Offprint from
Advances and Technical Standards in Neurosurgery, Vol. 33
Edited by J.D. Pickard

Tumor-biology and current treatment of skull-base chordomas

M. N. PAMIR and K. ÖZDUMAN

Marmara University Faculty of Medicine, Department of Neurosurgery,
Marmara University Institute of Neurological Sciences, Istanbul, Turkey

With 9 Figures

Contents

Abstract

Chordomas are rare, slow growing tumors of the axial skeleton, which derive from the remnants of the fetal notochord. They can be encountered anywhere along the axial skeleton, most commonly in the sacral area, skull base and less commonly in the spine. Chordomas have a benign histopathology but exhibit malignant clinical behavior with invasive, destructive and metastatic potential. Genetic and molecular pathology studies on oncogenesis of chordomas are very limited and there is little known on mechanisms governing the disease. Chordomas most commonly present with headaches and diplopia and can be readily diagnosed by current

neuroradiological methods. There are 3 pathological subtypes of chordomas: classic, chondroid and dedifferentiated chordomas. Differential diagnosis from chondrosarcomas by radiology or pathology may at times be difficult.

Skull base chordomas are very challenging to treat. Clinically there are at least two subsets of chordoma patients with distinct behaviors: some with a benign course and another group with an aggressive and rapidly progressive disease. There is no standard treatment for chordomas. Surgical resection and high dose radiation treatment are the mainstays of current treatment. Nevertheless, a significant percentage of skull base chordomas recur despite treatment. The outcome is dictated primarily by the intrinsic biology of the tumor and treatment seems only to have a secondary impact. To date we only have a limited understanding this biology; however better understanding is likely to improve treatment outcome.

Hereby we present a review of the current knowledge and experience on the tumor biology, diagnosis and treatment of chordomas.

Keywords: Chordoma; chondrosarcoma; skull base; operative technique; Gamma-Knife; radiation therapy.

Definition

Chordomas are rare, slow growing bone tumors of the axial skeleton. Due to their invasive, destructive growth characteristics and metastatic potential they are considered malignant tumors. Since their first description chordomas have been and continue to be a treatment challenge. As a tumor, that frequent arises in the central skull base, and is widely invasive in this delicate and intricate anatomy, the surgical resection of chordomas is very challenging even for the experienced skull base surgeon. Some chordomas do well even after simple limited resection, while others continue their relentless growth despite aggressive surgery and multimodal adjuvant treatment protocols, finally to result in the patient's demise. Determinants of this difference in behavior is not known, however is assumed to depend on the intrinsic biology of chordomas.

Chordomas derive from remnants of the notochord and arise along the axial skeleton anywhere from the visceral cranium to the sacrococcygeal bone, where these remnants are present. The outcome after diagnosis of skull base chordomas varies considerably. There are at least two subsets of patients with distinct clinical behavior: some with a benign course and another group with an aggressive and rapidly progressive course over 3–5 years. As the suffix "oma" denotes, chordomas have a differentiated morphological phenotype and appear "benign" under the microscope. However, in many cases this phenotype obscures the malignant tumor biology. Progressive chordomas have an indolent but relentlessly progressive course and are very challenging to treat. The outcome is clearly dictated primarily by the intrinsic biology of the tumor and treatment seems only to have a secondary impact. However, determinants of

this biology are still unknown to us and this excludes the possibility of a rational or patient based treatment.

Today there is no single best treatment option, or combination, for chordomas and the current favor is a wide resection followed by high dose radiotherapy. Existing literature can only provide level-4 and very limited level-3 evidence. This is mostly a consequence of the rarity of this disease. Since its first description in 1856 there have been only 24 studies of skull-base chordomas that reported cohorts larger than 30 patients. Skull base chordomas grow widely invasive in the skull base and the patients usually succumb to progressive tumor growth despite multimodal treatment. This is because of their widely invasive nature, which makes them difficult surgical targets and because of their poor response to any available adjuvant therapy.

Hereby we will provide a comprehensive review of the existing knowledge on tumor biology and treatment options for chordomas.

History

We owe the description of chordoma to the important work done in the second half of the 19th century [296]. The famous German pathologist Rudolph Virchow in 1846 found gelatoinous nest like formations in the spheno-occipital synchondrosis and gave the first description of the "physaliferous cells", the large vesicular cells characteristic of chordomas [356]. Speculating a possible relationship to other cartilaginous tumors he called the lesion "ecchondrosis (originating from cartilage) physillaphora (vacuole containing) spheno-occipitalis" and described them as: " growth and mucoid metamorphosis of remains of the sphenooccipital cartilage" [356]. Hubert von Luschka in his article in 1857 [208] and Virchow in his book [356] were the first to report their findings on this pathology in 1857. Hasse [139] and Zenker [376] in the same year confirmed the findings and with reference to Virchow, referred to them as the "mucous or gelatinous tumors of the clivus Blumenbachi". In the following years Kölliker [177] came up with the concept that the mammalian nucleus pulposus was derived from notochord. Subsequently, Heinrich Müller [237] in 1858, rejected the theory that these lesions are cartilagenous tumors and suggested a possible origin from the primitive notochord and induced a nomenclature change to ecchordosis (originiating from Chorda dorsalis) physaliphora. These ideas caused much controversy in morphological sciences and caused a division among the pathologists with some calling these "jelly tumors" a neoplasia while others considering them developmental abnormalities. Klebs [172] gave the first description of pontine compression from a skull base chordoma in 1864. The term "chordoma" was first used by Ribbert [279, 281] in 1894. Ribbert punctured the anterior intervertebral ligament in rabbits and successfully produced experimental chordomas, essentially classifying them as developmental tumors. In 1904 he

published his opinion on the origin of chordomas [280]. In his laboratory Fischer and Steiner [325] confirmed Müller's theory by creating a malignant chordoma in rabbits. In 1909 Linck [205] for the first time established criteria for histopathological diagnosis of chordoma and defined formation of mucus, presence of physaliphorous cells, lobular arrangement, nuclear vacuolation and resemblance of notochordal tissue as characteristic findings. The first succesful resection of a skull base chordoma was reported by Harvey Cushing in his 1912 monograph on pituitary adenomas [72]. The operation, performed in 1909, provided symptomatic improvement for motnths and the tumor was initially misdiagnosed as teratoma. With advancements in surgical technique a more radical approach to skull base has been proposed by several authors. In 1914, Alezais and Peyron [6, 7] gave a detailed description of histogenesis and evolution of chordomas. Stewart and Morin [328] were the first to suggest that chordomas may be derived from ecchordosis physaliphora. The experiments of Ribbert were replicated by Congdon [61] in 1952 in a similar rabbit model. Zülch [379] in 1956 noted variable clinical behavior among chordomas and differentiated between slowly growing benign chordomas and rapidly growing malignant chordomas. In the same book, Zülch also proposed that chordomas arise at anatomical locations where the notochord tissue is not surrounded by cartilage [379]. Heffelfinger, analyzing 155 cases of chordoma and all other cartilaginous tumors treated at Mayo clinic from 1910 to 1973, described a "chondroid" subtype in 1973 [141]. Despite major progress in microneurosurgery in the 1960's, a hundred years after the first description of chordomas, the treatment was still very disappointing. In 1975 Krayenbühl and Yaşargil [182] reported an analysis of 221 cases of skull base chordomas collected from the literature until 1970 and 4 cases of theirs. The results of this analysis were discouraging with 17.5% operative- and another 27% late postoperative mortality [182, 375]. The advent of sophisticated neuroimaging techniques in the 1980's brought better preoperative planning and the development skull base surgery in the early 1990's made total resection possible with acceptable morbidity and mortality. Together with advances in radiotherapy the treatment of chordomas has improved significantly in the last 25 years.

Accumulating experience and sophisticated molecular biology techniques brought a better understanding of the tumor biology. Today we know that the major determinant of the disease course of a chordoma is the tumor biology. The treatment, how aggressive or powerful it may be, does only modulate but does not change this behavior.

Pathogenesis

Etiology of chordomas is not known, nor there any predisposing conditions. Current scientific knowledge supports the theory that chordomas originate

from the remnants of notochord (from the Greek notos: "back", chorde: "string"). The notochord is a rod shaped body that defines the primitive axis of the embryo. In higher vertebrates, the notochord exists transiently during embryogenesis provides structural support and secretes signaling molecules to provide position and fate information to the surrounding structures [326]. The human notochord originates from ectoderm during the third week of embryogenesis [269, 369]. It influences the development of peri-notochordial mesenchymal elements, however, being a primitive relative of cartilage, also serves as the axial skeleton of the embryo until the formation of other elements, such as the vertebral bodies. Without a fully developed notochord embryos fail to elongate [326]. Ultimately the notochord that runs through the middle of each vertebra, which is identified by type X collagen expression, is dismantled and replaced by bone, similar to the enchondral bone formation, in which Collagen II rich extracellular matrix (ECM) is deposited by type X collagen and finally replaced by bone [206]. However, between the vertebrae the notochord does not express collagen-X and eventually expands forming the nucleus pulposus [13]. The cranial extension of this embryonic structure extends as far as the sella turcica. In the skull base the notochord is incorporated into the caudal part of the sphenoid and the basilar part of the occipital bone [296, 297]. It is possible for the notochord to bend towards the pharyngeal wall, forming secondary unions with the pharyngeal epithelium [264].

The notochord most likely is a primitive relative of cartilage and shares many characteristics with it such as expression of type II and type IX collagens, aggrecan, Sox9 and chondromodulin [126]. Chondrocytes normally secrete a highly hyrdrated extracellular matrix, which gives cartilage its main structural properties [326]. Notochordal cells, on the contrary, retain hydrated materials in large cellular vacuoles [326].

Benign chordal ectopias (ecchordosis physaliphora) are commonly encountered in the skull base in asymptomatic adults. It is widely believed that these benign chordal ectopias are also precursors of chordomas. Some authors have proposed a progressive tumorigenesis from benign notochordal tumors while others advocated a de-novo origin from notochordal remnants [372, 373]. The hypothesis on the origin of chordomas from pre-malignant lesions (ecchordosis physillaphora) is supported by similar morphology (light microscopy and electron microscopy [148]), similar immunophenotype [126, 295] and similar localization [370, 371]. Ecchordosis physillaphora are reported with an incidence of 0.5 to 2% in autopsy studies [3, 221]. Similar incidences are reported in radiological studies [221]. Alhough most common in the skull base, ecchordosis physillaphora (EP) may also be seen in other locations along the axial skeleton [245, 277, 348]. The supposed origin of ecchordosis physillaphora from the notochord is supported by similar electron microscopy findings and immunohistochemical profile [143, 148, 368].

Genetics and molecular biology

Familial chordomas

Familial chordomas are exceptionally rare. However, the presence of several cases in two or more close relatives suggested that the disease may be caused by possible genetic alterations. In 1958, Foote *et al.* [105] reported the familial occurrence of chordoma for the first time in a brother and sister, who presented with metastatic sacrococygeal chordomas. This was flowed by a report of two young brothers with nasopharyngeal chordoma [93], a man, his mother and daughter with nasopharyngeal chordomas [167], a man with sacrococygeal chordoma whose sister and niece developed clival chordomas and whose first cousin had a nasopharyngeal chordoma [327], and a father and daughter with clival chordomas [73, 231]. Stepanek *et al.* [327] reported an autosomal dominant inheritance pattern. This was followed by a genome-wide linkage analysis in an extended pedigree of 10 affected individuals of the same family and the defect was localized to 7q33 [166]. In a recent study the authors reconfirmed this disease region in the same 3 families by linkage analysis, however were unable to detect the same changes in a fourth family [374]. Dalpra *et al.* [73] reported a father and a daughter with recurrent chordoma. Another daughter also had a cerebellar astrocytoma. Cytogenetic analysis revealed pronounced heterogeneity of the karyotypes, with a number of unbalanced translocations leading to 1p losses [73, 231]. An analysis of this family and several other sporadic cases mapped the genetic defect to a 25cM segment between 1p36.31 and 1P36.13 and possibly involving a tumor suppressor gene [231]. A list of reported disease loci in chordomas is presented in Table 1.

Telomere maintenance

Telomere length is an important regulator of cell life span and is deregulated in virtually all types of cancer to provide limitless replicative potential [19]. Reactivation of the cellular enzyme telomerase is the most common way utilized by tumor cells to maintain telomere length. This reactivation is strongly associated with genomic instability [19]. Butler *et al.* [42] showed increased telomere length in 4 of 4 chordomas they studied and telomerase activity in half of these cases. Pallini *et al.* [258] in their study of 26 skull base chordoma cases concluded that expression of hTERT correlated significantly with shorter recurrence-free survival. Interestingly the majority of the hTERT positive tumors in this study were also positive for p53 mutations, an association that results in increased incidence in human-like carcinomas in mice [54].

Genome wide studies and genomic integrity

There are only few genome-wide studies on chromosomal abnormalities in chordomas. The NCBI Cancer Chromosomes database, as accessed on

Table 1. *Reported disease loci in chordomas*

Ref.	Reported locus	Mode of analysis	Comments
Foote *et al.* [105]	–	Case report	Chordomas may be inherited. Brother and sister presenting with recurrent and metastatic chordomas
Stepanek *et al.* [327]	–	Genetic analysis	Autosomal dominant inheritance in a family
Dalpra *et al.* [73]	1p33	Linkage analysis	Deletion in familial recurrent chordoma
Miozzo *et al.* [231]	1p36	Linkage analysis	Tumor suppressor gene suggested at the locus
Kelley *et al.* [166]	7q33	Linkage analysis	Linkage analysis performed on the same family as Stepanek
Colli *et al.* [59]	–	Karyotype analysis	Abnormal karyotype is not correlated with recurrence. It is not different in chondroid chordomas or chondrosarcomas.
Scheil *et al.* [304]	3p, 1p, 7q, 20q, 5q and 12q	Comparative genomic hybridization	Analysis of 16 chordomas in 13 patients Frequent loss at 3p and 1p Frequent gain at 7q, 20q, 5q and 12q
Riva *et al.* [284]	1p36.13	Linkage analysis	LOH analysis in 27 sporadic chordomas.
Bayrakli *et al.* [20]	1p36, 1q25, 2p13, 7q33 6p12	iFish	Analysis of 7 primary tumors and 11 recurrences in 7 patients. Gains at 1q25 (66.6%), 1p36 (60%), and 7q33 (37.5%) 4q26-q27 (12.5%), 3p12-p14 (10%), 3p12-p14 (16.6%) in recurrent, 7q33 (33.3%), 3p12-p14 (16.6%), 1q25 (14.2%), and 1p36 (14.2%) in primary tumors. Losses at 1q25 (66.6%), 2p13 (55.5%), 1p36 (30%) in recurrent and 2p13 (83.3%), 6p12 (50%), 1q25 (32.7%), 17p13.1 (20%), 6p12 (12.5%), and 3p12-p14 (10%) and 1p36 (28.5%) 3p12-p14 (16.6%), 7q33 (16.6%), and 17p13.1 (14.2%) in primary tumor samples.

October 2006, reports chromosome aberrations of 34 chordomas [176]. In our literature analysis we came across 82 karyotypes reported in chordomas as presented in Table 2 [40, 51, 73, 75, 118, 119, 188, 226, 267, 303, 304, 334]. Fifty-one (62.2%) of these karyotypes were abnormal and a majority of those

were hypo-diploid or near-diploid. Very diverse chromosome aberrations were detected in the rest and no single characteristic karyotypic abnormality was described in primary or recurrent chordomas [303].

The incidecence of an aneuploid karyotype is comparable in classic and chondroid chordomas and ranges between 27% and 45% [40, 119, 124, 232, 303, 334]. Findings were similar for skull base and sacral chordomas [299]. Three studies reported complex, aneuploid/multiploid karyotypes in dedifferentiated chordomas [119, 150]. Genetic instability may be a late event in chordoma oncogenesis.

Other tumors such as meningiomas or gliomas contain areas with chordoid phenotype [173]. Interestingly, in chordoid meningiomas an unbalanced translocation t(1;3) was shown to be associated with this chordoid phenotype. Chordoid gliomas, in the other hand, have no chromosomal imbalances [276].

Some studies explored a correlation between ploidy and survival. Mitchell *et al.* [232] found polyploidy with similar incidences in chondroid and classic chordomas. In their study none of the tumors containing chondroid areas had aneuploidy and the diploid and aneuploid tumors had comparable survival. Colli *et al.* [59] conducted a ploidy analysis in 2 classic and 5 chondroid chordomas and a karyotype analysis in 11 classic-, 3 chondroid chordomas and 4 chondrosarcomas and confirmed the findings of Mitchell *et al.* [60]. Additionally they have found that patients with an abnormal karyotype had higher recurrence rates.

The largest series of genome wide analysis in chordomas was reported by Scheil *et al.* [304]. In their study the most commonly encountered losses were on 1p (50%) and 3p (44%). Most frequent gains were 7q in 69%, chromosome 20 in 50%, 5q in 38% and 12q in 38% of the cases in this series. Brandal *et al.* also reported similar findings: In their study the most frequently observed changes were 1q23 gain in 50%, 7p gain in 50%, 7q gain in 75%, 19p gain in 50% and loss of 9p in 50% of cases. So far, 4 cases of chordoma with single cytogenetic defects have been described, three with different translocations, 2 with involvement of 6q and 1 case with 1p [40, 50, 226, 267] Sawyer *et al.* [303] found cytogenetic abnormalities in 11 of their 22 skull base and cervical chordoma samples. All of these positive tumors were recurrent lesions and isochromosome1q was a recurrent abnormality in a number of tumor samples, however not the sole abnormality [303]. Bayrakli *et al.* [20] using interphase FISH, have studied 1p36, 1q25, 3p13-p14, 7q33, 17p13.1 (p53 gene locus), 2p13 (TGF-α), 6p12 (VEGF), and 4q26-q27 (bFGF/FGF2) loci in 18 primary and recurrent tumor samples from 7 patients. Common gains were found at 1q25 (66.6%), 1p36 (60%), and 7q33 (37.5%) and losses at 2p13 (83.3%), 6p12 (50%), 1q25 (32.7%), and 1p36 (28.5%) loci. In conclusion two loci, 1p36 and 7q33, were found to be associated with chordoma progression and recurrence. Two other newly reported loci, 1q25 and 2p13, displayed abnormalities both in primary chordomas and recurrences. The chromosome 6p12 aberration was only observed in primary chordomas.

Table 2. *Abnormal karyotypes reported in chordomas*

Case #	Study	Main study cohort	Abnormal karyotypes					
			Age/ gender	Tumor site	Tumor status	Histo-pathology	Radio-therapy	Karyotype
1	Chadduck *et al.* [51]	1 chordoma	?F	N/A	N/A	N/A	N/A	46,XX,t(1;16)(p34;p11)
2	Persons *et al.* [267]	2 SAC chrodomas	56M	SAC	R	N/A	N/A	44,XY,t(1;3)(q42;q11),−2, der(7)t(2;7)(q23;q32),−21/46, X,t(Y;6)(q12;q22), t(1;14)(q34;q32)t(5;10)(q13;p11)
3			77F	SAC	R	N/A	N/A	45,XX,−21
4	Gibas *et al.* [118]	2 SAC chrodomas	71F	SAC	P	N/A	N/A	36,X,−X,−1,−3,−4,−11,−13,−14, −18,−21,−22,+der(21)t(1;21)(q21;q22)
5			75F	SAC	P	N/A	N/A	72,XX,−X,−1,+del(1)(p22)×2,−2, −3,add(3)(p25),−4,del(5)(p13), add(5)(p15),add(5)(p13),−7, inv(7)(q11.2q22),der(9)t(9;?)(p24;?)×2, −10, −10,−10,+12,−13,−13, der(15)t(15;?)(p11;?),−17, der(18)t(18;?)(p11;?), der(19)t(19;?)(q13;?),der(20)t(20;?)(q13;?), +der(20)t(20;?)(q13;?),−21, +der(21)t(2;21)(q11;q22)×2,+9mar [cp]
6	DeBoer *et al.* [75]	1 SAC chordoma	69M	SAC	P	N/A	N/A	43,XY,−2,−3,del(4)(q32),−6,+7,−11, der(12)t(9;12)(q12;p11),add(16)(q23), −20,add(22) (q13),+mar

7	Mertens *et al.* [226] (also reported by Mandahl *et al.* [214])	8 SAC chordomas	51M	SAC	R	N/A	N/A	42,XY;add(1)(q31),del(2)(p21),−3, add(3)(p11),−4,t(5;7)(q33;q36), add(8) (q24),del(9)(p13),−10, add(11)(q11),dup(12)(q13q24),−16, −18,ins(18;t)(q21;?),add(19)(p13), der(22)t(4;22)(q11;p11),+mar [3]/46,Y,del(X)(q24),t(1;5)(p36;q33), del(2),der(3)t(3;14)(p21;q24), t(X;3)(q24;q11),der(6)t(3;6)(p21;p21), del(9),10,add(11),del(12)(q13q15), +add(12)(q24),der(14)t(3;14) (q21;q24),der(15)t(6;15)(p21;p13), −16,?add(17)(p11),add(19), +mar [4]/48,XY,del(2), der(2)t(2;?;12)(p14;?;q13), inv(4)(p16q31),add(5)(p15),+7,+8, del(9), 10,del(11)p12),del(12), add(16)(p13),add(17)(q21),add(19), +mar [4]
8			61M	SAC	R	N/A	N/A	46,XY(1;6)(q44;q11) [5]/46,XY [20] on recurrence: 46,XY [12]
9			62M	SAC	P	N/A	N/A	40,XY,der(1)t(1;21)(p11;q11),−3,−4, −8,der(8)t(1;8)(q21;q23),add(9)(q22), −13,−14, der(20)t(2;20)(q21;q13), del(2)(q35),−21 [13]/77–84,idem×2, +3,+8,+2mar [3]/46,XY [3]

(*continued*)

Table 2 (*continued*)

Case #	study	Main study cohort	Abnormal karyotypes					
			Age/ gender	Tumor site	Tumor status	Histo-pathology	Radio-therapy	Karyotype
10	Bridge et al. [35]	1 SAC chordoma	70M	SAC	P	N/A	N/A	42,XY,add(1)(p11),−3, der(4)t(4;?;?18;?)(q12;?;?;?),−6,−9, −14,der(16)t(4;?;16)(q12;?;q11), der(17)add(17)(p12) t(17;18)(q11;p11), der(18)del(18)(p11)add(18)(q?) [6]/42, idem,der(9)t(6;9)(q11;p11) [4]/46,XY [10]
11	Butler *et al.* [41]	5 SAC chordomas	34F	SAC	P	N/A	N/A	46,X,−X,t(5;12)(q13;p13), t(6;7)(q25;q22),+14
12	Buonamici *et al.* [40]	3 SB, 1SPI chordomas	47M	SP	P	classic	N/A	46,XY,(6;11)(q12;q23)
13	Dalpra *et al.* [73]	1 SB chordoma	39M	SB	R	Classic	No	39,XY,dic(1;9)(p36.1;p21),add(1)(p12), del(3)(p13),−4,−4,der(6)t(1;6;14) (6pter →6q2:1p36 →1p13:14pter →14qter), −7,−8,−8,−11,−17, −17,−18,−18, −19,−20,−20,−22,−22,+8mar on recurrence 46,XY [18]/40,XY, del(2)(p12pter),del(3)(q21qter), del(3)(q21qter),−3,−6,−9, del(12)(q21qter),−13,−13,−15, −19,−19,−20,+mar1,+mar2, +mar3/45,X,−Y,add(6)(p25)/46,XY, del(7)(q32qter)/47,XY,+mar1/48, XY,+r1, +r2,(ace and dmin)/44,X,

−Y,−2,del(2)(q31qter),
t(2;Y)(p25;q11.2),add(10) (q26),−13,
−14,−15,del(15)(q15ter),+20,+22,
+mar1/45,XY,−4,add(10) (q26)/46,
XY,del(6)(q21qter),add(D)(q?)/46,XY,
add(6)(q27),add(10)(q26)/44,XY,-D,
−16,−17,−18,+21,+mar1/45,XY,
inv(1)(p21;q32-44),−4,−20,+mar/46,
XY,add(1)(q21),add(10)(q26)/48,XY,
del(3)(q21qter),−7,add (9)(q34),
t(9;10)(q11;p15)+add(20)(q13.3)/43,
XY,del(2)(p12pter),−6, add(10)(p15),
−11,−13,−16,+mar1/46,XY,
del(2)(p12pter),add(11)(q14 o q22)/
46,XY,−2,−7,t(15;15)(p?;p?),−19,
+mar1,+mar2,+mar3/46,XY,−4,
+add(10)(q26),del(12)(q22qter)/45,
Y,−X,add(1)(p12),−20,+mar/45,XY,
del(6)(q25qter),del(10)(q23-24qter),
−12,der(16)t(q12-13;q23-24)/46,XY,
del(3)(q21qter),add(9)(q34)/44,XY,
add(1)(p?),del(2)(p12pter),−6,−8,−11,
−18,+mar1,+mar2/46,XY,−2,
add(11)(p?),−12,+iso(12p),
+mar1/43,XY, −2,add(3)(p23),−4,
−21/46,XY,−6,+mar1/45,XY,
del(3)(p21),−16,+mar1/43,XY,
del(1)(q11qter),add(1)(p12-p13) [2],

(*continued*)

Table 2 (*continued*)

Case #	study	Main study cohort	Abnormal karyotypes					
			Age/ gender	Tumor site	Tumor status	Histo-pathology	Radio-therapy	Karyotype
								−15,−17,−20/46,XY,add(6) (q27), del(4)(q21.3qter) or t(4;6)(q21.3;q27)/44,XY,del(4)(p12), −5,t(5;11) (q12;p15),−7,−8, +10/46,XY,add(10)(q26) [2]/46,XY, +mar1/46,XY,del(2) (p12pter), add(16)(p12-p13)/47,XY,t(1;10)(p36;q24)
14	Scheil *et al.* [304]	7 SAC,5 SB, 1 SP chordomas	46M	SAC	R	N/A	Yes	gains: 7; 8p;9q34; 12q34; 15q; 17, 20 q Losses: 1p34-p21; 3; 10; 11; 14q; 18; 22
15			77F	SAC	R	N/A	Yes	gains: 7q36, 20 Losses: 1p31.3-p22; 3p21-p12; 13q21-q32; 18q22-q23
16			70F	SAC	R	N/A	Before 2nd surgery	gains: 1p34.2-p36; 7p21-qter; 12p; 15q; 22qLosses: 1p31-p21; 3p; 6q11-q21; 9p; Xp On recurrence(1 year later) gains: amp1p34.2-p36; 7; 12p; 15q; 22qLosses: 1p31-p21; 2q33-q36; 3p; 6q11-q21; 9p-q31; Xp
17			69F	SAC	R	N/A	Before 2nd surgery	gains: 7q22-qter; 12pLosses: On recurrence gains: 7q22-qter Losses: 3; 4; 5; 9p; 10
18			61F	SAC	R	N/A	Yes	gains: 17; 20q Losses: 1p31; 4p; 9p21-p24; 13q21

19			46F	SAC	R	N/A	Before 2nd surgery	gains: 5q23-qter; 7; 12q24; 20 Losses: 3; 4q35 On recurrence 6 years later gains: 5q31-qter; 7q34-qter; 12q24; 20; 22q; Xq23-qter
20			74F	SAC	P	N/A	No	gains: 1q, 3p, 4q12-q27, 5q, 7, 8pter-q21.1, 8q24, Losses: 9q22-qter, 11pter-q22, 12, 13q22-qter, 15q, 17q, 21, 22
21			26M	SB	P	N/A	No	gains: 20; 21q22; 22q; Xp, Xq26-q28 Losses:-
22			66F	SB	R	N/A	Yes	gains: 11q24-q25; 12q24; 14q21-qter; 17q; 20q; 21q21-q22 losses: 6q; 12p; 13q
23			51F	SB	R	N/A	Yes	gains: 7q34-qter; 20q Losses: 1p31-p21; X
24			37M	SB	P	N/A	No	gains: 12q24Losses: 13q21-q31; Xq25-Xqter
25			58F	SB	P	N/A	No	gains: 1q; 11q24-q25Losses: 1p; 3; 4; 9p; 10; 13q; 14q; X
26			80F	SP	P	N/A	No	gains: 5p15; 7q34-qter; 9q34; 22qLosses: 3p12-p14; 13q; 18q
27	Sawyer *et al.* [303]	22 SB chordomas	57F	SB	R	Chondroid	Yes	46,XX,inv(1)(q23q42),t(1;10)(q32;p11), t(3;14)(p21;q13),inv(4)(p14q31), add(12)(q22),del(14)(q32) [5] 46–48,XX,add(1)(q?32),del(3)(p25), del(5)(q31),del(6)(q15),add(11)(p13), +del(12)(q22),−13,

(*continued*)

Table 2 (*continued*)

Case #	study	Main study cohort	Abnormal karyotypes					
			Age/ gender	Tumor site	Tumor status	Histo-pathology	Radio-therapy	Karyotype
								add(16)(p11),add(16)(q24),+17, der(18)t(1;18)(q12;q23)x2, add(19)(q13) [cp3]46,X,del(X)(p22.1), t(1;9)(p36.1;p13),t(4;9)(p12;q34), t(6;16)(p11;q24) [2] 45,X,del(X)(p11.2p11.4), der(5)t(5;14)(p13;q11),?add(11)(q22), del(12)(q22),−13, der(17)t(13;17)(q14;p13),add(21)(q22) [3]
28			25M	SB	R	Chondroid	No	48,XY,+5,+7,+12,−13, add(13)(q34),−18,+20 [2]49,idem, +19 [16]
29			34M	SB	R	Classic	No	44–45,XY,t(2;14)(p23;q11), ?t(3;12)(p21;p13),del(4)(q?23),−5, −6,der(11)t(6;11)(q11;p12) [cp2]
30			58F	SB	R	Classic	Yes	46,XX,t(4;17)(q23;q21), t(8;9)(q11;q11) [3] 46,XX,t(2;20)(p31;p11.2), t(3;22;16)(p21;q11.2;q22),del(6)(p23) [2]
31			41M	SB	R	Classic	Yes	52–66,−X,−X,−Y,add(1)(q22)x2,i(1)(q10), +2,−3,der(3)t(3;4)(p?24;q?13)t(1;3)(q21;q21)X2, 4,der(4)del(4)(p12)add(4)(q13)x2,add(6)(q?21)+7,

						−9,−10,add(11)(q13)x2,add(11)(q25),+add(11)(q25), −12,13,add(13)(?q13),?del(15)(q11.1q13)×2, ?dup(15)(q11.1q13),add(17)(q24),−18,+19, −20,+21,+22 [cp9] 46,XY,1,der(1)?t(1;4)(p13;q?27), +der(3)t(3;11)(q29;q11)add(3)(p13),del(4)(p12), der(4)add(4)(p16)t(1;4),inv(7)(p?21q?34),add(8)(p22), del(9)(q21),del(10)(q22),der(11)add(11)(p15)?del(11) (q13q22),?inv(14)(q11.2q32),+add(15)(q22), der(15;16)(q10;q10),?t(17;20)(q?23;q?13.3) [cp4]
32	33M	SB	R	classic	Yes	38,X,−X,i(1)(q10),−3,−4,add(6)(q27),+7,−9, −10,−13,−14,−18,−22 [cp5]
33	65M	SP	R	Classic	Yes	43–45,−Y,del(X)(q?26),t(2;17)(q21;p13),del(6)(q?25), add(9)(p24),inv(14)(q13q24) [cp10] 46–47,XY,t(1;2)(q44;q13),inv(3)(p?24.2q29), t(4;9)(q33;q22),t(8;16)(q24.1;q24),t(10;13) (p13;q12) [cp5]
34	15F	SB	R	Classic	Yes	44–46,XX,t(1;22)(p32;q11.2),?t(2;20)(q33;q11.2), der(3)t(3;4)(p21;q?31;1)t(3;22)(q21;q13),der(4)t(3;4), ?t(9;15)(p22;q22),t(17;18)(q21;q23) [cp15]
35	52M	SB	R	Classic	Yes	45–47,Y,del(X)(p22.1),del(1)(q24),?t(8;18)(q24.1;q23), add(9)(q34),?inv(9)(p11q22),del(16)(q?22),add(17)(p11), add(19)(q13),del(20)(q11.2) [cp20]
36	69M	SB	R	Classic	Yes	45–46,XY,der(1)t(1;1)(q42;p34.1), der(1)t(1;1)t(1;14)(q24;q11.2),t(3;5)(p23;p11), t(3;10)(q21;q24),t(4;6)(q31.1;p11.2), t(4;16)(q25;p11.2),der(?6)del(6)(p12p21.2)t(6;12) (q?27;?21.2),t(13;16)(q12;q22),der(14)t(1;14) [cp10]

(*continued*)

Table 2 (*continued*)

Case #	study	Main study cohort	Abnormal karyotypes					
			Age/ gender	Tumor site	Tumor status	Histo-pathology	Radio-therapy	Karyotype
37			47F	SB	R	Classic	Yes	46,X,?del(X)(q26q26),inv(3)(p23q?25),inv(7)(p22q22), add(8)(p23),der(8)t(8;9)(p11.2;q22)t(8;13)(q13;q11), der(9)t(8;9),t(10;15)(q26;q12),der(13)t(8;13), del(17)(p11.2p11.2),t(21;22)(q11.2;q13) [cp11]46, XX,inv(20(p13q11.2),del(7)(q11.1q11.2), t(14;19)(q11.2;p13.3),del(16)(q23)46, der(X)del(X)(p11.4)del(X)(q21),der(X)t(X;X)(q26;p11.4) der(5)t(5;9)(q11.2;q32),inv(6)(p23q?13), der(7)t(7;9)(p15;p24),t(7;15)(p12;q15), t(8;12)(q24.1;q22),?t(8;19)(p22;p11), der(9)t(7;9)(p15;p24)t(5;9)(q11.2;q?32), t(10;20)(p13;q11.2),del(22)(q13) [3] 37–40,XX,i(1)(q10),−3,?t(3;13)(p26;q11), −4,?t(4;5)(p14;q33),der(5)t(?4;5)(q?21;q?33),−6, +7,der(9)add(9)(p24)del(9)(q22),−10,−13,−14, del(15)(q21),−18,add(20)(p11.2),−22,+mar [cp3]
38	Tallini *et al.* [334]	SAC chordomas	80 M	SAC	N/A	N/A	N/A	add(1)(p11),−3,−4,−10,−11,−14, der(14;15)(q10;q10),−22,−mar
39			60 F	SAC	N/A	N/A	N/A	43,t(X;1)(q28;p31),der(X;7)(q10;p10),add(1)(p11), add(3)(p13),add(3)(p25),add(5)(p15), _der(7)t(1;7)(p21;p22),add(8)(q24),−10,add(11)(p11), der(12)t(7;12)(q11;p11),ins(12;?)(q13;?),−13, del(14)(q32),−17,−18,−mar

40			55 M	SAC	N/A	N/A	N/A	44,X −3, −9,−Y, -mar
41			60 M	SAC	N/A	N/A	N/A	47,XY,+X/46,XY
42			61 M	SAC	N/A	N/A	N/A	46,XY,t(1;16)(q44;q11)/46,XY
43	Gil *et al.* [119]	3 SB chordomas	66 F	SB	R	Classic	N/A	45–46,X,del(X)(q23) [3],t(2;9)(p23;p24) [5],t(3;19)(q26;q13) [4],t(5;15)(p13;q26) [5],+der(8) [3] [cp7]
44			47 M	SB	P	Dediffer-entiated	N/A	71,XY,+X,+1,+1,+2,+2,+5,+6,+6,+7,+7,+8,+9,−11,add(11)(p15),+12,+14,+14,+16,+7mar,3dmin
45	Kuzniacka *et al.* [188]	7 SP and SAC chordomas	74M	SAC	P	N/A	N/A	40–42,XY,−3,der(6)t(6;9)(q?25–27;q11-12),−8,−9,der(9)t(9;10)(p24;?) or der (9)t(9;16)(p24;?),−10,dic(12;?16)(?p1?3;?)?inv(12)(p11p13),der(21)t(8;21) (q11;p13),−22
46			60F	SAC	P	N/A	N/A	43,−X,der(X;1)(q22-24;p13),der(1)t(1;11)(p1?3;p1?3),der(1;22)(q10;q10),add (3)(p1213),der(3)t(3;12)(p25;?p11),der(5)ins(5;19)(p15;p11p12) or der (5)ins(5;19)(p15;q11q12),der(7)t(2;7)(p15-16;q21-22) or der(7)t(2;7)(q31-32;q2122),+der(7)t(7;13)(p15;?q14)t(1;13)(p22;q22),der(8)t(7;8)(?q32;q24),?der(10)del(10)(p11)del(10)(q22),der(11)t(11;16)(p11;q11),der (12)t(7;12)(q11;p11),?inv(12)(q13q15),−13,del(14)(q32),−16,−17,−18
47			51M	SAC	R	N/A	N/A	42,X,−Y,der(1)t(1;3)(p31;p11-12),der(2)t(2;3)(p21;?),−3,der(3)t(2;3)(?;p12), −4,der(5)t(5;16)(q33;?p?),der(7)t(5;7)(q33;q36),+der(8)t(1;8)(?;q24),del(9)(p13),−10,del(11)(q13),dup(12)(q13q24),+del(12)(q13),−16,−18,dup(18)(q?), ?add(19)(q13),der(22)t(4;22)(q11;p11)/40,X,−Y,der(1)t(1;3),der(2)t(2;3),der (2)t(2;7)(p?;?),−3,der(3)t(2;3),

(*continued*)

Table 2 (*continued*)

Case #	study	Main study cohort	Abnormal karyotypes					
			Age/ gender	Tumor site	Tumor status	Histo-pathology	Radio-therapy	Karyotype
								der(4)t(4;7)(p?;?),der(5)t(5;16),der(6)t (6;7)(q?;?),der(7) t(5;7),del(9),−10,del(11),dup(12),+del(12),der(13)t(8;13) (q?;q?),−16,der(17)t(6;17)(?;q?),der(19)t(3;19),der(22) t(4;22)/46,del(X) (q24),−Y,der(1)t(1;9)(p36;?),der(2) t(2;16)(p21;?),der(3)t(3;14)(p21;q24)t (3;16)(q11;?)t(2;16) (?;?),der(4)t(4;13)(q3?;?),der(5)t(5;16),der(6)t(6;8) (p23;?p21),?del(7)(q?),der(8)t(6;8)(?;p?),del(9),del(11), der(12)t(7;12) (q?;q24)t(5;7)(q33;?),+del(12)(q13q15), der(14)t(3;14)(q21;q24),−16,der(16)t (Y;16)(q11;p13), der(17)t(9;17)(q?;p?),?add(17)(p11),der(19)t(X;19) (?q24;p13)
48			71M	SP	P	N/A	N/A	47–48,XY,+2,inv(9)(p11q12)c,+13,−14,−16, −16,+2mar
49			71M	SP	R	N/A	N/A	40–44,XY,−1,der(3)t(1;3)(q11;q11),?−4, der(9)t(9;14)(p11;p13),−22
50			59M	SP	P	N/A	N/A	47,X,−Y,+6,+7
51			50M	SAC	MET	N/A	N/A	33–40,X,−Y,−1,add(1)(p11)x1-2,+2, der(2;14)(q10;q10),−3,add(4)(p15),−5,−6, ins(6;?1)(q24;q25q44),−8,−9,−10,add(11)(p15), −12,der(12)t(8;12)(q13;q24), −13,−13,−15, add(16)(q22),−17,−18,−20,−21,−21,−22, +der(?)t(?;13)(?;q13), +1−4r,+4mar

P: primary, R: recurrent, SAC: Sacral, SB: skull base, SP: spinal, MET: metastatic.

Several solid tumors are known to have microsatellite instability (MIN), a term used for allelic size alterations in microsatellites, oligonucleotide tandem repeats dispersed throughout the genome. This is a signal of defective DNA mismatch repair and resultant genomic instability. Klingler *et al.* [174] found MIN in 6 of their tumor samples. In contrast Pallini *et al.* [258] found no MIN in the 9 tumor tissues they studied.

Cell cycle control

The retinoblastoma (Rb) gene is a well characterized tumor suppressor gene which is shown to have several important roles in oncogenesis. Eisenberg *et al.* [90] demonstrated LOH at intron 17 of the retinoblastoma gene in 2 of 7 chordomas they studied but in none of the 2 chondrosarcomas.

Naka *et al.* [244] found alterations in cyclin D1, and pRb proteins, all of which take roles in the G1-S checkpoint of the cell cycle in 10–45% of primary chordomas.

Tumor suppressor genes

Riva *et al.* [284] performed a linkage analysis in 27 sporadic chordoma cases and mapped a defect to 1p36.13, common to 85% of the cases [231, 284]. By performing RT-PCR analysis on candidate genes in this region the authors suggested that Caspase 9, Ephrin-2A and DVL1 (which is also a candidate for neuroblastoma transformation) genes may play a role in chordoma tumor-suppression [284]. Defects at 1p may be an early change in chordoma oncogenesis.

P53 plays an important role in the response to genetic damage and metabolic disturbance and modulates, cell cycle arrest, repair and apoptosis. Deregulation of this tumor suppressor gene is found in majority of human cancers. Bergh [26], Kilgore and Prayson [168], Naka *et al.* [244], Pallini *et al.* [258] found p53 overexpression in 0, 27%, 30%, 40% of the chordoma cases in their cohorts respectively. In a comprehensive analysis, Naka *et al.* [244] showed that high p53 levels in this 30% of their cases correlated well with increased mitotic index and decreased patient survival. In a significant proportion of human cancers increased p53 levels result from mutations in the p53 gene. However, the authors found no mutations in the p53 gene in cases with increased p53 levels, possibly indicating an alternative mechanism for p53 protein accumulation. Mdm2 overexpression is a common mechanism of p53 inactivation in sarcomas, but not in chordomas [244].

There are numerous case reports on occurrence of chordomas in patients with the tuberous sclerosis complex [32, 43, 178, 201]. Lee-Jones *et al.* [201] showed somatic mutation of corresponding alleles in patients with TSC-1 or TSC-2 tumor suppressor gene germ line mutations. A causal relationship is not proven.

Oncogene activation

Most studies on oncogene activation in chordomas were motivated by the availability of small molecule receptor tyrosine kinase (RTK) inhibitors and the prospect of the use in recurrent/refractory chordomas [364]. No studies on the significance or downstream signaling of these or RTK's is available. Weinberger *et al.* [364] in their study 10 chordomas (30% skull base, 50% sacral, 20% sacral) found consistent immunoreactivity for EGFR and c-Met receptors, robust expression in 50% and 70%, respectively. HER2/neu receptor expression was present in 70% of the tumors [364].

Experimental models of chordoma

Spontaneous chordomas are documented in several animals including rats rats, ferrets, cats, dogs and minks, however currently there are no animal models with spontaneous chordomas. Explant cultures of chordoma cells have been performed by Horten and collegues [147] who also have generated several commonly used human glioma cell lines. Another cell line, U-CH1, was generated from a recurrent sacral chordoma by Scheil *et al.* [304], who also described its chromosomal abnormalities in detail.

Pathology

Chordomas are slow growing, unencapsulated, extraaxial tumors that are locally invasive within bone of the skull base (Table 3). They have an extradural origin; however, few completely intradural cases have also been reported [261].

Table 3. *Definitions*

Chordoma	A rare neoplasm of skeletal tissue mostly in adults, derived from persistent portions of the notochord; composed of cells arranged in lobules, with abundant myxoid stroma with some clear vacuolated cells
Chondrosarcoma	A sarcoma derived from cartilage cells which produce cartilage matrix May develop de-novo or secondarily from a preexisting benign cartilaginous neoplasia such as such as enchondroma or osteochondroma. This is the third most common primary malignant tumor of the bone but only 2% arises in the skull base
Chondroma	A benign neoplasm derived from mesodermal cells that form cartilage
Parachordoma	A neoplasm that develops outside the axial skeleton in muscle, adjacent to tendons, synovium and bone and has morphological features identical to chordoma

On gross examination they have a smooth or lobulated surface, gelatinous. The cut surface is usually homogenous, and inside the tumor is often soft with occasional semi-translucent gray and blue areas, focal hemorrhages, cyst formations cartilage and calcifications. The high mucin content is responsible for the semi-fluid consistency. Chordomas are unencapsulated and grow infiltrative along the lines of least resistance in the bone [141]. However a pseudocapsule may be seen, especially in skull base cases that grow into soft tissues or the dura mater.

Skull base chordomas are not primary tumors of the nervous system and classified among tumors that involve the nervous system by local extension. Three histopathological variants are recognized: Classic (International classification for disease-oncology [ICD]: M-9370/3), chondroid (ICD: M-9371/3) and dedifferentiated chordomas (ICD: M-9372/3). Light microscopy of chordomas shows a differentiated morphological phenotype, despite the malignant biology in most cases. Light microscopy of the **classic chordoma** reveals cells with a clear but granular appearance (Fig. 1). The cytoplasm is eosinophilic and stains positive with the periodic-acid Schiff (PAS) stain [283]. Distinct, larger cells with eccentric nuclei abundant vacuolated and reticulated cytoplasms due to intracellular accumulation of glycoseaminoglycans are called physaliferous cells and are typical of chordomas [283]. The nuclei are eccentric, hyperchromatic, have prominent nucleoli and rarely demonstrate atypia. These cells rarely present the majority [283]. The biological nature of physaliphorous cells is still not clear. It is widely accepted that the vacuoles are droplets of mucoid material in the cytoplasm. An ultrastructural and histochemical study showed intracellular enrichment in the enzymes leading to synthesis of stromal glycosamino-

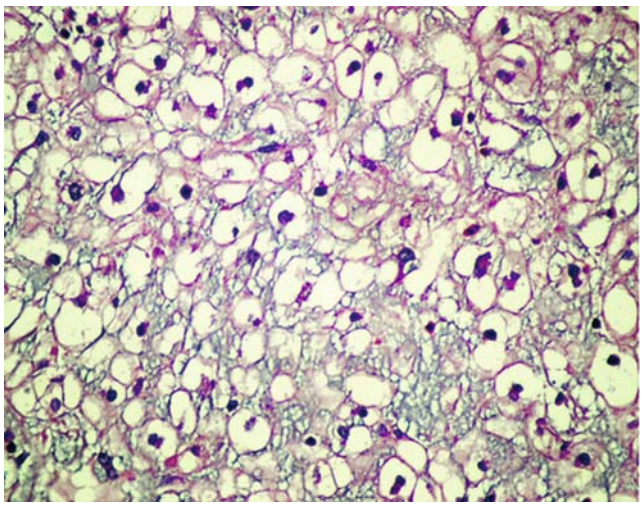

Fig. 1. Light microscopy of chordoma. Cells with vacuolated cytoplasm and small, uniform hyperchromatic nuclei are seen (Hematoxylin-eosin stain)

glycans and the excessive synthesis and storage of sulfated glycosaminoglycans, which suggests that the vacuoles result from the breakdown and utilization of membrane-bound glycogen in sulfated glycosaminoglycans biosynthesis [191]. Signet-ring appearance may be seen in cells containing an intermediate quantity of mucin [141]. Electron microscopy also reveals parallel bundles of criss-crossing microtubules within the rough endoplasmic reticulum, but the significance of these structures is not known [156].

A lobular configuration may be marked with cell clusters divided by thin fibrous septa in the myxoid extracellular matrix. The fibrous septa may be thin or thick and hyalinized Naka *et al.* [243] found fibrous septa in 79 (64.8%) of the 122 chordoma samples they studied. Forty-two per cent of the tumors with septa had also a lobular growth pattern and a more favorable prognosis when compared to those without a lobular pattern. The lobules either contain a sheet of cells or a pool of mucin [141]. The mucoid matrix stains strongly with Alcian blue.

Mitoses, necrosis, hypervascularity or spindle cells are typically absent or rare in the classic chordoma. Pools of mucin containing cords of eosinophilic syncytial cells can be found. These cords often attach peripherally to the septa and are projected toward the center, giving an impression of a continuum from polyhedral cells containing little mucin. **Cellular chordomas** have very little extracellular matrix while others contain numerous cells resembling adipocytes and are called **lipoid chordomas** [291] None of these pathological subtypes are associated with distinct tumor biology and likely represent individual variations of the classic chordoma.

Low grade chondrosarcomas and chordomas can have similar localization, imaging characteristics and pathological appearance and have traditionally been analyzed together to create sufficiently large artificial cohorts to enable conclusive analyses. Accumulating evidence has shown, however, that chondrosarcomas have a more benign and predictable tumor biology and therapeutic response when compared to chordomas [290]. Low-grade chondrosarcomas respond much better to surgical resection, to conventional, stereotactic, charged particle therapies and recur less frequently. In selected cohorts more than 99% of patients with chondrosarcomas were still alive 10 years after diagnosis [290]. Chondrosarcoma patients also fare much better than patients with chordoma in terms of median and long-term survival. Therefore, to come up with realistic conclusions, chordomas and chondrosarcomas should be considered separately.

The distinction of chordoma, pleomorphic adenoma, mucinous adenocarcinoma, and chondrosarcoma may pose difficulties to the neuropathologist but immunohistochemical techniques are usually adequate to establish the diagnosis [273]. Chordomas exhibit an epithelial phenotype [232, 289]. Morphologically they possess atypical epithelial markers in conventional microscopy and desmosomes and simple cell junctions in electron microscopy. Immunohistochemical analysis also presents an epithelial phenotype with staining for EMA [33, 223,

Table 4. *Immunohistopathological findings in chordomas*

	Classic chordoma	Chondroid chordoma	Chondro-sarcoma	Ref.
EMA	88–94	24–33	0	[223, 232, 289]
Cytokeratin	94–100	32–33	0	[223, 232, 289]
S100	44–94	85–100	20–100	[2, 223, 232, 289]
Vimentin	94	92	100	[2, 223, 232, 289]

232], low molecular weight cytokeratins 7, 8, 18, and 19 (simple epithelial), as well as high molecular weight 4, 5, and 6 (mucosal epithelial). In contrast chondrosarcomas do not express epithelial markers. Despite this clear distinction there were no survival difference between cytokeratin positive and negative tumors [232]. There are very conflicting reports on the incidence of S-100 or CEA positivity in chordomas, so we presented the results of large studies in Table 4.

In 1973 Heffelfinger *et al.* [141] described a variant of chordomas that contained islands of chondroid differentiation, resembling chondrosarcomas. The authors called this **chondroid chordoma** and also documented lower rates of recurrence and longer survival when compared to classic chordomas. Since this observation there has been an ongoing debate about existence and the prognostic significance of this phenotype. Chondroid chordomas contain areas of typical chordoma intermixed with islands of stellate cells in lacunar spaces, resembling chondrocytes. The chondroid component may be in the form of small scattered foci or even dominate the picture [141]. As in classic chordoma, anaplastic features are lacking. Electron microscopical studies supported the dual nature (epithelial-mesenchymal) of these neoplasms by showing that the chondrocyte-like cells have mesenchymal features while other cells have epithelial features [353].

Some authors speculated that chondroid chordoma may be in fact a low grade myxoid chondrosarcoma with good prognosis [157]. As the conclusion of an analysis of 7 chondroid chordomas, 18 classic chordomas, 2 peripheral chondromas, 8 peripheral chondrosarcomas, fetal notochord and fetal cartilage of 9-week and 12-week gestational age, Brooks *et al.* [36] even questioned the existence of any cartilaginous differentiation in chordomas. In the contrary later studies from Mayo clinic did not replicate the prognostic findings of the previous study by Heffelfinger *et al.* and it was suggested that this difference in survival might be related to the younger age of the chondroid chordoma patients in that study [106, 232]. The immunopositivity of classic and chondroid chordomas for epithelial markers was demonstrated by Mitchell *et al.* [232], who analyzed 16 classic chordomas, 25 chondroid chordomas and 12 condrosarcomas at the Mayo clinic. In this study the authors found immunopositivity for EMA in 88%, 24%, 0, for cytokeratins in 100%, 32%, 0, for S100

Table 5. *Comparison of chondroid tissues, tumor and chordomas*

	Fetal chorda dorsalis	Pediatric nucleus pulposus	Adult nucleus pulposus (cartilage)	Classic chordoma and Chordoid areas in chondroid chordoma	Chondroid areas in chondroid chordoma	Chondrosarcosma
Primary cell type	Physalipherous cells	Chondrocyte like rounded cells	Chondrocytes	Physalipherous neoplastic cells	Chondrocyte like rounded neoplastic cells	Chondrocyte like rounded neoplastic cells
Typical ECM molecules expressed	Collagen VI, (focal Collagen I and III) Chondroitin Sulphate and Keratan Sulphate rich Proteoglycan	Collagen II	Collagen IIB	Collagen VI (focal Collagen I, II and III) Chondroitin Sulphate and Keratan Sulphate rich Proteoglycan	Collagen II Aggrecan	Collagen II, Collagen X Aggrecan
Typical immuno-histochemical markers	EMA pan-cytokeratin cytokeratin 19 vimentin S-100	EMA pan-cytokeratin cytokeratin 19 vimentin S-100	Vimentin S-100	EMA pan-cytokeratin cytokeratin 19 vimentin S-100	Vimentin S-100	Vimentin S-100

44%, 88% and 100 and for vimentin in 94%, 92% and 0% for classic chordomas, chondroid chordomas and chondrosarcomas respectively. Rosenberg *et al.* [289] reported a comparative analysis of 38 classic chordomas, 12 chondroid chordomas, 28 chondrosarcomas, fetal notochord, ecchordosis physaliphora, and fetal hyaline cartilage. All classic and chondroid chordomas in this study were positive for cytokeratin, and the majority was also positive for EMA and CEA. In contrast, none of the chondrosarcomas stained for cytokeratin, EMA, or CEA. Vimentin and S-100 were positive in more than 95% of both classic chordomas and chondroid chordomas, and chondrosarcomas. Histopathological findings and immunoistochemical profiles of the tumors correlated well with their proposed physiological counterparts (Table 5). The authors concluded that chondroid chordoma is a subtype of chordoma and not chondrosarcoma. In another study on chondrosarcomas by Rosenberg *et al.* [290] the authors found S100 positivity in 96 of 97 (98.9%), cytokeratin expression in 0 of 97 (0%) and a faint staining for epithelial membrane antigen in 7 of 88 tumors (7.95%). Chordomas have chondrogenic potential as demonstrated by the expression of Collagen II protein expression in the tumors, even in the absence of chondroid areas [336, 365]. It has also been shown that chondroid areas in chondroid chordomas mimic nucleus pulposus development. In an elegant immunohitochemical study, Gottschalk *et al.* [126] showed that the physalipherous cells in the fetal chorda dorsalis expressed collagen VI (focally I and III), Chondroitin- and keratin-sulphate rich proteoglycan and was positive for EMA, epithelial cytokeratin, vimentin and S100. The pediatric nucleus pulposus had chondrocyte like rounded cells and was positive for Collagen II expressed EMA, Epithelial Cytokeratin, Vimentin and S100 while the adult nucleus pulposus had round chondrocytes, Collagen II, vimentin and S-100. Classical chordomas, chordoid areas of chondroid chordomas, fetal chorda dorsalis have similar cellular features and matrix composition while chondrosarcomas have a different pattern. Additionally the expression of intercellular adhesion molecule (NCAM, VCAM-1, CD44, N-Cadherin, B-Catenin) expression in chordomas also mimics fetal notochord. Neural cell adhesion molecule (NCAM) expression is associated with the formation and maintenance of chordoma tissue architecture. NCAM is not expressed by chondrosarcomas and therefore of important value in the differential diagnosis of chordoma versus CS. In their tissue comparison with microarray Fujita *et al.* [111] found CD24 overexpression in the nucleus pulposus. The same study also reported CD24 immunoreactivity in 6 of 7 studied chordomas, however in none of the chondrosarcomas. CD 24 is a P-Selectin (CD62P) ligand, however its role in chordomas is not known. Valderrama *et al.* [353] studied ultrastructural characteristics of chordomas and found that the presence of well-formed tonofilament desmosome complexes as well as complexes composed of alternating profiles of rough endoplasmic reticulum and mitochondria were seen only in

chordoma and chondroid chordoma, but not in cartilaginous tumors. Deniz *et al.* [79] studied the expression of several extracellular matrix proteins and growth factors (basic fibroblast growth factor, transforming growth factor α, vascular endothelial growth factor, fibronectin, collagen III, and collagen IV) that take part in oncogenesis in chordomas with aggressive and benign courses. This descriptive data from immunohistochemical analyses of chordomas suggested that high levels of transforming growth factor α and basic fibroblast growth factor expression, ligands of two important cellular kinase pathways that are shown to be important in a wide variety of cancers, were linked to higher rates of recurrence and an aggressive behavior [79].

Taken together, these clinical, immunohistochemical and ultrastructural findings quite strongly support the hypothesis that chordoid chordomas are a subtype of chordomas and not of chondrosarcomas. However, it remains unproven still if chondroid chordomas, in fact, have a better outcome than classic chordomas.

In a minority of patients chordomas exhibit atypical histopathological features of a round cell tumor or spindle cell sarcoma. Such tumors are usually composed of sheets of relatively small epitheloid cells with oval to irregular nuclei with a minimal amount of eosinophilic to clear cytoplasm and commonly exhibit tumor necrosis. Atypical chordomas usually have higher mitotic activity (1–3/10 hpf) and more commonly demonstrate cellular atypia than conventional chordoma, chondroid chordoma or cellular chordoma. This histology is commonly observed in the pediatric population and is almost exclusively associated with aggressive behavior [31, 58, 144]. Chordomas with such a sarcomatous component are called **dedifferentiated chordomas** [104, 207, 222]. Only very few cases have been reported in the literature, mostly in sacrococcygeal location and in pediatric population. Dedifferentiated chordomas constitute less than 4% of chordomas at initial presentation and are documented through the course of a chordoma in 4–9% of the cases [341].

There is scant information on the evolutionary process of a dedifferentiated chordoma in comparison with classic chordomas. The clonality of the two tumor components has not been analyzed. Some authors suggested that dedifferentiated chordomas might arise secondary to sarcomatous transformation after radiotherapy, or even be a collision tumor. However roughly ¼ of the dedifferentiated chordomas arise in patients who did not receive any radiation and this speaks against the exclusive role of radiation in causality [119]. Other authors postulated that a sarcomatous progression could be regarded as a failure of differentiation rather than a reversal of differentiated cell to an embryonic undifferentiated cell. Sarcomatous areas of dedifferentiated chordomas are negative for the epithelial markers such as cytokeratin and EMA [119]. The usual finding in dedifferentiated chordomas is such that the high-grade malig-

nant spindle cells stain strongly for vimentin and weakly for cytokeratin, S-100 protein, and epithelial membrane antigen (EMA), whereas the areas of conventional chordoma in these same neoplasms stain moderately for vimentin and S-100 protein, and strongly for cytokeratin and EMA [150]. Immunohistochemistry studies in dedifferentiated chordomas report that the transitional areas between conventional and dedifferentiated chordoma exhibited EMA and CK positivity, despite an absence of the same markers in the center of the sarcomatous areas [150, 294]. Vimentin and alpha1-antichymotrypsin are also reported positive in these areas and this supports the pathogenesis of sarcomatous transformation from chordoma [294].

Local invasion

Chordoma is a locally aggressive tumor and almost exceptionally invades the surrounding bone. The process of bone invasion requires active proteolytic activity, and Heackel *et al.* [130] showed that chordomas were positive for Cathepsin K, an osteoclast protease. In their study of 44 chordomas, 10 chondrosarcomas and 10 fetal specimens the authors showed that Cathepsin K and its mRNA were present in the advancing tumor front in chordomas [130]. This protease was not present in fetal notochord or in skull base chondrosarcomas, except for in entrapped osteoclasts. Naka *et al.* [242] studied the expression of extracellular matrix proteases MMP-1, MMP2, MMP9, Cathepsin B and urokinase plasminogen activator in non-skull base chordomas and found that patients with high MMP2 activity has a significantly worse prognosis.

Although they are widely invasive in the bone, skull base chordomas do not invade, but simply displace surrounding soft tissues [253]. This is especially noteworthy from the surgical standpoint, because adjacent vessels, nerves and dura are not invaded [101]. In 6 cases involving the cavernous sinus Goel *et al.* [122] did not find any vessel wall invasion.

Metastasis

Metastases occur in 3–48% of adult patients with chordomas and sacrococcygeal and vertebral chordomas are more likely to metastasize than intracranial cases [26, 52, 252, 320]. One study reporting post mortem results in 27 skull base chordomas found a 37% incidence of metastases [209]. Borba *et al.* [31], in their extensive review of pediatric chordoma cases in the literature found the incidence to be 57.9% in patients younger than 5 years. Interestingly 87.5% of these cases had atypical histopathology. Metastases usually are encountered late in the disease course, usually years after the initial presentation and most commonly become manifest in the bone and skin [52]. However lesions in lungs and lymph nodes are also frequently seen. Most common sites of involvement in the pediatric population were lungs followed by lymph nodes,

bone, liver, dura mater, kidney, adrenal glands, cerebrospinal fluid, and heart (7.1%). Seeding through the cerebrospinal fluid has been reported [329, 347]. Surgical seeding of chordoma is reported in 7.3% of the cases along the operative route or even at distal sites such as fat tissue graft harvest site [11].

Intraopertative diagnosis and cytology

Smear preparations from chordomas are generally satisfactory. Usually chords or clusters of discohesive cells set in an abundant mucinous background is observed. Tumor cells are uniform and have rounded nuclei. Physaliphorous cells can be seen but these must be differentiated from freezing artifacts. The ECM stains metachromatically with toluidine blue.

Fine needle aspiration biopsies (FNAB) are seldom possible in skull base chordomas but are of significant diagnostic importance especially when retropharyngeal extension is present [34, 140]. Studies on the cytology of chordomas most consistently report moderate to hypercellular smears of typical physaliphorous cells in a myxoid background [64, 140, 181, 234, 355]. However hypocellular smears have also been reported [246]. In addition to the physilaphorous cells, a second population of non-vacuolated epitheloid cells is also commonly reported [64]. Tumor cells are usually clustered in groups and have indistinct cytoplasmic borders [64, 360]. Occasionally well demarcated cells surrounded by the myxoid background are seen [64, 360]. Cytoplasmic vacuolization in pysaliphorous cells in a minority of cases leads to nuclear indentation or even "signet ring-like" cells [64]. Layfieled *et al.* [200] reported the cytological diagnosis of a dedifferentiated chordoma in a patient with radiographic appearance of a conventional chordoma, emphasizing the importance of cytological diagnosis.

Incidence

Chordoma is a rare bone tumor of the axial skeleton. The incidence varies considerably among studies and is dependent on the methods used for analysis. Clinical studies report incidences between 0.2% and 6.15%. However, most studies are affected by selection bias associated with referral and treatment patterns. Population-based studies avoid these type of bias and report incidences ranging from 0.18 to 0.8 per million (Table 6). A detailed list of population based studies on chordomas is presented in Table 6. The prevalence of chordoma has been stable in the last 3 decades [220] The incidence increases with advancing age [141, 349]. The peak incidence is reported to be in the 4^{th} to 7^{th} decades [220] decades. Mean age at diagnosis ranged 48 to 55 years among studies [96, 141, 251, 256, 349]. Median age reports vary between 58.5 and 62 years (range 3–95 years) [85, 89, 220, 270]. Although chordomas may be encountered in virtually any age group congenital or infant cases are exceptional and pediatric cases are rare [88, 217]. Patients younger than 20 years only

Table 6. *Population based studies on chordoma*

Study	Origin of registry or study cohort	Study period	Total number of cases	incidence	F/M ratio	Age at diagnosis (years)	Peak Incidence (decades)	Anatomical localization			Follow-up (years)	Median survival (years)	5 and 10 year survival (%)
								Sacral	Spinal	Skull-base			
Paavolainen and Teppo [256]	Finland	1953–1971	20	$0.3/10^6$ in males $0.18/10^6$ in females	1:1.5	Mean 55.5	6–7	75	15	10	Complete*	N/A	35/18
Eriksson [96]	Sweden	1958–1970	51	$0.51/10^6$	1:1	Mean 57	6–7	57	16	27	8–20	4.6 for sacral 3.3 for S/B 3.5 for spinal	N/A
O'Neil [251]	Scotland	1953–1971	34	N/A	1:1 in S/B 2.6:1 in sacral	Mean 49.6	N/A	52.9	11.8	35.3	N/A	7.2 for sacral 7.7 for S/B	N/A
Price and Jeffree [270]	England	1946–1974	11	N/A	N/A	Median 59	N/A	45	37	18	N/A	N/A	N/A
Dreghorn [89]	England	1958–1989	13	N/A	N/A	Median 62	N/A	70	30	Not included	Mean 6.2	3.75	N/A
Dorfman and Czerniak [85]	USA	1973–1987	221	$0.3/10^5$ for 75–79 years age group	1:1.6	Median 59	6–7	N/A	N/A	N/A	N/A	N/A	63.8/–
McMaster *et al.* [220]	USA	1973–1995	400	$0.08/10^5$	1:1.7	Median 58.5	7–8	29.2	32.8	32	N/A	6.29	67.6/39.9

* Patients were followed until all were deceased. S/B: Skull base.

make up 5% of the cases [31, 144, 217, 261, 320]. Pediatric cases constituted 5.5% of our cohort and only 35.71% of the patients were younger than 40 years at presentation [261]. Female to male ratio ranged from 1:1 to 1:2 [85, 89, 96, 141, 204, 220, 251, 256, 270, 349, 358]. Chordomas were very rarely reported in the black race [85, 220]. In a study of 221 chordomas Dorfman and Czerniak [85] found only 4 cases (1.8%) in blacks.

Chordomas represent 3–8.4% of all primary bone tumors, 17.5% of the primary bone tumors of the axial skeleton, 0.2% of all intracranial tumors and 6% of all skull base tumors [141, 209, 220, 357]. Among primary bone cancers chordomas are the fourth most common pathology [85, 209, 220]. In their analysis of 2627 histologically verified primary malignant bone tumors, Dorfman and Czerniak reported that chordomas comprised 8.4% of the cases [85]. Unni [349] analyzed 11087 cases of malignant bone tumors seen at the Mayo clinic from 1901 to 1994 and reported that chordomas comprised 4%. There is no gender predilection for skull-base cases.

Although chordomas can be seen anywhere along the axial skeleton, where remnants of the notochord are present, they are more commonly localized at the two craniocaudal extremes (Table 7). Most studies report a higher incidence for sacral chordomas but comparable incidences for sacral and skull base cases have also been reported by other authors both population based and clinical studies [220]. Young age (<26 years; $p = 0.0001$) and female sex ($p = 0.037$) were associated with greater likelihood of cranial presentation [220]. McMaster *et al.* [220] reported a higher incidence of skull base cases in the youngest age quartile and a higher incidence of sacral cases in the oldest group. Heffelfinger *et al.* [141] and Unni [349] both reporting Mayo clinic experience found that the average age at presentation was a decade earlier in skull base chordomas when compared to spinal or sacral cases. This may be related to the late presentation for treatment in nonskull base chordomas, which tend to be symptomatic

Table 7. *Anatomical localization of chordomas along the axial skeleton*

Study	*n*	Mean age at diagnosis	Skull base (%)	Sacral (%)	Spinal (%)
Harvey and Dawson [138]	240		37	12	51
Heffelfinger *et al.* [141]	155	48	36	49	15
Paavolainen and Teppo [256]	20	55	10	75	10
Price and Jeffree [370]	11	59	18	45	37
Eriksson *et al.* [96]	51	57	27	57	16
O'Neil *et al.* [251]	34	49.6	35.3	52.9	11.8
Unni [349]	356	48	38.2	47.5	14.3
McMaster *et al.* [220]	400	55.8	32	29.2	3
Total	1124		39	41	20

much longer and considerably larger in size at the time of presentation [141, 241, 349]. Alternatively the difference may be explained by different biological nature and behavior of chordomas in two different localizations.

Analyzing 128 skull base cases that have been diagnosed in the USA 1973 through 1995, McMaster *et al.* [220] reported that 51.8% of the patients were treated surgically alone, 44.6 with a combination of surgery and radiotherapy, 1.8% with radiotherapy alone. Another 1.8% did not receive any treatment. Median survival reported in this analysis was 6.29 years; 5- and 10-year relative survival rates were 67.6% and 39.9%, respectively. Dorfman and Czerniak reported a five year relative survival rate of 63.8% [85]. The 5 year survival numbers have not changed in the last 3 decades [220]. There was no overall increased risk for second primary cancers after the diagnosis of chordoma [220].

Clinical manifestations and natural course of disease

There are no exclusive signs or symptoms of skull base chordomas and the presentation depends on the localization, extent and direction of expansion of the tumor [225]. The usual presentation is of vague complaints of headache and/or neck pain, followed by rapid progression of one or more of the symptoms [225]. The average time between the onset of symptoms and clinical presentation reported for all chordomas is 3.44 years. However there is much variation in this and presentations as quick as 1 week and as late as 16 years have been reported. Acute presentations are however rare and related to unusual complications such as intratumoral hemorrhage [110]. Skull base chordomas present to clinical attention in average one decade earlier than sacral chordomas [349]. Diplopia and headache are the most common symptoms in patients with skull base chordomas [114, 282]. Diplopia is present in the majority of patients. Symptoms may be persistent or intermittent [16]. On examination CN-VI is the most commonly involved nerve followed by CN-III and CN-IV. Ptosis may be seen in up to 50% of the patients.

Headaches are of aching character and are most commonly poorly localized. Retroorbital pain or pressure sensation is also frequently reported. Bone destruction and neuralgia are the most common causes of pain. Trigeminal nerve is the most frequently affected. Visual loss is reported in only a minority of patients. Facial numbness may also be reported in up to 30% of the patients. Facial paresis may also be encountered. Lower cranial nerve involvement most commonly presents as hoarseness and dysphagia. Dizziness, hearing loss and vertigo may be encountered due to CN VII and CN VIII traction, compression or cervicomedullar junction compression. Neural axis impingement by lower clival tumors may result in spastic paresis in the extremities. Compression at the craniovertebral junction can cause hydrocephalus, syringobulbia and syringomyelia and resultant symptomatology.

Natural course of chordomas after they become symptomatic is dismal. Kamrin *et al.* [162], estimated that the average survival of an untreated chordoma would be between 6 and 24 months. Eriksson and colleagues reported a less than 1 year survival without treatment [96]. Menezes *et al.* [225] reported an average survival of 28 months after the onset of symptoms.

Diagnosis

Neuroradiology of chordomas

Preoperative diagnosis of chordoma mainly relies on neuroradiology. Computerized tomography (CT) and magnetic resonance imaging (MRI) are the backbone of modern neuroradiological imaging of chordoma. Sensitivity of CT and MRI for chordomas are similar and the information provided is complementary [332]. MRI is superior in delineating the extent of the tumor, its relation to surrounding structures including neural parenchyma, cranial nerves, vessels and the CT is superior in imaging bone involovement [332, 362]. Current neuroradiological technology can reliably diagnose chordomas and chondrosarcomas, however differential diagnosis between chordomas and chondrosarcomas or between classic and chondroid chordomas is not reliable [87, 229, 255, 261, 317, 362].

The classic appearance of intracranial chordoma on CT is that of a centrally located, well-circumscribed but invasive, lytic soft tissue lesion within the clival bone [87]. Bone margins are not sclerotic. The mass usually contains large calcifications and bone sequestra [87, 261, 332, 362]. The lesion is usually slightly hypodense to brain parenchyma and usually enhances well after injection of iodinated contrast agents [95]. Single or multiple small hypodense areas may be seen [95]. CT is of great importance in evaluating erosion of cranial foramina.

MRI is the single best imaging modality for chordomas of the skull base [38, 87, 195, 203, 229, 255, 261, 332]. The typical small chordoma will arise within the clivus, cause expansion of the bone, will have a homogenous hypointense T1 and bright hyperintense T2 signal, enhance moderately and heterogeneously after contrast injection [38, 87, 95, 195, 203, 229, 255, 332].

MRI and CT correlates of pathological findings

Physaliphorous cells contain intracytoplasmic mucopolysaccharide accumulations and have a high water content [141]. Most chordomas and chondrosarcomas appear iso- to hypointense to adjacent brain parenchyma on conventional spin echo T1w images [38, 87, 95, 195, 203, 229, 255, 261, 332]. In our analysis only 4.8% of cases had a hyperintense signal on T1w images [261]. Such hyperintense signal on T1W images in a minority of patients has also been demonstrated by other authors, however the pathological correlate is

not known [87, 299]. On T2w images most chordomas exhibit high to very-high signal intensity [229, 261].

Chordomas are the second most common mass lesion within the clivus after metastases [170]. Normal clivus has a uniformly low signal on T1w images which changes to uniformly high signal intensity in the third to fourth decades [170, 254]. This incidence of a T1 bright clivus increases with advancing age. Especially in the elderly the chordoma will thus appear as a clear cut hypointense focus within the hyperintense signal of the fatty bone marrow of clivus [95]. In larger lesions the clear demarcation from the surrounding tissue may be lost [170]. Doucet *et al.* [87] suggested that the incomplete delineation of chordomas on MRI may indicate microscopic distal extension of tumor cells. Meyers *et al.* [229] indicated that indistinct and irregular borders are found at sites of marrow invasion. Enhancement of the normal clivus is mild, howeve the contrast enhancement of the hypoientese tumor tends to be intense [170].

Majority if chordomas have a homogenous cut surface and in our experience 64.3% of cases had also homogenous signal on T1w images. Lobule formation is also a hallmark of chordomas, and this feature is more readily appreciated on T2w images, where hypointense fibrous septae will separate highly hyperintense lobules [195, 229, 261, 332]. Lobulation is seen in approximately half of the cases and with the same incidence both in chordomas and chondrosarcomas [261]. In less than half of the cases areas of recent and old hemorrhage, collections of mucin, necrotic regions, dystrophic calcification, and/or entrapped bone trabeculae will result in a heterogenous signal intensity on MRI [87, 225, 229]. Some chordomas show focal areas of low attenuation, and these are thought to represent myxoid and gelatinous material found in pathology specimens [227]. This feature is more commonly observed in spinal chordoma variants [227]. Small hemorrhagic foci, which are common in chordomas, appear as hyperintense in T1w images will appear hypointense in spin echo sequences [95]. Bone sequestrae, hemorrhages or mucus pools with high protein content will appear as hypointense foci on T2w images.

Major vascular structures in the region such as the ICA and the basilar artery are easily appreciated as flow-voids on T2W MRI [229, 261]. Meyers *et al.* [229] indicated that 79% of skull base chordomas displaced or encased major vascular structures. Vascular flow voids must be differentiated from a speckled pattern of low signal, which most likely represent calcifications. The absence of the flow voids of major vessels should prompt for angiography as this might indicate vascular narrowing, however this is very rare [229, 261]. Abnormal vascularity or tumor staining is generally absent on angiography.

Chordomas and chondrosarcomas show varying degrees of contrast enhancement [87, 332]. Enhancement is usually moderate and only a very small proportion of chordomas do not enhance [229, 261]. Strong enhancement is seen only in a small minority of cases [261]. Heterogenous contrast enhancement

creates the known "honeycomb" pattern [87, 95, 362]. Intravenous contrast can effectively demonstrate meningeal, cavernous sinus or sellar involvement, intracranial or retropharyngeal extension as well as invasion of cranial foramina. Strong enhancement of the dura may also help aid in indirect demonstration of the tumor extent and will strongly facilitate diferential diagnosis [229]. Fat suppression can aid in differentiating between enhancing tumor mass and the surrounding fatty marrow or fat grafts from previous surgery, however susceptibility artifacts, especially around the paranasal sinuses can be a limiting factor. Several studies reported similar contrast enhancement patterns in CT and MRI. In our analysis contrast enhancement was less frequently observed on CT [261].

Osseous invasion

Bone destruction is demonstrated in 95% of chordomas and chondrosarcomas and this is almost always accompanied by expansion of involved bone and no reactive bony changes surrounding the area of destruction [182, 261]. This finding is lost with further enlargement of the tumor [87].

We detected advanced erosion of the occipital condyle on CT in roughly 26% of our cases that involved the inferior clivus and 60% of these cases required postoperative occipitocervical fusion [261].

Chordomas and chondrosarcomas may feature bone sequestra as well as dystrophic calcification or mineralization of the chondroid matrix (ring-and-arc pattern). CT is reported to demonstrate calcification in 41% to 88.1% of chordomas [87, 114, 229, 261, 332]. It is not always possible to differentiate bone sequestrae from calcification on CT. Weber *et al.* [362] suggested that linear, globular, or arc-like calcifications may help differentiate chordomas from chondrosarcomas. Erdem *et al.* [95] found that dystrophic calcification was more common in chondroid chordomas than in classic chordomas. In our analysis there were no significant differences among the 3 groups (classic chordoma, chondroid chordoma, chondrosarcoma) with respect to proportions of lesions with calcification [261].

There are no characteristic radiological findings of chordoma subtypes

A differential diagnosis between skull-base chordomas and chondrosarcomas preoperatively using radiological methods would be extremely valuable but currently there are no reliable radiological markers to differentiate chondrosarcomas from chordomas or classic chordomas from chondroid chordomas [255, 261].

All three histopathological types of chordoma have a classic chordoma background or at least have some classic chordoma component to it. Chondorid chordomas have additional chondroid foci and atypical chordomas have sarcomatous foci. Sze *et al.* [332] reported that in their cohort chondroid

chordomas had shorter T1- and T2-signal when compared to classic chordomas and speculated that this may be related to the replacement of gelatinous-watery matrix by the chondroid foci. This has been largely cited in the literature despite the lack of any studies confirming this finding. On the contrary many studies, including three studies with large cohorts of 42, 28 and 22 patients, did not find such a difference [87, 228, 229, 255, 261, 317, 362].

Some authors argued that chordomas are midline pathologies whereas chondrosarcomas are more often located off the midline and speculated that this finding may be used for differential diagnosis [229, 362]. We and others did not find any differences concerning location relative to the midline between chordomas and chondrosarcomas [261, 285].

Tumor size and extent

It is extremely difficult to identify the site of origin of a chordoma or chondrosarcoma because neither of these neoplasms has a radial growth pattern. Both tumors tend to invade surrounding bone in rather unpredictable fashion, and only those that are confined to a specific anatomical compartment (intradural tumor, cavernous sinus, and others) exhibit radial growth. In our series, we observed no significant difference in tumor volume between skull-base chordomas and chondrosarcomas. To specifically define the extent of each mass, we divided the skull base into 18 zones and recorded whether tumoral tissue was present/absent in each. Our detailed analysis of the extent of the 42 tumors revealed no difference between chordomas and chondrosarcomas [261]. This finding is consistent with prior reports [69, 285]. We also observed no significant differences between the 2 chordoma subtypes (classic and chondroid) with respect to lesion volume or tumor extent [261].

Skull base chordomas occur at the spheno-ocipital synchondrosis and grow within the clival bone [305]. In an analysis of 28 chordoma cases, Meyers *et al.* [229] reported extension into the middle fossa in 32.1% of cases and into the posterior fossa in 78.5%. Albeit rare, other localizations outside the central skull base are also encountered and include purely intrasellar [161, 339], purely intracavernous [117, 123, 192, 193, 312, 318], within Meckel's cave [22, 261] and those that are purely intradural [261] chordomas.

Although the sella and parasellar area is very frequently involved, pure intrasellar chordomas are rare [261, 339]. Cavernous sinus is involved in 54 to 75% of the chordoma cases [375]. In addition to cases arising purely within the cavernous sinus larger tumors can involve the cavernous sinus secondarily. There is still no consensus on the nature of cavernous sinus invasion. Cases of chordomas arising within the cavernous sinus or those which secondarily invade the cavernous sinus are known]. Goel *et al.* [123] reported their observation that the cavernous sinus involvement was in the form of displacement rather than invasion while others like El-Kaliny *et al.* [92] concluded that

chordomas were invasive in the cavernous sinus. In our experience aggressive surgical resection for cavernous sinus involvement was associated with poor surgical outcome and high morbidity. Surgical results of chondrosarcomas were better than those achieved in chordomas [260].

The relation of the tumor to the petrous and intracavernous internal carotid artery is of clinical significance. Displacement or partial encasement is frequently observed, but complete encasement is exceptional [122, 123]. Chordomas displace the relatively immobile parts of the internal carotid artery in the petrous and precavernous segments along its anterolateral border [122]. In massive tumours, the entire intrapetrous segment of the artery can ne displaced. At the petrous apex, the fifth nerve is displaced superiorly while the carotid artery was displaced anteriorly [122]. Luminal narroving may be due to stretch but not due to invasion [122].

Intradural extension is a frequent feature of chordomas. Of the 38 chordomas in our series, only 47.2% were completely extradural [261]. The pathogenesis of this intradural extension is unknown. As with invasive pituitary adenomas, it is not known whether skull-base chordomas actually invade and penetrate the dura or extend through small dural defects or around cranial nerve sleeves [253]. Some reports have stated that chordomas do not penetrate the dura, and that the exact mechanism of this intradural extension is yet to be proven. Interestingly, several cases of intradural ecchordosis physillaphora have been reported within the pons which were connected with a pedicle to their intraclival part, however no such case has been documented in chordomas [3, 221]. MRI is the modality of choice for assessing intradural extension of chordomas and chondrosarcomas. CT myelography can also be used for this purpose, but this modality is seldom indicated given the extraordinary tissue resolution of MRI [332]. It is very rare for a chordoma to be purely intradural. Dow *et al.* [88] found a total of 19 reported purely intradural chordoma cases in the literature and we have also reported another case [261]. No age or gender predisposition is noted in cases reported so far. Median age of the reported cases is 38 (range 9–57 years). Males constituded 42.11% of the cases and 37.89% were females. Interestingly, it is easier to totally resect chordomas that are completely intradural than it is to totally remove other chordomas [88]. Complete resection is reported to be commonly achieved in intradural chordomas and no recurrence has been reported in any of the intradurally located chordomas with follow up periods ranging from 1 month to 12 years [5, 88, 229, 261, 367]. Our patient who had the strictly intradural chordoma is recurrence-free 10 years after complete surgical removal with no adjuvant therapy. MR spectroscopy may aid in differential diagnosis of purely intradural chordomas [215].

Skull base and cervical chordomas can spread by para- or retro-pharyngeal extension. Pharyngeal extension is seen in 7.1–25% of cases. We only observed

retropharyngeal extension in tumors that involved the inferior clivus. Chordomas have been reported within the craniofacial skeleton [125], frontal, ethmoid and maxillary sinuses [142, 319], mandible and scapula. Although extension into sphenoid or ethmoid sinuses is seen in chordomas, subfrontal extension has not been reported [228, 229, 261].

Metastatic chordomas are found in 3 to 48% of the cases but become manifest very rarely [252, 320]. Chordomas may seldom seed through cerebrospinal fluid pathways [329, 347]. Surgical seeding of chordoma is also documented in 7.3% of the cases along the operative route or even at distal sites of fat tissue graft harvest [11].

Differential diagnosis

Several different pathologies can mimic the radiological appearance of chordomas and chondrosarcomas in the skull base [87, 95, 115, 203, 283], however chordomas and chondrosarcomas of the skull base can be reliably differentiated from other tumors of the skull base with current neuroradiological technology. Meningiomas of the region are differentiated by their homogenously intense contrast enhancement on MRI, presence of a dural tail, and hyperostotic bone reaction on CT and frequent tumor blush on angiography [87]. Chordomas with sellar involvement should be differentiated from an invasive pituitary adenomas [301]. Although sellar encasement is very common in chordomas and chondrosarcomas, pure intra-sellar cases are exceptionally rare [339]. Endocrinological studies may be suggestive of an adenoma, however several endocrinological disturbances may also be seen in sellar chordomas [339]. Chordomas may also contain hemorrhages and mimic pituitary apoplexy [202]. Other pathologies that should be ruled out include malignant lesions such as plasmocytoma, lymphoma, metastasic as well as nasopharyngeal or paranasal carcinomas. Rhabdomyosarcomas should also be suspected in the pediatric population. Benign lesions that should be considered in the differential diagnosis are histiocytosis X, fibrous dysplasia, dermoid and epidermoid cysts as well as giant carotid aneurysms [87, 95, 115, 203].

Ecchordosis physaliphora (EP) are believed to be the precursors of chordoma. These benign lesions are common incidental findings and are found in roughly 2% autopsies or imaging studies for done for other reasons [3, 221]. Exceptionally rare symptomatic cases have been reported [3, 49, 186, 210, 286, 340]. To date there are only 12 reported EP cases with MRI findings [3, 49, 186, 210, 221, 286, 340, 361]. Eleven of the 12 cases were hypointense on T1W images and all were hyperintense on T2w images. In several cases a pedicle connecting the intradural lesion to the clivus was demonstrated [3, 221]. None of the cases showed contrast enhancement. At times an EP may be symptomatic and in these cases it may be difficult to differentiate these notochordal remnants from chordomas and clinical follow up may be needed. Wolfe *et al.*

[367] suggested that all such lesions should be considered intraaxial chordomas. Rodriguez *et al.* [286], in the contrary, stated that all MRI findings suggestive of symptomatic, intradural, extraosseous physaliphorous cell growth should be classified as giant or symptomatic EP as long as the existence of an intradural chordoma is not definitely proven.

Classification schemes

At present, aggressive surgical resection remains the most effective available treatment for chordomas [100, 199, 259]. Chordomas and chondrosarcomas vary much in their localization and extent in the skull base. Therefore, preoperative neuroradiological workup has an enormous impact on the choice of the optimum surgical approach to maximize resection and minimize morbidity. Through the years, several classification systems have been proposed to aid surgical planning (Table 8). The first scheme was described by Schisano and Tovi [305], who categorized skull-base chordomas as sellar or clival types. Falconer *et al.* [99] classified skull-base chordomas and chondrosarcomas as sellar, parasellar or clival subtypes. Subsequently, Sekhar and Janecka [314] classified chordomas as superior middle and inferior clival subtypes. Each of these classification schemes was very valuable in its time, but became less significant as operative approaches to the skull base evolved. This evolution continues.

With the need for an improved classification method and aware of the weaknesses of the current classification schemes, we devised a new method to quantify and define tumor extent within the skull base structures [261].

Table 8. *Surgical-anatomical classification schemes of chordomas reported in the literature*

Krayenbühl and Yasargil [182]	1. Clival 2. Parasellar 3. Sellar
Schisano and Tovi [305]	1. Basiocciput 2. Basicsphenoid
Raffel [274]	1. Basi-occiput 2. Basi-sphenoid
Falconer *et al.* [99]	1. Sellar 2. Parasellar 3. Clival
Sekhar and Janecka [314]	1. Superior clival 2. Middle clival 3. Inferior clival
Goel *et al.* [122]	1. Petroclival 2. Others

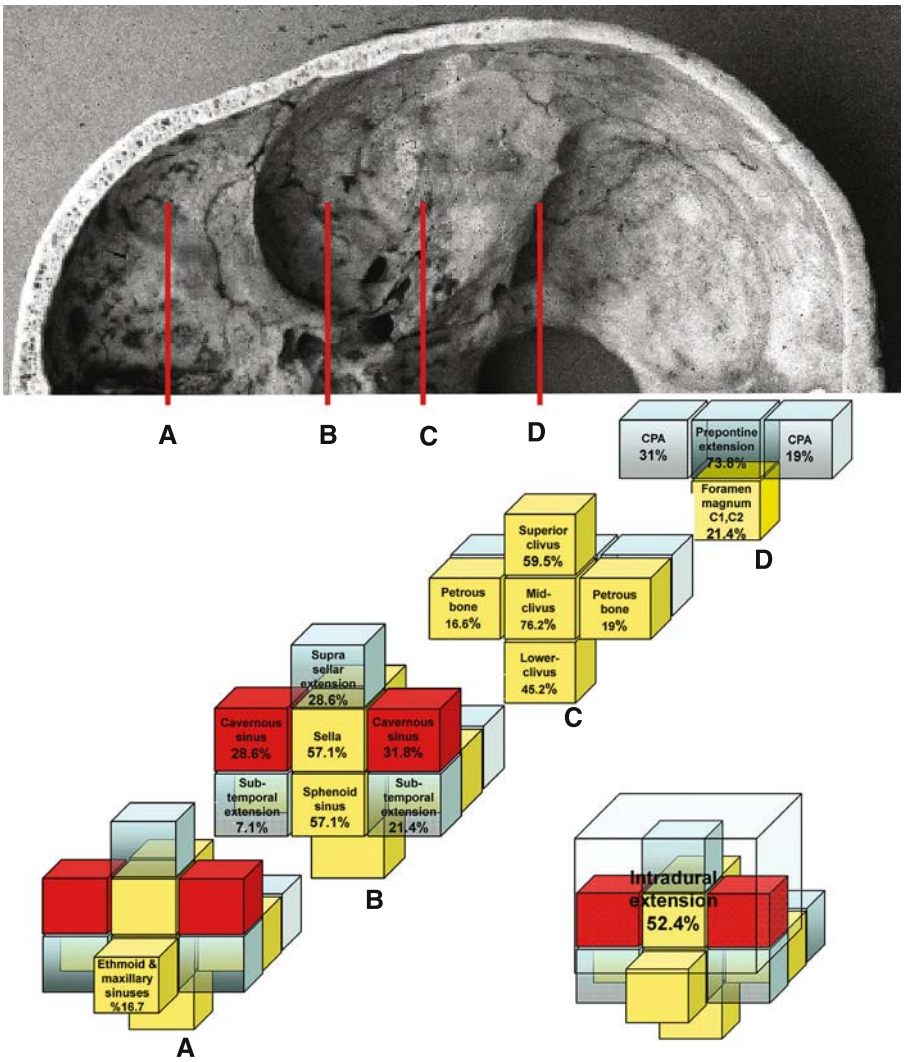

Fig. 2. Schematic representation of the 18 zones within the skull base. Red lines (A–D) represent the planes at which the schematic descriptions are made. Such a division of the skull base allows a detailed and objective description of the extent of each skull base chordoma to aid in surgical decision making, postoperative evaluation of resection and follows up. Please refer to the text or reference 273 for further details

For each tumor we analyze the presence/absence of tumor involvement in 18 distinct anatomical zones in the skull base (Fig. 2).This system addresses specifics of tumor location and extent, and thus provides very valuable information both for selecting the optimal surgical approach and systematic comparison. In our analysis of 38 skull base chordomas and 4 chondrosarco-

mas (42 tumors total) a mean of 6.7 (SD ± 2.9) zones was involved in each tumor [261].

Early and late postoperative imaging

Aggressive surgical debulking remains the most effective treatment option for chordomas Although total resection is rarely possible, extensive removal is correlated with a longer survival [60, 65, 114, 259, 345]. The extent of surgical removal is of crucial importance for planning of further treatment as recurrence is most commonly observed as persistent growth of a residual tumor mass [316]. Early postoperative MRI within the first 48 hours is performed in all neurooncological operations at our clinic. Its efficiency has been proven for several tumor types including chordomas and thus it has become a part of our current treatment paradigm for chordomas [91, 169, 259]. Early postoperative MRI led to a second attempt of surgical removal in 10.6% of our patients [259]. With increasing availability intraopertive MRI may supplement or substitute early postoperative MRI.

Despite modern treatment protocols a significant percentage of skull base-chordomas recur regardless the mode of therapy [259]. Recurrence is most frequently observed as hyper-intense mass in T2w images [95]. Most recurrences occur at the main tumor mass, most commonly as persistent growth of residual tumor. Recurrence along the surgical path has also been reported in 5% [103]. Distant metastasis is seen in up to 7–14% of patients, more so in children and with the dedifferentiated phenotype [31, 52, 252, 331].

Intraoperative imaging

Ultasonography, CT and MRI have all been used for intraoperative imaging for skull base tumors. Intraoperative MRI is used in both resective surgery or biopsy sampling of chordomas [29, 86, 219, 233, 262]. Intraoperative MRI caries a high potential to improve surgical result as it can show details, location and extent of known or unexpected residual tumor tissue and feed this information to neuronavigation equipment improving the extent of tumor removal [262]. Short term results of intraoperative MR imaging in different pathologies such as pituitary adenomas, low and high grade glial tumors, epilepsy surgery, suprasellar tumors are very encouraging [29, 39, 57, 98, 247, 248, 262]. Use of intraoperative MRI can be useful for chordoma surgery in several perspectives. First it has a high potential in assuring a safer and more extensive surgical resection, possibly decreasing the need for staged surgeries. In several approaches, and maybe most importantly in the transsphenoidal approach, it can provide dynamic image guidance. Finally the availability of objective feedback on operative success facilitates planning of further treatment.

We have been using an intraoperative 3 tesla MRI system for more than a year and early results have been reported [262]. We are using the Siemens 3T

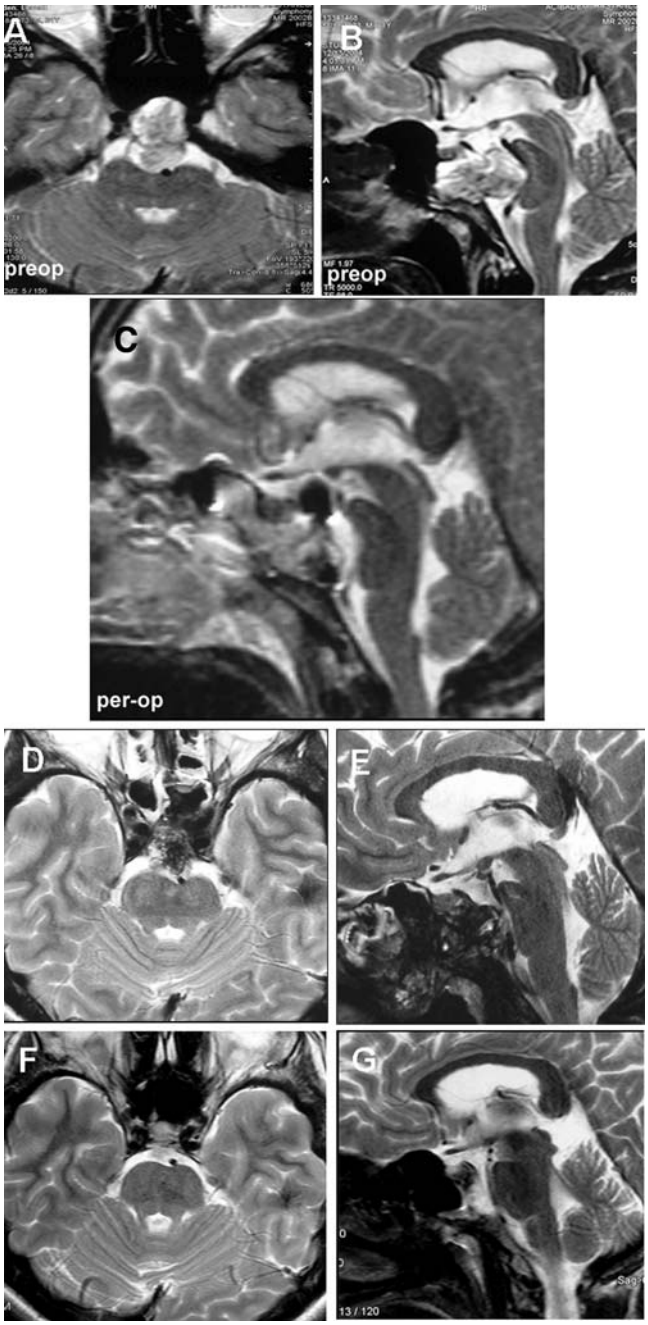

Fig. 3. Use of intraoperative MRI. for a clivus chordoma. T2w MRI of a patient showing preoperative (A and B), intraoperative (C), early postoperative (D and E) and postoperative 15th month (F and G) images

Trio (Erlangen-Germany) system which is capable of intraoperative imaging and functions as a clinical scanner as well. Our preliminary experience indicated that, as with many other tumors, the ioMR is very useful in the surgery for chordomas to help decrease complications and to increase the total resection rate. An exemplary figure of gross total chordoma resection without complications is demonstrated in Fig. 3.

Other diagnostic tests

Plain X-ray films may demonstrate an osteolytic lesion, osteosclerosis or may be normal in a minority of cases [351]. Calcifications or bone sequestrae are less readily diagnosed than with CT [229, 261]. Technetium Tc 99m bone scans are seldom performed but may reveal hot areas within the tumor. PET scans can also demonstrate chordomas, however are not routinely utilized.

For accessible lesions fine needle aspiration biopsies, with or without image guidance, may be performed to verify diagnosis. However, it should be kept in mind that such interventions will interfere with imaging findings. Presence of retropharyngeal tumor poses a unique opportunity for transpharyngeal biopsy in exceptional cases when preoperative radiology is not conclusive. However the incidence of retropharyngeal tumor extension is low (8.33–25%) and is only present in cases involving the lower clivus [5, 182, 229].

Treatment of chordomas

Current treatment options of skull base chordomas rest mostly on level-4 and very limited level-3 evidence. This is mostly a consequence of the rarity of this disease [220]. Since its first description in 1856 there have been only 24 studies of skull-base chordomas that reported cohorts larger than 30 patients [15, 28, 47, 65, 106, 114, 117, 142, 145, 152, 168, 211, 229, 234, 253, 254, 265, 278, 307, 313, 314, 350, 361b, 368].

There are three different philosophies regarding the treatment of chordomas: aggressive surgical resection, with radiotherapygiven only in patients who have remnants, aggressive resection followed by radiotherapy, and partial resection followed by radiotherapy. Sekhar and Crockard have followed the policy of aggressive surgical resection and no radiotherapy unless distinct remnants remain [315, 317, 345]. In contrast, Al-Mefty advocated administering radiotherapy to all patients postoperatively, regardless of extent of resection [5, 30, 60].

In a recent study Tzortzidis *et al.* [345] have presented the clinical outcome and recurrence rates of 74 cranial base chrome patients at long term follow-up after aggressive microsurgical resection. On the basis of the experience gained from this series, they have stated that tumor resections are much easier if the patient is seen initially, before the patient has had a previous resection or

radiotherapy and recurrent tumors are not only more difficult to remove, but also carry a higher complication rate. Thus, the surgeon's aim should be to administer the optional treatment during the initial treatment session, which may consist of tumor resection and/or radiotherapy. In this paper the thoughts of the senior author, Sekhar were stated as: "whenever possible, radiotherapy should be reserved for recurrences rather than initial therapy". In this series, better long-term results were obtained in primary tumors than recurrent tumors. However, they have also stated that this may be caused by more aggressive biological behavior (recurrent tumors) rather than complete removal (in primary patients). For the recurrent tumors their policy was summarised as:" when a patient presents with recurrent tumors, the approach should be different and more conservative. If the tumor can be removed completely without causing disability, it should be removed. However, the surgeon (and the patient) should be aware that the chances of long-term survival and the potential for complications (resulting in disability) are higher in reoperation cases. The treatment strategy should be planned appropriately".

It is widely accepted today, based on critical analysis of available data, that surgical resection is the mainstay of chordoma treatment. A more complete resection is correlated with longer survival. And It is possible that younger patients benefit from resection and its extent [259]. The importance of intraoperative or early postoperative MRI cannot be overemphasized in the shaping of adjuvant treatment. The surgeons assessment of the completeness of resection is often unreliable and MRI interpreted by a team consisting at least of the operating surgeon and a competent neuroradiologist is required to assess completeness.

Maybe the most important factor determining how a patient will fare from surgery is the biology of the tumor. Today we know very little on oncogenesis of chordomas, however it is well established that not all chordomas behave the same. There are at least two subsets of patients with distinct clinical behavior: Some with a benign course and another group with an aggressive and rapidly progressive course over 3–5 years. The outcome is clearly dictated primarily by the intrinsic biology of the tumor and treatment seems only to have a secondary impact. However understanding the oncogenesis and intrinsic behavior will enable us to shape our treatment protocols rationally or even tailor it to the needs of the individual. With advancing molecular biology and increasing knowledge of tumor biology such a possibility is not remote.

Most chordomas are not surgically treatable and recurrences create a clinical picture of ever increasing complexity. Surgical resection, even when gross total, cannot exclude the possibility of recurrence and some form of adjuvant therapy is almost always required. Therefore management of chordomas by a multidisciplinary team is of crucial importance. Particle based radiation treatment was shown to be the most effective adjuvant therapy for residual

chordomas after maximal surgical resection. However it is a very expensive treatment modality and most institutions do not have the luxury of particle based radiation therapies.

Few authors have reported such prospective management protocols. Protocols differ in the timing of postoperative imaging and the mode of postoperative radiation treatment and its timing. Increased understanding of chordoma biology and development of definitive conclusions on the optimal adjuvant therapy will eventually dictate optimal, patient based treatment protocols.

Surgical treatment

Patients benefit from aggressive but safe surgery

Accumulating evidence indicates that a simple debulking procedure is not the optimal surgical treatment for chordomas. Just in the contrary, an extensive resection of the tumor is shown to be of benefit to the patient. A subset of patients, if not all, benefits form the extent of surgical resection. This is especially true for the young patient population.

Extensive resection requires the use of more advanced surgical techniques. Chordomas arise in the center of the craniofacial skeleton and invade the surrounding structures with an unpredictable pattern, creating a very large and invasive tumor bulk. This oftentimes necessitates combination of several approaches or staged procedures to address tumor extension into different parts of the skull base [345, 346]. Facing such challenging tumors, Al-Mefty and Borba [5] classified chordomas according to their resectability. Type I chordomas can be resected along with a margin of normal bone and soft tissue. These tumors are small, symptomatic or asymptomatic and separated from critical structures. The most commonly encountered type is the Type II tumor which is larger and involves contiguous anatomic areas. Type II chordomas are still resectable with a single operative approach. Type III chordomas have extensive skull base involvement and require multiple approaches for resection.

It is commonly accepted that an extensive resection is feasible. However, there is no consensus to date regarding how aggressive the surgeon should be. Should a cavernous sinus involvement be addressed aggressively at the cost of cranial nerve morbidity? Does such an aggressive approach increase our chances of assuring local control? Can a similar outcome be obtained by "safe, maximal surgical resection" and adjuvant therapy? Current literature cannot provide definitive answers most of these questions [12, 84, 117, 132, 165, 193, 312]. However some facts have been proven by accumulating experience: Safe maximal resection is of benefit to the patient at initial resection, but is influenced by other factors such as history of prior surgery or radiotherapy, which greatly increase the risk of complications and force us to being more conservative [345, 346].

Evolution of the surgical technique

Surgical techniques used for the treatment of chordomas are in constant evolution. Forsyth *et al.* [106] reported 78% subtotal removal and an 11% biopsy rate in patients treated with conventional techniques between 1960 and 1984. Skull base surgery, as it entered our routine armamentarium in the 1990's has provided major improvements in treatment of chordoma, which grows widely invasive in the skull base. Cumulative experience of the last 20 years has proven the usefulness of several of these approaches. For treatment of lower clival lesions with lateral extension the far lateral transcondylar approach has been a major improvement over transoral approaches with a limited reach and high complication rate. During this evolution limitations have been defined and the degree of success defined for each approach and emergence and popularization of newer technologies have helped define more precise indications. For example the limited midline reach of the traditional transsphenoidal transseptal approach was considerably widened with the popularization of extended transsphenoidal approaches [63, 109, 163, 302]. Couldwell *et al.* [63] reported that the extended transsphenoidal approach can expose the skull base from the cribriform plate of the anterior cranial base to the inferior clivus in the anteroposterior plane, and laterally to expose the cavernous cranial nerves and the optic canal. Similarly Kouri *et al.* [180] described the modifications to the standard trasnsphenoidal approach for accessing to suprasellar tumors. Increased interest in surgical neuroanatomy [236], wider use of endoscopes [159, 160], image guidance, and development of inntraoperative MRI have been major driving factors in the field [29, 86, 219, 233, 262]. Jho *et al.* described routine successful use of endoscopy for transsphenoidal approaches and described endoscopic removal of large posterior fossa chordoma [158–160].

With advanced surgical techniques gross-total tumor removal is achieved in approximately 50–71.6% of these patients, with estimated rates of mortality and major complications at 5% and 10%, respectively [259, 345]. Our analysis showed that the initial tumor volume was also correlated with operative outcome. Tumor progression was almost the rule if initial tumor volume exceeded 20 cm^3 [259]. In most studies the extent of resection was inversely related to the risk of recurrence [60, 65, 114, 259, 345]. And in many cases the patients have residual, albeit controlled, disease. To achieve high rates of complete tumor removal, 16 to 50% of patients require multiple skull-base operations [5, 60, 114, 259, 345]. These above-mentioned results represent dramatic improvement over conventional surgeries. The 5-year rate of progression free survival after this aggressive skull-base surgery is approximately 76% [259, 345].

Several different studies on the postoperative functional performance status of patients indicated that there was no improvement postoperatively [60, 114]. It should be noted that there is a small but significant group of patients, who

experience functional deterioration due to the operative procedure and never improve [60].

Principles of tumor resection

When treating chordomas the aim of surgeon is to reach the most extensive resection with the least morbidity. Preoperative evaluation includes, in addition to detailed neurological examination, neuroopthalmological, otolaryngological and endocrinological testing if appropriate and general medical assessment. Electrophysiological testing is also of great value. Comprehensive neuroimaging should also be undertaken to delineate tumor location, extent, invasion and relation to vital structures both using MRI and CT and additional techniques such as CTA, MRA or DSA as needed. Basic concepts of skull base surgery apply in their entire to chordoma surgery. As one of the pioneers of the radical skull base surgery for chordomas, Sen *et al.* [316] indicated that the tumor resection should follow pathways created by the tumor and follow an intracapsular route. Removal of bone is preferred over retraction of neurovascular structures. When dura is opened into communication with nasopharyngeal or oropharyngeal spaces, repair with vascularized large pedicle-flaps is required to prevent cerebrospinal fluid (CSF) fistulas.

Choice of the surgical approach

With the current surgical techniques there is no single best operative approach to treat chordomas and all approaches have limitations as well as weaknesses. The choice of surgical approach is dictated by the tumor's location, extent, growth pattern, relation to the dura and surrounding vital structures. Other factors that must be taken into consideration are the general health of the patient, previous surgery or radiation treatment and the experience and choice of the surgeon.

We prefer to tailor the approaches according to the extension of each individual tumor. The extent of the tumor is analyzed according to our method, which simply marks the presence/absence of tumor tissue in 18 distinct anatomical zones in the skull base [261]. Details of this method and other previous classification schemes is described in the radiology section. Capabilities of each surgical approach to reach these 18 compartments are outlined in the Table 9. Details of each surgical approach are also presented below. Rough outlines are as follows: Midline central skull base can be reached by anterior or lateral transcranial approaches. Lateral extension of chordomas is best approached by lateral approaches. Tumors at the craniovertbral junction can be approached with midline subfrontal, maxillotomy or transoral approaches. Lateral extension of the tumor at the craniovertebral junction will necessitate

Table 9. Common surgical approaches to the skull base and extent of anatomical exposure. A positive sign denotes that the anatomical zone (columns) can be exposed with the corresponding surgical approach (rows).

Approaches	Intradural extension	Sellar encasement	Suprasellar extension	Subtemporal extension	Cavernoussinus involvement	Sphenoidsinus involvement	Ethmoid–maxillary sinusinvasion	Superiorclivus involvement	Middleclivus involvement	inferiorclivus involvement	Prepontine extension	Petrousbone involvement	Cerebellopontine angleextension	Foramenmagnum/atlas/axisinvasion
Anterior approaches														
Extended transbasal/subfrontal	+	+	+	–	+/–	+	–	+/–	+	+	+	–	–	+/–
Subcranial	–	+	–	–	+/–	+	–	+/–	+	+	+	–	–	+/–
Conventional transsphenoidal	–	+	+	–	–	+	–	+	+/–	–	–	–	–	–
Extended transsphenoidal	–	+	+	+/–	–	+	+	+	+	+	+	–	–	–
Transethmoidal-sphenoidal	–	+	–	–	–	+	+	+	+	–	+	–	–	–
Le-Fort I maxillotomy	–	+	–	–	–	–	+	+	+	+	+	–	–	+
(extended) Transoral	–	–	–	–	–	–	–	–	–	+	–	–	–	+
Anterolateral approaches														
Pterional	+	–	+	+	+	–	–	–	–	–	–	–	–	–
Fronto-orbitozygomatic	+	–	+	+	+	–	–	+/–	–	–	–	–	–	–
Cavernous sinus exploration	+	–	+	+	+	–	–	+/–	–	–	–	–	–	–
Lateral and posterolateral approaches														
Subtremporal	+	+	–	+	–	–	–	+	–	–	–	–	–	–
Transpetrous apex	+	+	–	+	+	–	–	+	+/–	–	–	–	–	–
Presigmoid-Retrolabyrinthine	+	–	–	–	–	–	–	+	+	–	+	+	+	–
Presigmoid-Translabyrinthine	+	–	–	–	–	–	–	+	+	–	+	+	+	–
Total petrosectomy	+	–	–	–	–	–	–	+	+	+	+	+	+	–
Retrosigmoid	+	–	–	–	–	–	–	+/–	–	–	+/–	+/–	+	–
Extreme lateral	+	–	–	–	–	–	–	–	+	+	+	+	+	+

the use of an extreme lateral approach. We have previously shown that use of tailored skull base techniques as opposed to conventional approaches decreased the postoperative residual tumor volume decreased from 20% to 9.2% [259]. Use of 3T intraoperative MRI and neuronavigation further improves surgical results [262].

Anterior approaches

Midline central skull base can be reached by anterior or lateral transcranial approaches. These approaches expose the whole clivus in its entire from different angles. Entry may be performed by a bicoronal or facial incisions or through nasal or oral cavities or the neck. Within the facial skeleton a subfrontal, ethmoidal, transnasal, transseptal, transfacial, transmaxillary or a transoral route may be taken, either alone or in combination. All anterior approaches are in essence midline approaches and are limited in their lateral exposure.

Midline Subfrontal approaches

Chordomas with significant suprasellar and anterior extension in addition to widespread disease in the clivus can be addressed with the transbasal, extended subfrontal approaches or their modifications [80]. These two approaches combine various degrees of bifrontal craniotomy and orbitonasal osteotomies. As described by Derome [80] in 1972 the transbasal approach is a capable and versatile anterior midline approach. Derome [81] published his experience with the results of 33 skull base chordomas and documented its versatility. This approach has been extended by several authors with the addition of varying orbital, nasal or ethmoidal osteotomies [53, 145, 187, 275, 313, 322, 377]. Sekhar *et al.* [313] described the extended subfrontal approach, and advocated a radical ethmoidectomy to improve exposure of the clivus. Spetzler *et al.* [323] further refined the approach by the addition of an osteotomy of the cribriform plate to preserve olfaction and facilitate the reconstruction of the floor of the anterior fossa. Several similar techniques involving varying slightly in their frontoorbito nasal osteotomies have been described. Cadaver dissection studies report that the transbasal approach increases the viewing angle twice and the extended subfrontal approach five times when compared to the simple subfrontal approach [145]. The extended subfrontal approach involves a bifrontal craniotomy, followed by orbital, frontal and ethmoidal osteotomies. Planum sphenoidale is removed and both optic nerves are exposed and protected. Laterally the internal carotid arteries are identified and protected. Piecemeal removal of the tumor starts from the core and tumor boundaries within clivus are drilled until normal bone architecture is seen. Possible tumor remnants at blind spots at the dorsum sella or the petrous apices can be addressed using endoscopic assistance. Such an invasive skull base exposure also requires careful reconstruction with closure of

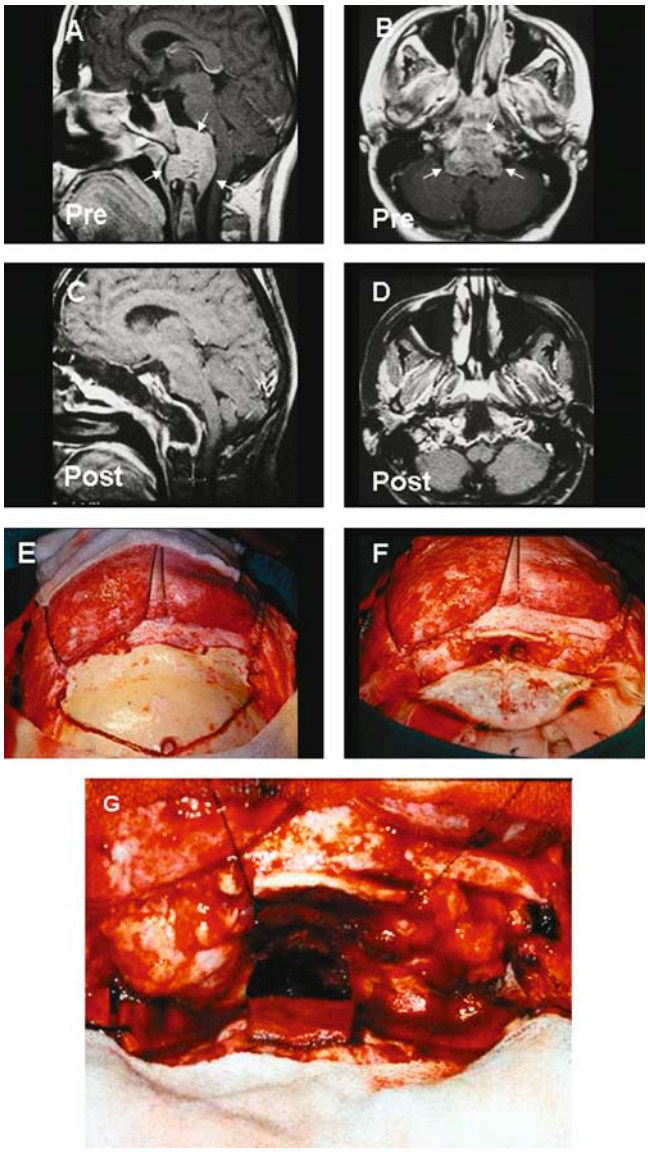

Fig. 4. Transbasal approach for the removal of an inferior clival chordoma. This approach is well suited for resection of midline tumors and provides access to as low as the axis. A and B present the preoperative T1w contrast enhanced images and show the inferior clival contrast enhancing chordoma impinging on the pontomedullar junction. C and D represent postoperative T1w contrast enhanced images with fat supression. E shows the monobloc bifrontal osteotomy. F shows the exposure after removal of the bone flap and (G) represents the deep exposure to the inferior clivus

dural defects, lying of a large pedicle-flap of pericranium along the surgical path and generous packing with fat on the cranial side.

Such midline subfrontal approaches provide an exceptionally deep view down to the skull base as low as the odontoid process of C2 (clival dura posteriorly and roof of the nasopharynx anteriorly) with very little brain retraction (Fig. 4) [81]. Superiorly the exposure of the superior clivus and the dorsum sella is limited by the dorsum sella [81]. Lateral boundaries of the approach decrease with the depth of exposure [80, 313]. Lateral boundaries in the ethmoid bone are formed by the orbital apices and the optic nerves. Within the sphenoid the lateral resection can extend into the cavernous sinus [80, 313]. Chordomas involving the medial wall of the cavernous sinus can be resected and venous bleeding which starts after resection of the tumor bulk can be stopped with surgical packing, however the risk of injury to the internal carotid artery and cranial nerves within the cavernous sinus becomes significant. Down at the clivus trigeminal roots and the hypoglossal nerves form the lateral boundaries [80].

These approaches are very versatile but they also have significant limitations. The exposure is deep and at times requires specialized equipment to reach the lesion that lies 8–10 cm away from the opening [53, 145, 187, 275, 313, 377]. These approaches are essentially designed to address lesions in a midline corridor but can be combined with some type of lateral approach to address for lateral extensions of the tumor. Possible complications of transbasal and subfrontal approaches are frontal lobe injury, CSF leak, injury to the optic, abducens and olfactory nerves, carotid rupture and hypopituitarism [70].

Transsphenoidal approaches

Their extradural origin, their predominantly extradural extension and little hemorrhage make chordomas attractive targets for endonasal approaches (Fig. 5). Traditionally, the conventional transseptal-transsphenoidal approach was considered appropriate only for biopsy or for subtotal removal of small midline lesions of the upper (retrosellar) clivus only [12, 136, 196, 198, 212, 317, 335]. However with the development of newer technologies such as image guidance, intraoperative MRI and neuroendoscopy endonasal and description of alternative techniques these approaches are gaining popularity and with more reports of success its role is being reconsidered. To date, despite all the encouraging preliminary results, only few reports exist on use of microsurgical transsphenoidal [63, 74, 190, 197] or the endoscopic transnasal approach [44, 74, 109, 159, 160] for the treatment of clival chordomas. Apart from its ever increasing use for resective surgery, the transsphenoidal technique also still maintains its valuable role for biopsy [29].

The main limitation of classical-midline approaches was their inability to address lateral extension adequately. Several new techniques have been proposed to overcome these shortcomings both for microsurgical and endoscopic

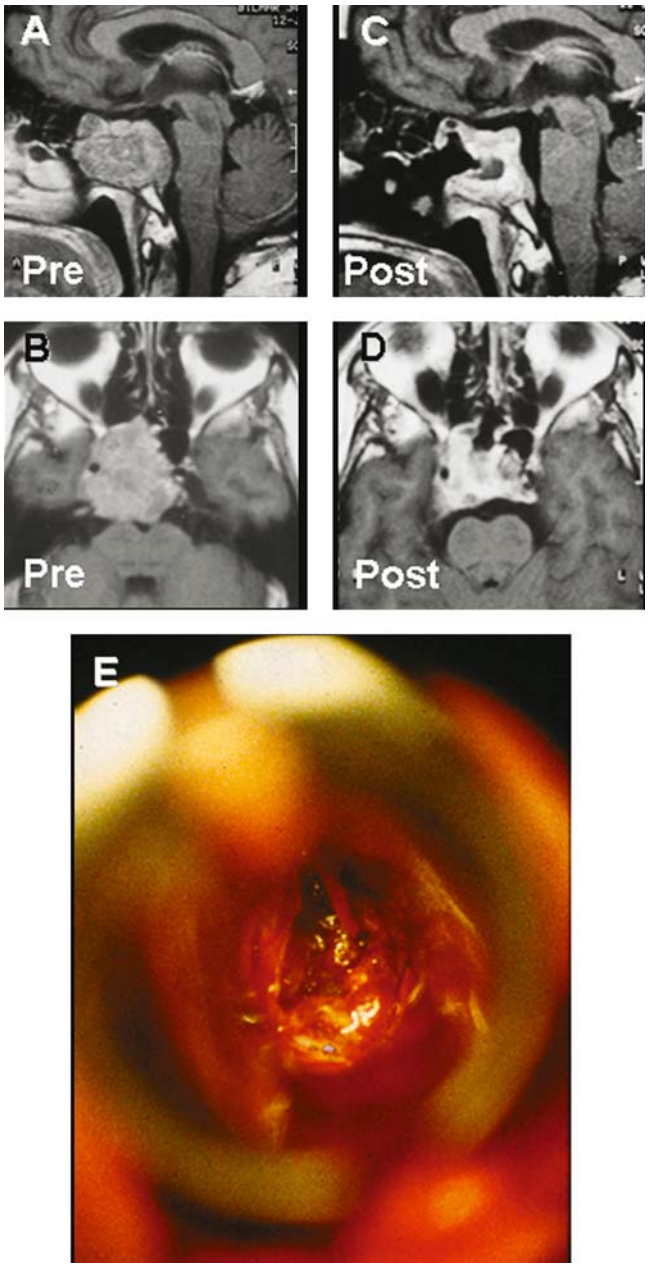

Fig. 5. Standard transseptal transsphenoidal approach to the sella for removal of a sellar chordoma. A and B represent sagittal and axial preoperative T1w contrast enhanced MRI's. C and D are the corresponding postsurgical 26th month images. E shows the visualization of the chordoma through the transnasal transseptal exposure

approaches [316]. Laws [63, 197, 198] was one of the pioneers of extended transsphenoidal approaches [197, 198, 366]. Couldwell *et al.* [63] described their experience of extended transsphenoidal approach for 18 chordomas of the inferior clivus and noted that the superior clivus can be accessed posterior to the sphenoid sinus and that the middle or inferior clivus can be reachedafter removal of the sphenoid floor. Kitano and Taneda [171] described the submucosal removal of the posterior ethmoid to gain access to gain a wider access to the suprasellar area or the cavernous sinus. Addition of transmaxillary approaches or addition of a maxillectomy in the endoscopic approach extends the lateral exposure and provides access to the medial compartment of the cavernous sinus [62, 108, 272, 293].

Radical resection of chordomas is possible with the transsphenoidal approach and its modifications in selected cases. In such suitable cases the technique is less invasive and results in fewer complications than craniotomy [63, 109, 197, 212]. Rates of macroscopic total resection for selected clival chordomas with transsphenoidal approaches ranges from 45% to 70% [63, 197]. Intraoperative MRI, neuronavigation and endoscopy can greatly facilitate resection of an invasive tumor in the skull base. The limitations of current transsphenoidal techniques, either endoscopic or microsurgical, are tumors primarily situated in the lower clivus with lateral extension into the occipital condyles. The course of the internal carotid artery and the brainstem narrow the surgical space to the petrous apex.

Complications reported with the transsphenoidal approaches for chordoma include carotid rupture (with resulting hemiparesis), basilar thrombosis, venous cavernous sinus hemorrhage (intra or postoperative), CSF leak, anosmia, CN III and CN VI palsies [63, 198]. Couldwell *et al.* [63] reported a very high incidence (3 of 18 cases) of carotid artery rupture during chordoma resection from the clivus. Laws *et al.* [198] noted that the complication risk in repeat surgery was significantly higher.

Anterior midface approaches

Anterior midface approaches take advantage of the fact that the clivus lies immediately posterior to the nasal cavity, paranasal sinuses and the nasopharynx. The entire length of the clivus can be accessed through the nose with a substantially shallow operative depth [137, 155]. Transethmoid and sphenoid approaches can expose the area from dorsum sella down to the hard palate [155]. Addition of a maxillotomy or maxillectomy extends the inferior down to the craniovertebral junction [155]. The superior and inferior limits of various transnasal approaches are similar and these approaches differ mainly in the extent of lateral exposure. A wider lateral exposure provides access to lateral extension of the tumor but also widens the surgical field, decreasing the working distance.

Incisions for midface approaches can be rhinal or mucosal [155]. Mucosal incisions include the posterior septal, septal transfixion, sublabial and "midfacial degloving" procedures and provide easy and relatively less invasive approaches to the midfacial skeleton with good cosmetic results. However, except for the "midfacial deglowing" procedure these procedures provide a more limited surgical field, being more suitable for the resection of smaller tumors or tumors that may be removed from a small window. The "midfacial deglowing" procedure was described by Casson *et al.* [46] in 1974 and provides a complete exposure of the visceral cranium without the need for facial skin incisions. Another very important advantage of this approach is that the submucosal dissesction for closure and repair decreasing the risk of a CSF fistula [189]. Facial-rhinal incisions can be limited to the superior, full, extended or bilateral extended [137, 155]. A lateral rhinotomy permits entry into ethmoid and sphenoid sinuses and the superior half of the clivus can be accessed through this approach [155]. Spanning the whole length from Glabella to philtrum, the Weber-Ferguson incision starts from the glabella, extends around the medial canthus deep into the orbicularis muscle, lateral aspect of the nose and down to the philtrum [155]. This incision provides access to the ethmoid, sphenoid and medial maxillary sinuses and makes lateral reflection of the nasal cartilage and bone possible [155]. This can expose the clivus in its entire length [155]. For mobilization of midfacial skeleton this incision may be extended laterally beneath the eye and the lower eyelid and from the lateral canthus to the preauricular area.

Exposure to the clivus can be gained with various facial osteotomies. Maxillary osteotomies, especially Le Fort-I or hemi-Le Fort-I osteotomy procedures have frequently been reported to approach clival lesions [10, 155, 189, 235, 352, 354] These procedures have in common a horizontal maxillary osteotomy. The drop-down maxillotomy procedure exposes the sphenoid bone, the superior and the middle clivus. The translocated maxilla, however, limits the visualization of the inferior clivus and the craniovertebral junction [155, 189]. On the axial plane the approach is limited by the carotid arteries. One of the important advantages of midline transfacial approaches is due to its embryological development the facial skeleton is quite symmetrical and each half has its own neurovascular supply. This creates a unique opportunity to "hinge" any part of the facial skeleton from the orbit down to the maxilla and mandible to create a midline surgical corridor [235]. The so called "swing approaches" were first described on the mandible by Spiro in 1981 [324]. A maxillary swing procedure involves an extended Weber fergusson incision followed by a hemi Le fort III osteotomy and mobilization of the nasal septum [324]. Alternatively the extended "open door maxillotomy" procedure consists of midfacial deglowing exposure, a Le-Fort I osteotomy and a midline division of the hard and soft palate. Each flap of the palate is supplied by its own palatal artery and

nerve. This approach provides a more extensive caudal exposure than the drop down maxillotomy and can visualize as low as the body of C2. Superior limits are formed by the sella superiorly, the optic canals superolaterally and the cavernous sinuses laterally. Lateral boundaries are the carotid arteries and the occipital condyles. Using a maxillotomy approach the carotid artery can be visualized from its bifurcation to the petrous canal, however proximal control is not possible.

Major disadvantages of anterior midface approaches are the contaminated surgical field, cosmetical concerns and functional problems (nasal crusting and chronic sinusitis) in the upper airway [155]. Maxillotomy approaches are of significant complexity and complications include carotid artery injury, cranial nerve injuries, CSF fistula, oral malocclusion, palatal and dental numbness, maxillar osteonecrosis and loss of tooth viability [10, 155, 189, 235, 352, 354].

Transoral approaches

The transoral transpharyngeal approach provides an easy and direct access to the extradural structures in the ventral aspect of the craniovertebral junction without the risk of manipulation of brainstem, spinal cord or the vertebral arteries [69, 94, 224, 343]. With the standard approach a midline corridor spanning from the inferior one third of the clivus down to the C3 can be exposed [224]. However exposure can be extended to as high as the middle clivus by splitting the soft and hard palate [224]. As for the lateral exposure, it can extend to the jugular foramina [224]. For tumors with larger lateral extension a posterolateral exposure is indicated, which also makes occipitocervical fusion possible in the same setting [224]. Alternatively a combination with transethmoidal, transmaxillary or maxillectomy procedures may be performed to increase superior and lateral exposure [224]. In case of limited oral exposure, in patients with small interdental space (<2.5 cm) or less commonly in those with micrognathia or macroglossia, addition of a glossotomy may be required [9, 78, 224, 240]. A glossotomy is more commonly required in children than in adults [134, 343]. A midline mandibular splitting procedure may also be used to increase inferior exposure. The removal of occipital condyles to resect tumor may necessitate an occipitocervical fusion, which must be done as a separate procedure. Tuite *et al.* reported several cases with acute neurological deterioration after the transoral procedure with possible injury occurring during repositioning for the posterior fusion procedure. Crockard *et al.* [67] described a one-stage procedure for transoral approach and fusion in cases with rheumatoid atlantoaxial subluxation.

This is an old and established approach with much accumulated experience. However despite initial optimism, transoral transpharyngeal-transpalatal approaches fell of favor for the treatment of chordomas at the craniovertebral junction, mostly due to their high infectious complication rate and limited

exposure [8, 70, 213, 224, 311, 343, 359]. The contaminated surgical field also precludes its use for chordomas with intradural extension. Such an approach is best suited for partial resection of purely extradural tumors located at the midline on the craniovertebral junction with no or very little lateral extension.

The overall complication rate for transoral approach is 18 to 26% and there is also a high mortality rate (6%). Surgical wound infection is of great concern with transoral approaches. Pulmonary infectious complications are also commonly seen. Other complications include CSF fistula, vertebral artery rupture, velopharyngeal insufficiency (with resultant hypernasal voice, nasal regurgitation, and dysphagia) and occipitocervical instability.

Anterolateral approaches

Parasellar structures are very commonly involved by chordomas. Fifty-four to 75% of chordomas involve the cavernous sinus. Pterional approach alone or in combination with orbital or orbitozygomatic osteotomies or frontotemporal interdural approaches (cavernous sinus exploration as described by Dolenc, Hakuba and Kawase) with or without addition of orbitozygomatic osteotomies are frequently utilized for resection of parasellar, suprasellar cavernous sinus extension of chordomas [12, 82, 84, 117, 123, 192, 193, 312, 318]. However, exposure of the clivus with these approaches is limited [82].

Tumor within the cavernous sinus are approached with frontotemporal interdural approaches [12, 84, 117, 132, 165, 193, 312]. These are collectively known as cavernous sinus explorations. The Dolenc approach involves an extradural anterior clinoid resection and stripping of the two layers of the lateral wall of cavernous sinus after an incision along the occulomotor nerve (Fig. 6) [82, 84]. The similar Hakuba approach exposes the cavernous sinus purely extradurally [164, 165]. The Kawase approach involves a frontotemporal-orbitozygomatic craniotomy (or alternatively a simple subtemporal craniotomy) [132]. Anterolateral approaches such as the transcavernous or Kawase approaches can only provide a very limited and narrow exposure of the dorsum sella and the petrous apex, far less than what is required for the average chordoma [82, 164, 165]. The approaches are well suited for lesions arising in the superior clivus and the petrous apex invading the posterior cavernous sinus and can be extended into the petrous apex or the posterior fossa [164, 165].

Lateral approaches

Lateral approaches use floor of the middle cranial fossa to approach the central skull base. They include the subtemporal approach, the standard middle fossa approach to the internal auditory canal and its extensions. The middle fossa approach was first described by House as an extradural, infratemporal approach to the internal acoustic canal for resection (with hearing preservation)

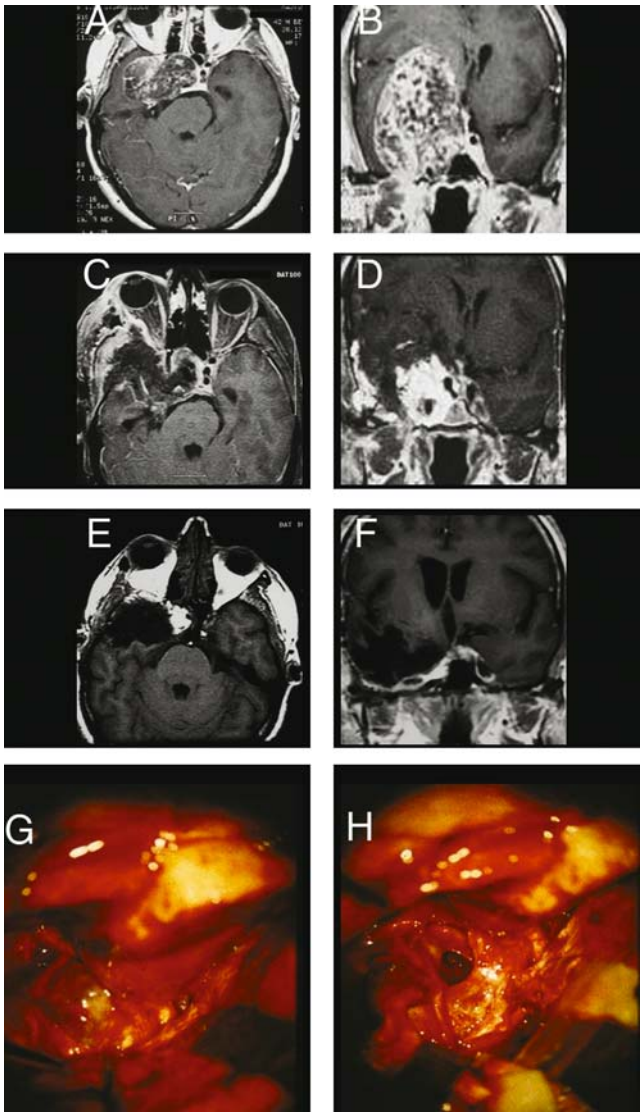

Fig. 6. Cavernous sinus exploration with the Dolenc procedure. A and B present the preoperative T1w contrast enhanced images and show the tumor within the left cavernous sinus. Early postoperative images show the tumor cavity. C and D which has collapsed at late postoperative imaging. G shows intraoperative exposure of the characteristic greenish looking chrodoma. H shows the resection cavity after piecemeal removal of the tumor

of small vestibular schwannomas with limited posterior fossa extension [149]. This approach because of its very limited exposure it is used in its extended form. The extension involves an anterior petrosectomy through a subtemporal

approach and exposes posterior cavernous sinus, anterolateral mesencephalon, pons and the upper half of the clivus [121]. Lateral inferior approaches divide the temporomandibular joint and reach the central skull base through the infratemporal fossa [23, 102].

Posterolateral and inferolateral approaches

Posterolateral and inferolateral approaches are mainly indicated for chordomas with marked lateral extension. Various presigmoid approaches can be used for chordomas invading the petroclival area [141, 315, 317, 344a, 345]. Lateral extension at the craniovertebral junction are best addressed with an extreme lateral approach, which involves mobilization of the vertebral artery, partial or complete resection of the occipital condyle and provides a lateral viewing angle to the caudal brain stem.

Presigmoid approaches

The transpetrosal approach was first described in the neurosurgical literature in 1985 by Hakuba *et al.* [131]. In this report they described the surgical technique and results of the transpetrosal transtentorial route used in 8 patients with a retrochiasmatic craniopharyngioma. In 1988 Al-Mefty *et al.* [4] and Samii and Ammirati [298] independently described their experience with the technique and the results of the transpetrosal approach. Al-Mefty reported on 13 patients with a petro-clival meningioma treated using, what he called the "petrosal" approach [4]. Al-Mefty's original work was a key literature in popularizing this approach.

Presigmoid approaches combine a simple mastodidectomy with various degrees of petrosectomy (Fig. 7). The extent of petrosectomy depends on both the desired exposure and the preoperative symptoms of the patient and includes partial labyrinthectomy, total labyrinthectomy (translabyrinthine approach) and petrosectomy (transcochlear approach). The translabyrinthine exposure exposes the anterolatral brainstem and the cerebellopontine angle and the transcochlear approach further exposes the anterior brainstem, however at the expense of hearing and transient facial nerve palsy. All levels of petrosectomy can be combined with middle fossa or far lateral approaches for resection of extensive tumors.

We are currently using small petrosal approach to petroclival region [344a]. The small petrosal approach allows safe access to this region without the need for brain resection or retraction [344a].

Extreme lateral approach

Extreme lateral approach is of great value for resection of chordomas of the lower clivus with lateral extension into the craniovertebral junction. The approach allows the surgeon to view the craniovertebral junction (CVJ) from a

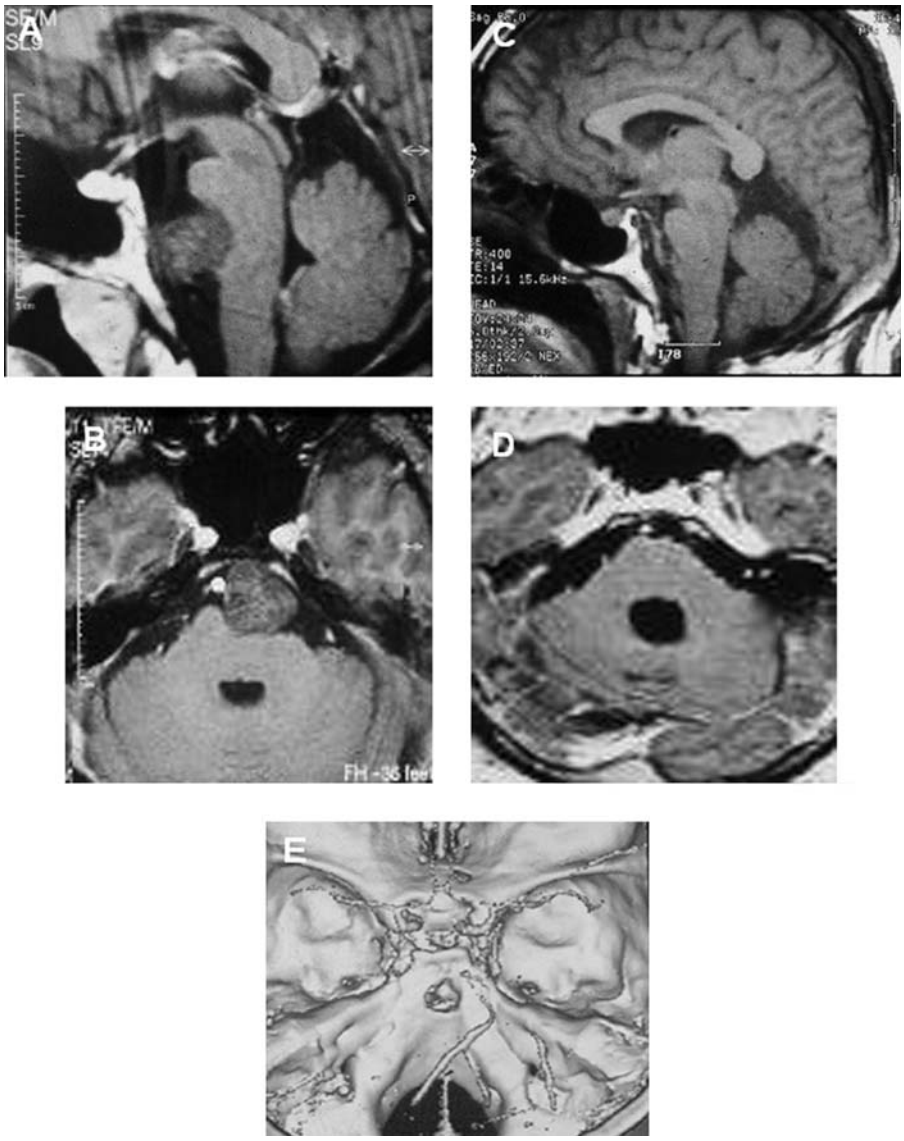

Fig. 7. Presigmoid approach for resection of a predominantly extraosseus prepontine chordoma. A and B represent sagittal and axial preoperative T1w contrast enhanced MRI's withsignificant impingement on pons. C and D are the corresponding postsurgical images. E presents a preoperative CT reconstruction of skull base showwing localized bone destrucion at the level of mid-clivus

lateral perspective and this is of great importance as most chordomas arise either anterior or anterolateral to the neuraxis [18]. The extreme lateral approach can be used alone or in combination with presigmoid or subtemporal approaches [18].

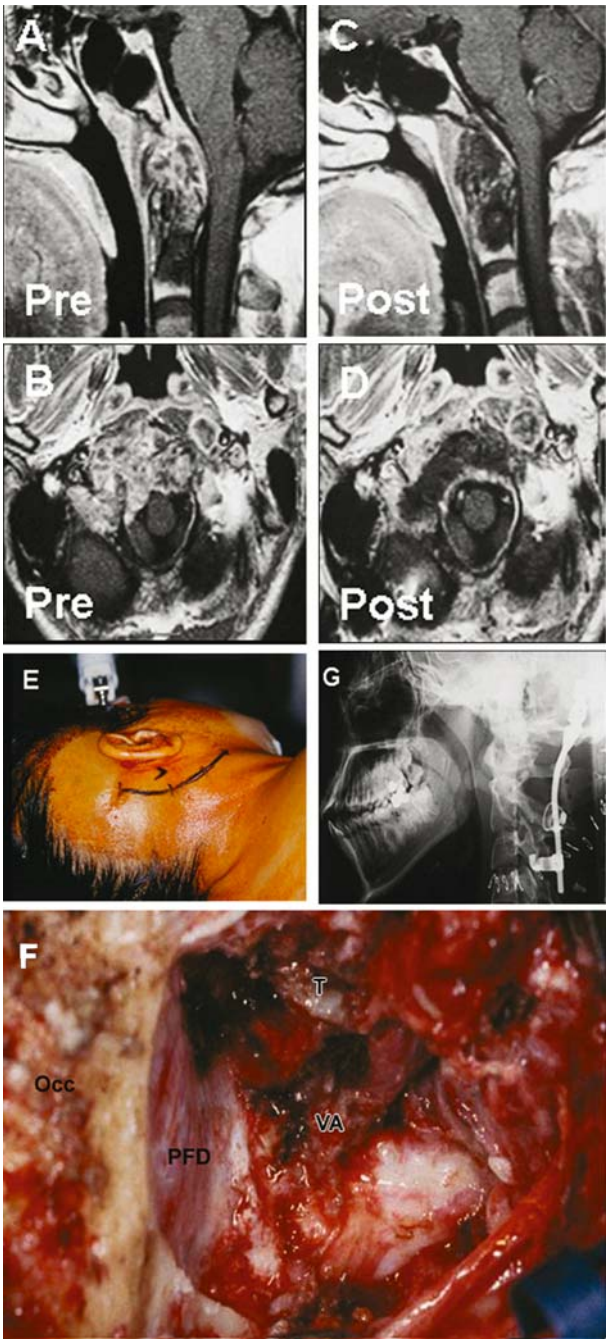

Fig. 8. Extreme lateral transcondylar approach for the removal of an inferior clival chordoma with significant lateral extension. A and B represent sagittal and axial preoperative T1w contrast enhanced MRI's with involvement of the craniovertebral junction. C and D are the corresponding postsurgical images. Through a retroauricular incission the craniovertebral junction is exposed (E). A demonstration of the surgical field is given in F. Extensive condylar resection necessitated a fusion procedure (G). *Occ* occipital bone, *PFD* Posterior fossa dura, *T* tumor, *LC VA* vertebral artery

The extreme lateral approach involves a vertical retromastoid incision extending down to the neck to expose the vertebral artery within the foramen transversarium of axis (Fig. 8).

Occipital bone, arch and lateral mass of atlas and the lamina of axis are exposed. The vertebral artery is identified within the suboccipital triangle and unroofed at the foramen transversarium of atlas. Exposure and subsequent mobilization of the vertebral artery for protection was first described by George *et al.* [116]. The V3 segment is identified using bony landmarks. Between atlas and axis the ventral ramus of the C2 nerve root passes lateral to the artery and at this portion (between the atlantooccipital membrane and the posterior fossa dura) the vertebral artery courses within a venous plexus. Parkinson [263] compared this venous plexus to the lateral sellar compartment and Arnavutovic *et al.* [11] called it "the occipital cavernous sinus". The exposure of the venous plexus greatly facilitates protection of the vertebral artery and minor bleeding form the plexus is easily controlled by packing with surgicell and gentle compression. A gentle posteromedial translocation of the artery exposes the lateral mass of C1 and subsequently a durotomy to explore intradural tumor extension may be performed. It is of extreme importance to avoid kinking of the vertebral artery as it may cause brainstem infarction. Calcification of the periosteal sheath and tunneling of the vertebral artery groove should be considered during mobilization of the artery, especially if the artery is the dominant one. The muscular branch of the VA above the posterior arch of the atlas is usually coagulated during exposure, and care must be taken not to confuse the muscular branch with the posterior inferior cerebellar artery which, although rarely, may originate from the extradural VA [344]. A retrosigmoid craniotomy is performed, followed by unroofing of the sigmoid sinus and the jugular bulb and a posterior fossa craniectomy involving the foramen magnum. Transcondylar approach caries a risk of injury to the hypoglossal nerve or the jugular bulb during drilling of the condyle. Extradural tumor removal is removed and invaded bone is drilled until healthy tissue is recognized. Intradural tumor extension can also be accessed after posteromedial mobilization of the vertebral artery.

A wide condylar resection (more than the posterior 2/3 of the condyle) either to resect involved bone or the gain exposure causes craniocervical instability. In our experience 60% of inferior clival cases with condylar involvement required craniocervical stabilization. Bejjani *et al.* [24] reported a need for fusion in 5 of 6 chordoma cases, all of which needed more than 70% resection of the condyle. The most devastating complications in this approach, however, are vertebral artery injury and lower cranial nerve palsies. The risk of lower cranial nerve injury is especially high in the case of tumor removal from the jugular and hypoglossal foramina and this may be very debilitating to the patient. Other complications include hemiparesis or quadriparesis, CSF fistula and pseudomeningocele [18].

Author's experience: We presented our experience with 26 pathologically confirmed skull-base chordomas which were managed by conventional or specialized skull-base surgery initially, and subsequent radiosurgery in selected cases [259]. The results of this study indicate that skull-base techniques should be used instead of conventional surgical approaches for first-line treatment of skull-base chordomas. According to data in this study, the residual tumor volume after specialized skull-base techniques is approximately half that associated with conventional surgical approaches. The second comment in this study is that the critical initial tumor volume at the time of diagnosis is $20\,cm^3$ and all patients with initial tumors which exceed this tumor volume developed recurrence or progression after the resection regardless of whether a conventional or specialized skull-base approach was used. We have also concluded that performing Gamma-knife surgery immediately after the initial operation yields better control of tumor growth than if this modality is used to treat tumor progression at a later date. Since this report our patient cohort grew and within 20 years (between September 1986 and December 2006) 44 patients with skull-base chordomas were treated at the Marmara University, Department of Neurosurgery; Institute of Neurological Sciences and Acibadem Medical center. The cohort included 27 females and 17 males and the median age was 39 years (range 3–82 years). Presenting symptoms were headache in 32 (72%), diplopia in 18 (41%), difficulty swallowing in 16 (36%), nausea-vomiting

Table 10. *Surgical approaches in 69 tumor excision procedures*

Surgical approaches	No. of patients	(%)
Conventional approaches (before 1992)		
Transoral	5	7
Transsphenoidal	4	6
Subtemporal	1	1
Suboccipital aramedian	4	6
Skull Base approaches (after 1992)		
Subfrontal	12	17
Transsphenoidal	10	15
Transfacial approach	2	3
Cavernous sinus exploration	12	17
Presigmoid (petrosal) approaches	13	20
Mastoidectomy	7	
Mastoidectomy + labirynthectomy	1	
Total petrosectomy	1	
Partial petrosectomy	4	
Transcondylar	6	9
Total	69 tumor excisions	

in 15 (33%), ataxia in 13 (29%), motor deficit in 10 (23%), slurred speech in 4 (8%). During the course of treatment a total of 78 operations (excluding Gamma-Knife procedures) were performed, and 69 of those were for tumor resection and 9 were for other purposes (4 occipitocervical fusions, 4 ventriculoperitoneal shunt placements, and 1 hematoma evacuation) (Table 10). In addition to these 78 operations, 16 of the patients underwent 19 stereotactic radiosurgery procedures with the Leksell Gamma-Knife system. All patients underwent T1-weighted (with and without gadolinium enhancement) and T2-weighted magnetic resonance imaging (MRI), as well as computerized tomography (CT) with bone density studies which included three-dimension skull-base constructions. Tumor volume was measured on an Image Analyzer (Image Inc., Canada). All tumors were pathologically diagnosed as chordoma. Conventional approaches were used in 14 of the 69 operations for tumor resection (20.3%) and skull-base approaches were used in the rest (Table 10). Complete tumor resection rate, as judged by early postoperative or intraoperative MRI, was 70% with conventional approaches and 84.8% with skull-base approaches. Surgical mortality is 2.6% and the morbidity rate was 28.2% (Table 13). Mean follow-up period is 67.6 months (range 6–88 months). A total of 25 patients (56.8%) experienced recurrence during this follow-up period. In subtotally resected cases recurrent was defined as persistent tumor growth after surgery. Nine of 44 patients (20.5%) died in the follow-up period. Eight of these 9 patients died due to tumor relate reasons (2 due to surgical complications, 6 due to related clinical deterioration) and 1 died of myocardial infarction. Complications seen are presented in Table 11. The data on our growing patient cohort still supports our conclusions we have drawn in our published study [259].

Table 11. *Surgical complications in 44 surgically treated chordoma cases*

Complications	No. of patients	(%)
Hydrocephalus (requiring VP shunt)	4	5.1
Lower cranial nerve palsy (transient in 2 cases, gastrostomy required in 2)	4	5.1
Craniocervical instability (requiring OC fusion)	3	3.8
CN-III palsy (2 transient, 1 permenant)	3	3.8
CSF fistula (treated with lumbar drainage)	2	2.6
Facial paresis	1	1.3
Hearing loss	1	1.3
Postoperative hematoma at resection bed	1	1.3
Vertebral artery rupture	1	1.3
Hemihypoesthesia (1 case)	1	1.3
Hemiparesis (1 case)	1	1.3
Total	22	28.2

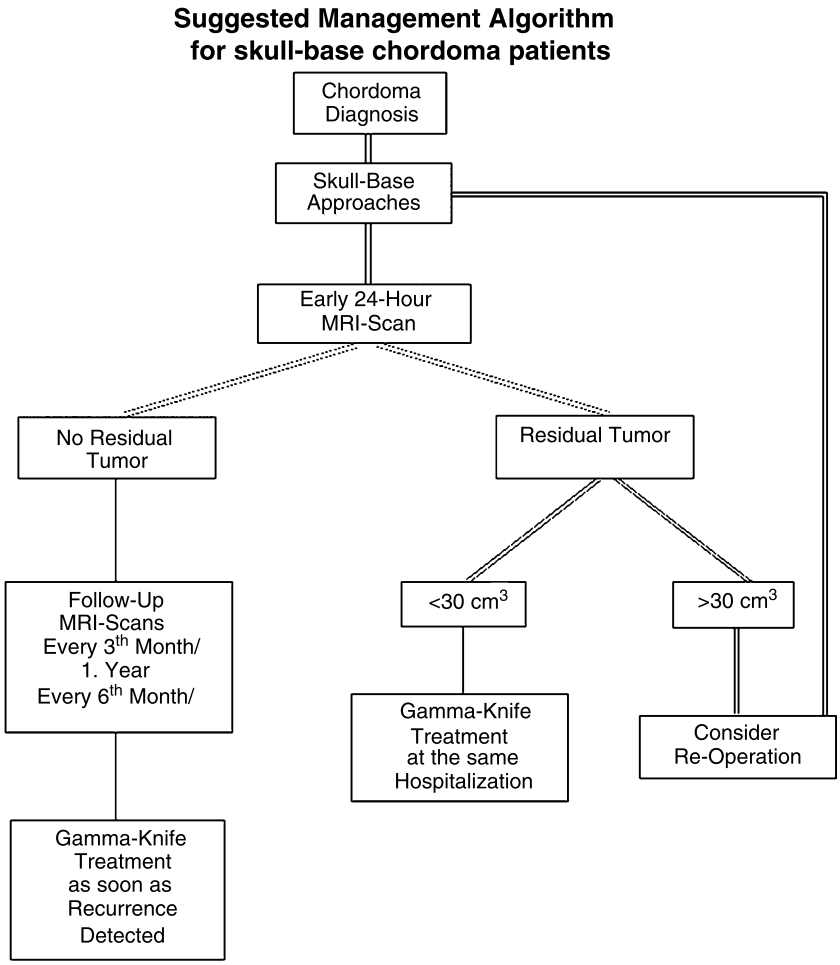

Fig. 9. An algorithm was formulated based on our institution's experience with skull-base chordomas

We have adopted a prospective algorithm for treatment of skull base chordomas which relies on maximal safe surgical resection followed by Gamma-Knife radiosurgery of residual lesions smaller than 30 cm^3 (Fig. 9). When the residual tumor volume exceeds 30 cm^3, immediate reoperation should be considered. The use of intraoperative MRI enabled us to decrease the residual tumor volume after maximal safe resection during the first operation [262].

Radiotherapy

Most chordomas recur after surgical resection and some form of adjuvant therapy is almost always needed. Radiation therapy is therefore used in an

Table 12. *Studies on radiation therapy of chordomas*

Study	Treatment method	n	Total dose (Gy/CGE)	Follow-up (months)	Overall survival rate %	Local control rate %		
						3y	5y	10y
Magrini *et al.* [211]	photon	12	Median 58 (48–60)	Median 72 (12–300)	58 at 5 years, 35 at 10 years	N/A	25	25
Forsyth *et al.* [106]	photon	39	Median 50 (22.93–67.42)	Median 99.6 (67.2–356.4)	51 for biopsy and 64 for resection at 5 years	N/A	39	31
Romero *et al.* [287]	photon	18	Median 50.1 (29.9–64.8)	Median 37.2 (4–240)	N/A	N/A	17	N/A
Catton *et al.* [48]	photon	24	Median 50 (25–60)	Median 62.4 (4–240)	N/A	N/A	23	15
Zorlu *et al.* [378]	photon	18	Median 60 (50–64)	Median 43.2 (12–96)	35 at 5 years	N/A	23	N/A
Austin Seymour *et al.* [15]	Particle (Proton beam) and photon combined	68	Median 69 (56.9–75.6)	Median 34 (17–152)	N/A	N/A	82	58
Benk *et al.* [25]	Particle (Proton beam) and photon combined	18	Median 69 (55.8–75.6)	Median 72 (19–120)	68%	N/A	78	N/A
Berson *et al.* [28]	Particle (Proton beam) and photon combined	45	59.4–80	33 patients longer than 12 months	62% at 5 years	N/A	59	N/A

Hug *et al.* [152]	Particle (Proton beam)	58	Mean 70.7 (66.6–79.2)	Mean 33 (7–75)	97 at 3 years, 79 at 5 years	67	59	N/A
Munzenrider and Liebsch [238]	Particle (Proton beam) and photon combined	621	66–83	Median 41 (1–254)	80 at 5 years and 54 at 10 years	N/A	73	54
Igaki *et al.* [154]	Particle (Proton beam) and photon combined	13	Median 72 (63–95)	Median 69.3 (14.6–123.4)	66.7 at 5 years	67.1	46	N/A
Noel *et al.* [250]	Particle (Proton beam) and photon combined	100	Median 67 (60–71)	Median 31 (0–87)	94.3 at 2 years, 80.5 at 5 years	86.3 at 2 years	53.8 at 4 years	N/A
Castro *et al.* [47]	Particle (Helium ion)	80*	Mean 65 (60–80)	Median 51 (4–191)	N/A	N/A	63	N/A
Shultz-Ertner *et al.* [308]	Particle (Carbon ion)	44	Mean 60	Median 16 (4–38.3)	89.4 at 3 years	87.1	N/A	N/A
Weber *et al.* [363]	Particle (Carbon ion)	29 (11 cases CS)	Mean 74 (67–74)	Median 26 (8–70)	93.8 at 3 years*	87.5	N/A	N/A
Muthukumar *et al.* [239]	Gamma-Knife	15* (6 cases CS)	Mean 20 Gy to margin	Median 40 (6–84)	N/A	N/A	N/A	N/A
Pamir *et al.* [259]	Gamma-Knife	7	Mean 16.2 Gy to margin	Mean 23.3 mo	N/A	N/A	N/A	N/A
Feigl *et al.* [100]	Gamma-Knife	13* (10 cases CS)	Mean 17 Gy to margin	Mean 17mo	N/A	N/A	N/A	N/A
Krishnan *et al.* [183]	Gamma-Knife	29* (4 cases CS)	Median 15 Gy to margin	Median 57.6mo	N/A	70	32	N/A

* Marked studies do not indicate results selectively for chordomas but report cumulative outcome data for chordomas, chondrosarcomas and (in one study) other tumors.

attempt to gain local control. However, failure of initial attempts at conventional radiation therapy to control chordomas resulted in the notion that chordomas are radioresistant. This concept was challenged by more recent series showing modest benefit with conventional radiotherapy and improved results with higher dose regimens and stereotactic methods (Table 12) [31, 106, 141, 333].

Conventional radiotherapy

Early studies showed that conventional radiotherapy after subtotal resection of chordomas was associated with a high rate of treatment failure and recurrence (Table 14). Progression free survival rates in these studies ranged form 17 to 39% at 5 years [48, 106, 112, 287, 378]. Some studies from the 1970's however, indicated better response rates with the use of escalated radiation doses [142, 265, 338]. Pearlman and Friedman [265] concluded that doses lower than 40 Gy were not effective and doses >80 Gy were more likely be of benefit. Despite reports of improved results with escalated doses, other studies failed to reconfirm this increase in efficacy [48, 333]. Cummings *et al.* [71] showed a survival benefit even with a low dose (40–55 Gy) radiotherapy compared to surgery alone. Currently it is fairly well established that conventional postoperative radiotherapy can result in approximately 50% 5-year survival and effective palliation [1]. However long-term local control and cure are not possible in most instances [1]. Salvage therapy is effective in alleviating symptoms, but is associated with a grim survival [97].

Conventional radiotherapy has frequently been combined with particle beam radiotherapies or radiosurgery and some authors claim that there may be an advantage to this as chordomas and chondrosarcomas have intermediate proliferative indices and presumably intermediate α/β ratios for linear quadratic modeling purposes [107]. Results from a recent Gamma-Knife study from Mayo clinic however reported complications only in patients who received a combination of radiosurgery and fractionated radiotherapy and not those who received their adjuvant therapy with radiosurgery alone [183].

Rhomberg *et al.* [278] showed promising results with the addition of the radiosensitizing agent razoxane to conventional radiotherapy. The authors presented 5 patients with chordoma who were alive with local control 5 years after this combination treatment.

LINAC based stereotactic radiotherapies

The need for higher doses and concern with complications associated with such high doses resulted in the adoption of advanced technologies such as particle irradiation and stereotactic radiosurgery with more conformal dose distributions [333]. Stereotactic techniques and radiosurgery allow for precise,

image guided, highly conformal and high dose radiation treatment of chordomas. Current radiosurgical modalities include Gamma-Knife radiosurgery; LINAC based fractionated stereotactic radiotherapy technologies and particle beam irradiation technologies such as proton beam, helium ion and carbon ion. Better results in treatment of skull base chordomas have been reported using radiosurgical technologies, when compared to conventional radiation treatment [175].

Use of stereotactic techniques, multileaf collimators and sophisticated inverse three-dimensional dose planning for sparing of critical structures in the delivery of intensity modulated radiotherapy is increasing the efficacy of LINAC based radiation treatments [175]. Debus *et al.* [76] reported the results of fractionated stereotactic therapy on 45 skull base chordomas and chondrosarcomas. After delivery of 66.6 Gy for chordomas and 64.9 Gy for chondrosarcomas, the authors reported complete local tumor control at 5 years in chondrosarcomas and 82% 2 year and 50% 5 year local control rates in chordomas. Gwak *et al.* [128] reported the results of hypofractionated Cyberknife stereotactic radiotherapy for skull base and upper cervical chordomas. A tumor dose of 21 to 43.6 Gy was delivered in 3 to 5 fractions and after a median follow up of 24 months only one asymptomatic recurrence was noted. The authors, however, also reported radiation induced myelopathy in 2 of 9 cases.

Gamma-Knife radiosurgery

Gamma-Knife radiosurgery is reported to be a safe and effective treatment for small chordomas [179]. However there are only a handful of studies using the Gamma-Knife and most of the studies lack long follow-up periods, which prevents us from drawing definitive conclusions. Kondziolka and coworkers [239] showed no progression after Gamma-Knife treatment with a dose of 20 Gy to the tumor margin in chordomas less than 30 cm^3, however with only a very short follow up period (mean, 22 months; range, 8–36 months). A newer study by the same group reported a cohort of 9 chordomas and 6 chondrosarcomas with a median follow-up of 40 months (range 6–84) [100]. In this study 73% of patients either improved clinically or remained stable following treatment, and two thirds showed either a reduction or stabilization of tumor size on follow-up imaging with no patients having any complications related to the treatment. We have reported the treatment of 7 patients with adjuvant Gamma-Knife therapy after maximal surgical resection [259]. This treatment for residual lesion is administered in the same hospital admission after maximal radical surgical excision if the residual tumor volume does not exceed 30 cm^3. Feigl *et al.* [100] used adjuvant Gamma-Knife radiosurgery 2 to 10 months after radical surgery for skull base chordomas and chondrosarco-

mas and reported a 93.3% tumor control rate at a mean of 17 months after the treatment. Krishnan *et al.* [183] reported 25 chordomas and 4 chondrosarcomas with a 15 Gy marginal dose. Nineteen patients had prior conventional radiation therapies. Actuarial tumor control rates were 89 and 32% at 2 and 5 years.

Previously we reported the results of 7 patients with adjuvant Gamma-Knife therapy after maximal surgical resection [268]. A total of 30 patients underwent 38 Gamma-Knife radiosurgery at our clinic from January 1997 through December 2006. Of these 30 patients 22 were male, 8 patients were female and the median age was 50 years (range 25–82). All patients had pathologically confirmed diagnosis of chordoma. A mean dose of 15.8 Gy was delivered to 50% isodose line. The patients were followed for 36 ± 41 months and 7 of 30 patients showed progression after the first Gamma-Knife radiosurgery session and a second Gamma-Knife procedure was performed. Only one of these continued to progress after the second radiosurgery and a third Gamma-Knife procedure was performed. We should stress the unlucky localization of skull-base chordomas here. Because these tumors are very close to eloquent areas, such as brain stem, very limited dose can be delivered to tumors for protecting the brain stem from radiation related complications. Two patients (6.6%) died during the follow-up. We did not experience any adverse reactions related to the Gamma-Knife treatment such as brain necrosis, vascular damage, or cognitive dysfunction.

In conclusion Gamma-Knife radiosurgery is potentially useful in the treatment of small sized residuel chordomas, but it is not so effective in treatment of recurrence. However, the definitive role needs to be addressed in larger studies with adequate follow-up durations.

Brachytherapy

There are only few anectodal reports on the use of brachytherapy for skull base chordomas [27, 127, 184, 185]. Orecchia *et al.* reported combination of brachytherapy with external beam radiotherapy. Although it is an appealing technology due to very high local dose delivery and sparing of surrounding structures it is invasive, does not have any superiority to existing noninvasive stereotactic radiation treatment modalities and therefore used only by very few centers.

Charged particle radiation therapies

Charged particle irradiation technologies are capable of a sharp cut-off outside the target volume and therefore deliver higher doses to the lesion with relative sparing of the surrounding normal tissue when compared to conventional radiotherapy. This sharp dose escalation curve is both due to a finite range in tissue and a sharply defined lateral beam edge. Charged particles deposit a dose along their path, however much more so at the end of their range. This is due

to the "Bragg peak" effect which denotes that the maximum dose delivery to the tissue occurs shortly before the particle lost all its energy and stops [268] and because of their heavy mass the particles.

The largest experience with charged particle irradiation is with proton radiotherapy (Table 14). Proton-beam radiotherapy does not produce resolution of chordomas but provides local tumor control and the results are considerably improved over conventional radiotherapy. Radiotherapy schedules involving a mixed treatment with protons and photons have achieved an approximately 60% local control rate at 5 years [28, 152]. This rate ranged from 46% to 73% in different studies. The most recent study on 100 patients with skull base and upper cervical chordomas from Centre de Protontherapie d'Orsay in France reported 2 and 4 year local tumor control rates of 86.3% and 53.8% with a combination of photon and proton therapy [250]. Using spot scanning proton beam radiation therapy, Paul Scherrer Institute team in Switzerland reported a actuarial local control rate of 87.5% for skull base chordomas. Despite its superior results the proton beam radiotherapy is an expensive technology and the experience is limited to very few centers around the globe.

The results reported by the Carbon ion therapy team in Darmstadt-Germany were significantly better than with LINAC based methods [308, 363]. The authors reported 87.1% 3 year survival in 44 chordomas using a dose of 60 Cobald-Gray equivalent (CGE). This study.

These results are encouraging, however longer follow up is required to draw final conclusions.

Predictive factors on outcome after radiation treatment

Several prognostic factors for local control and overall survival have been reported. Few of these studies indicated better results with smaller tumors and the use of higher radiation doses [15]. Local control rates are correlated with homogeneity of the dose delivered to the tumor and inadequate dose delivery is associated with a high local failure rate [97]. The limit to the total prescribed dose is dictated by the proximity to surrounding radiation sensitive structures such as optic apparatus and brain stem. Frequently this is also the cause of local innadequate dose delivery. Austin-Seymour *et al.* [15] indicated that over 75% of the treatment failures were due to dose limitations. Only 25% of the failures were in areas that received the planned dose. Fagundes *et al.* [97] reported that one third of the patients had treatment failures after proton beam treatment. Ninety-five percent of these patients had a local recurrence, and in 78%, this was the only site of failure. The use of a dermal fat graft as a spacer to maintain a separation between the brain stem and the tumor bed during resective surgery has been described as a means to protect radiation injury to the surrounding parenchyma [66]. Tumor histology is also a very important

indicator of treatment response. Low grade chondrosarcomas seem to have a better treatment response but are commonly analyzed as a single group together with chordomas, which complicates the interpretation of the current results [194]. In several studies female sex was associated with a poorer prognosis, and a study analyzing several hypotheses concluded that it was most likely due to a statistical artefact [133]. Age was also commonly reported as a prognostic factor [25, 31, 129, 134, 153, 342, 366]. Forsyth *et al.* [106] reported a 5 and 10 year overall survival of 75% and 63% in patients under 40 years of age; these rated were 30% and 11% for older patients. This may be a reflection of poor tolerance of surgery by the elderly and choice of more conservative treatment options. Children are reported to have chordomas with more aggressive histopathology and also metastasize more frequently. Borba *et al.* [31] reported a poor prognosis for children under 5 years of age, but another study by Benk *et al.* [25] failed to replicate this finding.

Complications of radiation therapy

Present literature suggests that low to moderate doses of conventional radiotherapy are well tolerated. Serious complications are rarely encountered. Charged particle therapies, which delivery considerably higher doses to the brain also have higher complication rates. Most commonly reported complications are endocrine dysfunction, temporal lobe, brain stem or cord injury, visual loss, hearing loss and memory impairment. In the most recent clinical series on proton therapy of skull base chordomas, Noël *et al.* [249] reported hypopituitarism in 25%, occulomotor impairment in 3%, memory impairment in 2%, hearing loss in 2% and bilateral visual loss in 2% of the patients.

Temporal lobe or brain stem radiation injury are the most serious complications but are seldom encountered after proton beam therapy despite despite very high doses delivered to these structures. In a study of 96 patients, Santoni *et al.* [300] reported 8% and 13% temporal lobe complication rates 2 and 5 years after treatment, respectively. Complications were more common in males. Debus *et al.* [76] reported 12% 10 year incidence of brain stem complications. Ninety per cent of these complications occurred within the first 3 years after treatment. Wenkel *et al.* reported a 2.2% incidence of brainstem complications after proton beam therapy for skull base meningioma. Noël *et al.* [249] reported only 1 incidence (1%) of transient myelopathy after a dose of 55CGE to the spinal cord.

Harbrand *et al.* reported a 20% incidence of visual complications after a dose of 60 Gy to the optic apparatus. Noël *et al.* [249] reported a 8% visual complication rate, which was most commonly a decrease in visual acuity. Radiation injury to other cranial nerves is also commonly encountered. Radiation induced hearing loss is also reported in several series [238, 250, 257, 321].

Cognitive side effects are uncommon. Glosser *et al.* [120], in their study of 17 patients who were treated for skull base tumors with doses up to 66CGE, did not report any early or late cognitive side effects.

The incidence of endocrine dysfunction after proton beam therapy ranged between 26 and 84% among studies in the present literature and included hyperprolactinemia, hypothyroidism, hypogonadism and hypoadrenalism [257, 321]. Complications are reported to be most common 14 to 45 months after therapy, increase with time [257]. Doses of >50CGE to the pituitary axis and >70CGE to the pituitary gland are reported as risk factors [183].

There is only one study that reports complications related to Gamma-Knife radiosurgery for skull base chordoma [183]. This series from Mayo clinic reported a 34% incidence of radiation related complications which included cranial nerve deficits, radiation necrosis and pituitary dysfunction, all of which occurred only in patients who had previous radiation treatment [183].

Chemotherapy

The role of chemotherapy in the treatment of chordoma remains limited. There is no evidence at this stage that chemotherapy has any beneficial role in the treatment of patients with intracranial chordomas. It is mainly used as a salvage therapy in patients with widespread or recurrent disease not amenable to further surgery or radiotherapy.

As there was no obvious therapeutic target to guide a rational treatment, chordomas mostly have been treated with chemotherapy regimens intended for sarcomas and several of those reported either a lack of response or only a modest therapeutic response [17]. Sundaresan [330] reported treatment of 8 recurrent or disseminated chordomas with different chemotherapy regimens containing 5-fluorouracil, vinblastine, actinomycin-D, cyclophosphamide, methotrexate, epoxy-piperazine, and chlorambucil without any treatment response. Azzarelli *et al.* [17] reported treatment of 33 cases of chordoma with only limited success. Horton *et al.* described a pediatric patient without any response to chemotherapy. Chetty *et al.* [55] also described a pediatric case who responded to a combination of surgery, radiotherapy and chemotherapy, however the role of chemotherapy in this treatment response is not known. Fleming *et al.* [104] also reported two patients with sacral dedifferentiated chordoma and lung metastases. One of the patients was responsive to treatment with a regimen consisting of vincristine, dacarbazine, doxorubicin, etoposide, and cisplatin. The second patient did not respond to the combination treatment but only had a brief response to ifosfamide. Schönegger *et al.* [306] reported one patient treated with repeated surgery, radiotherapy and a subsequent short (2) course of chemotherapy with EVAIA protocol (Etoposide-Ifosfamide-doxorubicin-vinchristine) before he developed toxicity. Reportedly the patient

received isoretinoin and IFN-α for 12 months, thaliodomide and finally liposomal doxorubicin for systemic metastases and local progressive disease and was stable with a Karnofsky score of 80 at last follow up 8 years after first diagnosis. Casali *et al.* [45], after demonstrating the presence of PDGF receptors on a chordoma biopsy, reported the use of imatinib mesylate, a small molecule inhibitor of several receptor tyrosine kinases including PDGF receptors, BCR-ABL and KIT and described clinical benefit in treating patients with advanced sacral chordoma. The authors have taken this treatment to a phase II clinical trial. In the only prospective phase II trial of systemic chemotherapy in chordoma a Topoisomerase I inhibitor 9-Nitro-Camptothecin was tried in recurrent inoperable chordoma to show moderate benefit with moderate toxicity [51].

Chordomas in the pediatric age group

Most chordoma cases are seen in the adult population and patients younger than 20 years only make up 5% of the cases [31, 144, 153, 220]. So far, at least 159 cases of skull base chordomas have been reported in the pediatric population [31, 37, 51, 75, 87, 113, 144, 153, 217, 259, 271, 292, 320, 342, 343]. The youngest case is the congenital chordoma reported by Probst *et al.* [271]. Among those cases there is no gender predilection reported. In this age group skull base cases are more commonly seen than sacral chordomas [31]. Matsumoto *et al.* [217] analyzed 56 pediatric cases younger than 16 years. 63.3% were in the skull base, 21% were sacrococygeal and 16% were spinal. Common cranial localizations are orbital, maxillary, nasopharyngeal, clival and upper cervical regions and here they constitute 15% of pediatric brain tumors. Tumors usually become manifest with pain, headache, neurological dysfunction nasopharyngeal obstruction and/or failure to thrive and are reported to have more aggressive behavior than those observed in adult patients [31, 58]. In a large series of skull base chordomas reported neurological symptoms were intracranial hypertension, CN VI palsy, quadriparesis, dysphagia, dysarthria, torticollis, hydrocephalus, diplopia, nystagmus, palatal weakness, pneuomonia, CN III palsy, lower cranial nerve palsies, pathological laughter, deafness and ataxia [31].

There are 159 reported cases of pediatric chordomas in the literature. Several authors have indicated that the histopathological findings in pediatric chordomas, especially those in patients younger than 5 years are much different from those of the adult population [31]. In dedifferentiated chordomas of the pediatric population, commonly a very aggressive clinical behavior accompanies a tumor with abundant mitotic activity, hypercellularity, and pleomorphism [31]. Symptomatic metastases are also more commonly reported in the pediatric population and this is associated with the atypical phenotype in 85.7% of the cases [14, 31]. One study reported an even higher incidence of metastases in children younger than 5 years (57.9%) compared to those 5 years and older (8.5%) [14].

Treatment of skull base chordomas in the pediatric population does not differ much from the adult population. The value of a complete surgical excision in treatment is well established for all ages. However, Borba *et al.* [31] reported that there was no significant survival difference between radical or conservative surgery in atypical cases. They also reported a significantly better prognosis in pediatric patients with chordoma when they received adjuvant radiotherapy, regardless of the completeness of the surgical intervention [73].

Conclusions

- Chordomas are rare, slow growing tumors of the axial skeleton, derive from the remnants of the fetal notochord and occur most commonly in the sacral area, skull base and less commonly in the spine.
- Patients commonly present with headaches and diplopia and can be readily diagnosed with current neuroradiological methods.
- Chordomas have a benign histopathology but exhibit malignant clinical behavior with invasive, destructive and metastatic potential. There are 3 pathological subtypes: classic, chondroid and dedifferentiated.
- Chondrosarcomas are distinct from chordomas, respond better to treatment and have a better prognosis. Preoperative differential diagnosis form chordoma is not reliable.
- There are at least two subsets of chordomas, one with a benign and another with an aggressive course.
- The eventual prognosis is determined by intrinsic tumor biology. To date we only have a limited understanding of this biology.
- Patients with chordomas benefit from surgical resection and postoperative high dose radiation treatment. Young patients likely benefit form the extent of surgery.
- Currently the most effective adjuvant therapy is charged particle radiation therapy. Radiosurgery may also be of value.
- Current chemotherapy has no role in the first line treatment of chordomas.

References

1. (2000) Proton therapy for base of skull chordoma: a report for the Royal College of Radiologists. The Proton Therapy Working Party. Clin Oncol (R Coll Radiol) 12: 75–79
2. Abenoza P, Sibley RK (1986) Chordoma: an immunohistologic study. Hum Pathol 17: 744–747
3. Akimoto J, Takeda H, Hashimoto T, Haraoka J, Ito H (1996) A surgical case of ecchordosis physaliphora. No Shinkei Geka 24: 1021–1025
4. Al-Mefty O, Fox JL, Smith RR (1988) Petrosal approach for petroclival meningiomas. Neurosurgery 22: 510–517
5. Al-Mefty O, Borba LA (1997) Skull base chordomas: a management challenge. J Neurosurg 86: 182–189

6. Alezais MM, Peyron A (1914) Contrubution a letude des chordomes; chordomes de la region occipitale, Paris
7. Alezais MM, Peyron A (1914) Sur une tendence evolutive remarquable de certainc chordomes-passage de l'epitheliome au sarcome polymorphe, Paris
8. Alonso WA, Black P, Connor GH, Uematsu S (1971) Transoral transpalatal approach for resection of clival chordoma. Laryngoscope 81: 1626–1631
9. Arbit E, Patterson RH Jr (1981) Combined transoral and median labiomandibular glossotomy approach to the upper cervical spine. Neurosurgery 8: 672–674
10. Archer DJ, Young S, Uttley D (1987) Basilar aneurysms: a new transclival approach via maxillotomy. J Neurosurg 67: 54–58
11. Arnautovic KI, Al-Mefty O (2001) Surgical seeding of chordomas. Neurosurg Focus 10: E7
12. Arnold H, Herrmann HD (1986) Skull base chordoma with cavernous sinus involvement. Partial or radical tumour-removal? Acta Neurochir (Wien) 83: 31–37
13. Aszodi A, Chan D, Hunziker E, Bateman JF, Fassler R (1998) Collagen II is essential for the removal of the notochord and the formation of intervertebral discs. J Cell Biol 143: 1399–1412
14. Auger M, Raney B, Callender D, Eifel P, Ordonez NG (1994) Metastatic intracranial chordoma in a child with massive pulmonary tumor emboli. Pediatr Pathol 14: 763–770
15. Austin-Seymour M, Munzenrider J, Goitein M, Verhey L, Urie M, Gentry R, Birnbaum S, Ruotolo D, McManus P, Skates S, *et al* (1989) Fractionated proton radiation therapy of chordoma and low-grade chondrosarcoma of the base of the skull. J Neurosurg 70: 13–17
16. Aydin P, Ozek M, Kansu T (1994) Intermittent diplopia in chordoma. Ann Ophthalmol 26: 20–22
17. Azzarelli A, Quagliuolo V, Cerasoli S, Zucali R, Bignami P, Mazzaferro V, Dossena G, Gennari L (1988) Chordoma: natural history and treatment results in 33 cases. J Surg Oncol 37: 185–191
18. Babu RP, Sekhar LN, Wright DC (1994) Extreme lateral transcondylar approach: technical improvements and lessons learned. J Neurosurg 81: 49–59
19. Bailey SM, Murnane JP (2006) Telomeres, chromosome instability and cancer. Nucleic Acids Res 34: 2408–2417
20. Bayrakli F, Guney I, Kilic T, Ozek M, Pamir MN (2007) New candidate chromosomal regions for chordoma development. Surg Neurol 68(4): 425–430
21. Bayrakli FGI, Kilic T, Ozek MM, Pamir MN (accepted 1 November 2006) New candidate chromosomal regions for chordoma development. Surg Neurol (article in print)
22. Beck DW, Menezes AH (1987) Lesions in Meckel's cave: variable presentation and pathology. J Neurosurg 67: 684–689
23. Becker D, Ammirati M, Black K, Canalis R, Andrews J (1991) Transzygomatic approach to tumours of the parasellar region. Technical note. Acta Neurochir Suppl 53: 89–91
24. Bejjani GK, Sekhar LN, Riedel CJ (2000) Occipitocervical fusion following the extreme lateral transcondylar approach. Surg Neurol 54: 109–115; discussion 115–116
25. Benk V, Liebsch NJ, Munzenrider JE, Efird J, McManus P, Suit H (1995) Base of skull and cervical spine chordomas in children treated by high-dose irradiation. Int J Radiat Oncol Biol Phys 31: 577–581

26. Bergh P, Kindblom LG, Gunterberg B, Remotti F, Ryd W, Meis-Kindblom JM (2000) Prognostic factors in chordoma of the sacrum and mobile spine: a study of 39 patients. Cancer 88: 2122–2134
27. Bernstein M, Gutin PH (1985) Interstitial irradiation of skull base tumours. Can J Neurol Sci 12: 366–370
28. Berson AM, Castro JR, Petti P, Phillips TL, Gauger GE, Gutin P, Collier JM, Henderson SD, Baken K (1988) Charged particle irradiation of chordoma and chondrosarcoma of the base of skull and cervical spine: the Lawrence Berkeley Laboratory experience. Int J Radiat Oncol Biol Phys 15: 559–565
29. Bootz F, Keiner S, Schulz T, Scheffler B, Seifert V (2001) Magnetic resonance imaging – guided biopsies of the petrous apex and petroclival region. Otol Neurotol 22: 383–388
30. Borba L, Colli B, Al-Mefty O (2001) Skull base chordomas. Neurosurg Quart 11: 124–139
31. Borba LA, Al-Mefty O, Mrak RE, Suen J (1996) Cranial chordomas in children and adolescents. J Neurosurg 84: 584–591
32. Borgel J, Olschewski H, Reuter T, Miterski B, Epplen JT (2001) Does the tuberous sclerosis complex include clivus chordoma? A case report. Eur J Pediatr 160: 138
33. Bouropoulou V, Kontogeorgos G, Papamichales G, Bosse A, Roessner A, Vollmer E (1987) Differential diagnosis of chordoma immunohistochemical aspects. Arch Anat Cytol Pathol 35: 35–40
34. Bouvier D, Raghuveer CV (2001) Aspiration cytology of metastatic chordoma to the orbit. Am J Ophthalmol 131: 279–280
35. Bridge JA, Pickering D, Neff JR (1994) Cytogenetic and molecular cytogenetic analysis of sacral chordoma. Cancer Genet Cytogenet 75: 23–25
36. Brooks JJ, LiVolsi VA, Trojanowski JQ (1987) Does chondroid chordoma exist? Acta Neuropathol 72: 229–235
37. Brooks LJ, Afshani E, Hidalgo C, Fisher J (1981) Clivus chorodoma with pulmonary metastases appearing as failure to thrive. Am J Dis Child 135: 713–715
38. Brown RV, Sage MR, Brophy BP (1990) CT and MR findings in patients with chordomas of the petrous apex. Am J Neuroradiol 11: 121–124
39. Buchfelder M, Fahlbusch R, Ganslandt O, Stefan H, Nimsky C (2002) Use of intraoperative magnetic resonance imaging in tailored temporal lobe surgeries for epilepsy. Epilepsia 43: 864–873
40. Buonamici L, Roncaroli F, Fioravanti A, Losi L, Van den Berghe H, Calbucci F, Dal Cin P (1999) Cytogenetic investigation of chordomas of the skull. Cancer Genet Cytogenet 112: 49–52
41. Butler MG, Dahir GA, Hedges LK, Juliao HS, Sciadini M, Schwartz HS (1995) Cytogenetic, telomere, and telomerase studies in five surgically managed lumbosacral chordomas. Cancer Genet Cytogenet 85: 51–57
42. Butler MG, Sciadini M, Hedges LK, Schwartz HS (1996) Chromosome telomere integrity of human solid neoplasms. Cancer Genet Cytogenet 86: 50–53
43. Byrd SE, Harwood-Nash DC, Barry JF, Fitz CR, Boldt DW (1977) Coronal computed tomography of the skull and brain in infants and children. Part II. Clinical value. Radiology 124: 710–714
44. Cappabianca P, Cavallo LM, Colao A, Del Basso De Caro M, Esposito F, Cirillo S, Lombardi G, de Divitiis E (2002) Endoscopic endonasal transsphenoidal approach: outcome analysis of 100 consecutive procedures. Minim Invasive Neurosurg 45: 193–200

45. Casali PG, Messina A, Stacchiotti S, Tamborini E, Crippa F, Gronchi A, Orlandi R, Ripamonti C, Spreafico C, Bertieri R, Bertulli R, Colecchia M, Fumagalli E, Greco A, Grosso F, Olmi P, Pierotti MA, Pilotti S (2004) Imatinib mesylate in chordoma. Cancer 101: 2086–2097
46. Casson PR, Bananno PC, Converse JM (1974) The midface degloving procedure. Plast Reconst Surg 53: 102–103
47. Castro JR, Linstadt DE, Bahary JP, Petti PL, Daftari I, Collier JM, Gutin PH, Gauger G, Phillips TL (1994) Experience in charged particle irradiation of tumors of the skull base: 1977–1992. Int J Radiat Oncol Biol Phys 29: 647–655
48. Catton C, O'Sullivan B, Bell R, Laperriere N, Cummings B, Fornasier V, Wunder J (1996) Chordoma: long-term follow-up after radical photon irradiation. Radiother Oncol 41: 67–72
49. Cha ST, Jarrahy R, Yong WH, Eby T, Shahinian HK (2002) A rare symptomatic presentation of ecchordosis physaliphora and unique endoscope-assisted surgical management. Minim Invasive Neurosurg 45: 36–40
50. Chadduck WM (1973) Unusual lesions involving the sella turcica. South Med J 66: 948–955
51. Chadduck WM, Boop FA, Sawyer JR (1991) Cytogenetic studies of pediatric brain and spinal cord tumors. Pediatr Neurosurg 17: 57–65
52. Chambers PW, Schwinn CP (1979) Chordoma. A clinicopathologic study of metastasis. Am J Clin Pathol 72: 765–776
53. Chandler JP, Pelzer HJ, Bendok BB, Hunt Batjer H, Salehi SA (2005) Advances in surgical management of malignancies of the cranial base: the extended transbasal approach. J Neurooncol 73: 145–152
54. Chang S, Khoo C, DePinho RA (2001) Modeling chromosomal instability and epithelial carcinogenesis in the telomerase-deficient mouse. Semin Cancer Biol 11: 227–239
55. Chetty R, Levin CV, Kalan MR (1991) Chordoma: a 20-year clinicopathologic review of the experience at Groote Schuur Hospital, Cape Town. J Surg Oncol 46: 261–264
56. Chugh R, Dunn R, Zalupski MM, Biermann JS, Sondak VK, Mace JR, Leu KM, Chandler WF, Baker LH (2005) Phase II study of 9-nitro-camptothecin in patients with advanced chordoma or soft tissue sarcoma. J Clin Oncol 23: 3597–3604
57. Claus EB, Horlacher A, Hsu L, Schwartz RB, Dello-Iacono D, Talos F, Jolesz FA, Black PM (2005) Survival rates in patients with low-grade glioma after intraoperative magnetic resonance image guidance. Cancer 103: 1227–1233
58. Coffin CM, Swanson PE, Wick MR, Dehner LP (1993) Chordoma in childhood and adolescence. A clinicopathologic analysis of 12 cases. Arch Pathol Lab Med 117: 927–933
59. Colli B, Al-Mefty O (2001) Chordomas of the craniocervical junction: follow-up review and prognostic factors. J Neurosurg 95: 933–943
60. Colli BO, Al-Mefty O (2001) Chordomas of the skull base: follow-up review and prognostic factors. Neurosurg Focus 10: Article 1
61. Congdon CC (1952) Proliferative lesions resembling chordoma following puncture of nucleus pulposus in rabbits. J Nat Cancer Inst 12: 893–907
62. Couldwell WT, Sabit I, Weiss MH, Giannotta SL, Rice D (1997) Transmaxillary approach to the anterior cavernous sinus: a microanatomic study. Neurosurgery 40: 1307–1311
63. Couldwell WT, Weiss MH, Rabb C, Liu JK, Apfelbaum RI, Fukushima T (2004) Variations on the standard transsphenoidal approach to the sellar region, with emphasis on the extended approaches and parasellar approaches: surgical experience in 105 cases. Neurosurgery 55: 539–547; discussion 547–550

64. Crapanzano JP, Ali SZ, Ginsberg MS, Zakowski MF (2001) Chordoma: a cytologic study with histologic and radiologic correlation. Cancer 93: 40–51
65. Crockard A (1996) Chordomas and chondrosarcomas of the cranial base: results and follow-up of 60 patients. Neurosurgery 38: 420
66. Crockard A, Macaulay E, Plowman PN (1999) Stereotactic radiosurgery. VI. Posterior displacement of the brainstem facilitates safer high dose radiosurgery for clival chordoma. Br J Neurosurg 13: 65–70
67. Crockard HA, Calder I, Ransford AO (1990) One-stage transoral decompression and posterior fixation in rheumatoid atlanto-axial subluxation. J Bone Joint Surg Br 72: 682–685
68. Crockard HA, Cheeseman A, Steel T, Revesz T, Holton JL, Plowman N, Singh A, Crossman J (2001) A multidisciplinary team approach to skull base chondrosarcomas. J Neurosurg 95: 184–189
69. Crockard HA, Steel T, Plowman N, Singh A, Crossman J, Revesz T, Holton JL, Cheeseman A (2001) A multidisciplinary team approach to skull base chordomas. J Neurosurg 95: 175–183
70. Crumley RL, Gutin PH (1989) Surgical access for clivus chordoma. The University of California, San Francisco, experience. Arch Otolaryngol Head Neck Surg 115: 295–300
71. Cummings BJ, Hodson DI, Bush RS (1983) Chordoma: the results of megavoltage radiation therapy. Int J Radiat Oncol Biol Phys 9: 633–642
72. Cushing H (1912) The pituitary body and its disorders, clinical states produced by disorders of the hypophysis cerebri. J. B. Lippincott Company, Philadelphia, London
73. Dalpra L, Malgara R, Miozzo M, Riva P, Volonte M, Larizza L, Fuhrman Conti AM (1999) First cytogenetic study of a recurrent familial chordoma of the clivus. Int J Cancer 81: 24–30
74. de Divitiis E, Cappabianca P, Cavallo LM (2002) Endoscopic transsphenoidal approach: adaptability of the procedure to different sellar lesions. Neurosurgery 51: 699–705; discussion 705–707
75. DeBoer JM, Neff JR, Bridge JA (1992) Cytogenetics of sacral chordoma. Cancer Genet Cytogenet 64: 95–96
76. Debus J, Hug EB, Liebsch NJ, O'Farrel D, Finkelstein D, Efird J, Munzenrider JE (1997) Brainstem tolerance to conformal radiotherapy of skull base tumors. Int J Radiat Oncol Biol Phys 39: 967–975
77. Debus J, Schulz-Ertner D, Schad L, Essig M, Rhein B, Thillmann CO, Wannenmacher M (2000) Stereotactic fractionated radiotherapy for chordomas and chondrosarcomas of the skull base. Int J Radiat Oncol Biol Phys 47: 591–596
78. Delgado TE, Garrido E, Harwick RD (1981) Labiomandibular, transoral approach to chordomas in the clivus and upper cervical spine. Neurosurgery 8: 675–679
79. Deniz ML, Kilic T, Almaata I, Kurtkaya O, Sav A, Pamir MN (2002) Expression of growth factors and structural proteins in chordomas: basic fibroblast growth factor, transforming growth factor alpha, and fibronectin are correlated with recurrence. Neurosurgery 51: 753–760; discussion 760
80. Derome P (1972) Les tumeurs spheno-ethmoidales. Possibilites d'exerese et de reparation chirurgicale Neurochirurgie 18: 1–164
81. Derome PJ (1985) Surgical management of tumours invading the skull base. Can J Neurol Sci 12: 345–347
82. Dolenc VV, Skrap M, Sustersic J, Skrbec M, Morina A (1987) A transcavernous-transsellar approach to the basilar tip aneurysms. Br J Neurosurg 1: 251–259

83. Dolenc VV (1994) Frontotemporal epidural approach to trigeminal neurinomas. Acta Neurochir (Wien) 130: 55–65
84. Dolenc VV (1997) Transcranial epidural approach to pituitary tumors extending beyond the sella. Neurosurgery 41: 542–550; discussion 551–552
85. Dorfman HD, Czerniak B (1995) Bone cancers. Cancer 75: 203–210
86. Dort JC, Sutherland GR (2001) Intraoperative magnetic resonance imaging for skull base surgery. Laryngoscope 111: 1570–1575
87. Doucet V, Peretti-Viton P, Figarella-Branger D, Manera L, Salamon G (1997) MRI of intracranial chordomas. Extent of tumour and contrast enhancement: criteria for differential diagnosis. Neuroradiology 39: 571–576
88. Dow GR, Robson DK, Jaspan T, Punt JA (2003) Intradural cerebellar chordoma in a child: a case report and review of the literature. Childs Nerv Syst 19: 188–191
89. Dreghorn CR, Newman RJ, Hardy GJ, Dickson RA (1990) Primary tumors of the axial skeleton. Experience of the leeds regional bone tumor registry. Spine 15: 137–140
90. Eisenberg MB, Woloschak M, Sen C, Wolfe D (1997) Loss of heterozygosity in the retinoblastoma tumor suppressor gene in skull base chordomas and chondrosarcomas. Surg Neurol 47: 156–160; discussion 160–161
91. Ekinci G, Akpinar IN, Baltacioglu F, Erzen C, Kilic T, Elmaci I, Pamir MN (2003) Early-postoperative magnetic resonance imaging in glial tumors: prediction of tumor regrowth and recurrence. Eur J Radiol 45: 99–107
92. El-Kalliny M, van Loveren H, Keller JT, Tew JM Jr (1992) Tumors of the lateral wall of the cavernous sinus. J Neurosurg 77: 508–514
93. Enin IP (1964) Chordoma of the nasopharynx in 2 members of a family. Vestn Otorinolaringol 26: 88–90
94. Erbengi A, Tekkok IH, Acikgoz B (1991) Posterior fossa chordomas – with special reference to transoral surgery. Neurosurg Rev 14: 23–28
95. Erdem E, Angtuaco EC, Van Hemert R, Park JS, Al-Mefty O (2003) Comprehensive review of intracranial chordoma. Radiographics 23: 995–1009
96. Eriksson B, Gunterberg B, Kindblom LG (1981) Chordoma. A clinicopathologic and prognostic study of a Swedish national series. Acta Orthop Scand 52: 49–58
97. Fagundes MA, Hug EB, Liebsch NJ, Daly W, Efird J, Munzenrider JE (1995) Radiation therapy for chordomas of the base of skull and cervical spine: patterns of failure and outcome after relapse. Int J Radiat Oncol Biol Phys 33: 579–584
98. Fahlbusch R, Ganslandt O, Buchfelder M, Schott W, Nimsky C (2001) Intraoperative magnetic resonance imaging during transsphenoidal surgery. J Neurosurg 95: 381–390
99. Falconer MA, Bailey IC, Duchen LW (1968) Surgical treatment of chordoma and chondroma of the skull base. J Neurosurg 29: 261–275
100. Feigl GC, Bundschuh O, Gharabaghi A, Safavi-Abassi S, El Shawarby A, Samii M, Horstmann GA (2005) Evaluation of a new concept for the management of skull base chordomas and chondrosarcomas. J Neurosurg Suppl 102: 165–170
101. Ferry AP, Haddad HM, Goldman JL (1981) Orbital invasion by an intracranial chordoma. Am J Ophthalmol 92: 7–12
102. Fisch U (1978) Infratemporal fossa approach to tumours of the temporal bone and base of the skull. J Laryngol Otol 92: 949–967
103. Fischbein NJ, Kaplan MJ, Holliday RA, Dillon WP (2000) Recurrence of clival chordoma along the surgical pathway. Am J Neuroradiol 21: 578–583

104. Fleming GF, Heimann PS, Stephens JK, Simon MA, Ferguson MK, Benjamin RS, Samuels BL (1993) Dedifferentiated chordoma. Response to aggressive chemotherapy in two cases. Cancer 72: 714–718
105. Foote RF, Ablin G, Hall WW (1958) Chordoma in siblings. Calif Med 88: 383–386
106. Forsyth PA, Cascino TL, Shaw EG, Scheithauer BW, O'Fallon JR, Dozier JC, Piepgras DG (1993) Intracranial chordomas: a clinicopathological and prognostic study of 51 cases. J Neurosurg 78: 741–747
107. Fowler J (1989) The linear quadratic formula and progress in fractionated radiotherapy. Br J Radiol 62: 679–694
108. Fraioli B, Esposito V, Santoro A, Iannetti G, Giuffre R, Cantore G (1995) Transmaxillo-sphenoidal approach to tumors invading the medial compartment of the cavernous sinus. J Neurosurg 82: 63–69
109. Frank G, Sciarretta V, Calbucci F, Farneti G, Mazzatenta D, Pasquini E (2006) The endoscopic transnasal transsphenoidal approach for the treatment of cranial base chordomas and chondrosarcomas. Neurosurgery 59: ONS50–ONS57; discussion ONS50–ONS57
110. Franquemont DW, Katsetos CD, Ross GW (1989) Fatal acute pontocerebellar hemorrhage due to an unsuspected spheno-occipital chordoma. Arch Pathol Lab Med 113: 1075–1078
111. Fujita N, Miyamoto T, Imai J, Hosogane N, Suzuki T, Yagi M, Morita K, Ninomiya K, Miyamoto K, Takaishi H, Matsumoto M, Morioka H, Yabe H, Chiba K, Watanabe S, Toyama Y, Suda T (2005) CD24 is expressed specifically in the nucleus pulposus of intervertebral discs. Biochem Biophys Res Commun 338: 1890–1896
112. Fuller DB, Bloom JG (1988) Radiotherapy for chordoma. Int J Radiat Oncol Biol Phys 15: 331–339
113. Gadwal SR, Fanburg-Smith JC, Gannon FH, Thompson LD (2000) Primary chondrosarcoma of the head and neck in pediatric patients: a clinicopathologic study of 14 cases with a review of the literature. Cancer 88: 2181–2188
114. Gay E, Sekhar LN, Rubinstein E, Wright DC, Sen C, Janecka IP, Snyderman CH (1995) Chordomas and chondrosarcomas of the cranial base: results and follow-up of 60 patients. Neurosurgery 36: 887–896; discussion 896–897
115. Gehanne C, Delpierre I, Damry N, Devroede B, Brihaye P, Christophe C (2005) Skull base chordoma: CT and MRI features. Jbr-Btr 88: 325–327
116. George B, Dematons C, Cophignon J (1988) Lateral approach to the anterior portion of the foramen magnum. Application to surgical removal of 14 benign tumors: technical note. Surg Neurol 29: 484–490
117. George B, Ferrario CA, Blanquet A, Kolb F (2003) Cavernous sinus exenteration for invasive cranial base tumors. Neurosurgery 52: 772–780; discussion 780–782
118. Gibas Z, Miettinen M, Sandberg AA (1992) Chromosomal abnormalities in two chordomas. Cancer Genet Cytogenet 58: 169–173
119. Gil Z, Fliss DM, Voskoboinik N, Leider-Trejo L, Spektor S, Yaron Y, Orr-Urtreger A (2004) Cytogenetic analysis of three variants of clival chordoma. Cancer Genet Cytogen 154: 124–130
120. Glosser G, McManus P, Munzenrider J, Austin-Seymour M, Fullerton B, Adams J, Urie MM (1997) Neuropsychological function in adults after high dose fractionated radiation therapy of skull base tumors. Int J Radiat Oncol Biol Phys 38: 231–239

121. Goel A (1995) Extended middle fossa approach for petroclival lesions. Acta Neurochir (Wien) 135: 78–83
122. Goel A (1995) Chordoma and chondrosarcoma: relationship to the internal carotid artery. Acta Neurochir (Wien) 133: 30–35
123. Goel A, Muzumdar DP, Nitta J (2001) Surgery on lesions involving cavernous sinus. J Clin Neurosci 8 Suppl 1: 71–77
124. Gollin SM, Janecka IP (1994) Cytogenetics of cranial base tumors. J Neurooncol 20: 241–254
125. Gormley WB, Beckman ME, Ho KL, Boyd SB, Rock JP (1995) Primary craniofacial chordoma: case report. Neurosurgery 36: 1196–1199
126. Gottschalk D, Fehn M, Patt S, Saeger W, Kirchner T, Aigner T (2001) Matrix gene expression analysis and cellular phenotyping in chordoma reveals focal differentiation pattern of neoplastic cells mimicking nucleus pulposus development [see comment]. Am J Pathol 158: 1571–1578
127. Gutin PH, Leibel SA, Hosobuchi Y, Crumley RL, Edwards MS, Wilson CB, Lamb S, Weaver KA (1987) Brachytherapy of recurrent tumors of the skull base and spine with iodine-125 sources. Neurosurgery 20: 938–945
128. Gwak HS, Yoo HJ, Youn SM, Chang U, Lee DH, Yoo SY, Rhee CH (2005) Hypofractionated stereotactic radiation therapy for skull base and upper cervical chordoma and chondrosarcoma: preliminary results. Stereotact Funct Neurosurg 83: 233–243
129. Habrand JL, Mammar H, Ferrand R, Pontvert D, Bondiau PY, Kalifa C, Zucker JM (1999) Proton beam therapy (PT) in the management of CNS tumors in childhood. Strahlenther Onkol 175 (Suppl 2): 91–94
130. Haeckel C, Krueger S, Kuester D, Ostertag H, Samii M, Buehling F, Broemme D, Czerniak B, Roessner A (2000) Expression of cathepsin K in chordoma. Hum Pathol 31: 834–840
131. Hakuba A, Nishimura S, Inoue Y (1985) Transpetrosal-transtentorial approach and its application in the therapy of retrochiasmatic craniopharyngiomas. Surg Neurol 24: 405–415
132. Hakuba A, Tanaka K, Suzuki T, Nishimura S (1989) A comined orbitozygomatic infratemporal epidural and subdural approach for lesions involving the entire cavernous sinus'. J Neurosurg 71: 699–704
133. Halperin EC (1997) Why is female sex an independent predictor of shortened overall survival after proton/photon radiation therapy for skull base chordomas? Int J Radiat Oncol Biol Phys 38: 225–230
134. Handa J, Suzuki F, Nioka H, Koyama T (1987) Clivus chordoma in childhood. Surg Neurol 28: 58–62
135. Hara T, Kawahara N, Tsuboi K, Shibahara J, Ushiku T, Kirino T (2006) Sarcomatous transformation of clival chordoma after charged-particle radiotherapy. Report of two cases. J Neurosurg 105: 136–141
136. Hardy J, Vezina JL (1976) Transsphenoidal neurosurgery of intracranial neoplasm. Adv Neurol 15: 261–273
137. Harsh G, Ojemann R, Varvares M, Swearingen B, Cheney M, Joseph M (2001) Pedicled rhinotomy for clival chordomas invaginating the brainstem. Neurosurg Focus 10: E8
138. Harvey WF, Dawson EK (1941) Chordoma. Edinburgh Med J 48: 713–721
139. Hasse H (1857) Ein neuer Fall von Schleimgeschwulst am Clivus. Virch Arch 11

140. Hazarika D, Kumar RV, Muniyappa GD, Mukherjee G, Rao CR, Narasimhamurthy NK, Shenoy AM, Nanjundappa (1995) Diagnosis of clival chordoma by fine needle aspiration of an oropharyngeal mass. A case report. Acta Cytol 39: 507–510
141. Heffelfinger MJ, Dahlin DC, MacCarty CS, Beabout JW (1973) Chordomas and cartilaginous tumors at the skull base. Cancer 32: 410–420
142. Higinbotham NL, Phillips RF, Farr HW, Hustu HO (1967) Chordoma. Thirty-five-year study at Memorial Hospital. Cancer 20: 1841–1850
143. Ho KL (1985) Ecchordosis physaliphora and chordoma: a comparative ultrastructural study. Clin Neuropathol 4: 77–86
144. Hoch BL, Nielsen GP, Liebsch NJ, Rosenberg AE (2006) Base of skull chordomas in children and adolescents: a clinicopathologic study of 73 cases. Am J Surg Pathol 30: 811–818
145. Honeybul S, Neil-Dwyer D, Lang DA, Evans BT (2001) Extended transbasal approach with preservation of olfaction: ananatomical study. Br J Oral Maxillofac Surg 39: 149–157
146. Horiguchi H, Sano T, Qian ZR, Hirokawa M, Kagawa N, Yamaguchi T, Hirose T, Nagahiro S (2004) Expression of cell adhesion molecules in chordomas: an immunohistochemical study of 16 cases. Acta Neuropathol (Berl) 107: 91–96
147. Horten BC, Montague SR (1976) In vitro characteristics of a sacrococcygeal chordoma maintained in tissue and organ culture systems. Acta Neuropathologica 35: 13–25
148. Horten BC, Montague SR (1976) Human ecchordosis physaliphora and chick embryonic notochord. A comparative electron microscopic study. Virchows Arch A Pathol Anat Histol 371: 295–303
149. House WF, Shelton C (1992) Middle fossa approach for acoustic tumor removal. Otolaryngol Clin 25: 347–359
150. Hruban RH, Traganos F, Reuter VE, Huvos AG (1990) Chordomas with malignant spindle cell components. A DNA flow cytometric and immunohistochemical study with histogenetic implications. Am J Pathol 137: 435–447
151. Hug EB, Loredo LN, Slater JD, DeVries A, Grove RI, Schaefer RA, Rosenberg AE, Slater JM (1999) Proton radiation therapy for chordomas and chondrosarcomas of the skull base. J Neurosurg 91: 432–439
152. Hug EB (2001) Review of skull base chordomas: prognostic factors and long-term results of proton-beam radiotherapy. Neurosurg Focus 10: E11
153. Hug EB, Sweeney RA, Nurre PM, Holloway KC, Slater JD, Munzenrider JE (2002) Proton radiotherapy in management of pediatric base of skull tumors. Int J Radiat Oncol Biol Phys 52: 1017–1024
154. Igaki H, Tokuuye K, Okumura T, Sugahara S, Kagei K, Hata M, Ohara K, Hashimoto T, Tsuboi K, Takano S, Matsumura A, Akine Y (2004) Clinical results of proton beam therapy for skull base chordoma. Int J Radiat Oncol Biol Phys 60: 1120–1126
155. Jackson IT (1990) Craniofacial osteotomies to facilitate the resection of the tumors of the skull base. McGraw-Hill, Health Professions Division, New York
156. Jeffrey PB, Davis RL, Biava C, Rosenblum M (1993) Microtubule aggregates in a clival chordoma. Arch Pathol Lab Med 117: 1055–1057
157. Jeffrey PB, Biava CG, Davis RL (1995) Chondroid chordoma. A hyalinized chordoma without cartilaginous differentiation. Am J Clin Pathol 103: 271–279
158. Jho HD, Carrau RL, McLaughlin ML, Somaza SC (1996) Endoscopic transsphenoidal resection of a large chordoma in the posterior fossa. Case report. Neurosurg Focus 1: e3; discussion 1p following e3

159. Jho HD, Carrau RL (1997) Endoscopic endonasal transsphenoidal surgery: experience with 50 patients. J Neurosurg 87: 44–51
160. Jho HD, Carrau RL, McLaughlin MR, Somaza SC (1997) Endoscopic transsphenoidal resection of a large chordoma in the posterior fossa. Acta Neurochir (Wien) 139: 343–347; discussion 347–348
161. Kakuno Y, Yamada T, Hirano H, Mori H, Narabayashi I (2002) Chordoma in the sella turcica. Neurol Med Chir (Tokyo) 42: 305–308
162. Kamrin RP, Potanos JN, Pool JL (1964) An evaluation of the diagnosis and treatment of chordoma. J Neurol Neurosurg Psychiatry 27: 157–165
163. Kassam A, Snyderman CH, Mintz A, Gardner P, Carrau RL (2005) Expanded endonasal approach: the rostrocaudal axis. Part II. Posterior clinoids to the foramen magnum. Neurosurg Focus 19: E4
164. Kawase T (1990) Skull base approaches for clival tumors. No Shinkei Geka 18: 121–128
165. Kawase T (1997) Anatomical strategy of parasellar tumor surgery. No Shinkei Geka 25: 681–688
166. Kelley MJ, Korczak JF, Sheridan E, Yang X, Goldstein AM, Parry DM (2001) Familial chordoma, a tumor of notochordal remnants, is linked to chromosome 7q33. Am J Hum Genet 69: 454–460
167. Kerr WA, Allen KL, Haynes DR, Sellars SL (1975) Letter: familial nasopharyngeal chordoma. S Afr Med J 49: 1584
168. Kilgore S, Prayson RA (2002) Apoptotic and proliferative markers in chordomas: a study of 26 tumors. Ann Diagn Pathol 6: 222–228
169. Kilic T, Ekinci G, Seker A, Elmaci I, Erzen C, Pamir MN (2001) Determining optimal MRI follow-up after transsphenoidal surgery for pituitary adenoma: scan at 24 hours post-surgery provides reliable information. Acta Neurochir (Wien) 143: 1103–1126
170. Kimura F, Kim KS, Friedman H, Russell EJ, Breit R (1990) MR imaging of normal and abnormal clivus. Am J Neuroradiol 11: 1015–1021
171. Kitano M, Taneda M (2001) Extended transsphenoidal approach with submucosal posterior ethmoidectomy for parasellar tumors: technical note. J Neurosurg 94: 999–1004
172. Klebs E (1864) Ein Fall von Ecchondrosis spheno-occipitalise amylacea. Virchows Arch Path Anat 31: 396–399
173. Kleihues P, Louis DN, Scheithauer BW, Rorke LB, Reifenberger G, Burger PC, Cavenee WK (2002) The WHO classification of tumors of the nervous system. J Neuropathol Exp Neurol 61: 215–225; discussion 226–229
174. Klingler L, Shooks J, Fiedler PN, Marney A, Butler MG, Schwartz HS (2000) Microsatellite instability in sacral chordoma. J Surg Oncol 73: 100–103
175. Knisely JP, Linskey ME (2006) Less common indications for stereotactic radiosurgery or fractionated radiotherapy for patients with benign brain tumors. Neurosurg Clin N Am 17: 149–167, vii
176. Knutsen T, Gobu V, Knaus R, Padilla-Nash H, Augustus M, Strausberg RL, Kirsch IR, Sirotkin K, Ried T (2005) The interactive online SKY/M-FISH & CGH database and the Entrez cancer chromosomes search database: linkage of chromosomal aberrations with the genome sequence. Genes Chromosomes Cancer 44: 52–64
177. Kölliker A (1860) Über die Beziehungen der Chorda dorsalis zur Bildung der Wirbel der Selachier und einiger andern Fische. Verhandl. phys. med. Gesellsch. Würzburg 10: 193–242

178. Kombogiorgas D, St George EJ, Chapman S, English M, Solanki GA (2006) Infantile clivus chordoma without clivus involvement: case report and review of the literature. Childs Nerv Syst 22(10): 1369–1374
179. Kondziolka D, Lunsford LD, Flickinger JC (1991) The role of radiosurgery in the management of chordoma and chondrosarcoma of the cranial base. Neurosurgery 29: 38–45; discussion 45–46
180. Kouri JG, Chen MY, Watson JC, Oldfield EH (2000) Resection of suprasellar tumors by using a modified transsphenoidal approach. Report of four cases. J Neurosurg 92: 1028–1035
181. Koybasioglu F, Simsek GG, Onal BU, Han U, Adabag A (2005) Oropharyngeal chordoma diagnosed by fine needle aspiration: a case report. Acta Cytol 49: 173–176
182. Krayenbühl H, Yasargil MG (1975) Cranial chordomas. Progr Neurol Surg 6: 380–434
183. Krishnan S, Foote RL, Brown PD, Pollock BE, Link MJ, Garces YI (2005) Radiosurgery for cranial base chordomas and chondrosarcomas. Neurosurgery 56: 777–784; discussion 777–784
184. Kumar PP, Good RR, Leibrock LG, Mawk JR, Yonkers AJ, Ogren FP (1988) High activity iodine 125 endocurietherapy for recurrent skull base tumors. Cancer 61: 1518–1527
185. Kumar PP, Good RR, Skultety FM, Leibrock LG (1988) Local control of recurrent clival and sacral chordoma after interstitial irradiation with iodine-125: new techniques for treatment of recurrent or unresectable chordomas. Neurosurgery 22: 479–483
186. Kurokawa H, Miura S, Goto T (1988) Ecchordosis physaliphora arising from the cervical vertebra, the CT and MRI appearance. Neuroradiology 30: 81–83
187. Kurtsoy A, Menku A, Tucer B, Suat Oktem I, Akdemir H, Kemal Koc R (2004) Transbasal approaches: surgical details, pitfalls and avoidances. Neurosurg Rev 27: 267–273
188. Kuzniacka A, Mertens F, Strombeck B, Wiegant J, Mandahl N (2004) Combined binary ratio labeling fluorescence in situ hybridization analysis of chordoma. Cancer Genet Cytogenet 151: 178–181
189. Kyoshima K, Matsuo K, Kushima H, Oikawa S, Idomari K, Kobayashi S (2002) Degloving transfacial approach with Le Fort I and nasomaxillary osteotomies: alternative transfacial approach. Neurosurgery 50: 813–821
190. Lalwani AK, Kaplan MJ, Gutin PH (1992) The transsphenoethmoid approach to the sphenoid sinus and clivus. Neurosurgery 31: 1008–1014; discussion 1014
191. Lam R (1990) The nature of cytoplasmic vacuoles in chordoma cells. A correlative enzyme and electron microscopic histochemical study. Pathol Res Pract 186: 642–650
192. Lanzino G, Hirsch WL, Pomonis S, Sen CN, Sekhar LN (1992) Cavernous sinus tumors: neuroradiologic and neurosurgical considerations on 150 operated cases. J Neurosurg Sci 36: 183–196
193. Lanzino G, Sekhar LN, Hirsch WL, Sen CN, Pomonis S, Snyderman CH (1993) Chordomas and chondrosarcomas involving the cavernous sinus: review of surgical treatment and outcome in 31 patients. Surg Neurol 40: 359–371
194. Lanzino G, Dumont AS, Lopes MB, Laws ER Jr (2001) Skull base chordomas: overview of disease, management options, and outcome. Neurosurg Focus 10: E12
195. Larson TC 3rd, Houser OW, Laws ER Jr (1987) Imaging of cranial chordomas. Mayo Clin Proc 62: 886–893
196. Laws ER Jr, Trautmann JC, Hollenhorst RW Jr (1977) Transsphenoidal decompression of the optic nerve and chiasm. Visual results in 62 patients. J Neurosurg 46: 717–722

197. Laws ER Jr (1984) Transsphenoidal surgery for tumors of the clivus. Otolaryngol Head Neck Surg 92: 100–101
198. Laws ER Jr, Fode NC, Redmond MJ (1985) Transsphenoidal surgery following unsuccessful prior therapy. An assessment of benefits and risks in 158 patients. J Neurosurg 63: 823–829
199. Laws ER Jr (2001) Skull base chordomas: overview of disease, management options, and outcome. Neurosurg Focus 10(3): Article 12
200. Layfield LJ, Liu K, Dodd LG, Olatidoye BA (1998) "Dedifferentiated" chordoma: a case report of the cytomorphologic findings on fine-needle aspiration. Diagn Cytopathol 19: 378–381
201. Lee-Jones L, Aligianis I, Davies PA, Puga A, Farndon PA, Stemmer-Rachamimov A, Ramesh V, Sampson JR (2004) Sacrococcygeal chordomas in patients with tuberous sclerosis complex show somatic loss of TSC1 or TSC2. Genes Chromosomes Cancer 41: 80–85
202. Lee HJ, Kalnin AJ, Holodny AI, Schulder M, Grigorian A, Sharer LR (1998) Hemorrhagic chondroid chordoma mimicking pituitary apoplexy. Neuroradiology 40: 720–723
203. Leproux F, de Toffol B, Aesch B, Cotty P (1993) MRI of cranial chordomas: the value of gadolinium. Neuroradiology 35: 543–545
204. Lim GH (1975) Clivus chordoma with unusual bone sclerosis and brainstem invasion. A case report with review of the radiology of cranial chordomas. Australas Radiol 19: 242–250
205. Linck (1909) Chordoma malignum. Zieglers Beitr 46
206. Linsenmayer TF, Gibney E, Schmid TM (1986) Segmental appearance of type X collagen in the developing avian notochord. Dev Biol 113: 467–473
207. Losi L, Tomasich G (1996) Dedifferentiated (sarcomatoid) chordoma in the base of the skull. Report of a case. Pathologica 88: 514–518
208. Luschka H (1857) Über gallertartige Auswüchse am Clivus Blumenbachii. Virch Arch 11: 8–12
209. Mabrey R (1935) Chordoma: a study of 150 cases. Am J Cancer 25: 501–517
210. Macdonald RL, Deck JH (1990) Immunohistochemistry of ecchordosis physaliphora and chordoma. Can J Neurol Sci 17: 420–423
211. Magrini SM, Papi MG, Marletta F, Tomaselli S, Cellai E, Mungai V, Biti G (1992) Chordoma-natural history, treatment and prognosis. The Florence Radiotherapy Department experience (1956–1990) and a critical review of the literature. Acta Oncol 31: 847–851
212. Maira G, Pallini R, Anile C, Fernandez E, Salvinelli F, La Rocca LM, Rossi GF (1996) Surgical treatment of clival chordomas: the transsphenoidal approach revisited. J Neurosurg 85: 784–792
213. Makhmudov UB, Tcherekayev VA, Tanyashin SV (1992) Transoral approach to tumors of the clivus: report of two cases. J Craniofac Surg 3: 35–38
214. Mandahl N, Heim S, Arheden K, Rydholm A, Willen H, Mitelman F (1990) Chromosomal rearrangements in chondromatous tumors. Cancer 65: 242–248
215. Mapstone TB, Kaufman B, Ratcheson RA (1983) Intradural chordoma without bone involvement: nuclear magnetic resonance (NMR) appearance. Case report. J Neurosurg 59: 535–537
216. Marshman LA, Gunasekera L, Rose PE, Olney JS (2001) Primary intracerebral mesenchymal chondrosarcoma with rhabdomyosarcomatous differentiation: case report and literature review. Br J Neurosurg 15: 419–424

217. Matsumoto J, Towbin RB, Ball WS Jr (1989) Cranial chordomas in infancy and childhood. A report of two cases and review of the literature. Pediatr Radiol 20: 28–32
218. Matsumoto K, Tamesa N, Tomita S, Tamiya T, Furuta T, Ohmoto T (1997) Stereotactic brachytherapy for clival chordoma. No Shinkei Geka 25: 919–925
219. McDermott MW, Gutin PH (1996) Image-guided surgery for skull base neoplasms using the ISG viewing wand. Anatomic and technical considerations. Neurosurg Clin N Am 7: 285–295
220. McMaster ML, Goldstein AM, Bromley CM, Ishibe N, Parry DM (2001) Chordoma: incidence and survival patterns in the United States, 1973–1995. Cancer Causes Control 12: 1–11
221. Mehnert F, Beschorner R, Kuker W, Hahn U, Nagele T (2004) Retroclival ecchordosis physaliphora: MR imaging and review of the literature. Am J Neuroradiol 25: 1851–1855
222. Meis JM, Raymond AK, Evans HL, Charles RE, Giraldo AA (1987) "Dedifferentiated" chordoma. A clinicopathologic and immunohistochemical study of three cases. Am J Surg Pathol 11: 516–525
223. Meis JM, Giraldo AA (1988) Chordoma. An immunohistochemical study of 20 cases. Arch Pathol Lab Med 112: 553–556
224. Menezes AH, VanGilder JC (1988) Transoral-transpharyngeal approach to the anterior craniocervical junction. Ten-year experience with 72 patients. J Neurosurg 69: 895–903
225. Menezes AH, Gantz BJ, Traynelis VC, McCulloch TM (1997) Cranial base chordomas. Clin Neurosurg 44: 491–509
226. Mertens F, Kreicbergs A, Rydholm A, Willen H, Carlen B, Mitelman F, Mandahl N (1994) Clonal chromosome aberrations in three sacral chordomas. Cancer Genet Cytogenet 73: 147–151
227. Meyer JE, Oot RF, Lindfors KK (1986) CT appearance of clival chordomas. J Comput Assist Tomogr 10: 34–38
228. Meyers SP, Hirsch WL Jr, Curtin HD, Barnes L, Sekhar LN, Sen C (1992) Chondrosarcomas of the skull base: MR imaging features. Radiology 184: 103–108
229. Meyers SP, Hirsch WL Jr, Curtin HD, Barnes L, Sekhar LN, Sen C (1992) Chordomas of the skull base: MR features. Am J Neuroradiol 13: 1627–1636
230. Mills RP (1984) Chordomas of the skull base. J R Soc Med 77: 10–16
231. Miozzo M, Dalpra L, Riva P, Volonta M, Macciardi F, Pericotti S, Tibiletti MG, Cerati M, Rohde K, Larizza L, Fuhrman Conti AM (2000) A tumor suppressor locus in familial and sporadic chordoma maps to 1p36. Int J Cancer 87: 68–72
232. Mitchell A, Scheithauer BW, Unni KK, Forsyth PJ, Wold LE, McGivney DJ (1993) Chordoma and chondroid neoplasms of the spheno-occiput. An immunohistochemical study of 41 cases with prognostic and nosologic implications. Cancer 72: 2943–2949
233. Miyagi A, Maeda K, Sugawara T (1998) Usefulness of neuroendoscopy and a neuronavigator for removal of clival chordoma. No Shinkei Geka 26: 169–175
234. Mondal A, Mukherjee PK (1988) Cytological and cytochemical diagnosis of chordoma by fine needle aspiration biopsy – a case report. Indian J Pathol Microbiol 31: 64–66
235. Moreira-Gonzalez A, Pieper DR, Balaguer Cambra J, Simman R, Jackson IT (2005) Skull base tumors: a comprehensive review of transfacial swing osteotomy approaches. Plast Reconstr Surg 115: 711–720

236. Mortini P, Roberti F, Kalavakonda C, Nadel A, Sekhar LN (2003) Endoscopic and microscopic extended subfrontal approach to the clivus: a comparative anatomical study. Skull Base 13: 139–147
237. Müller H (1858) Über das Vorkommen von Resten des Chorda dorsalis bei Menschen nach der Geburt und über ihr Verhältniss zu den Gallertgeschwülesten am Clivus. Z Ration Med 2: 202–229
238. Munzenrider JE, Liebsch NJ (1999) Proton therapy for tumors of the skull base. Strahlenther Onkol 175 Suppl 2: 57–63
239. Muthukumar N, Kondziolka D, Lunsford LD, Flickinger JC (1998) Stereotactic radiosurgery for chordoma and chondrosarcoma: further experiences. Int J Radiat Oncol Biol Phys 41: 387–392
240. Nagib MG, Wisiol ES, Simonton SC, Levinson RM (1990) Transoral labiomandibular approach to basiocciput chordomas in childhood. Childs Nerv Syst 6: 126–130
241. Naka T, Boltze C, Samii A, Herold C, Ostertag H, Iwamoto Y, Oda Y, Tsuneyoshi M, Kuester D, Roessner A (2003) Skull base and nonskull base chordomas: clinicopathologic and immunohistochemical study with special reference to nuclear pleomorphism and proliferative ability. Cancer 98: 1934–1941
242. Naka T, Boltze C, Kuester D, Schulz TO, Samii A, Herold C, Ostertag H, Roessner A (2004) Expression of matrix metalloproteinase (MMP)-1, MMP-2, MMP-9, cathepsin B, and urokinase plasminogen activator in non-skull base chordoma. Am J Clin Pathol 122: 926–930
243. Naka T, Boltze C, Kuester D, Samii A, Herold C, Ostertag H, Iwamoto Y, Oda Y, Tsuneyoshi M, Roessner A (2005) Intralesional fibrous septum in chordoma: a clinicopathologic and immunohistochemical study of 122 lesions. Am J Clin Pathol 124: 288–294
244. Naka T, Boltze C, kuester D, Schulz T, Schneider-Stock R, Kellner A, Samii A, Herold C, Ostertag H, Roessner A (2005) Alterations of G1-S checkpoint in chordoma: the prognostic impact of p53 overexpression. Cancer 104: 1255–1263
245. Ng SH, Ko SF, Wan YL, Tang LM, Ho YS (1998) Cervical ecchordosis physaliphora: CT and MR features. Br J Radiol 71: 329–331
246. Nijhawan VS, Rajwanshi A, Das A, Jayaram N, Gupta SK (1989) Fine-needle aspiration cytology of sacrococcygeal chordoma. Diagn Cytopathol 5: 404–407
247. Nimsky C, Ganslandt O, Von Keller B, Romstock J, Fahlbusch R (2004) Intraoperative high-field-strength MR imaging: implementation and experience in 200 patients. Radiology 233: 67–78
248. Nimsky C, Ganslandt O, Buchfelder M, Fahlbusch R (2006) Intraoperative visualization for resection of gliomas: the role of functional neuronavigation and intraoperative 1.5 T MRI. Neurol Res 28: 482–487
249. Noel G, Habrand JL, Jauffret E, de Crevoisier R, Dederke S, Mammar H, Haie-Meder C, Pontvert D, Hasboun D, Ferrand R, Boisserie G, Beaudre A, Gaboriaud G, Guedea F, Petriz L, Mazeron JJ (2003) Radiation therapy for chordoma and chondrosarcoma of the skull base and the cervical spine. Prognostic factors and patterns of failure. Strahlenther Onkol 179: 241–248
250. Noel G, Feuvret L, Calugaru V, Dhermain F, Mammar H, Haie-Meder C, Ponvert D, Hasboun D, Ferrand R, Nauraye C, Boisserie G, Beaudre A, Gaboriaud G, Mazal A, Habrand JL, Mazeron JJ (2005) Chordomas of the base of the skull and upper cervical spine. One hundred patients irradiated by a 3D conformal technique combining photon and proton beams. Acta Oncol 44: 700–708

251. O'Neill P, Bell BA, Miller JD, Jacobson I, Guthrie W (1985) Fifty years of experience with chordomas in southeast Scotland. Neurosurgery 16: 166–170
252. Ogi H, Kiryu H, Hori Y, Fukui M (1995) Cutaneous metastasis of CNS chordoma. Am J Dermatopathol 17: 599–602
253. Oikawa S, Kyoshima K, Goto T, Iwashita T, Takizawa T, Kobayashi S, Ito M (2001) Histological study on local invasiveness of clival chordoma. Case report of autopsy. Acta Neurochir (Wien) 143: 1065–1069
254. Okada Y, Aoki S, Barkovich AJ, *et al* (1989) Cranial bone marrow in children: assessment of normal development with mr imaging. Radiology 171: 161–164
255. Oot RF, Melville GE, New PF, Austin-Seymour M, Munzenrider J, Pile-Spellman J, Spagnoli M, Shoukimas GM, Momose KJ, Carroll R, *et al* (1988) The role of MR and CT in evaluating clival chordomas and chondrosarcomas. AJR Am J Roentgenol 151: 567–575
256. Paavolainen P, Teppo L (1976) Chordoma in Finland. Acta Orthop Scand 47: 46–51
257. Pai HH, Thornton A, Katznelson L, Finkelstein DM, Adams JA, Fullerton BC, Loeffler JS, Leibsch NJ, Klibanski A, Munzenrider JE (2001) Hypothalamic/pituitary function following high-dose conformal radiotherapy to the base of skull: demonstration of a dose-effect relationship using dose-volume histogram analysis. Int J Radiat Oncol Biol Phys 49: 1079–1092
258. Pallini R, Maira G, Pierconti F, Falchetti ML, Alvino E, Cimino-Reale G, Fernandez E, D'Ambrosio E, Larocca LM (2003) Chordoma of the skull base: predictors of tumor recurrence. J Neurosurg 98: 812–822
259. Pamir MN, Kilic T, Ture U, Ozek MM (2004) Multimodality management of 26 skull-base chordomas with 4-year mean follow-up: experience at a single institution. Acta Neurochir (Wien) 146: 343–354; discusion 354
260. Pamir MN, Kilic T, Ozek MM, Ozduman K, Ture U (2006) Non-meningeal tumours of the cavernous sinus: a surgical analysis. J Clin Neurosci 13: 626–635
261. Pamir MN, Ozduman K (2006) Analysis of radiological features relative to histopathology in 42 skull-base chordomas and chondrosarcomas. Eur J Radiol 58: 461–470
262. Pamir MN, Peker S, Ozek MM, Dincer A (2006) Intraoperative MR imaging: preliminary results with 3 tesla MR system. Acta Neurochir Suppl 98: 97–100
263. Parkinson D (2000) Extradural neural axis compartment. J Neurosurg 92: 585–588
264. Patten BM (1968) Human ebryology. McGraw Hill, New York, pp 430–431
265. Pearlman AW, Friedman M (1970) Radical radiation therapy of chordoma. Am J Roentgenol Radium Ther Nucl Med 108: 332–341
266. Peker S, Kurtkaya-Yapicier O, Kilic T, Pamir MN (2005) Microsurgical anatomy of the lateral walls of the pituitary fossa. Acta Neurochir (Wien) 147: 641–648; discussion 649
267. Persons DL, Bridge JA, Neff JR (1991) Cytogenetic analysis of two sacral chordomas. Cancer Genet Cytogenet 56: 197–201
268. Petti PL (1996) Evaluation of a pencil-beam dose calculation technique for charged particle radiotherapy. Int J Radiat Oncol Biol Phys 35: 1049–1057
269. Placzek M (1995) The role of the notochord and floor plate in inductive interactions. Curr Opin Genet Dev 5: 499–506
270. Price CH, Jeffree GM (1977) Incidence of bone sarcoma in SW England, 1946–74, in relation to age, sex, tumour site and histology. Br J Cancer 36: 511–522
271. Probst EN, Zanella FE, Vortmeyer AO (1993) Congenital clivus chordoma. Am J Neuroradiol 14: 537–539

272. Rabadan A, Conesa H (1992) Transmaxillary-transnasal approach to the anterior clivus: a microsurgical anatomical model. Neurosurgery 30: 473–481; discussion 482
273. Radner H, Katenkamp D, Reifenberger G, Deckert M, Pietsch T, Wiestler OD (2001) New developments in the pathology of skull base tumors. Virchows Arch 438: 321–335
274. Raffel C, Wright DC, Gutin PH, Wilson CB (1985) Cranial chordomas: clinical presentation and results of operative and radiation therapy in twenty-six patients. Neurosurgery 17: 703–710
275. Raso JL, Gusmao S (2006) Transbasal approach to skull base tumors: evaluation and proposal of classification. Surg Neurol 65 (Suppl 1) S1: 33-1:37; discussion 1: 37-1:38
276. Reifenberger G, Weber T, Weber RG, Wolter M, Brandis A, Kuchelmeister K, Pilz P, Reusche E, Lichter P, Wiestler OD (1999) Chordoid glioma of the third ventricle: immunohistochemical and molecular genetic characterization of a novel tumor entity. Brain Pathol 9: 617–626
277. Rengachary SS, Grotte DA, Swanson PE (1997) Extradural ecchordosis physaliphora of the thoracic spine: case report. Neurosurgery 41: 1198–1201; discussion 1201–1202
278. Rhomberg W, Eiter H, Bohler F, Dertinger S (2006) Combined radiotherapy and razoxane in the treatment of chondrosarcomas and chordomas. Anticancer Res 26: 2407–2411
279. Ribbert H (1895) Über die experimentelle Erzeugung einer Ecchondrosis physalifora. Verhandl. d. XIII. Kongr f inn Med 13: 455–464
280. Ribbert H (1904) Geschwülstlehre für Arzte und studierende, Bonn
281. Ribbert H, Virchow R (1959) Chordoma
282. Rich TA, Schiller A, Suit HD, Mankin HJ (1985) Clinical and pathologic review of 48 cases of chordoma. Cancer 56: 182–187
283. Richardson MS (2001) Pathology of skull base tumors. Otolaryngol Clin North Am 34: 1025–1042
284. Riva P, Crosti F, Orzan F, Dalpra L, Mortini P, Parafioriti A, Pollo B, Fuhrman Conti AM, Miozzo M, Larizza L (2003) Mapping of candidate region for chordoma development to 1p36.13 by LOH analysis. Int J Cancer 107: 493–497
285. Roche PH, Malca SA, Payan MJ, Pellet W (1995) Chondrosarcoma of the skull base. Apropos of sphenotemporal localization and review of the literature. Neurochirurgie 41: 353–358
286. Rodriguez L, Colina J, Lopez J, Molina O, Cardozo J (1999) Intradural prepontine growth: giant ecchordosis physaliphora or extraosseous chordoma? Neuropathology 19: 336–340
287. Romero J, Cardenes H, la Torre A, Valcarcel F, Magallon R, Regueiro C, Aragon G (1993) Chordoma: results of radiation therapy in eighteen patients. Radiother Oncol 29: 27–32
288. Rone R, Ramzy I, Duncan D (1986) Anaplastic sacrococcygeal chordoma. Fine needle aspiration cytologic findings and embryologic considerations. Acta Cytol 30: 183–188
289. Rosenberg AE, Brown GA, Bhan AK, Lee JM (1994) Chondroid chordoma – a variant of chordoma. A morphologic and immunohistochemical study. Am J Clin Pathol 101: 36–41
290. Rosenberg AE, Nielsen GP, Keel SB, Renard LG, Fitzek MM, Munzenrider JE, Liebsch NJ (1999) Chondrosarcoma of the base of the skull: a clinicopathologic study of 200 cases with emphasis on its distinction from chordoma. Am J Surg Pathol 23: 1370–1378
291. Rosenberg AE, Nielsen GP, Keel SB (2000) Lipoid chordoma. Mod Pathol 13: 15a
292. Saad AG, Collins MH (2005) Prognostic value of MIB-1, E-cadherin, and CD44 in pediatric chordomas. Pediatr Dev Pathol 8: 362–368

293. Sabit I, Schaefer SD, Couldwell WT (2000) Extradural extranasal combined transmaxillary transsphenoidal approach to the cavernous sinus: a minimally invasive microsurgical model. Laryngoscope 110: 286–291
294. Saito A, Hasegawa T, Shimoda T, Toda G, Hirohashi S, Tajima G, Moriya Y (1998) Dedifferentiated chordoma: a case report. Jpn J Clin Oncol 28: 766–771
295. Salisbury JR, Isaacson PG (1985) Demonstration of cytokeratins and an epithelial membrane antigen in chordomas and human fetal notochord. Am J Surg Pathol 9: 791–797
296. Salisbury JR (1993) The pathology of the human notochord. J Pathol 171: 253–255
297. Salisbury JR, Deverell MH, Cookson MJ, Whimster WF (1993) Three-dimensional reconstruction of human embryonic notochords: clue to the pathogenesis of chordoma. J Pathol 171: 59–62
298. Samii M, Ammirati M (1988) The combined supra-infratentorial pre-sigmoid sinus avenue to the petro-clival region. Surgical technique and clinical applications. Acta Neurochir (Wien) 95: 6–12
299. Sandberg AA, Bridge JA (2003) Updates on the cytogenetics and molecular genetics of bone and soft tissue tumors: chondrosarcoma and other cartilaginous neoplasms. Cancer Genet Cytogenet 143: 1–31
300. Santoni R, Liebsch N, Finkelstein DM, Hug E, Hanssens P, Goitein M, Smith AR, O'Farrell D, Efird JT, Fullerton B, Munzenrider JE (1998) Temporal lobe (TL) damage following surgery and high-dose photon and proton irradiation in 96 patients affected by chordomas and chondrosarcomas of the base of the skull. Int J Radiat Oncol Biol Phys 41: 59–68
301. Sautner D, Saeger W, Ludecke DK (1993) Tumors of the sellar region mimicking pituitary adenomas. Exp Clin Endocrinol 101: 283–289
302. Sawamura Y, Terasaka S, Fukushima T (1999) Extended transsphenoidal approach with sigma-shape osteotomy of the maxilla: technical note. Skull Base Surg 9: 119–125
303. Sawyer JR, Husain M, Al-Mefty O (2001) Identification of isochromosome 1q as a recurring chromosome aberration in skull base chordomas: a new marker for aggressive tumors? Neurosurg Focus 10: E6
304. Scheil S, Bruderlein S, Liehr T, Starke H, Herms J, Schulte M, Moller P (2001) Genome-wide analysis of sixteen chordomas by comparative genomic hybridization and cytogenetics of the first human chordoma cell line, U-CH1. Genes Chromosomes Cancer 32: 203–211
305. Schisano G, Tovi D (1962) Clivus chordomas. Neurochirurgia (Stuttg) 5: 99–120
306. Schonegger K, Gelpi E, Prayer D, Dieckmann K, Matula C, Hassler M, Hainfellner JA, Marosi C (2005) Recurrent and metastatic clivus chordoma: systemic palliative therapy retards disease progression. Anticancer Drugs 16: 1139–1143
307. Schulz-Ertner D, Haberer T, Jakel O, Thilmann C, Kramer M, Enghardt W, Kraft G, Wannenmacher M, Debus J (2002) Radiotherapy for chordomas and low-grade chondrosarcomas of the skull base with carbon ions. Int J Radiat Oncol Biol Phys 53: 36–42
308. Schulz-Ertner D, Nikoghosyan A, Thilmann C, Haberer T, Jakel O, Karger C, Scholz M, Kraft G, Wannenmacher M, Debus J (2003) Carbon ion radiotherapy for chordomas and low-grade chondrosarcomas of the skull base. Results in 67 patients. Strahlenther Onkol 179: 598–605
309. Sefiani S, Amarti A, Maher M, Benkiran L, Saidi A (2002) Dedifferentiated chordoma of the skull base. A case report. Neurochirurgie 48: 436–439

310. Seifert G, Donath K (1998) [Cranial and cervical chordomas. A differential diagnostic problem]. Mund Kiefer Gesichtschir 2: 153–159
311. Seifert V, Laszig R (1991) Transoral transpalatal removal of a giant premesencephalic clivus chordoma. Acta Neurochir (Wien) 112: 141–146
312. Sekhar LN, Moller AR (1986) Operative management of tumors involving the cavernous sinus. J Neurosurg 64: 879–889
313. Sekhar LN, Nanda A, Sen CN, Snyderman CN, Janecka IP (1992) The extended frontal approach to tumors of the anterior, middle, and posterior skull base. J Neurosurg 76: 198–206
314. Sekhar LN, Janecka IP (1993) Surgery of cranial base tumors. Raven Press, New York
315. Sekhar LN, Pranatartiharan R, Chanda A, Wright DC (2001) Chordomas and chondrosarcomas of the skull base: results and complications of surgical management. Neurosurg Focus 10: E2
316. Sen C, Triana A (2001) Cranial chordomas: results of radical excision. Neurosurg Focus 10: E3
317. Sen CN, Sekhar LN, Schramm VL, Janecka IP (1989) Chordoma and chondrosarcoma of the cranial base: an 8-year experience. Neurosurgery 25: 931–940; discussion 940–941
318. Sepehrnia A, Samii M, Tatagiba M (1991) Management of intracavernous tumours: an 11-year experience. Acta Neurochir Suppl 53: 122–126
319. Shugar JM, Som PM, Krespi YP, Arnold LM, Som ML (1980) Primary chordoma of the maxillary sinus. Laryngoscope 90: 1825–1830
320. Sibley RK, Day DL, Dehner LP, Trueworthy RC (1987) Metastasizing chordoma in early childhood: a pathological and immunohistochemical study with review of the literature. Pediatr Pathol 7: 287–301
321. Slater JM, Slater JD, Archambeau JO (1995) Proton therapy for cranial base tumors. J Craniofac Surg 6: 24–26
322. Spallone A, Tcherekarjev VA, Korshunov AG (1996) Chondrosarcoma of the anterior cranial fossa. Report of two cases. J Neurosurg Sci 40: 115–120
323. Spetzler RF, Herman JM, Beals S, Joganic E, Milligan J (1993) Preservation of olfaction in anterior craniofacial approaches. J Neurosurg 79: 48–52
324. Spiro RH, Gerold FP, Strong EW (1981) Mandibular "swing" approach for oral and oropharyngeal tumors. Head Neck Surg 3: 371
325. Steiner and Fischer (1907) Über ein malignes chordom der Schaedel-Rückgradshöhle. Beitr Path Anat 40: 109–119
326. Stemple DL (2005) Structure and function of the notochord: an essential organ for chordate development. Development 132: 2503–2512
327. Stepanek J, Cataldo SA, Ebersold MJ, Lindor NM, Jenkins RB, Unni K, Weinshenker BG, Rubenstein RL (1998) Familial chordoma with probable autosomal dominant inheritance. Am J Med Genet 75: 335–336
328. Stewart M, Morin J (1926) Chordoma: a review, with report of a new sacrococcygeal case. J Pathol Bacterial 29: 41–60
329. Stough DR, Hartzog JT, Fisher RG (1971) Unusual intradural spinal metastasis of a cranial chordoma. Case report. J Neurosurg 34: 560–562
330. Sundaresan N (1986) Chordomas. Clin Orthop Relat Res: 135–142
331. Sweet MB, Thonar EJ, Berson SD, Skikne MI, Immelman AR, Kerr WA (1979) Biochemical studies of the matrix of craniovertebral chordoma and a metastasis. Cancer 44: 652–660

332. Sze G, Uichanco LS 3rd, Brant-Zawadzki MN, Davis RL, Gutin PH, Wilson CB, Norman D, Newton TH (1988) Chordomas: MR imaging. Radiology 166: 187–191
333. Tai PT, Craighead P, Bagdon F (1995) Optimization of radiotherapy for patients with cranial chordoma. A review of dose-response ratios for photon techniques. Cancer 75: 749–756
334. Tallini G, Dorfman H, Brys P, Dal Cin P, De Wever I, Fletcher CD, Jonson K, Mandahl N, Mertens F, Mitelman F, Rosai J, Rydholm A, Samson I, Sciot R, Van den Berghe H, Vanni R, Willen H (2002) Correlation between clinicopathological features and karyotype in 100 cartilaginous and chordoid tumours. A report from the Chromosomes and Morphology (CHAMP) Collaborative Study Group. J Pathol 196: 194–203
335. Tamaki N, Nagashima T, Ehara K, Motooka Y, Barua KK (2001) Surgical approaches and strategies for skull base chordomas. Neurosurg Focus 10: E9
336. Taniguchi K, Tateishi A, Higaki S, Igarashi M, Hayashi V, Inoue S, Shoji H (1984) Type of collagen in chordoma. Nippon Seikeigeka Gakkai Zasshi 58: 829–834
337. Terahara A, Niemierko A, Goitein M, Finkelstein D, Hug E, Liebsch N, O'Farrell D, Lyons S, Munzenrider J (1999) Analysis of the relationship between tumor dose inhomogeneity and local control in patients with skull base chordoma. Int J Radiat Oncol Biol Phys 45: 351–358
338. Tewfik HH, McGinnis WL, Nordstrom DG, Latourette HB (1977) Chordoma: evaluation of clinical behavior and treatment modalities. Int J Radiat Oncol Biol Phys 2: 959–962
339. Thodou E, Kontogeorgos G, Scheithauer BW, Lekka I, Tzanis S, Mariatos P, Laws ER Jr (2000) Intrasellar chordomas mimicking pituitary adenoma. J Neurosurg 92: 976–982
340. Toda H, Kondo A, Iwasaki K (1998) Neuroradiological characteristics of ecchordosis physaliphora. Case report and review of the literature. J Neurosurg 89: 830–834
341. Tomlinson FH, Scheithauer BW, Forsythe PA, Unni KK, Meyer FB (1992) Sarcomatous transformation in cranial chordoma. Neurosurgery 31: 13–18
342. Tsai EC, Santoreneos S, Rutka JT (2002) Tumors of the skull base in children: review of tumor types and management strategies. Neurosurg Focus 12: e1
343. Tuite GF, Veres R, Crockard HA (1996) Pediatric transoral surgery: indications, complications, and long-term outcome. J Neurosurg 84: 573–583
344. Ture U, Pamir MN (2002) Extreme lateral-transatlas approach for resection of the dens of the axis. J Neurosurg 96: 73–82
344a. Ture U, Pamir MN (2004) Small petrosal approach to the middle portion of the mediobasal temporal region: technical case report. Surg Neurol 61(1): 60–67
345. Tzortzidis F, Elahi F, Wright D, Natarajan SK, Sekhar LN (2006) Patient outcome at long-term follow-up after aggressive microsurgical resection of cranial base chordomas. Neurosurgery 59: 230–237; discussion 230–237
346. Tzortzidis F, Elahi F, Wright DC, Temkin N, Natarajan SK, Sekhar LN (2006) Patient outcome at long-term follow-up after aggressive microsurgical resection of cranial base chondrosarcomas. Neurosurgery 58: 1090–1098; discussion 1090–1098
347. Uggowitzer MM, Kugler C, Groell R, Lindbichler F, Radner H, Sutter B, Ranner G (1999) Drop metastases in a patient with a chondroid chordoma of the clivus. Neuroradiology 41: 504–507
348. Ulich TR, Mirra JM (1982) Ecchordosis physaliphora vertebralis. Clin Orthop Relat Res 163: 282–289

349. Unni KK (1996) Dahlin's bone tumors: general aspects and data on 11087 cases, 5 edn. Lippincot-Raven, Phhiladelphia, PA
350. Urie MM, Fullerton B, Tatsuzaki H, Birnbaum S, Suit HD, Convery K, Skates S, Goitein M (1992) A dose response analysis of injury to cranial nerves and/or nuclei following proton beam radiation therapy. Int J Radiat Oncol Biol Phys 23: 27–39
351. Utne JR, Pugh DG (1955) The roentgenologic aspects of chordoma. Am J Roentgenol Radium Ther Nucl Med 74: 593–608
352. Uttley D, Moore A, Archer DJ (1989) Surgical management of midline skull-base tumors: a new approach. J Neurosurg 71: 705–710
353. Valderrama E, Kahn LB, Lipper S, Marc J (1983) Chondroid chordoma. Electron-microscopic study of two cases. Am J Surg Pathol 7: 625–632
354. Van Loveren HR, Fernandez PM, Keller JT, Tew JM Jr, Shumrick K (1994) Neurosurgical applications of Le Fort I-type osteotomy. Clin Neurosurg 41: 425–443
355. Verma K, Murthy L, Kapila K (1986) Cytologic diagnosis of chordoma by fine needle aspiration. Indian J Pathol Microbiol 29: 189–191
356. Virchow RLK (1857) Untersuchungen über die Entwickelung des Schädelgrundes im gesunden und krankhaften Zustande, und über den Einfluss derselben auf Schädelform, Gesichtsbildung und Gehirnbau. G. Reimer, Berlin
357. Volpe NJ, Liebsch NJ, Munzenrider JE, Lessell S (1993) Neuro-ophthalmologic findings in chordoma and chondrosarcoma of the skull base. Am J Ophthalmol 115: 97–104
358. Volpe R, Mazabraud A (1983) A clinicopathologic review of 25 cases of chordoma (a pleomorphic and metastasizing neoplasm). Am J Surg Pathol 7: 161–170
359. Vougioukas VI, Hubbe U, Schipper J, Spetzger U (2003) Navigated transoral approach to the cranial base and the craniocervical junction: technical note. Neurosurgery 52: 247–250; discussion 251
360. Walaas L, Kindblom LG (1991) Fine-needle aspiration biopsy in the preoperative diagnosis of chordoma: a study of 17 cases with application of electron microscopic, histochemical, and immunocytochemical examination. Hum Pathol 22: 22–28
361. Watanabe A, Yanagita M, Ishii R, Shirabe T (1994) Magnetic resonance imaging of ecchordosis physaliphora – case report. Neurol Med Chir (Tokyo) 34: 448–450
361a. Watkins L, Khudados ES, Kaleoglu M, et al. (1993) Skull base chordomas: a review of 38 patients, 1958–1988. Br J Neurosurg 7: 241–248
362. Weber AL, Liebsch NJ, Sanchez R, Sweriduk ST Jr (1994) Chordomas of the skull base. Radiologic and clinical evaluation. Neuroimaging Clin N Am 4: 515–527
363. Weber DC, Rutz HP, Pedroni ES, Bolsi A, Timmermann B, Verwey J, Lomax AJ, Goitein G (2005) Results of spot-scanning proton radiation therapy for chordoma and chondrosarcoma of the skull base: the Paul Scherrer Institut experience. Int J Radiat Oncol Biol Phys 63: 401–409
364. Weinberger P, Yu Z, Kowalski D, Joe J, Manger P, Psyrri A, Sasaki C (2005) Differential expression of epidermal growth factor receptor, c-Met, and HER2/neu in chordoma compared with 17 other malignancies. Arch Otolaryngol Head Neck Surg 131: 707–711
365. Wojno KJ, Hruban RH, Garin-Chesa P, Huvos AG (1992) Chondroid chordomas and low-grade chondrosarcomas of the craniospinal axis. An immunohistochemical analysis of 17 cases. Am J Surg Pathol 16: 1144–1152

366. Wold LE, Laws ER Jr (1983) Cranial chordomas in children and young adults. J Neurosurg 59: 1043–1047
367. Wolfe JT 3rd, Scheithauer BW (1987) "Intradural chordoma" or "giant ecchordosis physaliphora"? Report of two cases. Clin Neuropathol 6: 98–103
368. Wyatt RB, Schochet SS Jr, McCormick WF (1971) Ecchordosis physaliphora. An electron microscopic study. J Neurosurg 34: 672–677
369. Yamada T, Placzek M, Tanaka H, Dodd J, Jessell TM (1991) Control of cell pattern in the developing nervous system: polarizing activity of the floor plate and notochord. Cell 64: 635–647
370. Yamaguchi T, Yamato M, Saotome K (2002) First histologically confirmed case of a classic chordoma arising in a precursor benign notochordal lesion: differential diagnosis of benign and malignant notochordal lesions. Skeletal Radiol 31: 413–418
371. Yamaguchi T, Suzuki S, Ishiiwa H, Shimizu K, Ueda Y (2004) 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 28: 756–761
372. Yamaguchi T, Suzuki S, Ishiiwa H, Ueda Y (2004) Intraosseous benign notochordal cell tumours: overlooked precursors of classic chordomas? Histopathology 44: 597–602
373. Yamaguchi T, Watanabe-Ishiiwa H, Suzuki S, Igarashi Y, Ueda Y (2005) Incipient chordoma: a report of two cases of early-stage chordoma arising from benign notochordal cell tumors. Mod Pathol 18: 1005–1010
374. Yang XR, Beerman M, Bergen AW, Parry DM, Sheridan E, Liebsch NJ, Kelley MJ, Chanock S, Goldstein AM (2005) Corroboration of a familial chordoma locus on chromosome 7q and evidence of genetic heterogeneity using single nucleotide polymorphisms (SNPs). Int J Cancer 116: 487–491
375. Yasargil MG (1996) Microneurosurgery. Thieme Verlag, Stuttgart, NewYork
376. Zenker FA (1857) Ueber die gallertgeschwülste des Clivus Blumenbachii (Ecchondrosis prolifera, Virchow). Virch Arch 12: 108–110
377. Zhou L, Guo H, Li S, Ji Y, Huang F (1995) An extensive subfrontal approach to the lesions involving the skull base. Chin Med J (Engl) 108: 407–412
378. Zorlu F, Gurkaynak M, Yildiz F, Oge K, Atahan IL (2000) Conventional external radiotherapy in the management of clivus chordomas with overt residual disease. Neurol Sci 21: 203–207
379. Zülch KJ, Christensen E (1956) Pathologische Anatomie der raumbeengenden intrakraniellen Prozesse. Springer, Berlin, Heidelberg New York