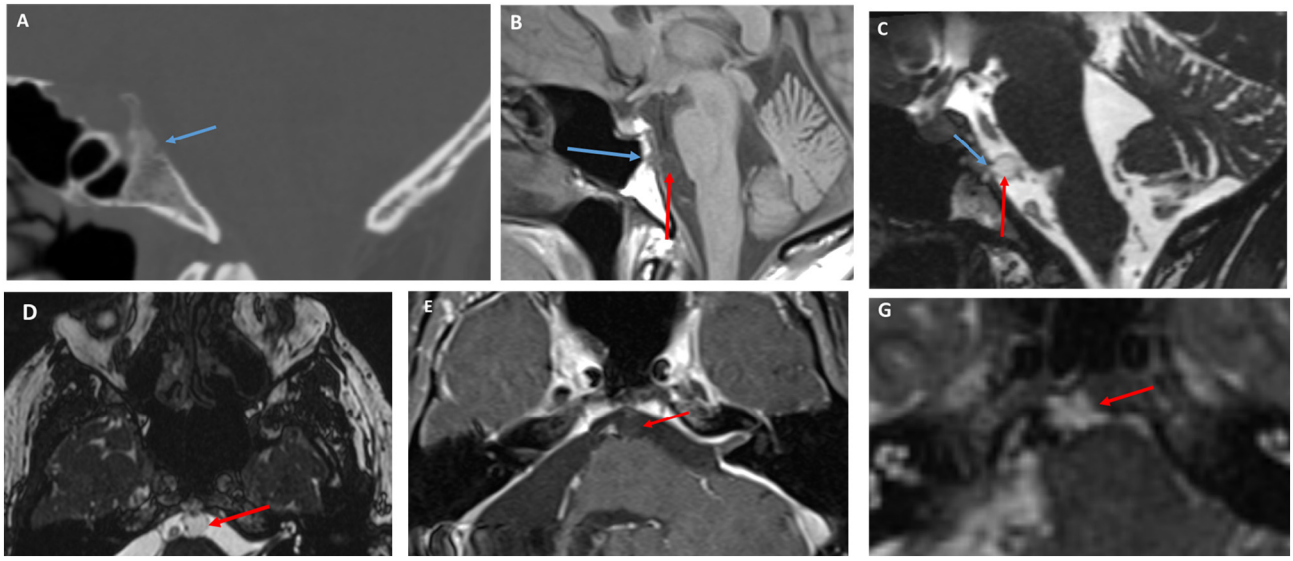

Fig. 3. A–G: Ecchordosis physalifora. 47-year-old male with right internal vestibular schwannoma with incidental EP. CT (A) shows subtle cortical irregularity of posterior clivus from which bulk of mass is attached (blue arrows). MRI shows a T1 hypointense (B and E) T2 hyperintense (C, D and G) exophytic mass with thin rim of tissue (red arrows) extends posteriorly from the clivus toward pons. There was slow growth of this mass which measured 0.6 × 0.4 cm in September of 2016 and 1.0 × 0.9 cm in April of 2017 (G and D, respectively). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

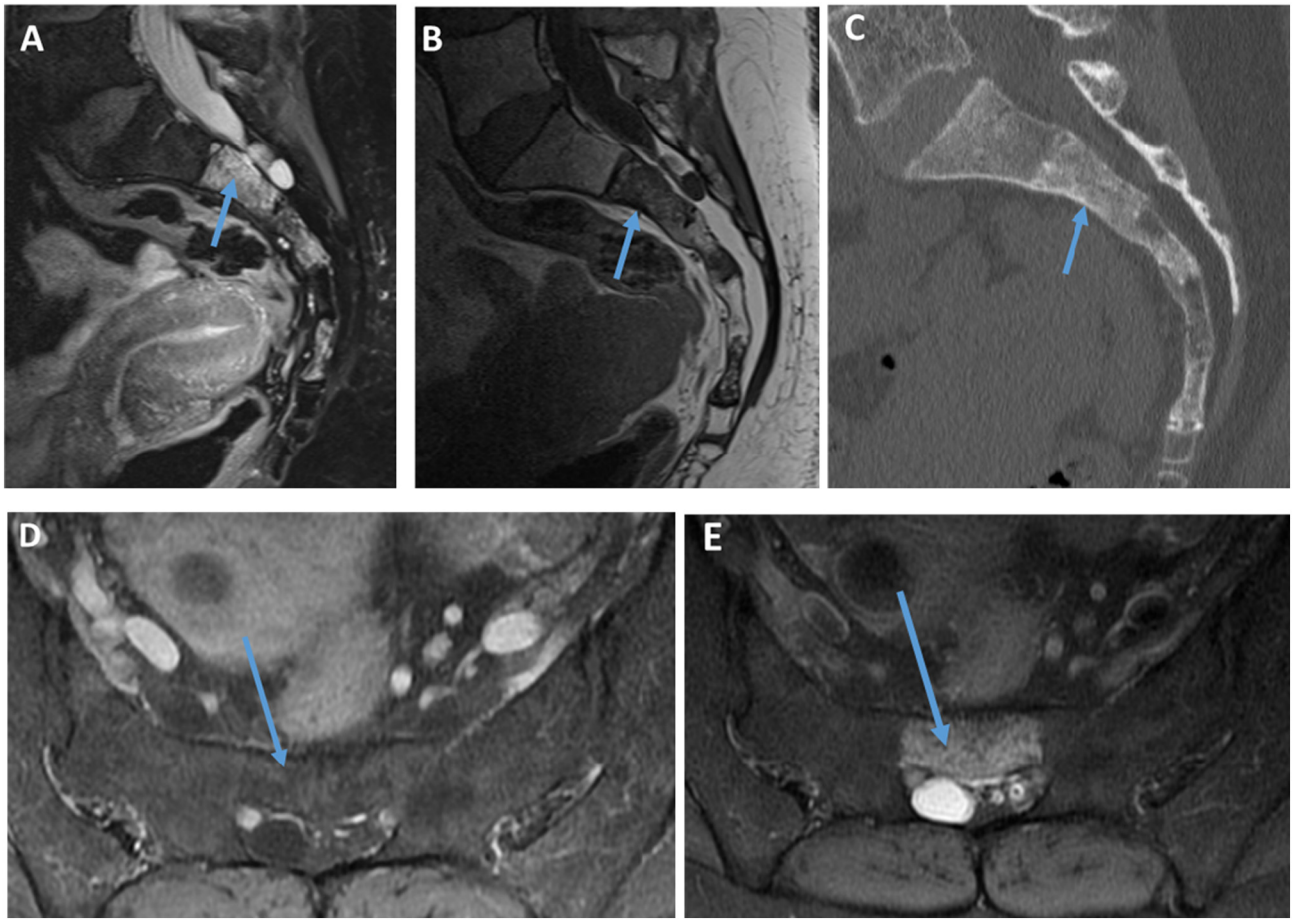

Fig. 4. A–E: Benign notochordal cell tumor. 57-year-old female with incidentally found sacral lesions on imaging workup of low back pain. Multiple T1 hypointense (B), T2 hyperintense (A and E), mildly sclerotic (C) non-enhancing (D) lesions in the S2, S3 and S4 segments with minimal intralesional fat (blue arrows). The lesion was biopsied which confirmed the diagnosis. Note that the images of D and E are at approximately the same level at S2 (no enhancement). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

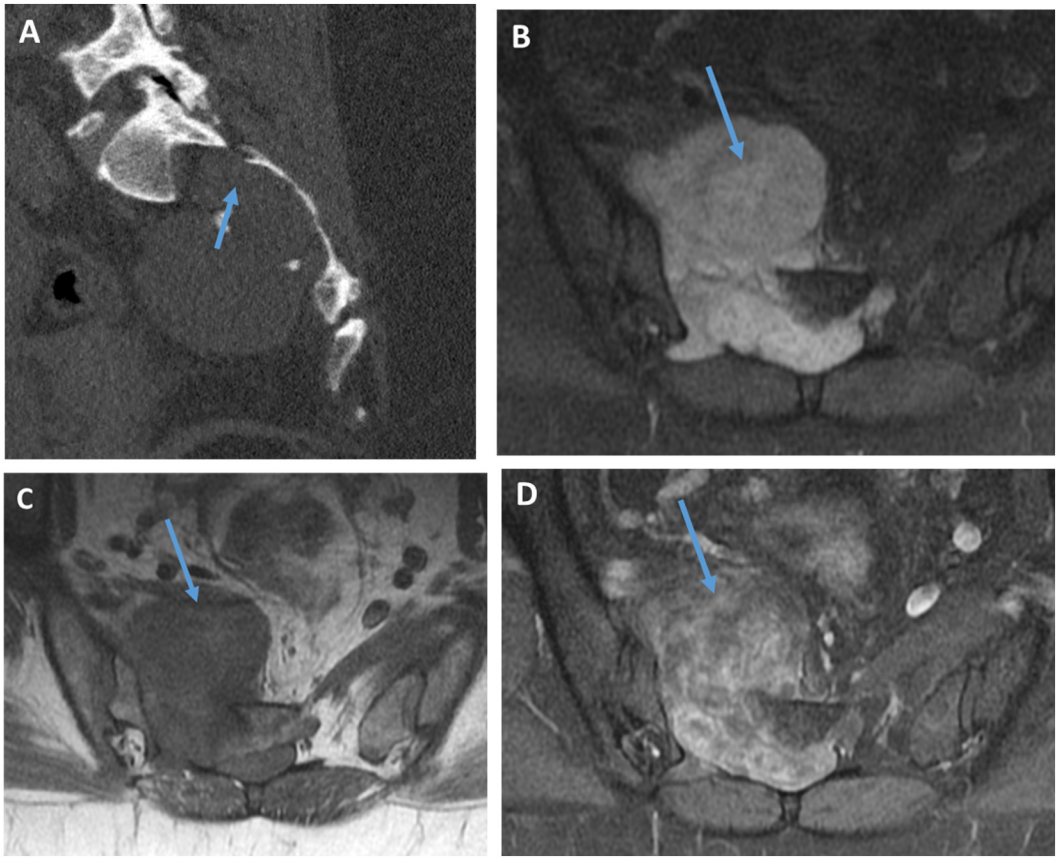

Fig. 5. A–D: Chordoma. 52-year-old female with large destructive (A) T2 hyperintense (B), T1 isointense (C) heterogeneously enhancing (D) tumor extending out from the canal and right side of the sacrum into the presacral soft tissues (blue arrows). CT shows bone destruction to a better advantage where the mass has a lytic appearance (A). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

of bone may be T2 hyperintense and avidly enhance after contrast administration [38].

3.3. Benign notochord cell tumor (BNCT)

Radiographically, BNCTs may present as occult axial lesions on radiographs [39] while CT examinations display mildly osteosclerotic lesions in the absence of destructive or osteolytic components [39]. In recent years, an increasing number of BNCT lesions have been identified on spinal MRI exams. On MR imaging, BNCTs appear as intraosseous lesions with nodular morphology [39] and are characterized with low-intermediate signal on T1-weighted images, heterogenous intermediate-high signal on T2-weighted images with minimal to no contrast enhancement (Fig. 4) [8,22,39]. Tiny foci of intralesional fat seen on MRI favors the diagnosis [39]. The lesions tend to be midline and may occur at multiple levels. While BNCTs are typically intraosseous lesions, large BNCT lesions may exhibit minimal soft tissue extension [22,39]. Biopsy is necessary to distinguish these lesions from chordoma.

3.4. Chordoma

Chordomas present as osteolytic, destructive lesions with soft tissue extension [40]. CT may show amorphous calcifications (seen in 40% of cases [24]) which are thought to be the result of associated osteolysis [27,41]. On MRI, chordomas arise from the midline and exhibit low to intermediate T1 signal characteristic and high T2 signal (Fig. 5) [33,41,42]. Intralesional hemorrhage and calcifications can lead to a heterogeneous “honeycomb” appearance [40,43,44]. The presence of hemorrhagic foci or calcification can be confirmed with gradient echo images or susceptibility weighted imaging (SWI) [40]. Poorly differentiated chordomas may show different imaging characteristics such as hypointense signal on T2-weighted images [40,44]. Extra-axial chordomas (Fig. 6) and metastasis (Fig. 7) tend to have imaging features similar to classical chordomas, but are located away from the spine and may not be associated with bone. Upon review of the current literature including 430 reported metastases, chordoma metastases occur most frequently in the lung, bone and liver (Fig. 8 and Appendix A).

The differential diagnosis for chordomas includes both primary bone tumors (including plasmacytoma/myeloma, giant cell tumor of bone, osteosarcoma and chondrosarcoma), meningioma, nerve sheath tumor, rhabdomyosarcoma and metastasis [45]. Clival meningiomas exhibit osseous sclerosis and bone remodeling instead of lytic lesions. Furthermore, homogeneous solid enhancement with presence of a dural tail is typical for meningiomas. Midline plasmacytomas and lymphomas can resemble intracranial chordomas on imaging [41]. Rhabdomyosarcomas should be considered in pediatric patients [41]. Sacral peripheral nerve sheath tumor (PNSTs) can also mimic chordomas on imaging, but PNSTs grow from and along the spinal nerves. About 10% will arise in the peri-foraminal region and may acquire the distinctive “dumbbell” shape [46]. Osteosarcomas present as lytic destructive lesions often containing osteoid matrix.

4. Management

4.1. Tornwaldt cyst

The management of Tornwaldt cyst is typically conservative. Surgical management, by means of excision or marsupilization, is reserved for symptomatic cysts such as those obstructing the Eustachian

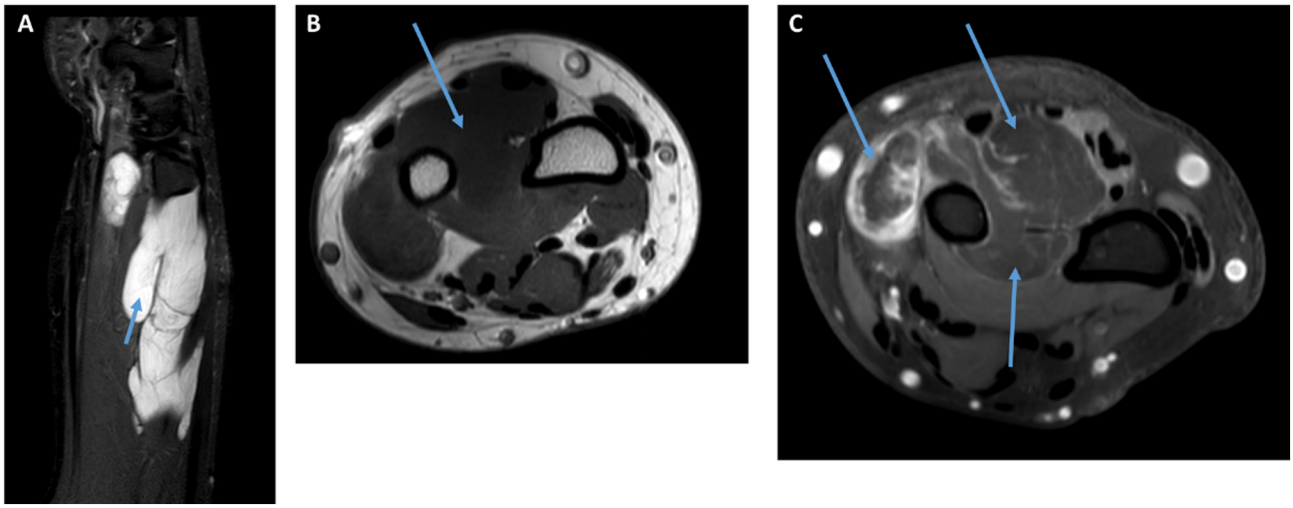

Fig. 6. A–C: Extra-axial chordoma. 51-year-old female with large lobulated T2 hyperintense (A) T1 isotense (B) heterogeneously enhancing C) mass in the forearm partially encasing the ulna and extending through the interosseous membrane into the volar forearm (blue arrows). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

tube orifice [9].

4.2. Ecchordosis physaliphora

Lagman et al. proposed a grading scheme based on clinical and radiologic findings for proper management of EP [15]. Conservative management (serial imaging and observation) is recommended for low grade asymptomatic EPs with classic MRI features (grades 1/2 and grade 2 tumors are characterized by presence of a stalk on imaging). Symptomatic lesions with volume < 6 cm^3 and typical imaging characteristics on MRI (grade 3) warrant biopsy and/or resection [15]. Surgical management is suggested for symptomatic lesions with atypical imaging features with examples including grade 4/5 and grade 5 tumors causing symptoms from compression of cranial nerves [15].

4.3. Benign notochord cell tumor

Recent studies have reported coexistence of intralesional BNCT tissue in resected sacral chordomas [19,47] as well as the existence of a disease continuum between BNCTs and classical malignant chordomas [8,47]. The transitional phase, referred to as incipient chordoma or atypical notochordal cell tumor, is believed to serve as a precursor lesion to chordoma [22,48]. Factors contributing to this transition are currently unknown [18]. However, since autopsy studies show a greater prevalence of BNCT lesions than chordomas, most BNCT lesions do not seem to undergo malignant transformation [22]. Typical management of BNCT lesions include serial imaging [8] and surgical excision is reserved for symptomatic lesions as well as those with atypical features such as osteolysis, soft tissue extension, and absence of fat and/or contrast enhancement on MRI examination [3,18,49,50].

4.4. Chordoma

Local aggressiveness is considered the most important negative prognostic factor [43,51]. Other negative prognostic factors include extreme age at time of diagnosis and metastasis at time of diagnosis [30] with Lee et al. reporting a median overall survival of approximately 2 years for patients with metastatic chordoma versus 10 years in non-metastatic disease [51], though metastasis is only seen in 5% of cases at the time of presentation [25,52]. Several studies have linked local aggressiveness with an increased risk of distant metastases [16,35,53]. Worse prognosis is also exhibited in patients with volume size > 25 cm^3 in volume or with a diameter > 4 cm and 8 cm in the case of skull base chordoma and mobile/sacrococcygeal tumors, respectively. Sacral chordomas reportedly have the shortest overall survival and the highest rate of metastases [25,53–56]. Iatrogenic tumor cell seeding has also been described most commonly in clival chordomas [25,43]. Kaisser et al. were first to provide evidence regarding recurrence as a result of chordoma cell seeding via wound contamination and this study reported a doubling of local recurrence in the setting of en-bloc excision with violation of the tumor capsule [25].

The mainstay of chordoma management, including for EAC, remains

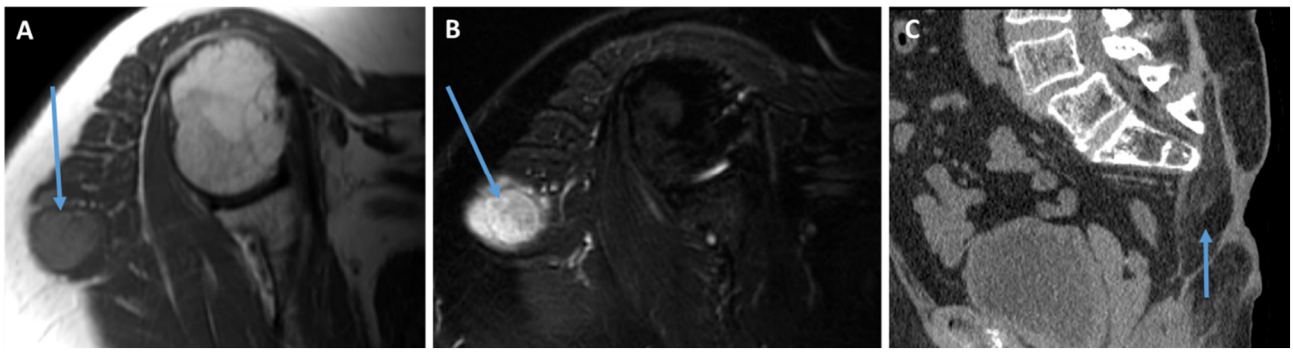

Fig. 7. A–C: Chordoma metastasis to soft tissue. 69-year-old female with history of sacral chordoma status post sacrococcygectomy (C) who presented with a mass in the right shoulder region. MRI showed a lobulated T2 hyperintense, T1 hyperintense mass embedded in the posterior deltoid which was proven to be a chordoma metastasis.

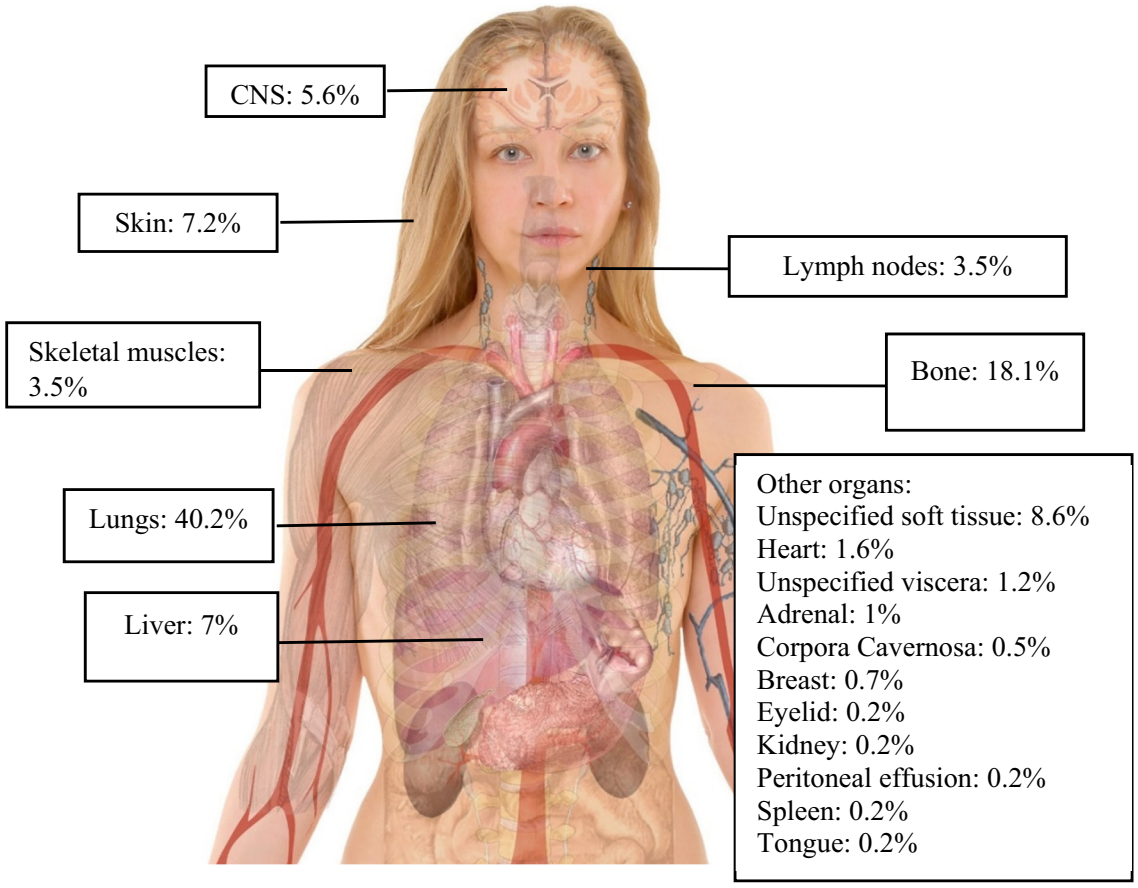

Fig. 8. Relative frequency of chordoma metastasis by location based on 430 metastases reported in the literature. The most frequent sites of involvement include (in descending order): lung: lung, bone, skin, and liver (please refer to appendix for references).

aggressive surgical resection with wide margins to decrease risk of local recurrence [36,57,58]. Tumor location affects treatment planning and a multispecialty team is needed to optimize decision making. For example, at our institution, orthopedic oncology may operate for sacral chordomas even when the mass involves regions above the S3 level and may combine surgery with proton therapy to help with local control. Other surgeons have reported the need to avoid surgical intervention for sacral chordomas above S3 level to decrease the risk of neurological sequelae [59]. Surgery followed by high dose radiation therapy is common for skull base and upper cervical spine chordomas. Alternative methods of treatment include carbon ion therapy, and radiosurgery [25]. While high dose-conformal radiotherapy can be considered a primary form of treatment for locally aggressive chordomas, it is often used post-resection for local control [25,58]. Systemic medical treatment is reserved for high grade/dedifferentiated chordomas and metastatic disease [60] with recent studies examining the role of tyrosine kinase and EGFR inhibitors in the management of advanced disease [60].

5. Conclusion

Notochordal derived tumors are commonly detected during routine advanced imaging. The majority of these lesions are benign and do not warrant aggressive surgical management. However, it is important to look for complications related to the benign lesions and to carefully assess for imaging findings suggestive of a chordoma.

Appendix A

Primary site							N cases & %
Lung	1. Shibuya et al. [61] 2. Agrawal et al. [62] 3. Fearon et al. [63] 4. Kanthan et al. [64]. 5. Kawahara et al. [65] 6. Collins et al. [66] 7. Lountzis et al. [67]. 8. Ruiz et al. [68] 9. Ogi et al. [69] 10. Riesco-martinez et al. [70]	11. Hall et al. [71] 12. Della et al. [72] 13. Mondaini et al. [73] 14. Lee et al. [74] 15. Rutkowski et al. [75] 16. Ashwood et al. [76] 17. Ferraresi et al. [77] (n = 3) 18. Kaiser et al. [78] (n = 8) 19. Hindi et al. [79] (n = 11) 20. Chetty et al. [80]	21. Sibley et al. [81] 22. Volpe et al. [82] (n = 2) 23. Renard et al. [83] 24. Samson et al. [84] (n = 2) 25. Hanna et al. [85] (n = 4) 26. Auger et al. [86] 27. Kearns et al. [87] 28. Lauer et al. [88] 29. Stacchiotti et al. [89] (n = 22)	30. Tudisco et al. [90] 31. von Witzleben et al. [91] (n = 5) 32. Crapanzano et al. [92] (n = 3) 33. Yasuda et al. [93] 34. Bjornsson et al. [94] (n = 2) 35. McPherson et al. [95] (n = 5) 36. Brooks et al. [96] 37. Nakamura et al. [96] 38. Sibley et al. [96]	39. Matsumoto et al. [96] 40. Sen et al. [96] 41. Wold & Laws [96] 42. Benk et al. [96] 43. Coffin et al. [96] (n = 2) 44. Kaneko et al. [96] 45. Ruggieri et al. [97] (n = 16) 46. Ridenour et al. [98] (n = 3) 47. Shinmura et al. [99]	48. Nong et al. [99] 49. Young et al. [100] (n = 8) 50. Radaelli et al. [101] (n = 16) 51. Ozaki et al. [102] 52. Isono et al. [103] 53. Dahl et al. [104] 54. Chang et al. [105] (n = 3) 55. Fagundes et al. [106] (n = 7) 56. Yang et al. [107] (n = 14)	173 (40%)
Bone	1. Resnik et al. [108] 2. Azarpira et al. [109] 3. Cui et al. [110] 4. Ashwood et al. [76] 5. Abdelwahab et al. [111] 6. Mondaini et al. [73]	7. Lee et al. [74] 8. Konuk et al. [112] 9. Bouvier et al. [113]. 10. Delank et al. [114] 11. Della et al. [72] 12. Makhdoomi et al. [115]	13. Kaiser et al. [78] (n = 2) 14. Riesco-martinez et al. [70] 15. Ferraresi et al. [77] (n = 3) 16. Hindi et al. [79] (n = 3) 17. Chetty et al. [80] 18. Volpe et al. [82] (n = 2)	19. Hanna et al. [85] (n = 6) 20. Stacchiotti et al. [89] (n = 5) 21. Jenkins et al. [116] 22. Yasuda et al. [93] (n = 3) 23. Gorysky et al. [117] 24. Woolf et al. [118]	25. Kaneko et al. [96] 26. Nakamura et al. [96] 27. Ridenour et al. [98] 28. Shinmura et al. [99] 29. Radaelli et al. [101] (n = 5) 30. Ozaki et al. [102]	31. Williams et al. [119] 32. Barrenechea et al. [120] 33. Maira et al. [121] 34. Chang et al. [105] (n = 15) 35. Fagundes et al. [106] (n = 6) 36. Yang et al. [107] (n = 3)	78 (18%)
Skin	1. Perschetti et al. [122] 2. Vergara et al. [123] 3. Su et al. [124] 4. Miller et al. [125] 5. Boneschi [126]	6. Cesinaro et al. [127] 7. Jones et al. [128] 8. Peramezza et al. [129] 9. Gagne et al. [130] 10. Chaabane et al. [131]	11. Collins et al. [66] 12. Lountzis et al. [67]. 13. Ruiz et al. [68] 14. Rubin et al. [132] 15. Ogi et al. [69]	16. Riesco-martinez et al. [70] 17. Mondaini et al. [73] 18. Rutkowski et al. [75] 19. Chetty et al. [80]	20. Elliot et al. [133] 21. Kishimoto et al. [54] (n = 7) 22. Ridenour et al. [98] 23. Gleghorn et al. [134]	**Cicatrix** 24. Wiacek et al. [135] **Port-site** 25. Highshaw et al. [136]	31 (7%)
Liver	1. Akyol et al. [137] 2. Tavernaraki et al. [138] 3. Lountzis et al. [67]. 4. Riesco-martinez et al. [70]	5. Della et al. [72] 6. Ashwood et al. [76] 7. Carey et al. [139]	8. Ferraresi et al. [77] 9. Kaiser et al. [78] (n = 2) 10. Hindi et al. [79] (n = 2)	11. Volpe et al. [82] (n = 2) 12. Hanna et al. [85] 13. Rubin et al. [132]	14. von Witzleben et al. (n = 3) 15. McPherson et al. [95] (n = 5) 16. Kaneko et al. [96]	17. Shinmura et al. [99] 18. Young et al. [100] (n = 3) 19. Fagundes et al. [106]	30 (7%)
CNS	1. Champeaux et al. [140] 2. Martin et al. [141] 3. Asano et al. [142] 4. Forsyth et al. [143]	5. Korinth et al. [144] 6. Uggowiter et al. [145] 7. Shinde& Monipanda [146] 8. Krol et al. [147] (n = 2)	9. Ji et al. [148] 10. Marigil et al. [149] 11. Raffel et al. 12. Kamel et al. [150]	13. Smith et al. [151] 14. Lountzis et al. [67]. 15. Hall et al. [71]	16. Della et al. [72] 17. Samson et al. [84] (n = 2) 18. Kaneko et al. [96]	19. Radaelli et al. [101] 20. Chang et al. [105] 21. Fagundes et al. [106] (n = 2)	24 (5%)
Lymph nodes	1. Sopta et al. [152] 2. Jain et al. [153]. 3. Ogi et al. [69]	4. Chetty et al. [80] 5. Singh et al. [154]	6. von Witzleben et al. (n = 3) 7. Coffin et al.	8. Nakamura et al. 9. Ridenour et al. [98]	10. Shinmura et al. [99] 11. Klingler et al. [155]	12. Radaelli et al. [101] 13. Derlin et al. [156]	15 (3%)
Skeletal muscles	1. Carey et al. [139] 2. Vu et al. [157]	3. Kishimoto et al. [54] (n = 9)	4. Ruiz et al. [68]	5. Robinson et al. [158]	6. Carey et al. [139]	7. Andronikou et al. [159]	15 (3%)
Other	**Kidney**: 1. Lountzis et al. [67]. **Adrenal** 2. Carey et al. [139] 3. Kishimoto et al. [54] 4. Matsumoto et al. [96] 5. Coffin et al. [96] **Spleen**: 6. Rubin et al. [132] **Tongue**	7. Biskin et al. [160] **Heart** 8. Oda et al. [161] 9. Lountzis et al. [67]. 10. Prompona et al. [162] 11. Tominaga et al. [163] 12. Kim et al. [164] 13. Harimoto et al. [165] 14. Pothineni et al. [166] **Breast**	15. Tot et al. 16. Gupta et al. [167] 17. Shakir et al. [168] **Ovary** 18. Zukerberg et al. [169] **Corpora cavernosa** 19. Mondaini et al. [73] 20. Chang et al. [105] **Eyelid**: 21. Malone et al. [170]	**Soft tissue (location unspecified)** 22. Kim et al. [164] 23. Agrawal et al. [62] 24. Emori et al. [171] 25. Ferraresi et al. [77] (n = 3) 26. Kaiser et al. [78] 27. Hindi et al. [79] (n = 3) 28. Samson et al. [84] 29. Stacchiotti et al. [89] (n = 4)	30. Crapanzano et al. [92] (n = 2) 31. Yasuda et al. [93] 32. Iwasa et al. [172] 33. Bjornsson et al. [94] 34. Young et al. [100] (n = 6) 35. Radaelli et al. [101] (n = 4) 36. Andronikou et al. [159] 37. Rutkowski et al. [75] 38. Dahl et al. [104] 39. Barrenechea et al. [120]	40. Chang et al. [105] 41. Fagundes et al. [106] (n = 2) **Unspecified viscera** 42. Kaiser et al. [78] (n = 3) 43. Samson et al. [84] 44. Lauer et al. [88] 45. Solini et al. [173] 46. Radaelli et al. [101] **Peritoneal effusion**: 47. Chopra et al. [174]	
Total number							430

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