3 Historical Overview, Demographics, and Clinical Presentation of Spinal Chordoma

Zach Pennington, Andrew Schilling, Joseph H. Schwab, and Daniel M. Sciubba

Abbreviations

BNCT	Benign notochordal cell tumor
CGE	Cobalt gray equivalent
Gy	Gray
MGH	Massachusetts General Hospital
NCI	National Cancer Institute
SEER	Surveillance, Epidemiology, and End Results
US	United States

Introduction

As discussed in Chap. 1, chordomas are malignant tumors derived from the notochord, a mesoderm-derived structure essential for normal embryonic patterning [1]. Originally described by Rudolph Virchow in the 1840s [2], chordomas are slow-growing lesions that commonly present with oncologic pain, mechanical pain (pain associated with movement), or neurologic dysfunction secondary to mass effect (e.g., urinary incontinence) [3]. Symptoms may be accompanied by a palpable mass. However, this is generally only seen in sacrococcygeal lesions [3] as the

Z. Pennington · A. Schilling · D. M. Sciubba (✉)
Department of Neurosurgery, Johns Hopkins University School of Medicine, Baltimore, MD, USA
e-mail: dsciubba1@northwell.edu

J. H. Schwab
Department of Orthopaedic Surgery, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

© The Author(s), under exclusive license to Springer Nature Switzerland AG 2021

D. M. Sciubba, J. H. Schwab (eds.), *Chordoma of the Spine*,
https://doi.org/10.1007/978-3-030-76201-8_3

notochordal remnants giving rise to chordomas of the mobile spine and skull base occupy deep positions within the axial skeleton. Consequently, the majority of patients with mobile spine lesions present with nonspecific back pain of insidious onset [4, 5]. Failure of conservative management then leads to radiographic workup, revealing a large mass of the ventral sacrum or vertebral bodies, oftentimes expanding outside the anatomic compartment defined by the vertebral body [5]. Involvement of multiple contiguous levels is also common [4].

Despite the fact that chordomas commonly present with localized pain, they are an overall uncommon cause of spine pain. In this chapter, we discuss the history of chordoma, its epidemiology, and its clinical presentation.

History of Chordoma

Pathologic and Embryonic Characterization

The first histologic description of chordoma was made by German pathologist Rudolf Virchow in 1846 based upon an incidentally discovered, small, myxoid exophytic lesion of the dorsum sella [2]. Virchow described the lesion as soft, transparent, and multi-lobulated with an underlying myxoid structure that appeared "slimy" [1]. Subsequently in 1856, a second German physician, Hubert Luschka [6], described a similar translucent mass invading the sella turcica. This led Virchow to further investigate these "chordomata" [2], that he described as "ecchondrosis physalifora spheno-occipitalis" – cartilaginous physaliphorous (bubbly) lesions arising from the spheno-occipital junction. Virchow posited that these lesions were cartilaginous in nature and resulted from hydropic degeneration of the spheno-occipital junction with concomitant softening of the cartilage matrix [7]. He posited that this hydropic degeneration led to the formation of vacuoles, which characterize the physaliphorous cell of chordoma [8].

The next year [9], Johnannes Müller – Virchow's doctoral advisor – argued that these chordomata were of notochordal origin, citing the persistence of notochordal tissue within the cartilaginous portions of the sacrum and skull base. This perspective was rejected by Virchow and contemporaries, sparking interest in determining the development of chordoma. Work published in 1880 by Leboucq suggesting all notochordal tissue involutes antenatally [10, 11] was cited as support for the cartilaginous origin of chordoma. However, work by others, including Kölliker [12] and Löwe [13] suggested that the nucleus pulposus of the intervertebral disc was derived from the embryonic notochord. Therefore, ongoing disagreement about the origin of chordoma persisted through the latter half of the nineteenth century [7].

In 1894, Hermann Steiner published a case of a spheno-occipital tumor demonstrating that chordomas were likely of notochordal origin [14]. This was followed shortly thereafter by laboratory support from Steiner's senior collaborator, Moritz Ribbert [15]. Using a rabbit model, Ribbert demonstrated that chordoma-like lesions could be reproduced by puncturing the intervertebral ligament and releasing a portion of the nucleus pulposus. The released tissue was noted to expand and form a

tumor histologically identical to the Ecchondrosis physalifora of Virchow, which Ribbert later called "chordoma" [16]. More than a half-century later, the findings of this experiment were replicated by Congdon working at the University of Michigan [17].

Ribbert additionally pointed out that the gelatinous texture of chordoma was wholly inconsistent with that expected of cartilaginous tumors. In aggregate, this evidence argued strongly for a notochordal origin and silenced debate about the embryological origin of chordoma [18, 19]. Shortly thereafter, Fischer and Steiner, working within Ribbert's group, described the occurrence of a malignant notochordal tumor [20], indicating that chordoma belonged to a family of notochord-derived tumors. In 1926, Stewart and Morin [21] made the formal proposal that benign notochord-derived lesions be called *ecchordosis physaliphora*, to differentiate them from chordoma. In modern descriptions, notochord-derived lesions are grouped as malignant chordomas and benign notochordal rests, now termed benign notochordal cell tumors (BNCTs) [22].

Clinical Descriptions

The first clinical description was made by Dr. Edwin Klebs of Berlin in 1864, who relayed a case of a probable chordoma of the spheno-occipital junction [23]. Shortly thereafter Trélat published on the first cervical chordoma, which was diagnosed as an "ecchondrome muqueux" [24]. The second case was subsequently published by Klebs in his text, "Die Allgemeine Pathologie" [25, 26]. In this case, the patient had presented with increased medullary pressure [8]; it was only later that the mass was determined to be malignant. The first sacrococcygeal lesion was diagnosed by Lothar Henning, who described its occurrence in a 7-month-old in 1900 [27]. Roughly 4 years later, Ribbert reported on findings from an autopsy series of 500 patients [16]. He reported notochord-derived lesions of the clivus in 2% of these patients, suggesting that said lesions might be present in a nontrivial proportion of the population.

The first large clinical review was published in 1923 by Burrow and Stewart [28], who reported the case of a 30-year-old man with an intrasellar chordoma along with a summary of 16 previously reported cases. Among these was the case of Grahl [29], who in 1903 reported the first death from chordoma. The patient, a 51-year-old woman, had presented with cranial polyneuropathy (deficits of cranial nerves 3, 4, 7, 9, and 10), headaches, and visual impairment consistent with elevated intracranial pressure. The patient's death was ultimately deemed secondary to medullary compression. Similar findings were reported shortly thereafter by Seiffer (1905) [30], Fischer and Steiner (1907) [20], Frenkel and Bassal (1910) [31], Eitel (1911) [32], and Wegelin (1911) [33]. In all cases, patients succumbed to pontine or medullary compression by their lesion.

Operative cases were notably sparse within the series, as the majority of described cases localized to the skull base. Most contemporary surgeons felt surgical resection of skull base masses was too dangerous. However, one operative case was noted in

the review of Burrow and Stewart – that of Linck, who in 1909 described the operative management of a clival chordoma [34]. The patient – a middle-aged man – originally presented with a pharyngeal swelling and right middle ear disease. He was treated with two open biopsies which revealed pathology consistent with chordoma. He later developed the progression of his tumor leading to multiple cranial neuropathies. Contemporaneously, three sacrococcygeal cases were reported [35–37]. Feldmann described the excision of a presacral chordoma in a 46-year-old female; the tumor was resected without issue and the patient was deemed "well" at 3 months postoperatively. Long-term follow-up was not reported. Mazzia [36] reported the case of a 54-year-old man who presented with a large (17 × 8 cm) coccygeal tumor associated with insidious-onset perirectal pain and discomfort. The lesion was excised but recurred at 19 months; local recurrence also occurred after the second operation, at which point the patient's lesion was felt to be inoperable. The next year Curtis and Le Fort [37] reported on the management of a 58-year-old man with a 10 × 8 cm presacral tumor. The lesion was treated with resection of the tumor and coccyx, but locally recurred with the patient passing at 30 months following initial resection. Of note, Moynihan treated a coccygeal chordoma at the same time as these reports; however, the mass was initially misdiagnosed as carcinoma with colloidal degeneration. It was only upon re-investigation of the pathology 9 years subsequent to resection that the mass was recognized as chordoma [38]. Unlike the prior reports, Moynihan's patient appears to have experienced good long-term local control following surgical resection.

The next surgically treated case was reported by Alézais and Peyron [39], who relayed the course of a 68-year-old woman presenting with a swelling of superior occipital lesion and cervicalgia. The occipital tumor was several inches in diameter and was noted to be eroding through the bone. Following resection, she had complete remission of her symptoms; no recurrence was noted. The subsequent year Albert [40] reported on the operative management of a 26-year-old man who presented with perirectal aching following a fall that was worsened by defecation. He was found to have a 10 × 6 × 5 cm sacrococcygeal chordoma compressing the rectum. The patient underwent multiple subtotal resections and ultimately succumbed 14 months after the presentation.

In 1919, Daland described the management of a 30-year-old woman who presented with hoarseness, headaches, and a retro auricular mass "the size of a hen's egg" [41]. The mass was treated with curettage, which resulted in the resolution of the patient's headaches. The patient also received adjuvant radiotherapy. In spite of this multimodal management, the mass recurred by 7-month follow-up, consistent with the known natural history of chordoma. The same year, Pototschnig [42] reported the first instance of metastatic chordoma. The patient was initially treated with surgical resection of his sacrococcygeal mass, but passed 2 days after his operation. On autopsy, the lesion was found to have spread to the regional lymph nodes and liver. Stewart subsequently described the spread of a sacrococcygeal chordoma to the right scapula 8 years after gross total excision [38]. At this point, it became apparent that chordoma had metastatic potential and was not simply limited to locally invasive disease.

As the pathology of chordoma became better defined, several authors began publishing reviews of the literature, including Coenen (1925) [43], Corsy and Sumont (1927) [44], and Mabrey (1935) [25]. The review of Mabrey has been widely cited and included the first 150 published cases with descriptions of tumor localization, patient epidemiology, clinical presentation, and pattern of metastatic spread. Among the reported cases, Mabrey noted a roughly 2:1 male predominance and a predilection for disease onset in the fifth or sixth decade of life. Additionally, lesions most commonly localized to either the spheno-occipital (33%) or sacrococcygeal regions (58%); mobile spine lesions were uncommon.

Extra-axial chordomas have also been described. The first such instance was the case of Alezais and Peyron, above, who described a chordoma of the left superior occipital region in 1914 [39]. Subsequent extra-axial cases have included those of Koritzki (alveolar process of mandible and maxilla) [45], Rubaschow (superior maxilla) [46], Hirsch (tonsillar region) [47], and Higinbotham et al. (scapula) [48]. Intradural [49] and purely epidural lesions of the spine [50–53] and intradural lesions [54–56] of the cranial vault have also been reported. Current radiographic and histopathologic diagnosis are discussed in Chaps. 4 and 5, respectively.

Management

Surgery for Skull Base Chordoma

As the majority of initial descriptions of chordoma were of lesions arising from the clivus and skull base, the majority of early case reports described histologic and pathologic findings on autopsy. Surgery was by-in-large felt to be a too high risk given the close proximity to the brainstem. However, with improvements in surgical techniques, case reports began to be published in the second and third decades of the twentieth century. The first by Linck [34] reported on the usage of open biopsies for a patient with clival chordoma. However, it was not until Daland in 1919 that an attempt at curative excision of a skull base chordoma was reported. As mentioned previously, this young woman experienced rapid local recurrence and death at 7 months in spite of complete excision of the mass and adjuvant radiotherapy. The same year Fabricius-Möller [57] and Argaud [58] described the treatment of retropharyngeal and clival chordomas, respectively. In the case of Fabricius-Möller, the patient experienced local recurrence after only a few months. As the 1920s progressed, additional reports of the surgical management of skull base chordomas were described. These include those of Hirsch, who in 1923 reported the use of palate splitting to treat a nasopharyngeal chordoma; the lesion recurred locally after 1 year of follow-up [7, 19]. Additionally, Argaud and Clermont [59] described resection of a small nasopharyngeal tumor via a transsinusofacial route without complications. Unfortunately, the lesion recurred after only a few months. The same year Loebell [60] reported the use of a transantral approach through the maxillary sinus to treat a nasopharyngeal chordoma involving the left nostril and obstructing the left Eustachian tube. The patient additionally received radium adjuvant brachytherapy; however, the lesion recurred after 1.5 years, leading to death.

These cases, among others, were reviewed by Mabrey, who documented an extremely high perioperative mortality, noted at 31% for large lesions. Congdon echoed similar findings in his series of 18 surgically treated patients [61]. Of the four patients treated for clival lesions, three died intraoperatively or within 1 day of attempted resection. A subsequent review of the spheno-occipital chordoma literature by Zoltán and Fényes in 1960 [62] also painted a morbid picture of surgery for skull base chordomas. They described surgical resection as "most discouraging" due to "the impossibility of complete surgical removal" and stated that conventional radiotherapy was "quite hopeless" [62]. They consequently recommended consideration of brachytherapy with yttrium-90 to help obtain local control. Surgical techniques improved steadily through the second half of the twentieth century though [63–65] and surgical resection became considered a standard part of treatment for most lesions. Al-Mefty and Borba [66] reported their experience with 23 patients treated in the early 1990s. All patients were treated with skull base approaches, of which 17 received adjuvant proton-photon radiotherapy; radiographic cure was seen in 71% of patients at a mean of 25 months. Subsequent follow-up using an expanded series found a 5-year recurrence-free survival rate of 50.7% and 5-year overall survival of 86% [67]. Gay et al. [68] reported similarly good results in their series of 60 patients with skull base chordomas or chondrosarcomas treated with surgical resection and adjuvant high-dose radiotherapy between 1983 and 1994. Five-year recurrence-free survival was 65% for patients with chordoma. Of note, it was also during the late 1980s and early 1990s that the first descriptions of transsphenoidal approaches for clival chordomas were described [69–72]. These evolved into the endoscopic transsphenoidal approaches [73–75] that are considered by some to be the approach of choice for clival chordomas [76, 77].

Surgery for Mobile Spine Chordoma

The first likely report of a chordoma of the mobile spine was reported by Trélat and Ranvier in 1868, who described a chordoma-like mass involving the cervical spine [78]. The mass was noted to be extremely large and extended from the angle of the mandible to the posterior pharyngeal wall. Resection was attempted, but the mass proved extremely adherent and surgery was aborted. The patient passed from pulmonary complication on post-operative day 2.

Then in 1924, the first confirmed case of mobile spine chordoma was made by Raul and Diss [79]. This was shortly followed by the reports of Cameron in 1926 [80], Syme and Cappell in 1926 [78], and Cappell in 1928 [81]. The case of Syme and Cappell [78], represents the first case of mobile spine chordoma treated by surgical management with histologic confirmation. They described a 59-year-old man presenting with neck stiffness, dysarthria, and dysphagia who was treated with curettage for a chordoma involving the anterior cervical spine. The patient experienced recurrence 6 months after resection and underwent repeat resection of the mass, which now extended from the occiput to C5 vertebral body. The patient, unfortunately, succumbed to septic pneumonia postoperatively and died on the third postoperative day. This high surgical morbidity was noted by Mabrey in his 1935 review [25]. Of the 14 patients in the literature who had undergone surgical

treatment of mobile spine chordomas, three (21%) had died in the perioperative period [25].

Surgery for mobile spine chordomas remained a contentious issue into the late-twentieth century as procedural morbidity remained high and was felt to be unjustified if cure could not be achieved. Through the 1960s and 1970s, surgery was almost exclusively performed for the relief of neurological symptoms rather than oncologic cure [82–86]. Then in 1981, Stener made the first report of *en* bloc vertebrectomy for mobile spine chordoma [87]. In this case, he resected an L3 chordoma causing cauda equina syndrome. The patient not only regained ambulatory function postoperatively, but she remained disease-free at last follow-up, 7 years post-resection. Such long-term control was particularly notable, as a contemporary series of 51 patients with chordoma showed extremely poor disease-free survival [88]. Of the treated patients, metastatic spread was observed in 25% of those treated for mobile spine lesions and 45% of those treated for sacrococcygeal lesions. The poor control seen in tumors treated with intralesional resection may have led Stener to subsequently argue for more aggressive resection of primary vertebral column lesions [87].

Several years passed before the additional description of these *en bloc* spondylectomies was issued [89]. By the early 1990s though, advances in modern imaging and surgical techniques allowed many groups to begin reporting favorable outcomes following *en bloc* resection of mobile spine lesions [89–92]. Of note are the contributions of Boriani and colleagues at the Rizzoli Orthopaedic Institute in Bologna, Italy [93]. Their experience with *en bloc* resection led to the formulation of the Weinstein-Boriani-Biagini staging system (see Chap. 6) that has become a standard part of surgical evaluation for patients with mobile spine lesions. Modern series, including the large multicenter AOSpine series [4], have indicated that while morbid, *en bloc* resection of mobile spine lesions is feasible. Additionally, where negative margins are achieved, *en bloc* surgical resection improves post-operative survival and local control; it is consequently considered to be the standard of care for these lesions. Current surgical approaches to lesions of the mobile spine are discussed in Chap. 7 (occipitocervical junction), Chap. 8 (cervical spine), Chap. 9 (thoracic spine), and Chap. 10 (lumbar spine).

Surgery for Sacrococcygeal Chordoma

Descriptions of total excision of sacrococcygeal chordoma started with the reports of Massia [36] and Curtis and Le Fort [37]. In both cases, gross total excision was thought to have been obtained, yet serial follow-up demonstrated local recurrence. The propensity for local recurrence among surgically treated tumors was subsequently noted by multiple authors [94]. Given the apparent proclivity for local recurrence, Stewart argued as early as 1922 that such lesions should be treated via total excision to achieve long-term control or even cure [38]. However, early surgical management was associated with high morbidity and mortality. In his 1935 review of the chordoma literature, Mabrey reported that perioperative mortality across all anatomic sites was 27% [25]. Additionally, local recurrence was seen in 66% of the 59 patients who survived the perioperative period, with an average time

to recurrence of 17.5 months [25]. Based upon this, Mabrey author argued for the surgical resection of sacrococcygeal chordomas, focusing on wide excision and without disruption of the tumor, if possible.

Such a treatment paradigm was later espoused in literature reviews by Mixter and Mixter in 1940 [94] and Shackelford and Rhode in 1955 [95]. Both author groups noted that lesions treated with gross total excision had longer times to local recurrence than other lesions and were far likelier to achieve cure. Additionally, Shackelford and Rhodes [95] noted that in cases where there was local recurrence, the intraosseous portion of the tumor had appeared to have been shelled out. In other words, local recurrence occurred more often in cases where excision had involved violation of the tumor capsule. Consequently, they argued that the best outcomes for sacrococcygeal chordoma were achieved through an *en bloc* resection that did not violate the integrity of the tumor capsule.

Subsequent studies demonstrated the superiority of this *en bloc* excision with negative margins in terms of local recurrence and post-operative survival [4, 5, 48, 96–99]. This led other groups to argue for *en bloc* resection with negative margins as the definitive treatment surgically amenable lesions beginning in the 1950s [95, 100]. Such studies serve as the evidentiary base for the treatment paradigm originally described by Enneking in 1980, which recommends *en bloc* resection with negative margins for chordoma [101, 102]. The Enneking system, also known as the Musculoskeletal Sarcoma Tumor Society (MSTS) System, remains the gold standard today for guiding the management of primary bone tumors of the mobile spine and sacrum [1]. More recently, Sim and colleagues provided further support for *en bloc* R0 resection with their experience treating 52 patients for sacrococcygeal chordoma at the Mayo Clinic [103]. When comparing patients treated with a wide margin resection (defined as a healthy cuff of tissue >1–2 cm) to those treated with marginal or intralesional margins, overall survival and local control were significantly better among those treated with wide margin resection. Interestingly though, a more recent 31-year experience published by the Rizzoli Institute [104] noted that long-term recurrence rates may be high even for patients treated with R0 resection. In their series of 99 patients, local control was seen in less than 25% of patients at 15-year follow-up. The reason for this is unclear, however, it may be due to the presence of "micro-skip" metastases – small tumor microfoci situated outside the tumor pseudocapsule. This was suggested by Akiyama et al. [105] who observed micro-skip lesions in over 40% of patients on histological examination. Consistent with this, the group at the Massachusetts General Hospital (MGH) [106] found that the use of adjuvant or neoadjuvant radiation, not surgical margin was the strongest predictor of local control among sacrococcygeal chordomas undergoing index surgery. It is unclear if the superior local recurrence was because the micro-skip lesions were covered by the adjuvant radiation though, and this remains an ongoing area of investigation. Current surgical techniques for sacrococcygeal chordomas are discussed in Chap. 11. Soft tissue and bony defect reconstruction techniques are described in Chaps. 12 and 13, respectively.

Radiotherapy for Chordoma

Radiation as adjuvant or primary therapy for chordoma has been described repeatedly since the earliest clinical patient series. The first such description was made by Daland [41] in his treatment of a skull base chordoma. The patient was initially treated with surgical resection, which was followed by "two massive x-ray treatments."

By the mid-1950s, most groups began to describe chordoma as highly radioresistant [62, 95, 107, 108] and indicated that radiotherapy was only of "palliative value" [107]. However, in the subsequent decade, it was suggested that extremely high doses of radiation could, in fact, reduce local recurrence. In 1964, Kamrin et al. reported a series of 30 patients treated for chordoma with a combination of biopsy or surgical resection and adjuvant radiation (3600–17,500 rad) [109]. They concluded that only sacrococcygeal chordoma could be reasonably be treated with surgical resection, and that mobile spine and intracranial chordoma should be biopsied and treated with "large tumor doses of therapeutic radiotherapy." They defined large doses as 5000 rad or greater and reported that their practice was to dose with 3000–5000 rad followed by 2000–3000 rad doses at each instance of recurrence. Shortly thereafter, Higinbotham and colleagues reported a 35-year experience of treating chordoma at Memorial Sloan Kettering [48]. Similar to Kamrin et al., the authors argued that high-dose radiation could be used to improve local chordoma control. The authors argued for an even more aggressive dosing schema, arguing that doses of 7000 rad or above were required for substantial benefit, although they acknowledged that such doses were associated with "acute radiation reactions."

Other series in the 1970s [86, 100, 110] and 1980s [111–113] argued for increasingly large radiation doses (60–70 Gy total dose over 6–7 weeks). Based upon the result in their series of 15 patients, Pearlman and Friedman [100] argued for tumor doses of 8000 rad or more; they found that doses ≤4000 rad were ineffective at killing tumor cells. Similar to Kamrin et al., the authors acknowledged the significant toxicities associated with such high levels of radiation and therefore stipulated that such lesions should likely be reserved for sacrococcygeal tumors. Unlike the Kamrin et al. though, Pearlman and Friedman argued against repeat radiation dosing, indicating that it would be unlikely to control the residual chordoma but would almost assuredly cause significant, irreparable radiation damage. The next decade, Amendola et al. [111] reported on the effectiveness of adjuvant hypofractionated radiation with 50–66 Gy in 180–220 cGy fractions for surgically managed chordoma. Though their experience was small, the authors reported that all nine of their cranial chordoma patients were able to tolerate radiotherapy without issue.

Beginning in the 1980s, several authors began to describe the benefits of proton therapy for chordoma [113]. The first report appears to have been by Suit and colleagues at the MGH, who described the use of high-dose proton radiotherapy in 10 patients with chordoma or chondrosarcoma of the skull base or cervical spine [113]. Patients in their series were treated with a combination of high-energy photons and 160-MV proton beams in 1.8–2.0CGE fractions to a total dose of 65.3–76.2CGE between the two modalities. Nine of the ten patients experienced acute radiation

reactions though, most commonly mucositis or skin changes (e.g., desquamation, erythema). None of the patients experienced recurrence over a follow-up period that ranged from 2 months to 6 years. Other early experiences included the expanded MGH series published by Fagundes et al. [114] and the experiences of Al-Mefty and Borba [66], Castro et al. [115], and Hug et al. [116]. Doses all ranged from 60 to 77CGE and a recent review of the chordoma literature supports superior outcomes in patients receiving high-dose (>65 Gy) radiotherapy with charged particles or stereotactic photon radiosurgery [117]. More modern experiences have since been described [118–120] and preliminary experiences using carbon ion and other charged particle radiotherapy modalities have been published [121–125]. Experiences with adjuvant stereotactic radiosurgery for chordoma have also been described, dating to the early 1990s [126–131]. The most recent consensus statements recommend the use of adjuvant high-dose charged particle therapy or stereotactic radiosurgery for local tumor control [132, 133]. Current usage of radiotherapy is discussed in Chap. 14 (photon therapy) and Chap. 15 (protons and charged particle therapy).

Chemotherapy

Owing to its relatively slow-growing nature, chordoma has generally not been considered to be a malignancy that is amenable to systemic chemotherapy [1]. Use of systemic therapy was first described by McSweeney and Sholl [134], who in 1959 published their use of mechlorethamine – a nitrogen mustard – in the treatment of a 78-year-old woman with metastatic sacrococcygeal chordoma. The mechlorethamine treatments led to improvement of the patient's sacrococcygeal pain; however, she progressed on therapy with new metastases to the forearm noted within 8 months of initiating therapy.

The next published description followed 5 years later with the series of Kamrin et al. in 1964 [109]. The authors described using intracarotid perfusion of methotrexate as a treatment adjuvant in two patients. One patient died within 8 days of treatment and the other experienced local recurrence within 1 year, making it unclear if there was any benefit. This was followed by the reports of Rissanen and Holsti in 1967 [135], and Pearlman et al. in 1972 [136] who reported the use of cyclophosphamide and actinomycin D, respectively, for recurrent disease. Both agents were found to be ineffective.

At the same time, these reports were published, Razis et al. [137] described the use of vincristine sulfate (2 mg week) in a patient with recurrent chordoma of the cervical spine. The patient experienced roughly 4 months of systematic improvement, but ultimately succumbed to their disease. Harwick and Miller [138] employed vincristine (1.4 mg/m^2 weekly) with similar results. The patient enjoyed symptomatic improvement after the first several doses; however, there was no clear survival benefit. Spratt et al. [139] published their case of a 49-year-old woman with recurrent sacrococcygeal chordoma who failed multiple regimens, including cyclophosphamide-doxorubicin-methotrexate triple therapy, cyclophosphamide-actinomycin D-dacarbazine triple therapy, cyclophosphamide-dacarbazine-vincristine triple therapy, and lomustine-doxorubicin-vincristine-bleomycin quadruple therapy.

The patient had a moderate radiographic benefit on the last line regimen, but was unable to tolerate associated toxicities and succumbed to *Pseudomonas* sepsis 2 years after initiating chemotherapy. Platinum-based agents were similarly found to be ineffective at producing long-term benefits [140].

Given this lack of success, chemotherapy has remained a last-ditch option. However, more recently there has been increased interest in small molecule agents, notably tyrosine kinase inhibitors, and immunotherapies for patients with recurrent or metastatic disease. These agents include erlotinib, sunitinib, lapatinib, imatinib, sorafenib, nivolumab, and ipilimumab. Various combinations of these agents are currently the subject of clinical trials [1]. More detailed discussion of modern systemic therapy and future directions is discussed in Chap. 16.

Epidemiology of Chordoma

Population-Level Data

Similar to other primary bone tumors of the spinal column, chordoma is a rare clinical pathology with previous estimates suggesting an overall prevalence of 0.08–0.5 per 100,000 persons worldwide [141]. Estimates vary widely though and little population-level data exist. Of that which is available, the best data come from the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute (NCI) [142–144]. The SEER registry of the NCI is a prospectively maintained database covering 28% of the US population [143], which has previously been found to be broadly representative of the US cancer population as a whole [145]. The most recent review of these data was published by Zuckerman et al. [143] based upon the data from 1616 patients with chordoma enrolled between 1973 and 2013. They found that the most common location for chordoma was the skull base (41.1%), followed by the sacrum (31.4%) and mobile spine (27.5%). For those with mobile spine lesions, 60% of patients were male, mean age was 57 years, and the majority of patients identified as white (93%) as opposed to black (2%) or other (6%). For sacral lesions, there was also a male predominance (62%) though the age at presentation was slightly older (mean 63 years) and a smaller proportion of patients identified as white (86%) as opposed to black (3%) or other (11%). No geographic biases were noted and the majority of both patients with mobile spine tumors (74%) and sacral tumors (70%) had their disease confined within the periosteum at the time of diagnosis, consistent with the relatively slow-growing nature of chordoma. Few patients had metastatic disease at presentation (8% of mobile spine; 7% of sacrum). Most patients underwent surgical resection (76% of mobile spine lesions; 67% of sacral lesions), and a large minority of both mobile spine (50%) and sacral lesions (37%) were treated with radiation. Analysis of the data by year suggested no trends in the proportion of patients being treated with surgical resection, though there was a significant decrease in the proportion of sacral lesions being irradiated. Median overall survival is relatively good for both mobile spine (median 95 months) and sacral lesions (median 87 months). In both cases, overall survival is

notably higher among patients treated with surgical resection (mobile spine: 105 vs 61 months; sacrum: 111 vs 56 months). The data from Zuckerman et al. [143] also suggest that prognoses may be better for more recently diagnosed patients; however, the trend they identified did not meet statistical significance. Older patients have been found to have poorer survival [143], though the effect size is small and it is unclear if this relationship is tied to the primary malignancy. Other small epidemiological series have been published based upon Scandinavian [3, 88], English [146], and Taiwanese populations [147], which are summarized in Table 3.1.

Table 3.1 Summary of population-based studies of chordoma epidemiology

Study	*n*	Population details	Epidemiology data
Eriksson et al., 1981 [88]	979	*Country*: Sweden *Time Period*: 1958–1970 *Recruitment*: Swedish Cancer Registry	*Age*: mean 57 yr *Sex*: 51% M *Incid*: 0.51 per 10^6 PY *Prev*: n.g. *Loc*: 27% SB, 16% MS, 57% Scrm *Surv*: mean 3.3 yr (SB), 3.5 yr (MS), 4.6 yr (Scrm)
Hung et al., 2014 [147]	1238	*Country*: Taiwan *Time Period*: 2003–2010 *Recruitment*: Taiwan Cancer Registry	*Age*: median >60 yr *Sex*: 67% M *Incid*: 0.40 per 10^6 PY *Prev*: n.g. *Loc*: n.g. *Surv*: n.g.
McMaster et al., 2001 [144]	400	*Country*: USA *Time Period*: 1973–1995 *Recruitment*: SEER database	*Age*: mean 54.8 yr *Sex*:60% M *Incid*: n.g. *Prev*: 0.8 per 10^6 *Loc*: 32% SB, 33%MS, 29%Scrm *Surv*: median 6.29 yr; 68% @ 5-yr; 40% @ 10-yr
Paavolainen and Teppo, 1976 [3]	<700	*Country*: Finland *Time Period*: 1953–1971 *Recruitment*: Finnish Cancer Registry	*Age*: mean 55.5 yr *Sex*: 60% M *Incid*: M = 0.30 per 10^6 PY; F = 0.18 per 10^6 PY *Prev*: per 10^6 *Loc*: 10% SB, 15% MS, 75% Scrm *Surv*: n.g.
Smoll et al., 2013 [142]	623	*Country*: USA *Time Period*: 1973–2009 *Recruitment*: SEER database	*Age*: median 58 yr *Sex*: 59% M *Incid*: n.g. *Prev*: 0.84 per 10^6 *Loc*: n.g. *Surv*: median 7.7 yr; 72% @ 5-yr; 49% @ 10-yr

Table 3.1 (continued)

Study	*n*	Population details	Epidemiology data
Stiller et al., 2013 [153]	45,568	*Country*: Europe (EU27 countries) *Time Period*: 1995–2002 *Recruitment*:	*Age*: n.g. *Sex*: n.g. *Incid*: <1 per 10^6 PY *Prev*: 4 per 10^6 *Loc*: n.g. *Surv*: ≈75% @ 5-yr
Whelan et al., 2012 [146]	11,002	*Country*: England *Time Period*: 1979–2007 *Recruitment*: National Cancer Data Repository; Office of National Statistics	*Age*: 75% >50 yr old *Sex*: n.g. *Incid*: 0.03–0.04 per 10^6 PY *Prev*: 0.3–0.4 per 10^6 *Loc*: 26% SB, 23% MS, 45% Scrm *Surv*: 49–59% @ 5-yr
Zuckerman et al., 2018 [143]	1616	*Country*: USA *Time period*: 1973–2013 *Recruitment*: SEER database	*Age*: mean 54.8 yr *Sex*:58% M *Incid*: n.g. *Prev*: n.g. *Loc*: 41% SB, 27% MS, 32% Scrm *Surv*: median 162mo (SB), 95mo (MS), 87mo (Scrm)

Key: *F* female, *incid* incidence, *loc* location, *M* male, *mo* month, *MS* mobile spine, *n* number, *n.g.* not given, *prev* prevalence, *PY* person-year, *SB* skull base, *Scrm* sacrum, *SEER* surveillance, epidemiology, and end results, *Surv* survival, *yr* year

Multicenter Cohort Data

Within the mobile spine, lumbar tumors appear to be most common [4]. In a retrospective review of the AOSpine Knowledge Forum Tumor prospective database [148], Gokaslan et al. [4] reported treatment outcomes of 166 patients with mobile spine chordomas who underwent surgical resection. Similar to the findings of Zuckerman et al., mean age was 59 years and two-thirds of patients were male. Half of all lesions localized to the lumbar spine, with the cervical spine being the second most common region (35%). Multilevel involvement is relatively common. Forty-two percent of lesions involve 2 or more consecutive vertebrae. Lesions are also large at diagnosis, with an average lesion size of 4.9 × 4.1 × 4.3 cm (anterior-posterior × transverse × craniocaudal) or 87.7 cm^3. The majority of tumors are low grade (63%) at presentation and there is a tendency to locally recur. This is reduced by *en bloc* resection tough, as 5-year local recurrence is 20% for tumors receiving *en bloc* resection with negative margins (Enneking-appropriate) compared to 65% for tumors receiving Enneking-inappropriate resection. To this end, Gokaslan et al. [4] found *en bloc* resection with negative margins to be the strongest protective factor against local recurrence.

Using this same prospective registry, Varga et al. [5] published a description of the AOSpine experience with surgically treated sacral chordomas. Among the 167 included patients, mean age was 57 years and 58% of patients were male, similar to the numbers from the SEER database. Perhaps unsurprisingly, mean tumor size is much larger for sacral lesions (mean 588.1 cm^3) and nearly all tumors (98%) had extracompartmental extension at the time of diagnosis. Multilevel disease is also common and 6% of lesions extend into the mobile spine. As with mobile spine lesions, local recurrence is common, even though 80% of lesions are low grade at the time of treatment. Median local recurrence-free survival is roughly 4 years, but this is significantly improved by *en bloc* resection with negative margins [5]. Varga et al. did not find Enneking-appropriate resection to improve overall survival, though the authors attributed this to short overall follow-up and the current consensus is that the best-available data support Enneking-appropriate resection as a means of improving survival in chordoma [133, 149, 150].

Clinical Presentation

Owing to the slow-growing nature of chordoma, patients commonly have an insidious symptom onset and some are even asymptomatic at the time of radiographic diagnosis [1]. The clinical picture varies depending upon the location of the lesion, but generally stem from mass effect or erosion of adjacent bony structures leading to compromise of the vertebral column's load-bearing capacity. The first attempt to summarize the literature on the clinical presentation of chordoma was performed by Mabrey in 1935, who summarized the data for 150 chordomas described in the literature to date [25]. Of the 86 sacrococcygeal tumors included, the most common symptoms were pain (69%) with (43%) or without (26%) an accompanying palpable mass. Seventeen percent of the identified patients had presented with a tumor without clinical symptoms. Among the 46 skull base lesions, 33% had presented with headache. Localized pain was also common among the 14 mobile spine lesions, occurring in 9 patients (64%). Consistent with the slow-growing nature of chordoma, Mabrey reported an average time between symptom onset and clinical presentation of 41 months for skull base chordomas and 36 months for sacrococcygeal chordomas.

Data from Multicenter Cohorts

In their multicenter review of 166 patients surgically treated for mobile spine chordomas, Gokaslan and colleagues found that the majority of patients (89%) presented with pain [4]. Only a minority of patients (18%) had evidence of pathological fracture though. Similarly, Varga et al. [5] found nearly all patients with sacral chordoma present with tumor-related pain (96%). Pathologic fracture was again uncommon, being seen in only 4% of patients. A significant minority also present with neurological deficits though. In the Varga et al. study, 24% had motor weakness at the time of presentation and 27% had symptoms consistent with cauda equina syndrome [5].

A smaller, population-based study of Swedish patients by Eriksson et al. [88] found 52% of patients with sacrococcygeal chordoma present with local pain, 31% present with bowel or urinary complaints, and 10% present with asymptomatic masses; 21% of patients presented with sensory deficits and 7% presented with concomitant motor deficits. They reported a median time from symptom onset to diagnosis of roughly 1 year, consistent with the slow-growing nature of chordomas. The authors [88] endorsed a distinct presentation for mobile spine lesions, with only 38% of patients having local pain and 25% having motor deficits at the time of diagnosis. In a second Scandinavian population, Paavolainen and Teppo [3] reported that 73% of sacral chordomas present with pain and 60% noted a palpable mass at the time of presentation; only 13% of patients had urinary complaints at presentation. Tumors of the other locations were too uncommon to derive conclusions about clinical presentation owing to the small population at risk. Median time from symptom onset to diagnosis was 6 months with a mean of 12.7 months [3]. Collectively, these data suggest that patients most commonly present with insidious-onset, localized, non-mechanical pain that in a minority of cases will be accompanied by neurological deficits.

Conclusion

As relayed in this chapter, chordomas are an extremely uncommon clinical entity, oftentimes known as a "one in a million" disease. Though first described more than 150 years ago, the continuous investigation into the origins and molecular genetics of chordoma (Chap. 2) has identified it as a malignant derivative of the embryonic notochord. Lesions of the spine and sacrum most commonly present with local pain, though neurological symptoms occur in a nontrivial proportion of patients secondary to tumor mass effect. While their overall rarity of chordoma makes it an unlikely cause of spine-related complaints, clinicians should have increased clinical suspicion in patients in the sixth or seventh decade of life with insidious onset, non-mechanical pain. Lesions are easily detected on diagnostic imaging (Chap. 4) and patients with these lesions benefit from earlier detection and referral to high-volume centers of excellence [151, 152].

References

1. Pennington Z, Ehresman J, McCarthy EF, Ahmed AK, Pittman PD, Lubelski D, Goodwin CR, Sciubba DM. Chordoma of the sacrum and mobile spine: a narrative review. Spine J. 2020;21(3):500–17. https://doi.org/10.1016/j.spinee.2020.10.009.
2. Virchow RLK. Untersuchungen über die entwickelung des schädelgrundes im gesunden und krankhaften zustande, und über den einfluss derselben auf schädelform, gesichtsbildung und gehirnbau. 1st ed. Berlin: G. Reimer; 1857.
3. Paavolainen P, Teppo L. Chordoma in Finland. Acta Orthop Scand. 1976;47:46–51.
4. Gokaslan ZL, Zadnik PL, Sciubba DM, et al. Mobile spine chordoma: results of 166 patients from the AOSpine Knowledge Forum Tumor database. J Neurosurg Spine. 2016;24:644–51.

5. Varga PP, Szövérfi Z, Fisher CG, et al. Surgical treatment of sacral chordoma: prognostic variables for local recurrence and overall survival. Eur Spine J. 2015;24:1092–101.
6. Luschka H. Über gallertartige auswüchse am clivus blumenbachii. Virchows Arch. 1857;11:8–12.
7. Hirsch EF, Ingals M. Sacrococcygeal chordoma. J Am Med Assoc. 1923;80:1369–70.
8. Sahyouni R, Goshtasbi K, Mahmoodi A, Chen JW. A historical recount of chordoma. J Neurosurg Spine. 2018;28:422–8.
9. Müller JP. Ueber das Vorkommen von Resten der Chorda dorsalis bei Menschen nach der Geburt, und über ihr Verhältnis zu den Gallertgeschwulsten der Clivus. Zeitschrift für Ration Med. 1858;2:202–29.
10. Leboucq H. Recherches sur la mode de disparition de la corde dorsale chez les vertébrés supérieurs. Arch Biol (Liege). 1880;1:718–36.
11. Williams LW. The later development of the notochord in mammals. Am J Anat. 1908;8:251–84.
12. Kölliker A. Über die Beziehungen der Chorda dorsalis zur Bildung der Wirbel der Selachier und einiger anderer Fische. In: Verhandlungen der Phys. Gesellschaft zur Würzbg. Würzburg. Würzburg: A. Stuber; 1860. p. 193.
13. Löwe L. Zur Kenntniss der säugethierchorda. Arch für Mikroskopische Anat. 1879;16:597–612.
14. Steiner H. Ueber die ecchondrosis physalifora spheno-occipitalis. Cent für Allg Pathol und Pathol Anat. 1894;5:457.
15. Ribbert MWH. Über die experimentelle Erzeugung einer Ecchondrosis physalifora. Verhandlungen der Kong f inn Med. 1895;13:455–64.
16. Ribbert H. Geschwulstlehre für Ärzte und Studierende. 1st ed. Bonn: Friedrich Coehn; 1904.
17. Congdon CC. Proliferative lesions resembling chordoma following puncture of the nucleus pulposus in rabbits. J Natl Cancer Inst. 1952;12:893–907.
18. Stewart MJ, Burrow JF. Ecchordosis physaliphora spheno-occipitalis. J Neurol Psychopathol. 1923;4:218–20.
19. Bailey P, Bagdasar D. Intracranial chordoblastoma. Am J Pathol. 1929;5:439–450.5.
20. Fischer B, Steiner H. Über ein malignes chordom der schädel-rückgratshöhle. Beiträge zur Pathol Anat und zer Allg Pathol. 1907;40:109–19.
21. Stewart MJ, Morin JE. Chordoma: a review, with report of a new sacrococcygeal case. J Pathol Bacteriol. 1926;29:41–60.
22. Yamaguchi T, Suzuki S, Ishiiwa H, Shimizu K, Ueda Y. Benign notochordal cell tumors: a comparative histological study of benign notochordal cell tumors, classic chordomas, and notochordal vestiges of fetal intervertebral discs. Am J Surg Pathol. 2004;28:756–61.
23. Klebs E. Ein fall von ecchondrosis spheno-occipitalis amylacea. Arch für Pathol Anat und Physiol und für Klin Med. 1864;31:396–9.
24. Hass GM. Chordomas of the cranium and cervical portion of the spine: a review of the literature with report of a case. Arch Neurol Psychiatr. 1934;32:300–27.
25. Mabrey RE. Chordoma: a study of 150 cases. Am J Cancer. 1935;25:501–17.
26. Klebs E. Die allgemeine Pathologie oder die Lehre von den Ursachen und dem Wesen der Krankheitsprocesse: Ein handbuch für studierende und aerzte. 1st ed. Jena: Verlag Von Gustav Fischer; 1889.
27. Henning L. Über congenitale echte Sakraltumoren. Beiträge zur Pathol Anat und zer Allg Pathol. 1900;28:593.
28. Burrow JF, Stewart MJ. Malignant spheno-occipital chordoma. J Neurol Neurosurg Psychiatry. 1923;4:205–17.
29. Grahl O. Eine Ecchondrosis physalifora spheno-occipitalis (Chordom des Türkensattels) ungewöhnlichen Umfangs mit interessanten klinischen. Inaugural-Dissertation 1903.
30. Seiffer. Ein Fall von seltenen Geschwulstbildung der Schädelbasis. Neurol Cent. 1905;24:469.
31. Frenkel H, Bassal L. Sur un cas de chordome malin sphéno-occipital. Arch médecine expérimentale d'anatomie Pathol. 1910;22:703.
32. Eitel W. Ein Beitrag zur Kasuistik der Chordome. Inaugural-Dissertation 1911.

33. Wegelin K. Über ein malignes chordom des clivus blumenbachii. Atti del Congr internazionale dei Patol. 1912;1:70.
34. Linck A. Chordoma malignum, ein Beitrag zur Kenntnis der Geschwülste an der Schädelbasis. Beiträge zur Pathol Anat und zer Allg Pathol. 1909;46:573–85.
35. Feldmann I. Chordoma ossis sacri. Beiträge zur Pathol Anat und zer Allg Pathol. 1910;48:630–4.
36. Mazzia O. Chordom der Sakralgegend. Zentralbl Allg Pathol. 1910;21:769–72.
37. Curtis F, Le Fort R. Tumeur de la région sacro-coccygienne chez un adulte: angio-sarcome a type périthélial développé aux dépens de la glande de Luschka. Rev Chir. 1911;43:1.
38. Stewart MJ. Malignant sacrococcygeal chordoma. J Pathol Bacteriol. 1922;25:40–62.
39. Alézais H, Peyron F. Contribution à l'étude des chordomes. Chordome de la région occipitale. Bull Assoc Fr Etud Cancer. 1914;7:194.
40. Albert H. Chordoma, with the report of a malignant case from the sacrococcygeal region. Surg Gynecol Obstet. 1915;21:766.
41. Daland EM. Chordoma. Bost Med Surg J. 1919;180:571–6.
42. Potoschnig G. Ein Fall von malignem chordom mit metastasen. Beiträge zur Pathol Anat und zer Allg Pathol. 1919;65:356–62.
43. Coenen H. Das chordom. Beitr Klin Chir. 1925;83:1–77.
44. Corsy F, Surmont J. Sur l'histogénèse, l'évolution des tumeurs de la notochorde. Bull Assoc Fr Etud Cancer. 1927;16:316–76.
45. Koritzki GE. Histiogenesis and localization of chordomata. Cent für Allg Pathol und Pathol Anat. 1914;25:638.
46. Rubaschow S. Zur onkologischen Kasuistik: Chordom mit ungewöhnlichem Sitz. Zentralbl Chir. 1929;56:137.
47. Hirsch C. Zur Frage des malignen chordoms. Zeitschrift für Hals-, Nasen-, und Ohren-heilkd. 1931;28:140.
48. Higinbotham NL, Phillips RF, Farr HW, Hustu HO. Chordoma. Thirty-five-year study at memorial hospital. Cancer. 1967;20:1841–50.
49. Rotter J, Mueller K, MacConnell A, McGowan J, Spitz S. Isolated cervical extraosseous intradural chordoma attached to the C5 nerve root: a case report. Chinese Neurosurg J. 2019;5:22.
50. Tomlinson FH, Scheithauer BW, Miller GM, Onofrio BM. Extraosseous spinal chordoma. Case report. J Neurosurg. 1991;75:980–4.
51. Pierre-Khan A, Sarkis A, Lellouch-Tubiana A, Sebag G, Finidori G, Hirsch JF. Epidural chordoma without bone involvement. A propos of a case in a child. Review of the literature. Neurochirurgie. 1991;37:258–63.
52. Kalish G, Rubin BP, Chew FS, Richardson ML. Epidural Chordoma of the cervical spine with secondary bone involvement. Radiol Case Rep. 2006;1:128–33.
53. Jallo J, Nathan D, Bierbrauer K, Farber E. Chordoma: a case report. Surg Neurol. 1997;48:46–8.
54. Katayama Y, Tsubokawa T, Hirasawa T, Takahata T, Nemoto N. Intradural extraosseous chordoma in the foramen magnum region. J Neurosurg. 1991;75:976–9.
55. Vinke RS, Lamers EC, Kusters B, van Lindert EJ. Intradural prepontine chordoma in an 11-year-old boy. A case report. Childs Nerv Syst. 2016;32:169–73.
56. Chang SW, Gore PA, Nakaji P, Rekate HL. Juvenile intradural chordoma: case report. Neurosurgery. 2008;62:E525–7.
57. Fabricius-Möller J. Chordoma of retropharyngeal region. Hospitalstid. 1919;62:849–57.
58. Argaud R. Chordome Malin. Arch médecine expérimentale d'anatomie Pathol. 1918;28:364–74.
59. Argaud R, Clermont D. Chordome primitif malin de la poche de Luschka. Ann Anat Pathol (Paris). 1928;5:145–52.
60. Loebell H. Zur Therapie der bösartigen Clivus- und Nasenrachenchordome. Zeitschrift für Hals-, Nasen-, und Ohren-heilkd. 1928;21:337–48.
61. Congdon CC. Benign and malignant chordomas; a clinico-anatomical study of twenty-two cases. Am J Pathol. 1952;28:793–821.

62. Zoltán L, Fényes I. Stereotactic diagnosis and radioactive treatment in a case of sphenooccipital chordoma. J Neurosurg. 1960;17:888–900.
63. Forsyth PA, Cascino TL, Shaw EG, Scheithauer BW, O'Fallon JR, Dozier JC, Piepgras DG. Intracranial chordomas: a clinicopathological and prognostic study of 51 cases. J Neurosurg. 1993;78:741–7.
64. Sen CN, Sekhar LN, Schramm VL, Janecka IP. Chordoma and chondrosarcoma of the cranial base. Neurosurgery. 1989;25:931–40. discussion 940–941
65. Atkins LW, Khudados ES, Kaleoglu M, Revesz T, Sacares P, Crockard HA. Skull base chordomas: a review of 38 patients, 1958–88. Br J Neurosurg. 1993;7:241–8.
66. Al-Mefty O, Borba LAB. Skull base chordomas: a management challenge. J Neurosurg. 1997;86:182–9.
67. Colli BO, Al-Mefty O. Chordomas of the skull base: follow-up review and prognostic factors. Neurosurg Focus. 2001;10:1–11.
68. Gay E, Sekhar LN, Rubinstein E, Wright DC, Sen C, Janecka IP, Snyderman CH. Chordomas and chondrosarcomas of the cranial base. Neurosurgery. 1995;36:887–97.
69. Lalwani AK, Kaplan MJ, Gutin PH. The transsphenoethmoid approach to the sphenoid sinus and clivus. Neurosurgery. 1992;31:1008–14.
70. Maira G, Pallini R, Anile C, Fernandez E, Salvinelli F, La Rocca LM, Rossi GF. Surgical treatment of clival chordomas: the transsphenoidal approach revisited. J Neurosurg. 1996;85:784–92.
71. Raffel C, Wright DC, Gutin PH, Wilson CB. Cranial chordomas: clinical presentation and results of operative and radiation therapy in twenty-six patients. Neurosurgery. 1985;17:703–10.
72. Laws ER. Transsphenoidal surgery for tumors of the clivus. Otolaryngol Neck Surg. 1984;92:100–1.
73. Frank G, Sciarretta V, Calbucci F, Farneti G, Mazzatenta D, Pasquini E. The endoscopic transnasal transsphenoidal approach for the treatment of cranial base chordomas and chondrosarcomas. Oper Neurosurg. 2006;59:ONS-50–7.
74. Jho H-D, Carrau RL, McLaughlin ML, Somaza SC. Endoscopic transsphenoidal resection of a large chordoma in the posterior fossa. Neurosurg Focus. 1996;1:E5.
75. Jho H-D. Endoscopic transsphenoidal surgery. J Neuro-Oncol. 2001;54:187–95.
76. Cannizzaro D, Tropeano MP, Milani D, Spaggiari R, Zaed I, Mancarella C, Lasio GB, Fornari M, Servadei F, Cardia A. Microsurgical versus endoscopic trans-sphenoidal approaches for clivus chordoma: a pooled and meta-analysis. Neurosurg Rev. 2020; https://doi.org/10.1007/s10143-020-01318-y.
77. Zoli M, Milanese L, Bonfatti R, et al. Clival chordomas: considerations after 16 years of endoscopic endonasal surgery. J Neurosurg. 2018;128:329–38.
78. Syme WS, Cappell DF. A case of chordoma of the cervical vertebræ with involement of the pharynx. J Laryngol Otol. 1926;41:209–22.
79. Raul P, Diss A. Chordome malin de la colonne vertebrale lambaire. Bull la Soc Anat. 1924;94:395–402.
80. Cameron JAM. Case of sacro-coccygeal chordoma. Glasgow Med J. 1926;106:38–43.
81. Cappell DF. Chordoma of the vertebral column with three new cases. J Pathol Bacteriol. 1928;31:797–814.
82. Jones RB. Chordoma of the third lumbar vertebra simulating carcinoma of the prostate with vertebral metastasis. Report of a case. Br J Surg. 1960;48:162–5.
83. Rosenqvist H, Saltzman G-F. Sacrococcygeal and vertebral chordomas and their treatment. Acta Radiol. 1959;52:177–93.
84. Dahlin DC, Maccarty CS. Chordoma. A study of fifty-nine cases. Cancer. 1952;5:1170–8.
85. Azzarelli A, Quagliuolo V, Cerasoli S, Zucali R, Bignami P, Mazzaferro V, Dossena G, Gennari L. Chordoma: natural history and treatment results in 33 cases. J Surg Oncol. 1988;37:185–91.
86. Sundaresan N, Galicich JH, Chu FCH, Huvos AG. Spinal chordomas. J Neurosurg. 1979;50:312–9.

87. Stener B. Complete removal of vertebrae for extirpation of tumors. A 20-year experience. Clin Orthop Relat Res. 1989;245:72–82.
88. Eriksson B, Gunterberg B, Kindblom L-G. Chordoma: a clinicopathologic and prognostic study of a Swedish National Series. Acta Orthop Scand. 1981;52:49–58.
89. Sundaresan N, Huvos AG, Krol G, Lane JM, Brennan M. Surgical treatment of spinal chordomas. Arch Surg. 1987;122:1479–82.
90. Sundaresan N, Steinberger AA, Moore F, Sachdev VP, Krol G, Hough L, Kelliher K. Indications and results of combined anterior—posterior approaches for spine tumor surgery. J Neurosurg. 1996;85:438–46.
91. Heary RF, Vaccaro AR, Benevenia J, Cotler JM. "En-bloc" vertebrectomy in the mobile lumbar spine. Surg Neurol. 1998;50:548–56.
92. Bas T, Bas P, Prieto M, Ramose V, Bas JL, Espinosa C. A lumbar chordoma treated with a wide resection. Eur Spine J. 1994;3:115–7.
93. Boriani S, Bandiera S, Biagini R, Bacchini P, Boriani L, Cappuccio M, Chevalley F, Gasbarrini A, Picci P, Weinstein JN. Chordoma of the mobile spine: fifty years of experience. Spine (Phila Pa 1976). 2006;31:493–503.
94. Mixter CG, Mixter WJ. Surgical management of sacrococcygeal and vertebral chordoma. Arch Surg. 1940;41:408–21.
95. Shackelford RT, Rhode CM. Sacrococcygeal chordoma: its surgical treatment. Ann Surg. 1955;141:952–66.
96. Boriani S, Chevalley F, Weinstein JN, Biagini R, Campanacci L, De Iure F, Piccill P. Chordoma of the spine above the sacrum. Treatment and outcome in 21 cases. Spine. 1996;21:1569–77.
97. Fujiwara T, Tsuda Y, Stevenson J, Parry M, Jeys L. Sacral chordoma: do the width of surgical margin and the use of photon/proton radiotherapy affect local disease control? Int Orthop. 2020;44:381–9.
98. Colangeli S, Muratori F, Bettini L, et al. Surgical treatment of sacral chordoma: En bloc resection with negative margins is a determinant of the long-term outcome. Surg Technol Int. 2018;33:343–8.
99. Kaiser TE, Pritchard DJ, Unni KK. Clinicopathologic study of sacrococcygeal chordoma. Cancer. 1984;53:2574–8.
100. Pearlman AW, Friedman M. Radical radiation therapy of chordoma. Am J Roentgenol. 1970;108:333–41.
101. Enneking WF. A system of staging musculoskeletal neoplasms. Clin Orthop Relat Res. 1986;204:9–4.
102. Enneking WF, Spanier SS, Goodman MA. A system for the surgical staging of musculoskeletal sarcoma. Clin Orthop Relat Res. 1980;153:106–20.
103. Fuchs B, Dickey ID, Yaszemski MJ, Inwards CY, Sim FH. Operative management of sacral chordoma. J Bone Joint Surg Am. 2005;87:2211–6.
104. Radaelli S, Stacchiotti S, Ruggieri P, et al. Sacral chordoma: long-term outcome of a large series of patients surgically treated at two reference centers. Spine (Phila Pa 1976). 2016;41:1049–57.
105. Akiyama T, Ogura K, Gokita T, et al. Analysis of the infiltrative features of chordoma: the relationship between micro-skip metastasis and postoperative outcomes. Ann Surg Oncol. 2018;25:912–9.
106. van Wulfften Palthe ODR, Tromp I, Ferreira A, Fiore A, Bramer JAM, van Dijk NC, DeLaney TF, Schwab JH, Hornicek FJ. Sacral chordoma: a clinical review of 101 cases with 30-year experience in a single institution. Spine J. 2019;19:869–79.
107. Greenwald CM, Meaney TF, Hughes CR. Chordoma – uncommon destructive lesion of cerebrospinal axis. J Am Med Assoc. 1957;163:1240–4.
108. Wood EH, Himadi GM. Chordomas: a roentgenologic study of sixteen cases previously unreported. Radiology. 1950;54:706–16.
109. Kamrin RP, Potanos JN, Pool JL. An evaluation of the diagnosis and treatment of chordoma. J Neurol Neurosurg Psychiatry. 1964;27:157–65.

110. Tewfik HH, McGinnis WL, Nordstrom DG, Latourette HB. Chordoma. Evaluation of clinical behavior and treatment modalities. Int J Radiat Oncol. 1977;2:959–62.
111. Amendola BE, Amendola MA, Oliver E, McClatchey KD. Chordoma: role of radiation therapy. Radiology. 1986;158:839–43.
112. Reddy EK, Mansfield CM, Hartman GV. Chordoma. Int J Radiat Oncol. 1981;7:1709–11.
113. Suit HD, Goitein M, Munzenrider J, Verhey L, Davis KR, Koehler A, Linggood R, Ojemann RG. Definitive radiation therapy for chordoma and chondrosarcoma of base of skull and cervical spine. J Neurosurg. 1982;56:377–85.
114. Fagundes MA, Hug EB, Liebsch NJ, Daly W, Efird J, Munzenrider JE. Radiation therapy for chordomas of the base of skull and cervical spine: patterns of failure and outcome after relapse. Int J Radiat Oncol. 1995;33:579–84.
115. Castro JR, Linstadt DE, Bahary J-P, Petti PL, Daftari I, Collier JM, Gutin PH, Gauger G, Phillips TL. Experience in charged particle irradiation of tumors of the skull base: 1977–1992. Int J Radiat Oncol. 1994;29:647–55.
116. Hug EB, Loredo LN, Slater JDJM, Devries A, Grove RI, Schaefer RA, Rosenberg AE, Slater JDJM. Proton radiation therapy for chordomas and chondrosarcomas of the skull base. J Neurosurg. 1999;91:432–9.
117. Dial BL, Kerr DL, Lazarides AL, et al. The role of radiotherapy for chordoma patients managed with surgery. Spine (Phila Pa 1976). 2020;45:E742–51.
118. Rotondo RL, Folkert W, Liebsch NJ, et al. High-dose proton-based radiation therapy in the management of spine chordomas: outcomes and clinicopathological prognostic factors. J Neurosurg Spine. 2015;23:788–97.
119. Yasuda M, Bresson D, Chibbaro S, Cornelius JF, Polivka M, Feuvret L, Takayasu M, George B. Chordomas of the skull base and cervical spine: clinical outcomes associated with a multimodal surgical resection combined with proton-beam radiation in 40 patients. Neurosurg Rev. 2012;35:171–83.
120. Cavallo LM, Mazzatenta D, D'Avella E, et al. The management of clival chordomas: an Italian multicentric study. J Neurosurg. 2020;4:1–10.
121. Iannalfi A, D'Ippolito E, Riva G, et al. Proton and carbon ion radiotherapy in skull base chordomas: a prospective study based on a dual particle and a patient-customized treatment strategy. Neuro-Oncology. 2020;22:1348–58.
122. Demizu Y, Imai R, Kiyohara H, et al. Carbon ion radiotherapy for sacral chordoma: a retrospective nationwide multicentre study in Japan. Radiother Oncol. 2021;154:1–5.
123. Bostel T, Mattke M, Nicolay NH, Welzel T, Wollschläger D, Akbaba S, Mayer A, Sprave T, Debus J, Uhl M. High-dose carbon-ion based radiotherapy of primary and recurrent sacrococcygeal chordomas: long-term clinical results of a single particle therapy center. Radiat Oncol. 2020;15:206.
124. Uhl M, Welzel T, Jensen A, Ellerbrock M, Haberer T, Jäkel O, Herfarth K, Debus J. Carbon ion beam treatment in patients with primary and recurrent sacrococcygeal chordoma. Strahlentherapie und Onkol. 2015;191:597–603.
125. Imai R, Kamada T, Araki N, et al. Carbon ion radiation therapy for Unresectable sacral chordoma: an analysis of 188 cases. Int J Radiat Oncol. 2016;95:322–7.
126. Debus J, Schulz-Ertner D, Schad L, Essig M, Rhein B, Thillmann CO, Wannenmacher M. Stereotactic fractionated radiotherapy for chordomas and chondrosarcomas of the skull base. Int J Radiat Oncol. 2000;47:591–6.
127. Kondziolka D, Lunsford LD, Flickinger JC. The role of radiosurgery in the management of chordoma and chondrosarcoma of the cranial base. Neurosurgery. 1991;29:38.
128. Muthukumar N, Kondziolka D, Lunsford LD, Flickinger JC. Stereotactic radiosurgery for chordoma and chondrosarcoma: further experiences. Int J Radiat Oncol. 1998;41:387–92.
129. Tanaka T, Kobayashi T, Kida Y, Oyama H, Niwa M. The results of gamma knife radiosurgery for malignant skull base tumors. No Shinkei Geka. 1996;24:235–9.

130. Miller RC, Foote RL, Coffey RJ, Gorman DA, Earle JD, Schomberg PJ, Kline RW. The role of stereotactic radiosurgery in the treatment of malignant skull base tumors. Int J Radiat Oncol. 1997;39:977–81.
131. Kocher M, Voges J, Staar S, Treuer H, Sturm V, Mueller R-P. Linear accelerator radiosurgery for recurrent malignant tumors of the skull base. Am J Clin Oncol. 1998;21:18–22.
132. Stacchiotti S, Gronchi A, Fossati P, et al. Best practices for the management of local-regional recurrent chordoma: a position paper by the Chordoma Global Consensus Group. Ann Oncol. 2017;28:1230–42.
133. Stacchiotti S, Sommer J, Chordoma Global Consensus Group. Building a global consensus approach to chordoma: a position paper from the medical and patient community. Lancet Oncol. 2015;16:e71–83.
134. McSweeney AJ, Sholl PR. Metastatic chordoma. Use of mechlorethamine (nitrogen mustard) in chordoma therapy. AMA Arch Surg. 1959;79:152–5.
135. Rissanen PM, Holsti LR. Sacrococcygeal chordomas and their treatment. Radiol Clin Biol. 1967;36:153–64.
136. Pearlman AW, Singh RK, Hoppenstein R, Wilder J. Chordoma: combined therapy with radiation and surgery: case report and new operative approach. Bull Hosp Joint Dis. 1972;33:47–57.
137. Razis DV, Tsatsaronis A, Kyriazides I, Triantafyllou D. Chordoma of the cervical spine treated with vincristine sulfate. J Med. 1974;5:274–7.
138. Harwick RD, Miller AS. Craniocervical chordomas. Am J Surg. 1979;138:512–6.
139. Spratt JS, Martin AE, McKeown J. Sacral chordoma: a case study and review. J Surg Oncol. 1981;18:101–3.
140. Jacob HE. Chemotherapy for cranial base tumors. J Neuro-Oncol. 1994;20:327–35.
141. Passias PG, Pierce KE, Lafage V, et al. At what point should the thoracolumbar region be addressed in patients undergoing corrective cervical deformity surgery? Spine J. 2020;20:S2–3.
142. Smoll NR, Gautschi OP, Radovanovic I, Schaller K, Weber DC. Incidence and relative survival of chordomas: the standardized mortality ratio and the impact of chordomas on a population. Cancer. 2013;119:2029–37.
143. Zuckerman SL, Bilsky MH, Laufer I. Chordomas of the skull base, mobile spine, and sacrum: an epidemiologic investigation of presentation, treatment, and survival. World Neurosurg. 2018;113:e618–27.
144. McMaster ML, Goldstein AM, Bromley CM, Ishibe N, Parry DM. Chordoma: incidence and survival patterns in the United States, 1973–1995. Cancer Causes Control. 2001;12:1–11.
145. Kuo T-M, Mobley LR. How generalizable are the SEER registries to the cancer populations of the USA? Cancer Causes Control. 2016;27:1117–26.
146. Whelan J, McTiernan A, Cooper N, Wong YK, Francis M, Vernon S, Strauss SJ. Incidence and survival of malignant bone sarcomas in England 1979–2007. Int J Cancer. 2012;131:E508–17.
147. Hung G-Y, Horng J-L, Yen H-J, Yen C-C, Chen W-M, Chen PC-H, Wu H-TH, Chiou H-J. Incidence patterns of primary bone cancer in Taiwan (2003–2010): a population-based study. Ann Surg Oncol. 2014;21:2490–8.
148. Fisher CG, Goldschlager T, Boriani S, et al. An evidence-based medicine model for rare and often neglected neoplastic conditions. J Neurosurg Spine. 2014;21:704–10.
149. Dea N, Fisher CG, Reynolds JJ, et al. Current treatment strategy for newly diagnosed chordoma of the mobile spine and sacrum: results of an international survey. J Neurosurg Spine. 2019;30:119–25.
150. Radaelli S, Fossati P, Stacchiotti S, et al. The sacral chordoma margin. Eur J Surg Oncol. 2020;46:1415–22.
151. Malik AT, Alexander JH, Khan SN, Scharschmidt TJ. Is treatment at a high-volume center associated with an improved survival for primary malignant bone tumors? Clin Orthop Relat Res. 2020;478:631–42.

152. Ogura K, Yasunaga H, Horiguchi H, Ohe K, Shinoda Y, Tanaka S, Kawano H. Impact of hospital volume on postoperative complications and in-hospital mortality after musculoskeletal tumor surgery: analysis of a national administrative database. J Bone Joint Surg Am. 2013;95:1684–91.
153. Stiller CA, Trama A, Serraino D, Rossi S, Navarro C, Chirlaque MD, Casali PG, Group TRW. Descriptive epidemiology of sarcomas in Europe: report from the RARECARE project. Eur J Cancer. 2013;49:684–95.