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Chordoma and Chondrosarcoma – Skull Base

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This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 101008548

Chordoma

Rare cancer that accounts for 1–4% of all bone malignancies (annual incidence of 0.1/100.000)

The median age at diagnosis ranges between 44 and 61 years

Typically considered low-grade, but locally invasive malignancy

Almost equal distribution in the skull base, mobile spine, and sacrum

The effect of the disease is more a function of its local aggressiveness than its potential to metastasize

Small number of familial cases of chordoma have been reported

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Chordoma

- Conventional chordoma (classic chordoma, most cases)
- Chondroid chordoma
- Dedifferentiated chordoma (highly undifferentiated cells or cells resembling osteosarcoma)

Brachyury: diagnostic hallmark for chordoma helpful for distinction of chordoma from from histological entities with similar morphological or immunophenotypic features

Dedifferentiated chordomas lose expression of brachyury, cytokeratin and other markers

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Chondrosarcoma

20% of primary bone malignancies (annual incidence of 1/200.000)

Group of heterogeneous, generally slow-growing, primary malignant tumors of bone arising from the chondrocytes or their precursor cells involved in the endochondral ossification

Primary intracranial chondrosarcomas are rare: 0.15% of tumors of the skull base

In the skull base, chondrosarcomas usually involve temporo occipital junction, parasellar area and spheno-ethmoid complex

De novo or in a pre-existing enchondroma (in Ollier disease or Maffucci syndrome; secondary central tumors) and osteochondroma (secondary peripheral tumors)

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Chondrosarcoma

Three histological classes:

- grade I (well differentiated, 90%)
- grade II (moderately differentiated)
- grade III (poorly differentiated)

The vast majority of cranial tumors are low to intermediate grade with indolent growth and low metastatic potential

CHSs stain positive for S-100 and vimentin, but fail to express epithelial markers such as cytokeratin and epithelial membrane antigen

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Skull base chordoma and chondrosarcoma: clinical presentation

Usually present with nonspecific and sometimes confusing symptoms

Often diagnosed at the development of symptoms caused by the presence of larger tumors

The initial presentation depends on the location, extension, and proximity of the lesion to critical structures

- Headache
- Neuro-ophthalmological signs (double vision, loss of vision, ptosis, visual field defects)
- Hearing loss, vertigo
- Dysphonia, dysphagia
- Hypopituitarism
- Larger tumors may also compress the brainstem and cerebellum, causing gait disturbances, ataxia, dysmetria, and motor weakness

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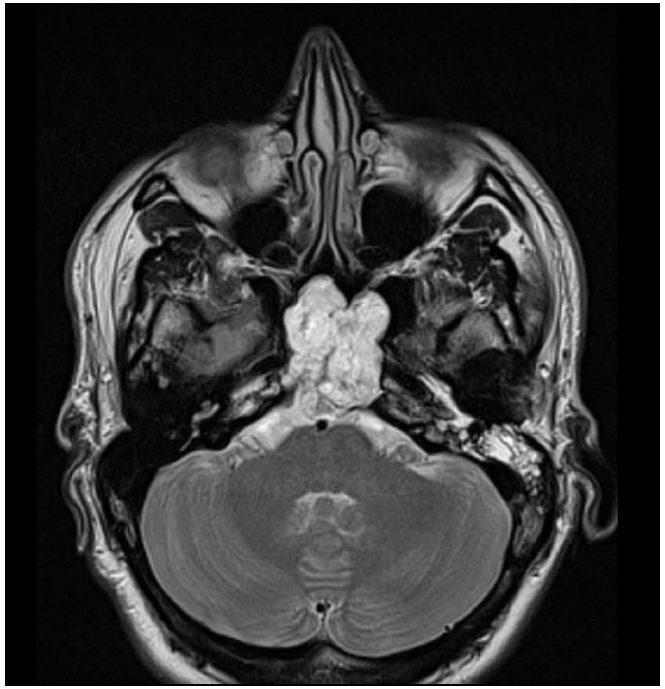
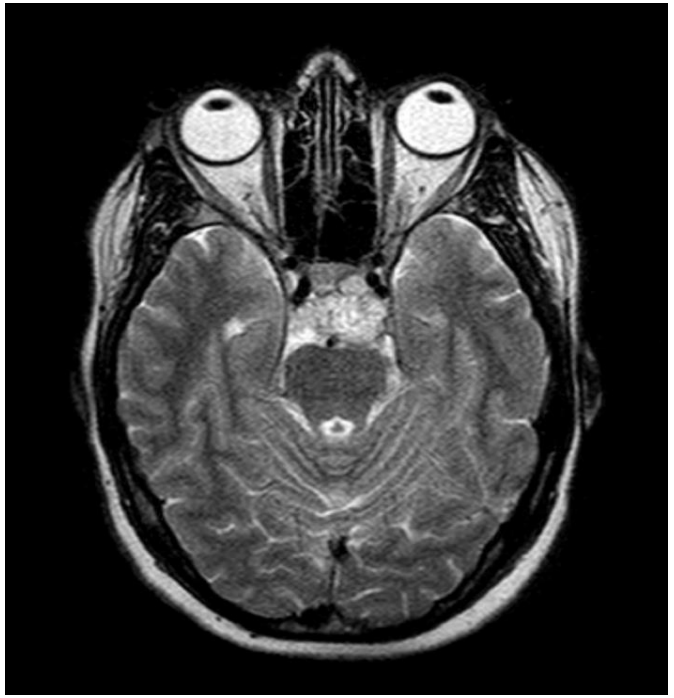
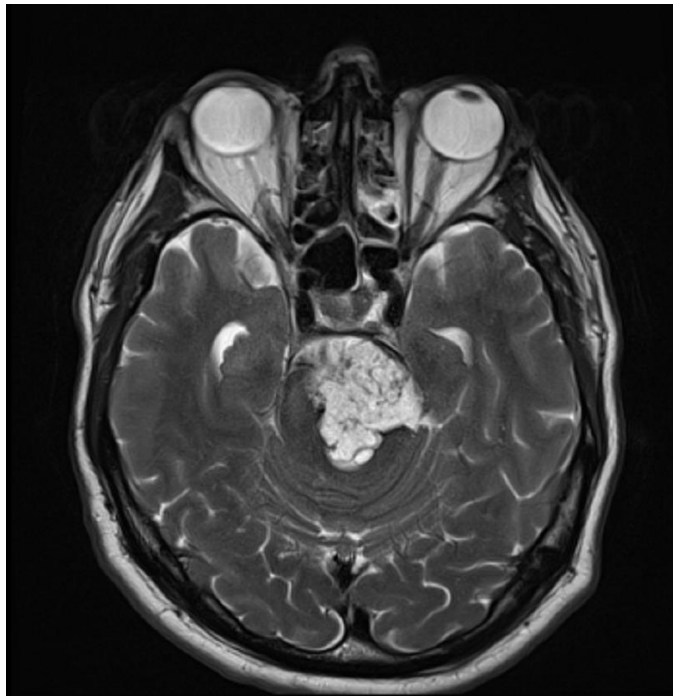
Chordoma

- Osteolytic, destructive lesions with associated cortical destruction and soft tissue extension
- Axial T2-weighted hyperintense signal
- Low-moderate gadolinium contrast enhancement
- Centrally located in the clivus, predominantly along the midline







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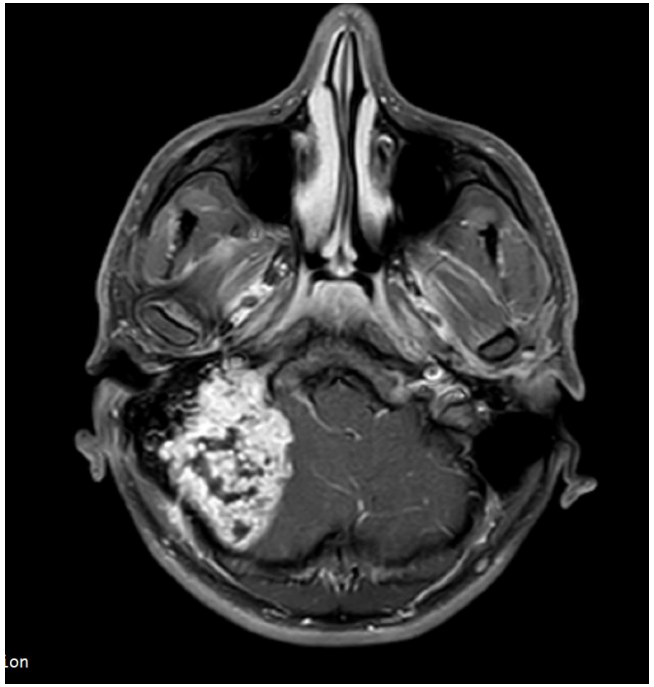
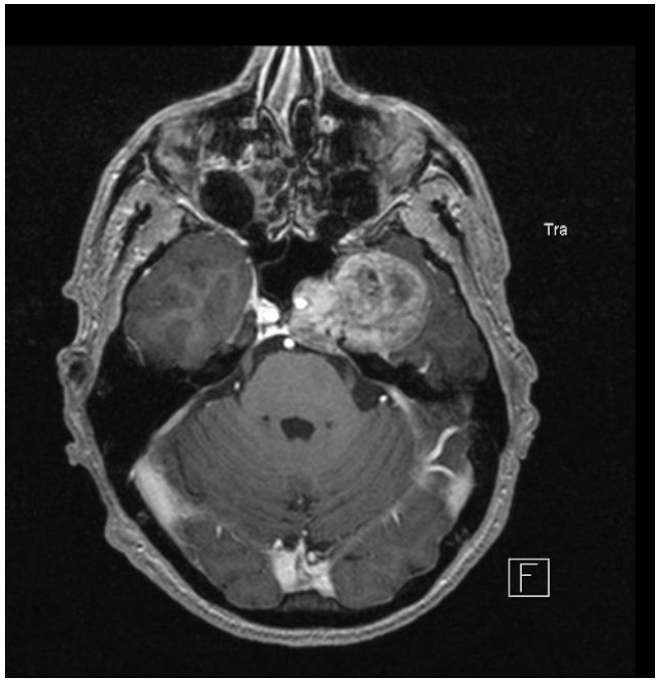
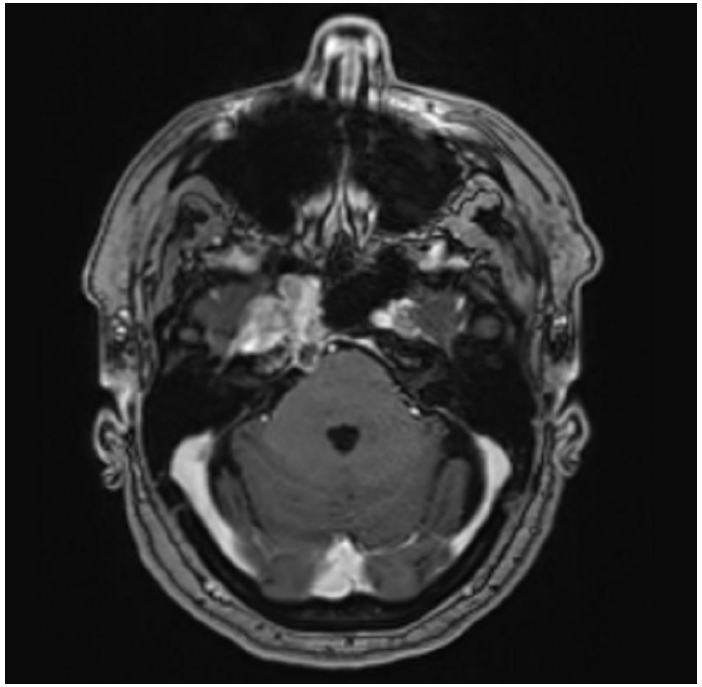
Chondrosarcoma

- High signal intensity on T2-weighted MRI
- Usually a marked degree of heterogenous enhancement with gadolinium contrast
- Apparent diffusion coefficient values higher than chordoma
- Tending to arise laterally







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Skull base chordoma and chondrosacoma: surgery

En-bloc R0 resection is the recommended treatment, however R0 resection can rarely be done in the skull base

Surgery should aim towards maximum tumor resection combined with preservation of neurological function and quality of life optimizing target geometry for postoperative RT: maximal safe resection

Endoscopic endonasal approaches can provide a powerful means for tumor removal (midline tumors)

Lateral approaches (eg, transpetrous, far lateral) are necessary for substantial lateral extensions

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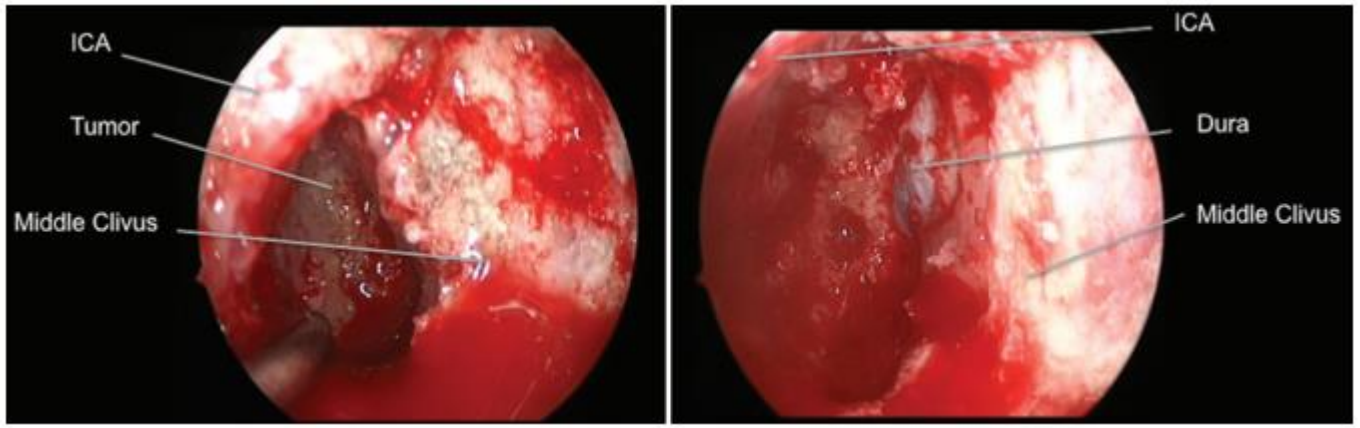
Skull base chordoma and chondrosacoma: surgery

Endoscopic endonasal approaches:

- exploit a natural corridor (direct approach)
- reducing surgical morbidity by avoiding any manipulation of neural and vascular structures
- possibilities to alleviate particularly disturbing symptoms (es diplopia)



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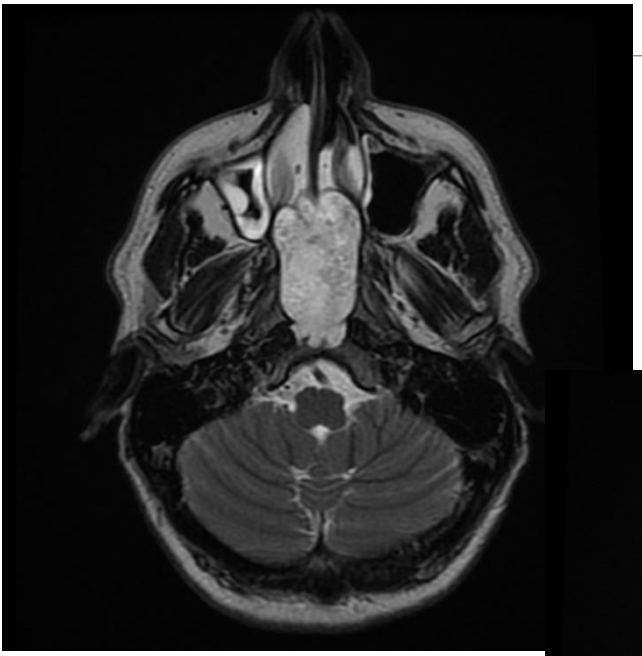
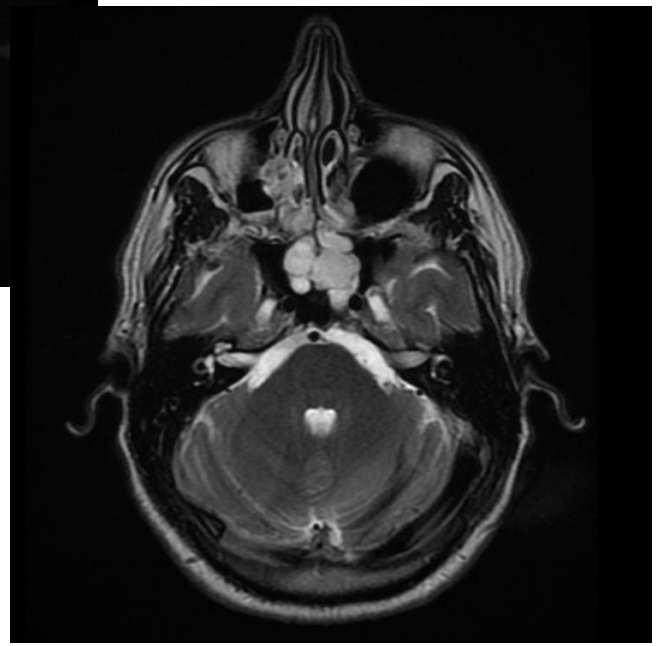
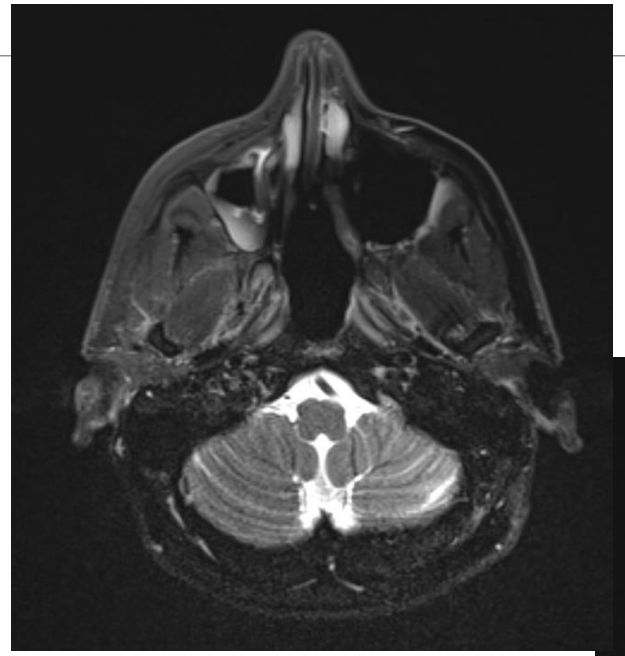
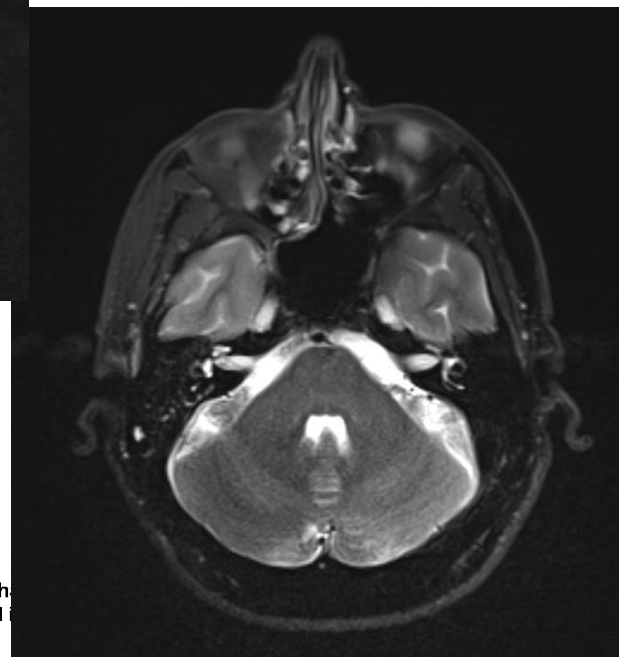
Skull base chordoma and chondrosacoma: surgery





Complete resection





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Skull base chordoma and chondrosacoma: surgery

Despite their extradural origin, clival chordomas and chondrosarcomas can often have dural or subdural invasion in over 50% of patients, with the resultant risk of a postoperative cerebrospinal fluid (CSF) leak.

Other surgical complications include:

- Meningitis
- Cranial nerve palsy
- Hearing loss
- Visual decline
- Consequences of vascular injury

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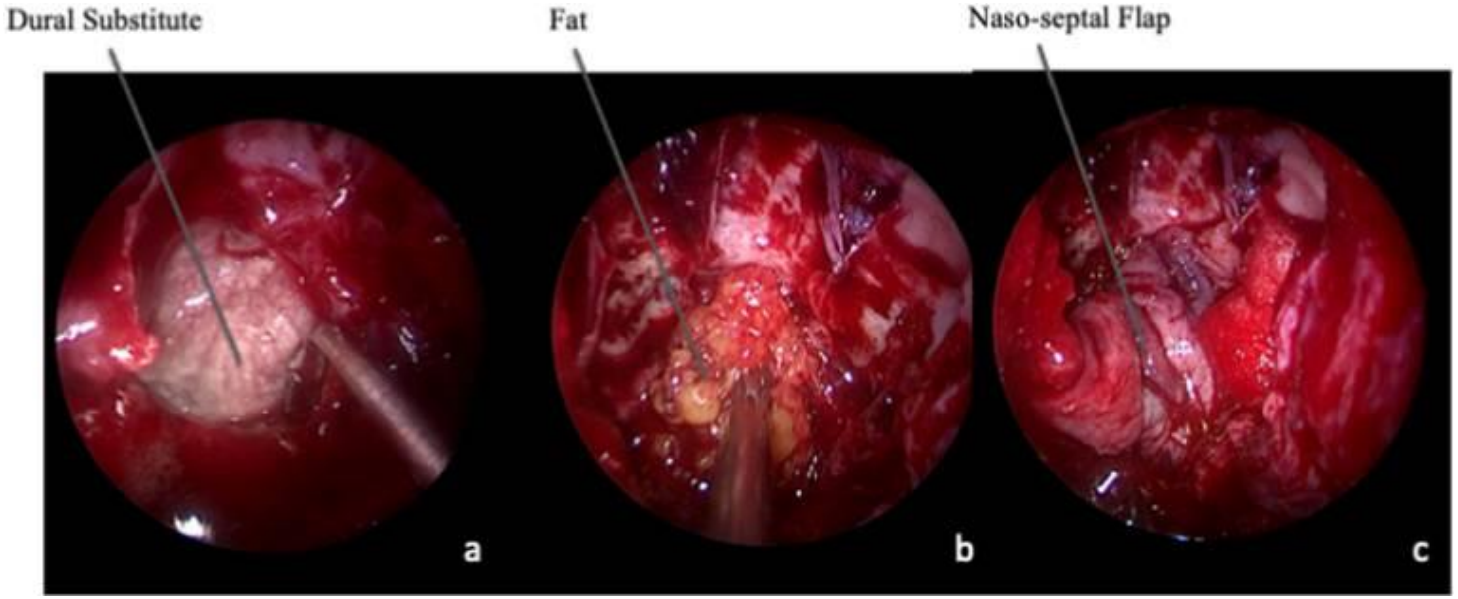
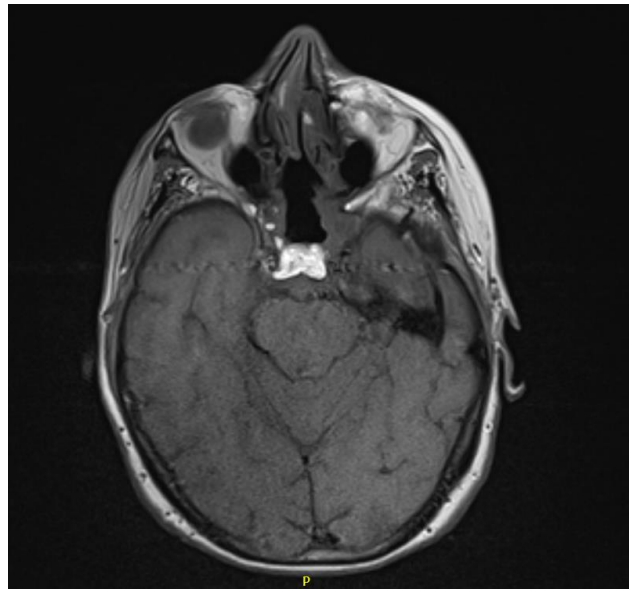
Skull base chordoma and chondrosacoma: surgery

Typically, modern reconstruction is multilayered, consisting of a combination of synthetic graft materials, autologous adipose, and fascia lata tissue as well as coverage with a pedicled flap obtained from the septum or by rhinopharynx for lower clivus tumors





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Skull base chordoma and chodrosarcoma: radiotherapy

Chordomas and chondrosarcomas are relatively radioresistant and respond best to high radiation doses above 70 Gy.

The required doses to control the disease significantly exceed the dose constraints for critical organs

This presents a challenge when using conventional RT because of the close proximity to dose-limiting neural structures (ie, brainstem, spinal cord and optic structures).

Particle beam therapy including proton therapy (PT) and carbon ion therapy (CIRT), is usually administered to these challenging patients because these radiation modalities can deliver high-dose radiation, while sparing organs at risk (OARs) next to the target volume

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Skull base chordoma and chodrosarcoma: radiotherapy

Usually, in particle centers:

- patients were positioned and immobilized using a thermoplastic mask
- CT performed with 1-2 mm slice thickness, based on institutional practice, without contrast media
- MRI obtained with contrast media in the treatment position (T2-weighted and contrast-enhanced T1-weighted MRI).

The contouring of GTV and OAR was performed on CT-MRI correlation

- GTV – residual macroscopic disease
- CTV HD
- CTV LD – risk for microscopic disease including preoperative extension

Protons: 1.8-2 GyRBE/fraction
Chordoma: CTV HD: 74 – 78
Chondrosarcoma: CTV HD 68-72 GyRBE

Carbon ions: 3-4.4 GyRBE/fraction
CTV HD: 66-70.4 GyRBE

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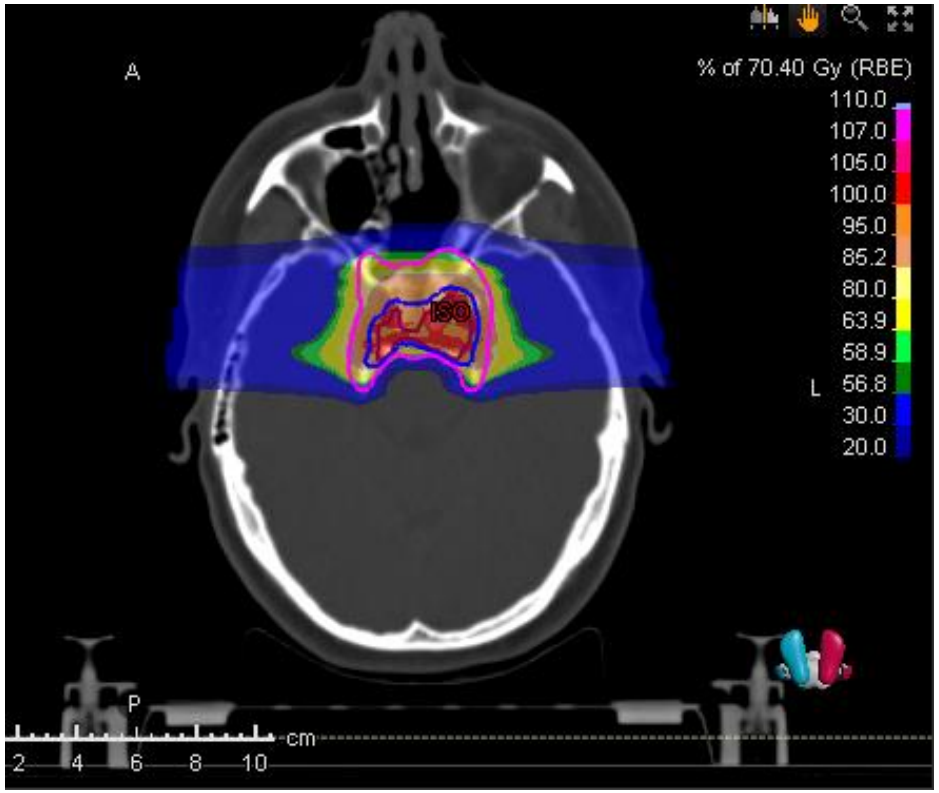
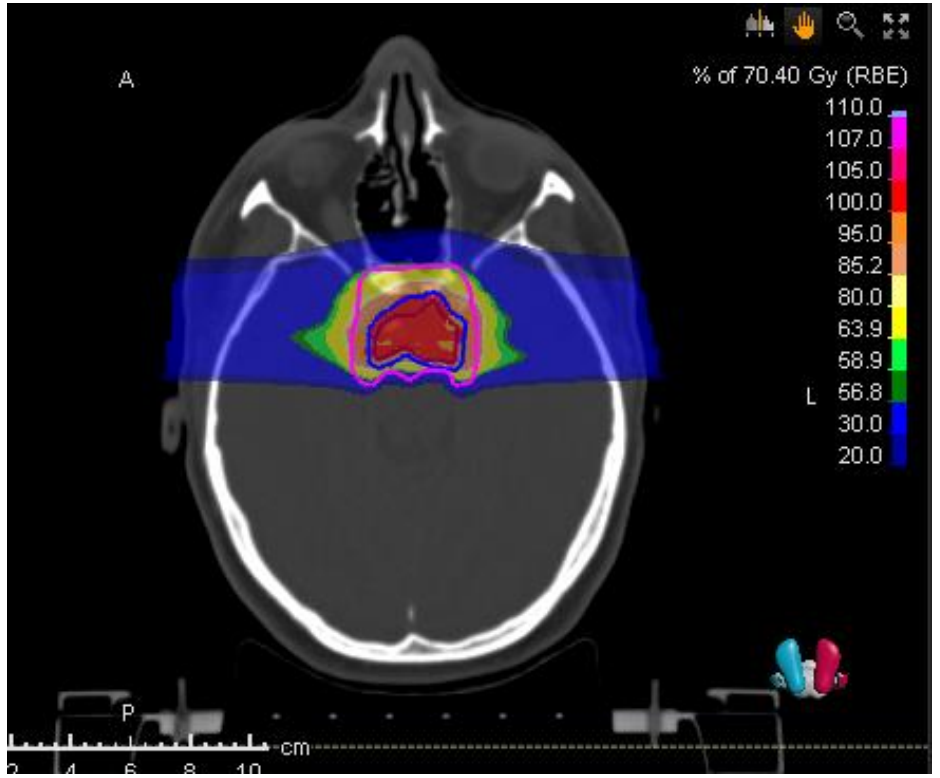
Skull base chordoma and chodrosarcoma: radiotherapy





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Chordoma – prognostic factors

Worse local control in case of:

- Larger Gross Tumor Volume (= residual macroscopic disease after surgery)

LBL (Berson et al, 1988):< 20cc vs. <35 vs. > 35 cc (80% vs. 33%) p=signif.

LLUMC (Hug et al, 1999): ≤ 25 ml vs. > 25 ml (100% vs. 56%) p=signif.

MGH (Munzenrider et al, 1999) < 70 ml vs. > 70 ml (disease-free survival) p=signif

CPO (Noel et al, 2003): < 29ml vs. > 29ml p=signif

PSI (Weber et al, 2016): ≤ 25 ml vs. > 25 ml (86% vs 65%) p=signif.

GSI/HIT (Uhl et al 2014): < 75ml (PTV2) vs. > 75 ml (84% vs 54%) p=signif

CNAO (Iannalfi et al 2020): ≤ 10.4 cm3 vs > 10.4 cm3 (94% vs 71%) p=signif (PT)

CNAO (Iannalfi et al 2020): ≤ 23.1 cm3 vs > 23.1 cm3 (81% vs 56%) p=signif (CIRT)

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Chordoma – prognostic factors

Worse local control in case of:

- Brainstem and Optic pathways involvement

(Hug et al, 1999; Munzenrider et al 1999; Weber et al, 2016; Iannalfi et al, 2020)

- RT dose target coverage: under coverage and inhomogeneity to the target

(Terahara et al, 1999; Noel et al, 2005; McDonald et al, 2016; Iannalfi et al, 2020)

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Study (Istitution)	Radiation Type	RT Total Dose (TD) (range) , Dpf : Dose per fractions ; (GyRBE)	No. of patients	Follow-up Months (median)	GTV	LC (%)	OS (%)
Munzenrider, 1999 (HCL-MGH, Boston, USA)	Photon+ Proton	TD: median 66-83 Dpf : 1,8-1,92	169	41	NR	5-y: 73 10-y: 54	5-y: 80 10-y: 54
Noel, 2005; (CPO; Orsay, France)	Photon+ Proton	TD: 67 median (60–71, range) ;Dpf: 1.8-2	100 (1993–2002)	31	23 cm3 (median)	4-y: 53	4-y: 90
Mizoe, 2009 (NIRS, Chiba, Japan)	Carbon Ions	TD: 48-60,8 ; Dpf : 3-3.8	33 (1995-2007)	53 (mean)	NR	5-y: 85 10-y: 64	5-y: 88 10-y: 67
Uhl, 2014 (GSI, Darmstadt, Germany)	Carbon Ions	TD: 60 median (54-70) Dpf : 3	155	72	NR	3-y: 82 5-y: 72	3-y: 95 5-y: 85
Weber, 2016 (PSI, Villigen, Switzerland)	Proton	TD: 74 (72.5 ± 2.2) Dpf: 1,8-2	151	50	35.4 cm3 (mean)	5-y: 75,8 7-y: 70.9	7-y: 72.9
Fung , 2018 (CPO; Orsay, France)	Photon+ Proton	TD levels: 68.4 -> 73.8 Dpf : 1.8	106 (2006-2012)	61	25 cm3 (mean)	4-y: 78,3 5-y: 75,1	4-y: 90.2 5-y: 88.3
Koto, 2020 (NIRS, Chiba, Japan)	Carbon Ions	TD: 60.8 ; Dpf : 3.8	34 (2002-2016)	108	18.7 (median)	5-y: 76.9 9-y: 69.2	5-y: 76.9 9-y: 69.2
Iannalfi , 2020 (CNAO, Pavia, Italy)	Proton or Carbon ions	P- TD: 74 median Dpf: 2 C - TD: 70,4, Dpf: 4,4	P: 70 ; C: 65	49	P: 3.5 cm3 (median) C: 12.9 cm3 (median)	P: 3-y: 89 5-y: 84 C: 3-y: 77 5-y 71	P: 3-y: 93 5-y: 83 C: 3-y: 90 5-y: 82
Mattke , 2023 (HIT, Heidlberg, Germany)	Proton or Carbon ions	P - TD: 74 median Dpf: 2 C - TD: 66 Gy; median Dpf: 3	P: 36 C: 111	49.3		P : 3-y: 79,8 5-y: 60,7 C: 3-y: 80.4 5-y : 64.5	P: 3-y: 91.7 5-y: 91.7 C: 3-y: 91.2 5-y : 83.3
Tubin, 2023 (MedAustron, W. Neustadt, Austria)	Proton or Carbon ions	P - TD: 74-78 Dpf: 2 C - TD: 66 Gy Dpf: 3	44	34.4	28.1 cm3 (median)	3-y: 90	3-y: 93

Study Year	Particle	Number of patients	Prescription dose (GyRBE)	Median time of follow-up (months)	LC rate	Late Toxicity
Hug 1999 (Loma Linda, USA)	Protons	25	70.2* (median)	33.2*	3y LC: 94%	7% (G3-G4)
Munzenrider 1999 (HCL-MGH, Boston, USA)	Protons	229	72* (mean)	41*	5y LC: 98%	-
Ares 2009 (PSI, Villigen, Switzerland)	Protons	22	68.4 (median)	34 *	5y LC: 94%	6.2%
Fuji 2011 (Shizuoka Cancer Center, Nagaizumi, Shizuoka)	Protons	8	63* (median)	42*	3y LC: 86%	No G ≥3
Weber 2016 (PSI, Villigen, Switzerland)	Protons	71	72.5* (median)	50 *	5y LC: 93.6%	8.1 % (G3-G4)
Mattke 2018 (HIT, Heidlberg, Germany)	Protons Carbon ions	22 79	70 (median) 60 (median)	30.7 43.7	4y LC: 100% 4y LC: 90.5%	No G ≥3
Holtzman 2019 (Jacksonville, USA)	Protons	43	73.8 (median)	44	4y LC: 89%	4.6 % (G3) + 9% G3 expected hear loss
Riva 2021 (CNAO, Pavia, Italy)	Protons Carbon ions	32 16	70 70.4	31 66	3y LC: 100% 3y LC	8% (G3) No G4-G5

Skull base chordoma and chodrosarcoma: radiotherapy

Acute toxicity: headache, loss of appetite, mucositis, fatigue, nausea, vomiting, and alopecia

Late toxicity:

- cranial nerve injuries
- visual deficits and rare cases of blindness
- pituitary insufficiency
- brain necrosis
- hearing loss

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Skull base chordoma and chodrosarcoma: radiotherapy and TLN

Temporal lobe necrosis (TLN) is one of the most dreaded late adverse events in high-dose PT and CIRT therapy for chordoma and chondrosarcoma of the skull base

TLN is histologically defined as cellulosic vascular necrosis and with persistent inflammation

There are currently three accepted hypotheses for the occurrence and development of:

- vascular injury
- glial cell and white matter injury
- inflammatory response and abnormal cytokine expression

TLN usually occurs half a year to a year after radiotherapy (up to 20% of cases)

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Skull base chordoma and chodrosarcoma: radiotherapy and TLN

TLN clinical presentation is often difficult to ascertain because of its vague and nonspecific presentation.

Majority of patients with TLN were asymptomatic even at late stage

Clinical symptoms of other patients:

- seizure
- cognitive decline
- change in consciousness
- memory impairment

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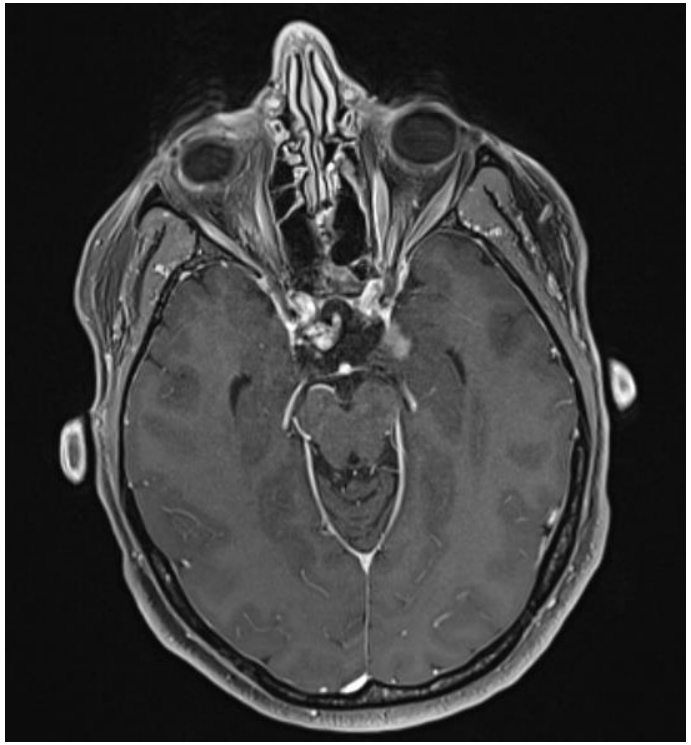
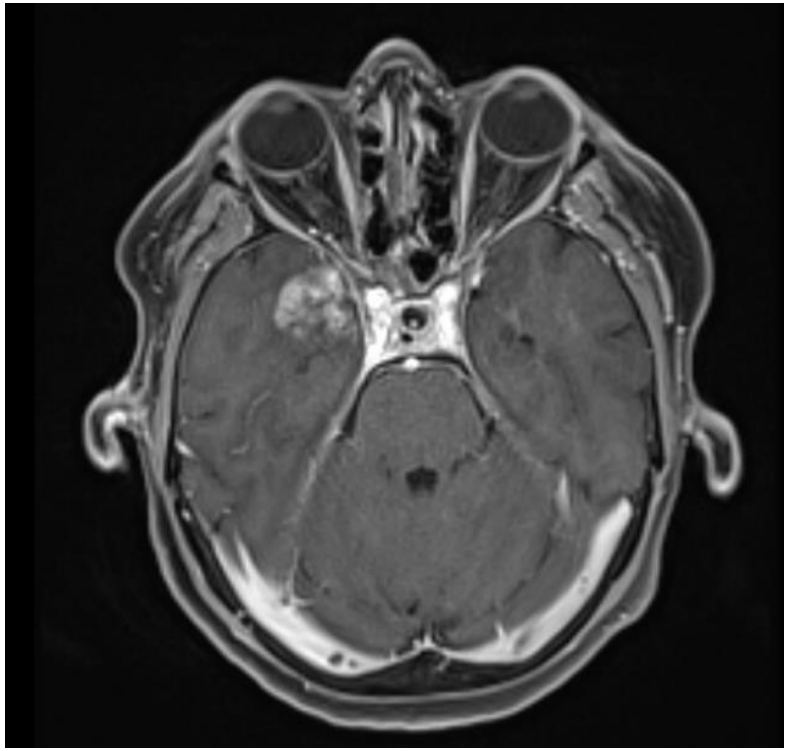
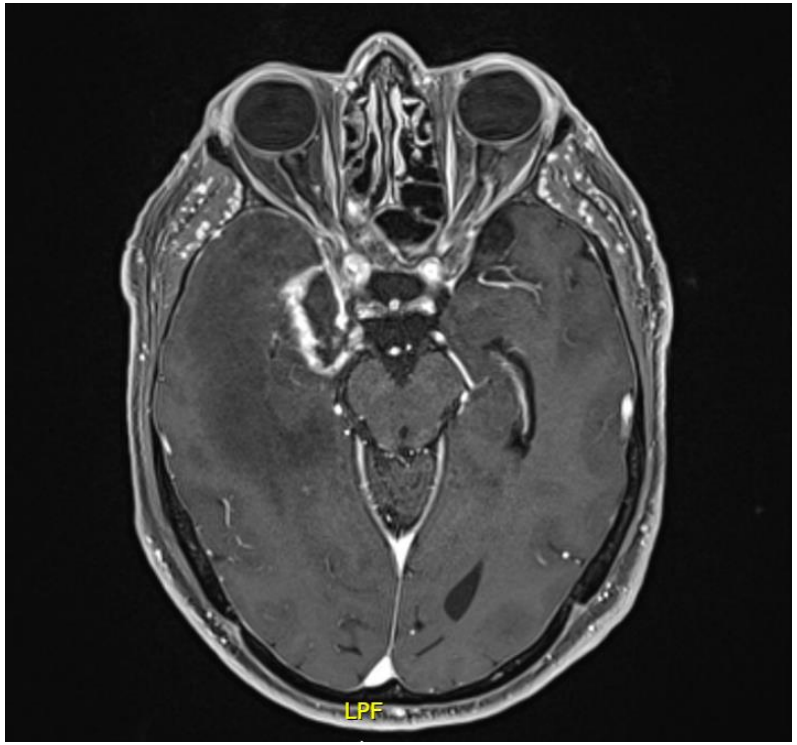
Skull base chordoma and chodrosarcoma: radiotherapy and TLN







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Skull base chordoma and chodrosarcoma: radiotherapy and TLN

For small and asymptomatic TLN, an observational wait strategy can be adopted

For symptomatic brain necrosis can be used:

- steroids (decrease cytokines and inflammatory reaction)
- anticoagulants.
- bevacizumab (monoclonal antibody that blocks VEGF, introduced recently, with the understanding of the pathophysiology of TLN)
- surgery (usually reserved as the last resort in patients with significant increase in intracranial pressure or in those with progressive neurological deficits despite steroids or other medical therapy)

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Skull base chordoma and chodrosarcoma: systemic therapy

Traditionally, chordomas and chondrosarcomas are not sensitive to chemotherapy

Chordoma:

- some studies have demonstrated that imatinib, erlonitib, cetuximab and gefitinib have a beneficial effect on the treatment of advanced or metastatic chordomas
- studies immunotherapy are currently underway

Chondrosarcoma:

- resistant to cytotoxic chemotherapy
- novel approaches employing antiangiogenics, including pazopanib, have a role in the management of unresectable or metastatic conventional chondrosarcoma
- IDH1 inhibition may serve as an alternative treatment option in IDH-mutant, conventional chondrosaroma
- limited benefit to doxorubicin-based chemotherapy particularly in dedifferentiated chondrosarcoma

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