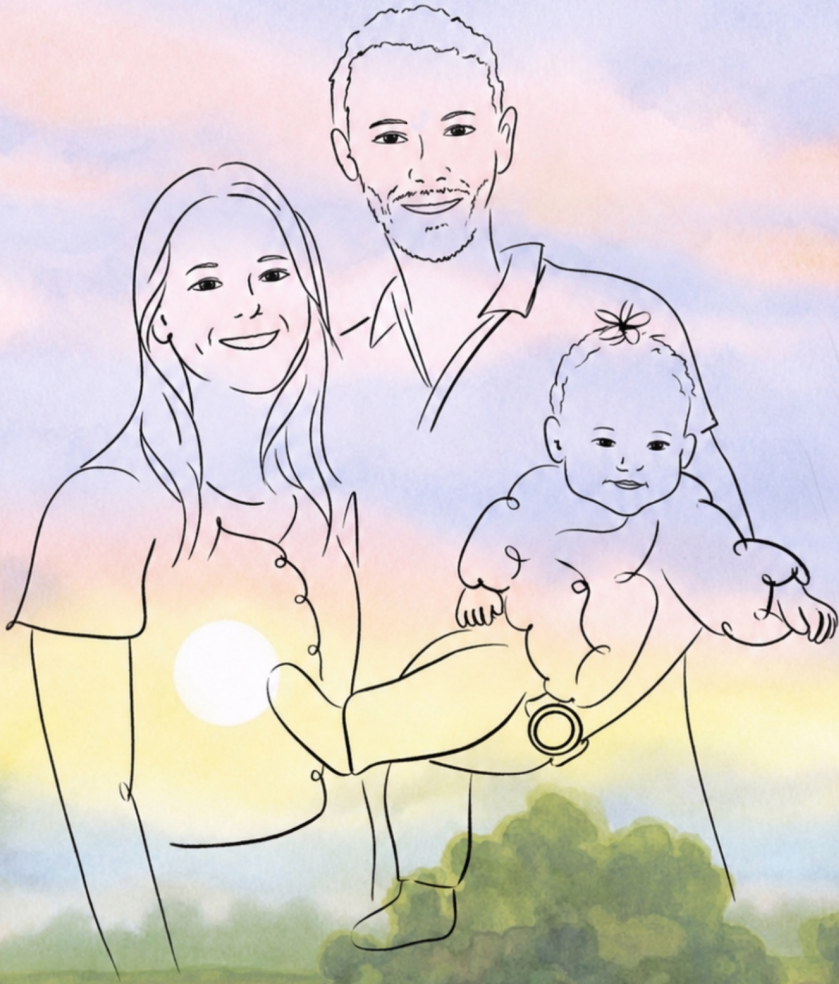


SURGICAL AND RADIOTHERAPEUTIC NUANCES IN SKULL BASE TUMORS



Max Keizer

Surgical and Radiotherapeutic Nuances in Skull Base Tumors

Maxim Edgar Keizer

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ISBN: 978-94-6534-475-1

Cover design: Valérie Schuermans

Production: ProefschriftMaken

The research described in this thesis was conducted at the department of neurosurgery of the Maastricht University Medical Center + and the Mental Health and Neuroscience Research Institute of the University of Maastricht, located in Maastricht, The Netherlands.

Surgical and Radiotherapeutic Nuances in Skull Base Tumors

PROEFSCHRIFT

Voor het behalen van de graad van Doctor aan de Universiteit Maastricht, onder gezag van Rector Magnificus, prof. dr. Jan Smits, overeenkomstig met het besluit van het College van Decanen, te verdedigen in het openbaar op dinsdag 23 juni 2026 om 13:00 uur.

door

Maxim Edgar Keizer

Promotor

Prof. dr. Y. Temel, Maastricht University, Maastricht, The Netherlands

Copromotoren

Prof. dr. H.P.M. Kunst, Maastricht University, Maastricht, The Netherlands

Dr. K.E. Hovinga, Maastricht University, Maastricht, The Netherlands

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Dit proefschrift draag ik op aan alle patiënten, nu en in de toekomst, zonder wie wetenschappelijk onderzoek niet zou kunnen plaatsvinden. Mijn dank en diepe respect voor uw inzet naast alle behandelingen en uitlagen die reeds al z'n grote impact op uw leven hebben.

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1

Introduction

INTRODUCTION

BACKGROUND

The skull base represents the osseous border between the neurocranium and viscerocranium. It consists of several bones which are connected by sutures. Numerous foramen and fissures provide passage for critical vessels and nerves between the brain and the rest of body. This entity is a complex anatomical 3D structure which may host countless different pathologies, possibly endangering these critical neurovascular structures. This leads to symptoms such as vision loss, double vision, loss of smell, facial paralysis or numbness. Treatment of skull base tumors is done by neurosurgeons, otorhinolaryngologists, neurologists, radiation oncologists, medical oncologists and ophthalmologists, often in multimodal paradigms. This thesis addresses the advancements of treating skull base tumors, more specifically chordoma, vestibular schwannoma, chondrosarcoma and sinonasal carcinomas. Additionally, the shift in treatment philosophy which has gone from aggressive, complete resections to functional preservation and partial resection is delineated. The introduction starts with explaining the different pathologies discussed in the chapters and in-depth information on the evolution of skull base tumor treatment. Then, the individual chapters will be briefly introduced, concluding with the aim of this thesis.

TUMORS OF THE SKULL BASE

Tumors of the skull base may arise from the meninges, cranial nerve sheath, bone, skull synchondrosis, sinus epithelium or, as a metastasis from a distant malignancy. This thesis focuses on four types of tumors: Vestibular schwannoma, Chordoma, Chondrosarcoma and Sinonasal carcinoma. Hereafter, a detailed description of each tumor is provided.

Vestibular schwannoma

Schwannomas are benign tumors arising from Schwann cells of the nerve sheaths and account for 8% of all intracranial neoplasms(1). Vestibular schwannoma is the most common, it originates from the vestibular nerve and has an incidence of 1 per 100,000 persons per year(2). The vestibular nerve is part of the eighth cranial nerve and is divided into an inferior and superior portion. Over 90% of vestibular schwannoma arise from the inferior vestibular nerve(3). Four percent of vestibular schwannoma present bilateral, which is highly associated with neurofibromatosis type 2(4). The vestibular nerve is responsible for balance and motion signal transfer between the labyrinth and

the brain stem(5). Consequently, vertigo and balance disorders are common presenting symptoms(6). However, the majority of patients (86%) present with progressive, unilateral hearing loss(6).

The Koos grading system is a commonly used tool to differentiate vestibular schwannoma based on their size and location, see figure 1(7). Grade 1 tumors are purely intracanalicular. Grade 2 extent into the cerebellopontine angle but do not reach the brain stem. Grade 3 touch the brainstem but do not displace it. Grade 4 are the largest and compress and displace the brainstem and cranial nerves, sometimes occluding the fourth ventricle.

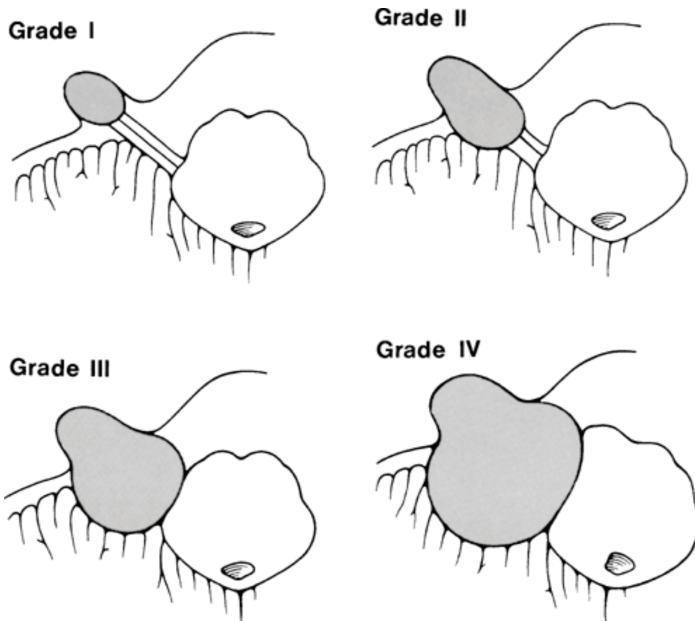


Figure 1: Koos grading system for vestibular schwannomas

Treatment paradigms consist of wait and scan policy, radiotherapy, surgical resection or multimodal therapies. The natural course of vestibular schwannoma has been extensively documented; however, it demonstrates variable growth behavior. Some tumors show continuous growth; others grow then stabilize or even shrink. Furthermore, symptom progression is not always linked to tumor growth. Two-thirds of incidental vestibular schwannomas do not grow during a 5-year follow-up. This makes patient counseling challenging. Additionally, tumor management is a heavily debated subject with varying opinions regarding treatment goals, focusing on tumor control and symptom outcome. Some surgeons advocate hearing sparing operations

in small intracanalicular schwannomas. Series demonstrate serviceable hearing rates after surgery between 63% and 88%. However, this does expose the patient to complications and treatment morbidity. Common surgical corridors are the middle fossa, translabyrinthine and retrosigmoid approach. The choice depends on the surgeon's preference, location and size of the tumor and the availability of an ENT surgeon. Radiotherapy has been increasingly applied over the last decades, even in large Koos 4 schwannoma, demonstrating excellent tumor control rates. However, treatment complications have been described: increased hearing deterioration, facial palsy or spasm and radiation necrosis. The development of a hybrid construction, which combines a partial resection followed by stereotactic radiotherapy has demonstrated excellent tumor control rates with limited therapeutic complications. However, the optimal timing of post-operative radiotherapy remains unknown. Chapter 2 further explores this multimodal treatment.

Chordoma

Chordoma is formed by remnants of the embryonic notochord. It is a pre-dominantly low grade, malignant, locally invasive tumor. Chordoma, together with chondrosarcoma is a primary osseous tumor of the axial skeleton. It may present in each spinal segment but shows a preference for the clivus and sacrum with a respective proportion of 41% and 31%(8). Patients typically present with cranial nerve deficits, headaches or diplopia. Diagnostic work-up includes a CT-scan and MRI-scan to differentiate chordoma from other osseous entities such as a benign notochordal cell tumor (BNCT) which does not require treatment. Lesions may not always present with characteristic radiological features; in such lesions a biopsy may be considered to confirm the diagnosis. Brachyury is a transcription factor protein which is normally only active during notochordal development. In chordoma this protein is re-activated and is a definitive tool for diagnosis, and a possible target for systemic therapies. In chapter 6 of this dissertation, we present a rare case of a spontaneously shrinking off mid-line chordoma.

Median overall survival is 102 months, but varies significantly by location, with skull base lesions demonstrating greater overall survival (median 162 months) relative to mobile spine lesions (95 months) and sacral lesions (87 months). For skull base lesions, overall survival is 65% and 32% at 5 and 10 years, respectively; disease-specific survival at the same time points are 73% and 42%(9). For lesions of the mobile spine, overall survival and disease-specific survival are 80.5% and 89.0% at 3 years, 68.4% and 80.9% at 5 years, and 39.2% and 60.1% at 10 years, respectively(10). Five-year overall survival is 60% for patients with sacral lesions(11). Several factors influence the risk of progression free- and overall survival: the most important factor is a

radical resection with free margins, followed by age at presentation and the extent of the tumor(12). Particularly in skull base lesions a radical resection is often not possible due to the involvement of critical neurovascular structures. Still, surgical resection is the main treatment for skull base chordoma. The goal is to achieve maximum resection, while preserving neurological function, sometimes in multiple stages. Adjuvant radiotherapy is increasingly applied the last decades(13). Even though chordoma is a radiation insensitive tumor, radiotherapy has demonstrated improved local control and is therefore included in the international guidelines(14). Primary radiotherapy is of limited value and may only be applied in non-surgical palliative settings. There is still discussion on the type of radiotherapy. Particle radiotherapy such as proton and carbon-ion has a high Bragg's peak, which may be beneficial for tumors that require high doses, with radiosensitive structures in close proximity, compared to photon radiotherapy. This will be explained in more detail in the paragraph radiotherapy and skull base tumors. Chapter 4 presents the results of the treatment outcome in skull base chordoma patients at the Maastricht University Medical Center.

Chondrosarcoma

Chondrosarcoma is a tumor originating from chondrocytes and like chordoma can present throughout the vertebral column, however it can also appear in the appendicular skeleton unlike chordoma. There is a great variety of histological subtypes; the conventional chondrosarcoma is the most prevalent at 87.5% of cases(15). There are three WHO grades: WHO grade I chondrosarcoma typically demonstrate no mitotic figures and only mild atypia and are therefore the least likely to recur or metastasize. WHO grade II are more malignant, showing higher probability of metastasizing and lower overall survival rates, histologically it shows an increase in mitotic figures and less abundant matrix. Lesions that demonstrate high levels of atypia, nuclear pleomorphism, and abundant mitotic figures are said to be dedifferentiated and are categorized as WHO grade III. These tumors have the poorest prognosis and portray high recurrence and low survival rates(16).

Diagnostic workup consists of CT and MRI scans to evaluate skull base destruction, neurovascular involvement and surgical strategies. A full body CT may be used to detect metastatic disease. Patients with skull base chondrosarcoma demonstrate 5- and 10-year overall survival rates of 82% and 50%, respectively, and disease-specific survival rates are 88% and 62%, respectively(9). Surgical resection is the main treatment modality, and survival mostly depends on WHO grade and negative tumor margins(17). Because this is rarely possible in skull base lesions adjuvant radiotherapy is increasingly applied to improve local control. Primary radiotherapy is only for non-surgical cases and shows limited success rates(18). As is the case with chordoma, in

chondrosarcoma there is also much debate about which radiotherapy type is most successful, photon or particle therapy. Nevertheless, good outcomes have been reported for both modalities, with local control rates of 83% to 100%, 80% to 94%, and 90% to 96% at 5 years for photon, proton, and carbon ion therapies, respectively(19-21). In chapter 5 this topic is further evaluated in a systematic review.

Sinonasal cancer

Sinonasal neoplasms are rare entities and account for approximately 2-3% of all head and neck malignancies(22). It is a large, heterogeneous group of tumors consisting mainly of squamous cell carcinoma (SCC), adenocarcinoma, olfactory neuroblastoma (ON), and adenoid cystic carcinoma (ACC)(22). Early symptoms, such as nasal congestion, epistaxis, rhinorrhea and anosmia, mimic those of more benign diseases, leading to patient and diagnostic delay(23). Up to 60% of patients present in an advanced stage which is correlated with a poorer prognosis(24). Involvement of the orbit, cranial nerves and brain categorically worsens the progression free- and- overall survival rates(25).

Epidemiologic studies have linked several risk factors to the formation of sinonasal cancers(26, 27). The most common factor is smoking; with more than doubling the odds after long term exposure. Cessation of smoking has a beneficial effect on people even after long term consumption(26). Occupational hazards are more difficult to definitively link to the formation of sinonasal cancers. However, there seems to be substantial data on the cumulative exposure to hardwood dust and the formation of adenocarcinomas(28-30). Nickel exposure is related to squamous cell carcinoma(31). Improved working environments have demonstrated decreased incidences of sinonasal cancers in employee pools(32).

Due to the large variety of tumors in the sinonasal region and subsequently different biological behavior, assessing survival outcomes is difficult. The first papers in the 1980's report a 5 year overall survival rate of just 30%(33). The development of craniofacial resection had a significant effect on survival rates as demonstrated by an international collaborative study of 1307 patients. They were treated at 17 institutions with anterior craniofacial resection, and the researchers found a 5-year overall survival, DSS, and recurrence-free survival rates of 54%, 60%, and 53%, respectively(34).

Treatment choice is largely dependent on tumor type, extent of disease, the presence of distant metastasis and the iatrogenic damage patients may receive from different treatment modalities. The cornerstone of treatment is a macroscopic complete resection. Depending on the extent of the tumor growing in the orbit, through the skull base or into the brain, different surgical procedures may be applied, sometimes

in multiple stages. For T4 tumors with cranial extension a bifrontal craniotomy combined with endonasal, endoscopic assistance is the most common procedure in our center. Smaller tumors may be resected using extended endoscopic trans nasal approaches. Reconstruction of the skull base is essential to limit the chance of liquor-rhea and infection. Orbital exenteration is a topic of debate; some experts advocate that involvement of the lamina papyracea is a mandate for complete exenteration to maximize tumor control, whereas others are less aggressive and prefer quality of life above absolute tumor control. If the orbital contents are involved exenteration becomes a necessity to achieve complete resection.

Radiotherapy is an important second treatment modality, applied either adjuvant after surgery or as a primary therapy in inoperable cases. As an adjuvant therapy it has demonstrated its benefit in local control and is said to augment survival rates by 10-15% in comparison to surgery alone(35-38). However, high dose radiotherapy may have serious negative side-effects on organs near the target area, more specifically the eye and optic nerve or the pituitary gland(39). This can lead to blindness or endocrine deficits. Developments in the field of radiotherapy such as intensity modulated radiotherapy (IMRT) and particle radiotherapy may improve survival rates and complication severity(39, 40). A meta-analysis comparing photon radiotherapy and particle radiotherapy demonstrated a significantly higher 5-year survival rate and local control rate in the particle therapy group. However, this is based on retrospective cohorts, and the authors encourage clinicians to set up prospective trials to further elucidate these results(41).

Systemic treatment mainly consists of chemotherapy and is mostly applied in palliative and metastatic settings. Some institutes apply neo-adjuvant chemotherapy regimes in locally advanced cases to try and create margins to critical organs such as the orbit and cavernous sinus(42).

In chapter 3 I report the outcomes of our cohort of large sinonasal cancers with intracranial extension.

THE EVOLUTION OF SKULL BASE TUMOR SURGERY

The field of skull base surgery has drastically changed over the last 125 years. Early pioneers such as Harvey Cushing and Walter Dandy first started exploring this area in the early 1900's.

Surgery at the skull base at that time was extremely dangerous due to limited anesthesiologic methods, intraoperative patient monitoring, lack of antibiotics and developing understanding of neuroanatomy. Tumors such as meningiomas and pituitary adenomas were often con-

sidered inoperable until Cushing and Dandy developed and published their progress(43-45). Early pioneers began limited cranial approaches, but mortality rates were very high(44, 46-50). The development of transsphenoidal surgery by Herman Schloffer to the hypophysis had a tremendous impact on operative mortality rates(51). Furthermore, new imaging techniques such as pneumoencephalography and angiography led to targeted surgical approaches and improved pre-operative planning(52, 53).

After the second world war in the latter half of the 20th century the foundations of “modern” neurosurgery were laid. Dedicated tools for microsurgery such as the operating microscope and micro instruments (bipolar forceps) developed by Gazi Yasargil are still being used today(54). The skull base anatomy was meticulously explored and described by Rhoton et al to enable new transcranial approaches to be developed(55-62). It was a time where this advanced understanding of the complex 3D anatomy of the skull base led to a conceptual shift in surgical approaches. Instead of retracting the brain aggressively, surgeons began to remove the bone to access tumors from below or the side. Arachnoid dissection planes were utilized by Yasargil to navigate the fissures and follow natural routes through the brain(63). Ugo Fisch and Takeshi Kawase developed new corridors around and through the temporal bone to better approach lesions around the inner ear, clivus and brainstem otherwise inaccessible(64-67).

Ossama Al-Mefty dedicated his efforts to further develop the treatment of skull base meningiomas and the preferred routes to resect them(68-71).

Skull base surgery became a stand-alone subspecialty within the neurosurgery. The next step was the formation of multidisciplinary skull base teams with collaboration between otolaryngology, neurosurgery, ophthalmology and maxillofacial surgeons to better treat complex tumors involving multiple craniofacial compartments. Technological advancements in diagnostics with high resolution CT and MRI imaging revolutionized preoperative planning(72). Additionally intraoperative neurophysiological monitoring improved cranial nerve preservation(73).

From the 1990's and onwards the endoscopic era took flight. The introduction of endoscopy in skull base surgery would revolutionize the field and in the following decades it would become standard practice in most skull base centers. The initial implementation of endoscopy was in pituitary surgery. Providing clear images and the ability to look around a corner. The initial phase was colored by high numbers of CSF leakage, but advancements in skull base defect closure such as autologous fat, pedicled flaps and multilayered reconstruction improved outcomes. Presently a great variety of extended endonasal approaches are available to cover the entire anterior, clival and craniovertebral skull base. Its advantages in comparison to large craniotomies are shorter recovery time, improved perioperative morbidity, no need for brain retraction and better visibility of the lesion and surrounding neurovascular structures. In

some skull base centers combined approaches are used, where the endoscope is applied to better visualize the anatomy in open surgery.

The following paradigm shift came in the current century and is still a point of discussion in international society; it is the philosophy of partial tumor surgery combined with adjuvant (radio) therapy to reduce surgical neurological morbidity and improve quality of life. This is especially relevant in benign lesions which may be cured with complete resection such as vestibular schwannoma and grade 1 meningioma. However, aggressive resection is associated with higher levels of iatrogenic neurological deficits. Which, in benign lesions, may lead to decades of impaired quality of life. A multimodal approach of surgery and adjuvant radiotherapy could provide a desired combination of tumor control while preserving neurological function. By surgically decreasing the tumor volume the effect of radiotherapy is increased, thereby improving local control of the tumor remnant. Developments in the field of radiotherapy have substantially improved the accuracy and safety of radiation which made this multimodal approach more feasible. This will be described in more detail in the next paragraph.

Future developments are likely to involve improved pre- and intra-operative imaging and navigation with augmented reality overlays to portray the relationship between tumors and surrounding neurovascular structures. Knowing the location of the deviated optic or facial nerve before real-life visualization could be of vital importance in sparing its function.

The rapidly growing possibilities of DNA sequencing and molecular profiling are going to improve prediction models, providing clinicians with tools to help them decide which tumors to treat more aggressively or to simply follow-up. The benefits of large data collections and AI powered computational analysis could help create tailored treatment schemes based on individual patient characteristics.

RADIOTHERAPY AND SKULL BASE TUMORS

Radiation therapy is an ever-growing field in oncological care and it has definitively claimed its position in the treatment of various skull base tumors. As a primary treatment option for small or inoperable lesions, adjuvant after resection or as a palliative option in extensive lesions. In the contemporary period, two main radiation types exist; namely photon and particle therapy. The former involves high-energy X-rays or gamma rays to destroy cancer cells and shrink or stabilize tumor size; the latter involves using the energy from protons or heavy ions. Radiotherapy has improved significantly in the last decades, with the advent of techniques such as intensity-modulated radiotherapy (IMRT) or volumetric arc therapy (VMAT) further optimizing radiation delivery. Below is a summary of how radiotherapy has developed over the years to shape its current state and use in skull base oncology.

1. Early Era: Conventional External Beam Radiotherapy (1950s–1980s)

Early treatment used two-dimensional (2D) planning with simple X-ray imaging.

Characteristics

- Large radiation fields
- Limited ability to spare critical structures
- Modest tumor control for many skull base tumors

Typical techniques

- Orthovoltage and later megavoltage photon beams
- Basic lateral or opposed fields

Limitations

- High toxicity to nearby organs (optic nerves, brainstem)
- Poor conformity to complex skull base anatomy
- Dose constraints limited effective tumor dosing

This made radiotherapy mainly adjuvant or palliative for many skull base tumors such as chordomas, meningiomas, and pituitary adenomas.

2. CT-Based Planning and 3D Conformal Radiotherapy (1980s–1990s)

The introduction of computed tomography revolutionized radiation planning.

Key innovations

- 3D treatment planning
- Beam shaping with multileaf collimators
- Improved tumor targeting

Important advance

- Three-dimensional conformal radiotherapy (3D-CRT)

Impact

- More accurate delineation of skull base tumors
- Ability to escalate dose slightly while reducing toxicity
- Better outcomes for tumors such as meningiomas and pituitary adenomas

However, conformality was still limited for irregular tumors wrapping around critical structures.

3. Stereotactic Radiosurgery (Late 1980s–2000s)

A major breakthrough came with stereotactic precision.

Key technique

- Stereotactic radiosurgery (SRS)

Important technologies

- Gamma Knife
- CyberKnife
- LINAC-based stereotactic systems

Advantages

- Submillimeter accuracy
- High-dose single fraction (or hypofractionated)
- Excellent for small skull base tumors

Common indications

- Vestibular schwannoma
- Small meningiomas
- Pituitary adenomas
- Residual or recurrent disease after surgery

Impact

- Tumor control rates are often >90% for benign tumors
- Reduced morbidity compared with open surgery in selected cases

Limitations

- Less suitable for large tumors
- Dose constraints near optic apparatus

4. Intensity-Modulated Radiotherapy (IMRT) and Advanced Photon Therapy (2000s)

The next step was inverse planning and beam modulation.

Key technique

- Intensity-modulated radiotherapy

Related development

- Volumetric modulated arc therapy (VMAT)

Advantages

- Highly conformal dose distribution
- Ability to sculpt dose around cranial nerves and brainstem
- Better sparing of organs at risk

Clinical benefits

- Dose escalation for malignant skull base tumors
- Lower toxicity to optic nerves and temporal lobes

This became the standard photon-based technique for many skull base malignancies.

5. Particle Therapy Era: Proton and Heavy Ion Therapy (1990s–Present)

Particle therapy has been particularly transformative for skull base tumors.

Proton Therapy

Key modality:

- Proton therapy

Physics advantage:

- Bragg peak allows dose deposition at precise depth

Benefits

- Reduced exit dose
- Improved sparing of brainstem and optic pathways
- Ability to deliver higher tumor doses

Major indications

- Chordomas
- Chondrosarcomas
- Pediatric skull base tumors

Carbon Ion Therapy

More advanced particle therapy:

- Carbon ion radiotherapy

Advantages:

- Higher relative biological effectiveness (RBE)
- Effective against radioresistant tumors

Often used for:

- chordomas
- chondrosarcomas
- adenoid cystic carcinoma

Centers in Japan and Europe have reported improved local control for these tumors.

6. Modern Era: Image-Guided and Adaptive Radiotherapy (2010s–Present)

Current radiotherapy integrates advanced imaging and adaptive workflows.

Key developments:

Image-guided radiotherapy

- Image-guided radiotherapy (IGRT)

Uses:

- cone-beam CT
- MRI guidance

Benefits:

- Daily positioning accuracy
- Reduced safety margins

MRI-guided radiotherapy

Emerging systems:

- MR-Linac

Advantages:

- Real-time visualization of soft tissues
- Adaptive replanning during treatment

Adaptive radiotherapy

Allows treatment plan modification during the course of therapy, particularly important when tumors shrink or anatomy changes.

AIM AND OUTLINE OF THIS THESIS

This thesis aims to describe our center's experience treating skull base tumors, specifically chordoma, vestibular schwannoma, sinonasal cancers and chondrosarcoma. To develop your expertise and improve your patient's outcome it is important to assess your own results and to build on these lessons learned. Skull base tumor surgery is an ever-developing field where most treatment paradigms are under international discussion, because most ideas are based on small retrospective series and expert opinions and seldomly on large prospective cohorts, let alone randomized trials.

In **chapter 2** I present our results on the combined approach to treating large Koos IV vestibular schwannoma. It combines a planned partial resection followed by Gamma Knife radiotherapy. Primary outcome is local tumor control and secondly, we look at treatment toleration. This chapter aims to add data to the discussion about which treatment plan is optimal for patients with large VS.

In **chapter 3** I present the treatment outcome of patients with cranially extended sinonasal carcinoma. These rare tumors are typically treated using radical resection followed by high dose radiotherapy. We portray the results of this treatment on tumor control and adverse effects. I discuss the balance between treatment aggression and quality of life, and whether there are ways to optimize this balance.

Chapter 4 depicts our experience of treating skull base chordoma. This rare and locally aggressive malignancy proves a fierce opponent in many skull base practices. The goal of this study was to evaluate the survival rates in our cohort and compare open vs endoscopic approaches. We also looked at treatment complications and results of salvage therapies. With this study we aim to contribute to further understanding this tumor's behavior.

We conducted a systematic review on the role of post-operative radiotherapy in skull base chondrosarcoma. There is international debate about when adjuvant radiotherapy is indicated in these lesions. In **chapter 5** I present our findings and delineate our current evidence on the added value of radiotherapy and in which form. This review may guide future decision making for clinicians and demonstrates knowledge gaps for future research endeavors.

The differential diagnosis of a clival lesion encompasses multiple entities, ranging from dormant dysplasia to highly malignant sarcoma. An experienced neuroradiologist with advanced multimodal diagnostics is of utmost importance for an academic skull base center. Still lesions may demonstrate atypical behavior or mimic other tumors. A pathology report may provide a definitive diagnosis. In **chapter 6** I describe a case report in which a patient with a clival lesion presents with paroxysmal abducens palsy. The tumor demonstrates growth and regression coupled with the patient's symptoms. Histopathology shows a chordoma. This

case illustrates the importance of pathological confirmation in uncertain radiological cases, which could aid colleagues in decision making.

The evolution of skull base surgery, as is elaborated on in the previous paragraph, is a continuous process. The goal of decreased morbidity and improved recovery after surgery is always demanding. In our center we developed a simple and rapid technique to close small clival defects without the need for vascularized flaps. In **chapter 7** this is presented in a case series. The aim is to provide surgeons with different options for skull base closure techniques. Concluding remarks and critical reflection on the findings are provided in **chapter 8**.

REFERENCES

1. Lanser MJ, Sussman SA, Frazer K. Epidemiology, pathogenesis, and genetics of acoustic tumors. *Otolaryngol Clin North Am.* Jun 1992;25(3):499-520.
2. Propp JM, McCarthy BJ, Davis FG, Preston-Martin S. Descriptive epidemiology of vestibular schwannomas. *Neuro Oncol.* Jan 2006;8(1):1-11. doi:10.1215/S1522851704001097
3. Khrais T, Romano G, Sanna M. Nerve origin of vestibular schwannoma: a prospective study. *J Laryngol Otol.* Feb 2008;122(2):128-31. doi:10.1017/S0022215107001028
4. Kentala E, Pyykko I. Clinical picture of vestibular schwannoma. *Auris Nasus Larynx.* Jan 2001;28(1):15-22. doi:10.1016/s0385-8146(00)00093-6
5. Benoudiba F, Toulgoat F, Sarrazin JL. The vestibulocochlear nerve (VIII). *Diagn Interv Imaging.* Oct 2013;94(10):1043-50. doi:10.1016/j.diii.2013.08.015
6. Mackle T, Rawluk D, Walsh RM. Atypical clinical presentations of vestibular schwannomas. *Otology & neurotology : official publication of the American Otological Society, American Neurotology Society [and] European Academy of Otology and Neurotology.* Jun 2007;28(4):526-8. doi:10.1097/mao.0b013e3180340a4d
7. Koos WT, Day JD, Matula C, Levy DI. Neurotopographic considerations in the microsurgical treatment of small acoustic neurinomas. *Journal of neurosurgery.* Mar 1998;88(3):506-12. doi:10.3171/jns.1998.88.3.0506
8. Zuckerman SL, Bilsky MH, Laufer I. Chordomas of the Skull Base, Mobile Spine, and Sacrum: An Epidemiologic Investigation of Presentation, Treatment, and Survival. *World Neurosurg.* May 2018;113:e618-e627. doi:10.1016/j.wneu.2018.02.109
9. Bohman LE, Koch M, Bailey RL, Alonso-Basanta M, Lee JY. Skull base chordoma and chondrosarcoma: influence of clinical and demographic factors on prognosis: a SEER analysis. *World Neurosurg.* Nov 2014;82(5):806-14. doi:10.1016/j.wneu.2014.07.005
10. Pan Y, Lu L, Chen J, Zhong Y, Dai Z. Analysis of prognostic factors for survival in patients with primary spinal chordoma using the SEER Registry from 1973 to 2014. *J Orthop Surg Res.* Apr 6 2018;13(1):76. doi:10.1186/s13018-018-0784-3
11. Yu E, Koffer PP, DiPetrillo TA, Kinsella TJ. Incidence, Treatment, and Survival Patterns for Sacral Chordoma in the United States, 1974-2011. *Front Oncol.* 2016;6:203. doi:10.3389/fonc.2016.00203
12. Mukherjee D, Chaichana KL, Parker SL, Gokaslan ZL, McGirt MJ. Association of surgical resection and survival in patients with malignant primary osseous spinal neoplasms from the Surveillance, Epidemiology, and End Results (SEER) database. *Eur Spine J.* Jun 2013;22(6):1375-82. doi:10.1007/s00586-012-2621-4
13. Alahmari M, Temel Y. Skull base chordoma treated with proton therapy: A systematic review. *Surg Neurol Int.* 2019;10:96. doi:10.25259/SNI-213-2019
14. Stacchiotti S, Sommer J, Chordoma Global Consensus G. Building a global consensus approach to chordoma: a position paper from the medical and patient community. *Lancet Oncol.* Feb 2015;16(2):e71-83. doi:10.1016/S1470-2045(14)71190-8
15. Arshi A, Sharim J, Park DY, et al. Chondrosarcoma of the Osseous Spine: An Analysis of Epidemiology, Patient Outcomes, and Prognostic Factors Using the SEER Registry From 1973 to 2012. *Spine (Phila Pa 1976).* May 1 2017;42(9):644-652. doi:10.1097/BRS.0000000000001870
16. Bergh P, Gunterberg B, Meis-Kindblom JM, Kindblom LG. Prognostic factors and outcome of pelvic, sacral, and spinal chondrosarcomas: a center-based study of 69 cases. *Cancer.* Apr 1 2001;91(7):1201-12. doi:10.1002/1097-0142(20010401)91:7<1201::aid-cnrc1120>3.0.co;2-w
17. Fiorenza F, Abudu A, Grimer RJ, et al. Risk factors for survival and local control in chondrosarcoma of bone. *J Bone Joint Surg Br.* Jan 2002;84(1):93-9. doi:10.1302/0301-620x.84b1.11942

18. Indelicato DJ, Rotondo RL, Begosh-Mayne D, et al. A Prospective Outcomes Study of Proton Therapy for Chordomas and Chondrosarcomas of the Spine. *International journal of radiation oncology, biology, physics*. May 1 2016;95(1):297-303. doi:10.1016/j.ijrobp.2016.01.057
19. Gatfield ER, Noble DJ, Barnett GC, et al. Tumour Volume and Dose Influence Outcome after Surgery and High-dose Photon Radiotherapy for Chordoma and Chondrosarcoma of the Skull Base and Spine. *Clin Oncol (R Coll Radiol)*. Apr 2018;30(4):243-253. doi:10.1016/j.clon.2018.01.002
20. Holliday EB, Mitra HS, Somerson JS, et al. Postoperative proton therapy for chordomas and chondrosarcomas of the spine: adjuvant versus salvage radiation therapy. *Spine (Phila Pa 1976)*. Apr 15 2015;40(8):544-9. doi:10.1097/BRS.0000000000000804
21. Schulz-Ertner D, Nikoghosyan A, Hof H, et al. Carbon ion radiotherapy of skull base chondrosarcomas. *International journal of radiation oncology, biology, physics*. Jan 1 2007;67(1):171-7. doi:10.1016/j.ijrobp.2006.08.027
22. Turner JH, Reh DD. Incidence and survival in patients with sinonasal cancer: a historical analysis of population-based data. *Head Neck*. Jun 2012;34(6):877-85. doi:10.1002/hed.21830
23. Robin PE, Powell DJ, Stansbie JM. Carcinoma of the nasal cavity and paranasal sinuses: incidence and presentation of different histological types. *Clin Otolaryngol Allied Sci*. Dec 1979;4(6):431-56. doi:10.1111/j.1365-2273.1979.tb01776.x
24. Alvarez I, Suarez C, Rodrigo JB, Nunez F, Caminero MJ. Prognostic factors in paranasal sinus cancer. *Am J Otolaryngol*. Mar-Apr 1995;16(2):109-14. doi:10.1016/0196-0709(95)90041-1
25. Euteneuer S, Sudhoff H, Bernal-Sprekelsen M, Theegarten D, Dazert S. [Malignomas of the nasal cavity and the paranasal sinuses: clinical characteristics, therapy and prognosis of different tumor types]. *Laryngorhinootologie*. Jan 2004;83(1):33-9. Malignome der inneren Nase und der Nasennebenhohlen, Klinik, Therapie und Prognose verschiedener Tumorentitäten. doi:10.1055/s-2004-814108
26. Greiser EM, Greiser KH, Ahrens W, et al. Risk factors for nasal malignancies in German men: the South-German Nasal cancer study. *BMC Cancer*. Nov 6 2012;12:506. doi:10.1186/1471-2407-12-506
27. Zheng W, McLaughlin JK, Chow WH, Chien HT, Blot WJ. Risk factors for cancers of the nasal cavity and paranasal sinuses among white men in the United States. *Am J Epidemiol*. Dec 1 1993;138(11):965-72. doi:10.1093/oxfordjournals.aje.a116816
28. Gordon I, Boffetta P, Demers PA. A case study comparing a meta-analysis and a pooled analysis of studies of sinonasal cancer among wood workers. *Epidemiology*. Sep 1998;9(5):518-24.
29. Holmila R, Cyr D, Luce D, et al. COX-2 and p53 in human sinonasal cancer: COX-2 expression is associated with adenocarcinoma histology and wood-dust exposure. *Int J Cancer*. May 1 2008;122(9):2154-9. doi:10.1002/ijc.23360
30. Pesch B, Pierl CB, Gebel M, et al. Occupational risks for adenocarcinoma of the nasal cavity and paranasal sinuses in the German wood industry. *Occup Environ Med*. Mar 2008;65(3):191-6. doi:10.1136/oem.2007.033886
31. Doll R, Morgan LG, Speizer FE. Cancers of the lung and nasal sinuses in nickel workers. *Br J Cancer*. Dec 1970;24(4):623-32. doi:10.1038/bjc.1970.76
32. Rourke T, Grover S, Wager N, Capper J. Decreasing incidence of nasal adenocarcinoma in Wycombe woodworkers. *Laryngoscope*. May 2014;124(5):1078-82. doi:10.1002/lary.24495
33. Sisson GA, Sr., Toriumi DM, Atiyah RA. Paranasal sinus malignancy: a comprehensive update. *Laryngoscope*. Feb 1989;99(2):143-50. doi:10.1288/00005537-198902000-00005
34. Patel SG, Singh B, Polluri A, et al. Craniofacial surgery for malignant skull base tumors: report of an international collaborative study. *Cancer*. Sep 15 2003;98(6):1179-87. doi:10.1002/cncr.11630

35. Gabriele P, Besozzi MC, Pisani P, et al. [Carcinoma of the paranasal sinuses. Results with radiotherapy alone or with a radio-surgical combination]. *Radiol Med.* Apr 1986;72(4):210-4. Carcinomi dei seni paranasali. Risultati del trattamento con radioterapia sola o con associazione radio-chirurgica.
36. Anniko M, Franzen L, Lofroth PO. Long-term survival of patients with paranasal sinus carcinoma. *ORL J Otorhinolaryngol Relat Spec.* 1990;52(3):187-93. doi:10.1159/000276132
37. Dirix P, Nuyts S, Vanstraelen B, et al. Post-operative intensity-modulated radiotherapy for malignancies of the nasal cavity and paranasal sinuses. *Radiother Oncol.* Dec 2007;85(3):385-91. doi:10.1016/j.radonc.2007.10.001
38. Duthoy W, Boterberg T, Claus F, et al. Postoperative intensity-modulated radiotherapy in sinonasal carcinoma: clinical results in 39 patients. *Cancer.* Jul 1 2005;104(1):71-82. doi:10.1002/cncr.21100
39. Moreno AC, Frank SJ, Garden AS, et al. Intensity modulated proton therapy (IMPT) - The future of IMRT for head and neck cancer. *Oral Oncol.* Jan 2019;88:66-74. doi:10.1016/j.oraloncology.2018.11.015
40. Vasudevan SS, Deeb H, Katta A, et al. Efficacy and safety of proton therapy versus intensity-modulated radiation therapy in the treatment of head and neck tumors: A systematic review and meta-analysis. *Head Neck.* Oct 2024;46(10):2616-2631. doi:10.1002/hed.27877
41. Patel SH, Wang Z, Wong WW, et al. Charged particle therapy versus photon therapy for paranasal sinus and nasal cavity malignant diseases: a systematic review and meta-analysis. *Lancet Oncol.* Aug 2014;15(9):1027-38. doi:10.1016/S1470-2045(14)70268-2
42. Hanna EY, Cardenas AD, DeMonte F, et al. Induction chemotherapy for advanced squamous cell carcinoma of the paranasal sinuses. *Arch Otolaryngol Head Neck Surg.* Jan 2011;137(1):78-81. doi:10.1001/archoto.2010.231
43. Cushing H. III. Partial Hypophysectomy for Acromegaly: With Remarks on the Function of the Hypophysis. *Ann Surg.* Dec 1909;50(6):1002-17. doi:10.1097/00000658-190912000-00003
44. Dandy WE. Contributions to Brain Surgery: A. Removal of Certain Deep-Seated Brain Tumors B. Intracranial Approach with Concealed Incisions. *Ann Surg.* Oct 1925;82(4):513-25. doi:10.1097/00000658-192510010-00001
45. Bailey P, Cushing H. Studies in Acromegaly: VII. The Microscopical Structure of the Adenomas in Acromegalic Dyspituitarism (Fugitive Acromegaly). *Am J Pathol.* Nov 1928;4(6):545-564 13.
46. Cushing H. Landmark article April 28, 1900: A method of total extirpation of the Gasserian ganglion for trigeminal neuralgia. By a route through the temporal fossa and beneath the middle meningeal artery. By Harvey Cushing. *JAMA.* Jul 22-29 1983;250(4):519-28. doi:10.1001/jama.250.4.519
47. Cushing H. I. The Control of Bleeding in Operations for Brain Tumors: With the Description of Silver "Clips" for the Occlusion of Vessels Inaccessible to the Ligature. *Ann Surg.* Jul 1911;54(1):1-19. doi:10.1097/00000658-191107000-00002
48. Dandy WE. Benign Encapsulated Tumors in the Lateral Ventricles of the Brain: Diagnosis and Treatment. *Ann Surg.* Nov 1933;98(5):841-5. doi:10.1097/00000658-193311000-00005
49. Dandy WE. Intracranial Tumors and Abscesses Causing Communicating Hydrocephalus. *Ann Surg.* Aug 1925;82(2):199-207. doi:10.1097/00000658-192508000-00002
50. Dandy WE. The Treatment of Trigeminal Neuralgia by the Cerebellar Route. *Ann Surg.* Oct 1932;96(4):787-95. doi:10.1097/00000658-193210000-00026
51. Schmidt RF, Choudhry OJ, Takkellapati R, Eloy JA, Couldwell WT, Liu JK. Hermann Schloffer and the origin of transsphenoidal pituitary surgery. *Neurosurgical focus.* Aug 2012;33(2):E5. doi:10.3171/2012.5.FOCUS12129

52. Dandy WE. Rontgenography of the Brain after the Injection of Air into the Spinal Canal. *Ann Surg.* Oct 1919;70(4):397-403. doi:10.1097/00000658-191910000-00004
53. Dandy WE. Ventriculography Following the Injection of Air into the Cerebral Ventricles. *Ann Surg.* Jul 1918;68(1):5-11. doi:10.1097/00000658-191807000-00002
54. Yasargil MG, Krakenbuhl HA, Jacobson JH, 2nd. Microneurosurgical arterial reconstruction. *Surgery.* Jan 1970;67(1):221-33.
55. Buza RC, Rhoton AL, Jr. Microsurgical anatomy of the jugular foramen. *Surg Forum.* 1972;23(0):442-4.
56. Gudmundsson K, Rhoton AL, Jr., Rushton JG. Detailed anatomy of the intracranial portion of the trigeminal nerve. *Journal of neurosurgery.* Nov 1971;35(5):592-600. doi:10.3171/jns.1971.35.5.0592
57. Habal MB, Maniscalco JE, Lineaweaver WC, Rhoton AL, Jr. Microsurgical anatomy of the optic canal: anatomical relations and exposure of the optic nerve. *Surg Forum.* 1976;27(62):542-4.
58. Harris F, Rhoton AL, Jr. Microsurgical anatomy of the cavernous sinus. *Surg Forum.* 1975;26:462-3.
59. Perlmutter D, Rhoton AL, Jr. Microsurgical anatomy of anterior cerebral anterior communicating recurrent artery complex. *Surg Forum.* 1976;27(62):464-5.
60. Renn WH, Rhoton AL, Jr. Microsurgical anatomy of the sellar region. *Journal of neurosurgery.* Sep 1975;43(3):288-98. doi:10.3171/jns.1975.43.3.0288
61. Rhoton AL, Jr., Buza R. Microsurgical anatomy of the jugular foramen. *Journal of neurosurgery.* May 1975;42(5):541-50. doi:10.3171/jns.1975.42.5.0541
62. Rhoton AL, Jr., Harris FS, Renn WH. Microsurgical anatomy of the sellar region and cavernous sinus. *Clin Neurosurg.* 1977;24:54-85. doi:10.1093/neurosurgery/24.cn_suppl_1.54
63. Yasargil MG. Intracranial microsurgery. *Clin Neurosurg.* 1970;17:250-6. doi:10.1093/neurosurgery/17.cn_suppl_1.250
64. Kawase T, Shiobara R, Toya S. Middle fossa transpetrosal-transtentorial approaches for petroclival meningiomas. Selective pyramid resection and radicality. *Acta neurochirurgica.* 1994;129(3-4):113-20. doi:10.1007/BF01406489
65. Kawase T, Shiobara R, Toya S. Anterior transpetrosal-transtentorial approach for sphenopetroclival meningiomas: surgical method and results in 10 patients. *Neurosurgery.* Jun 1991;28(6):869-75; discussion 875-6.
66. Kawase T, Toya S, Shiobara R, Mine T. Transpetrosal approach for aneurysms of the lower basilar artery. *Journal of neurosurgery.* Dec 1985;63(6):857-61. doi:10.3171/jns.1985.63.6.0857
67. Fisch U. Infratemporal fossa approach to tumours of the temporal bone and base of the skull. *J Laryngol Otol.* Nov 1978;92(11):949-67. doi:10.1017/s0022215100086382
68. Bikmaz K, Mrak R, Al-Mefty O. Management of bone-invasive, hyperostotic sphenoid wing meningiomas. *Journal of neurosurgery.* Nov 2007;107(5):905-12. doi:10.3171/JNS-07/11/0905
69. Cho CW, Al-Mefty O. Combined petrosal approach to petroclival meningiomas. *Neurosurgery.* Sep 2002;51(3):708-16; discussion 716-8.
70. Heth JA, Al-Mefty O. Cavernous sinus meningiomas. *Neurosurgical focus.* Jun 15 2003;14(6):e3. doi:10.3171/foc.2003.14.6.3
71. Mahmoud M, Nader R, Al-Mefty O. Optic canal involvement in tuberculum sellae meningiomas: influence on approach, recurrence, and visual recovery. *Neurosurgery.* Sep 2010;67(3 Suppl Operative):ons108-18; discussion ons118-9. doi:10.1227/01.NEU.0000383153.75695.24
72. Grevers G, Assal J, Vogl T, Wilimzig C. Three-dimensional magnetic resonance imaging in skull base lesions. *Am J Otolaryngol.* May-Jun 1991;12(3):139-45. doi:10.1016/0196-0709(91)90143-4

73. Sobottka SB, Schackert G, May SA, Wiegler M, Reiss G. Intraoperative facial nerve monitoring (IFNM) predicts facial nerve outcome after resection of vestibular schwannoma. *Acta neurochirurgica*. 1998;140(3):235-42; discussion 242-3. doi:10.1007/s007010050090

2

Vestibular Schwannoma

Tumour Shrinkage and Good Facial Nerve Function After Planned Partial Resection and Gamma Knife Radiosurgery in Koos 4 Vestibular Schwannoma

Keizer M*, Al-Ahmari M*, Al-Dhafery B, Eekers D, Hovinga K, Kunst H, Temel Y.
Tumour Shrinkage and Good Facial Nerve Function After Planned Partial Resection and Gamma Knife Radiosurgery in Koos 4 Vestibular Schwannoma. Turk Neurosurg. 2025;35(2):265-273.

*Both authors contributed equally.

ABSTRACT

Aim: To evaluate clinical and radiological outcome in surgically treated Koos 4 vestibular schwannomas.

Material and methods: Volumetric analysis of the tumour volumes before surgery, after surgery (before radiation), and at follow-up time-points after radiation was performed. Clinical data on facial nerve function and complications were collected. Approximately 6 months after surgery, all patients were treated with a single fraction of SRS using the Gamma Knife radiosurgery with a mean marginal dose of 12.9 Gy to the residual tumour volume.

Results: Mean tumour volume was 11.64 cm³ which was reduced to a mean volume of 4.17 cm³ after partial resection. After a mean follow-up of 100 months, residual tumour showed a decrease in volume in 20 patients, stable disease in one patient and two patients showed progressive tumour volume requiring a second operation in one patient. Facial nerve function was preserved in all patients. One patient suffered from a trigeminal neuralgia after radiation.

Conclusion: Planned partial resection followed by radiation for patients with Koos 4 vestibular schwannoma is an effective strategy to preserve facial nerve function and achieve tumour control. Residual tumours after planned partial resection showed a mean decrease in volume of 50% at the last follow-up time point.

Keywords: Vestibular schwannoma, Partial resection, Gamma knife, Tumour volume, Facial nerve

INTRODUCTION

Vestibular schwannoma (VS) is a benign skull base tumour resulting from the proliferation of Schwann cells of the vestibulocochlear nerve (56). VS is a slow growing tumour that usually expands from the internal auditory canal (IAC) toward the cerebellopontine angle (CPA). VS accounts for 10% of all intracranial tumours and approximately 90% of all tumours in the CPA (24,56). In the last two decades, the use of magnetic resonance imaging (MRI) has contributed to more incidental detection of VS. In up to 0.07% of individuals undergoing an MRI of the brain, a VS was detected (24,46).

recent study suggested that within the United States alone, the incidence rate has increased significantly from 1.5 over the past half-century to 4.2 per 100,000 persons in the last decade (31). Since the vestibulocochlear nerve is responsible for hearing and balance, VS patients usually show symptoms related to these functions, such as tinnitus, hearing loss, vertigo, and headache (35,47,50,55). Symptoms vary from one patient to another and are mostly dependent on tumour volume (43). Common treatment strategies are the 'wait and scan policy', surgical resection, and/or stereotactic radiosurgery (SRS) (43). Taking into account differences in patient characteristics, treatment selection is highly dependent on tumour volume and unilateral or bilateral (neurofibromatosis type 2 (NF2)) occurrence (59). VS size is classified into four grades using the Koos grading scale: intracanalicular (Koos 1), intra-/extrameatal (Koos 2), tumour touching the brainstem (Koos 3), and tumour compression of the brainstem (Koos 4) (20). This study focuses predominantly on Koos 4 VS.

Large VS compress the brainstem and may cause symptoms of cranial nerve disorders [MK1.1], ataxia, hydrocephalus and cerebrospinal tract impairment and therefore prompts a surgical decompression. Over the past decades, complete tumour resection has been considered the treatment of first choice (26,30). This strategy has shown high rates of VS control, ranging between 90.9–100% (49). However, as the tumour is often adjacent to the facial nerve (FN) in large VS, preserving this critical structure combined with the goal of leaving no residual tumour creates a major challenge. In a recent systematic review, the pooled overall gross-total resection rate was estimated to be 77%, with higher rates associated with surgeon's experience (49). Good facial nerve function House-Brackmann (HB) Grade 1 or 2 after total resection fluctuated between 27% and 85% (11,26,30,45,57,60,61). Leaving a residue of VS around the FN (partial or subtotal resection) ensures better preservation of neurological and sensory functions. Yet, partial resection alone was found to be associated with a higher probability of tumour growth in up to 53% of cases (3,10,16,42,51).

In large VS, SRS alone may cause transient swelling, adding more compression to the brainstem and is therefore not the preferred first treatment (54); however, it has shown to better control small to medium VS (on a scale ranging from 87% to 97%) with favourable FN function outcomes (5,6,29). Therefore, a combined approach of partial resection with

irradiation of the residual tumour seems to be a logical treatment for large VS. Throughout the last two decades, Gamma Knife (GK) radiosurgery after partial resection, with a marginal dose between 12–13 Gy to the residual tumour, has shown beneficial FN function outcomes, ranging between 86% and 100%, with tumour control rates of 79% and higher (7,15,22,23,39,40,41,53,58). This slightly more conservative approach has gained gradual attention among the skull base surgical community. Nine studies (7,15,22,23,39,40,41,53, 58) have reported on using this combined approach.

The aim of our retrospective study is to illustrate local control, FN outcomes, surgical complications, and radiotherapy side effects in managing Koos 4 VS using this combined approach.

MATERIAL AND METHODS

Inclusion and Exclusion Criteria

After obtaining permission from the medical ethical committee (METC 2018-0843), data were collected retrospectively. All patients harbouring histopathologically confirmed Koos 4 VS treated via a partial resection followed by GK radiosurgery, with preoperative and postoperative MRI scans, were included in the study. This study included patients from 2007 until 2018 with all required treatment data available.

Imaging Protocol and Clinical Workflow

All patients received a 1 mm T1-weighted contrast-enhanced brain MRI and a T2-weighted 0.6 mm (cochlea sequence) axial imaging of the cerebellopontine area. This protocol was performed preoperatively and during follow-up. All surgically treated patients with VS were discussed in the multidisciplinary skull base team. According to the local protocol, patients with Koos 4 and occasionally Koos 3 VS (if the patient had a strong preference for surgery) were treated with the combined approach. All patients presented with severe hearing loss. Therefore, tumour resection was conducted via the translabyrinthine route with the aim of achieving tumour volume reduction and FN preservation. This approach included dissection of the internal auditory meatus, besides mastoidectomy and labyrinthectomy, with secure exposition of the FN. To avoid any damage to FN, electromyography based two-channel facial monitoring was used during surgery. Surgeries were performed in a joint effort involving experienced surgeons from both otorhinolaryngology (ENT) and the neurosurgery departments. The ENT surgeon started with the labyrinthectomy, and the neurosurgeon resected the tumour. After surgery, the patient was discharged within 3–5 days and a follow up appointment was scheduled after approximately three months.

GK Radiosurgery

Within six months after surgery the residual VS was treated with GK radiosurgery, a dose between 12.0 and 13.0 Gy (mean: 12.9 Gy) was prescribed, covering 99% of the residual tu-

mour. All radiosurgery treatments were performed using the Leksell Gamma Knife 4C and, from 2008 onwards, the Leksell Gamma Knife Perfection, and from 2015 the Gamma Knife Icon. To ensure the exact delivery of the prescribed dose, the GK centre used a volumetric 1 mm (without slice gap) T1weighted contrast-enhanced MRI and 0.8 mm T2 weighted MRI for planning purposes.

Definition of Radiological and Clinical Control

In order to assess tumour volumes, four MRI scans were retrieved from the database system for each patient. These scans represented a chronological sequence of when the tumour was initially diagnosed (VT1), after surgery ((VT2) tumour volume at the time of GK), first MRI scan after GK (VT3), and at the last available follow-up (VT4). Based on the literature, VS patients might have an increase in tumour volume following GK (pseudo-progression or transient swelling), which will resolve in time (19). The first and second authors (radiologist with neuro imaging expertise) performed all volume measurements manually using 3DSlicer (<https://www.slicer.org/>), (Figure 1) (12).

Radiological control refers to the status of the tumour volume at VT4 in relation to VT2 by calculating the change. A difference of 20% between scans was considered the measurement error (38,52). Therefore, the tumour status at VT4 was classified into three categories: regression when VT4 is less than 80% of VT2; stable when the VT4 is within a margin of $\pm 20\%$ from VT2; progression when VT4 is larger than 120% of the VT2. Clinical control refers to the absence of the need for further treatment (GK or surgery) after completing the initial treatment approach.

Statistical analyses

Forward stepwise ANOVA regression was applied to find any predictive variable in relation to the tumour volume at the last follow-up (VT4). The tumour volume VT4 was the dependent variable and included the following variables in the candidate pool of predictors: age, sex, tumour location, tumour volume before and after surgery, tumour volume directly after GK, time interval between surgery and GK, and time interval between GK and the last follow-up. The level of significance was set at $p\text{-value} \leq 0.05$, and all statistical tests were performed using the IBM Statistical Package for Social Science (SPSS) software, version 26.0.

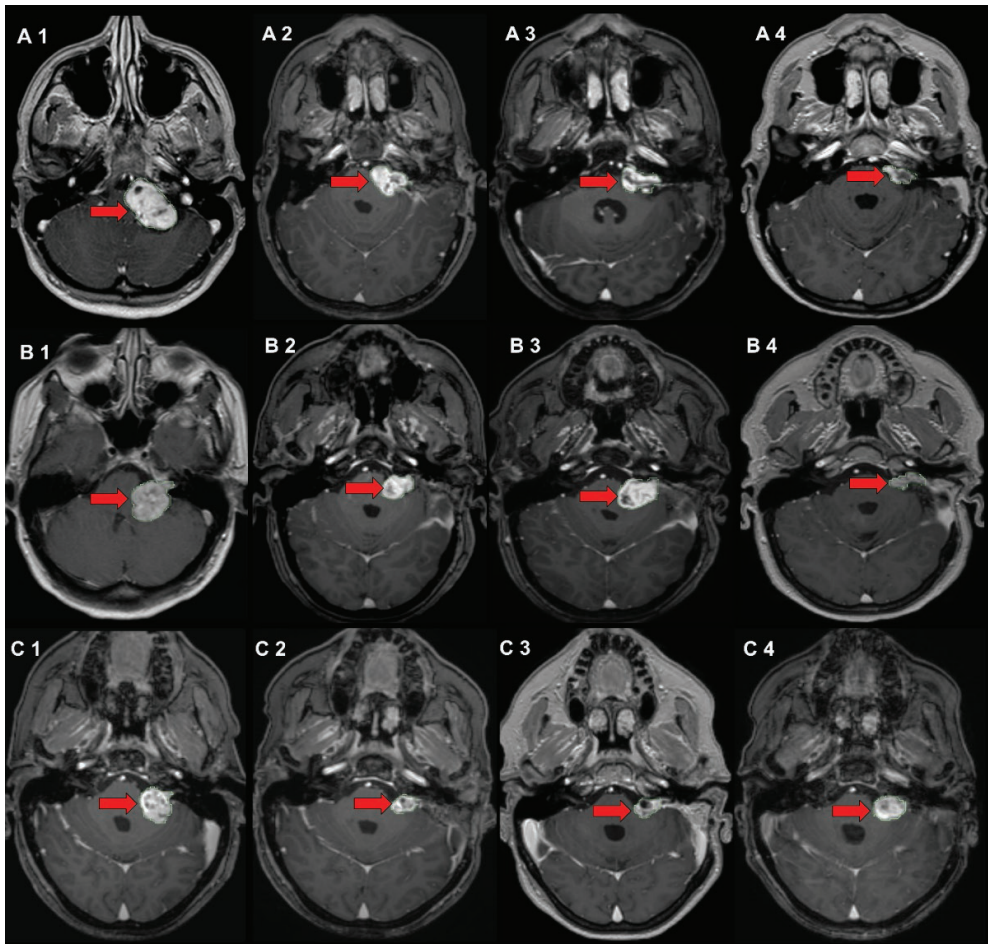


Figure 1: Transverse T1 3D MRI scans with gadolinium contrast in three patients (A, B, C) with left side VS, representing tumour shrinkage (A), transient swelling followed by shrinkage (B), and progression (C). 1 = pre-operative tumour, 2 = tumour before Gamma Knife, 3 = tumour 15 months after Gamma Knife, 4 = last follow-up.

RESULTS

Demographic and Treatment Data

A total of 23 patients with complete datasets were included in the analysis. This group consisted of 13 (57%) females and 10 (43%) males, with a mean age of 49 (range 22-73 years). Prior to surgery, all patients presented with hearing loss. Other symptoms included ataxia, vertigo, and tinnitus. Most of the VS tumours (74%) were located on the left side of the brain (17 left versus 6 on the right), and the mean tumour volume before surgery was 11.64 cm³ (range 4.59 – 31.02 cm³). All patients underwent planned partial resection, and the mean residual volume was 4.17 cm³ (range 1.29 – 10.99 cm³). Following surgery by a mean (SD)

time of 6 ($\pm$ 2) months, all patients received a marginal dose of 12- 13 Gy covering 99% of the tumour volume.

Tumour Control

After a mean follow-up time of 100 months (range 42–170) after GK, tumour control was achieved in 21 patients (91% control rate), and two patients showed tumour volume increase requiring re-operation in one (4%). Interval between GK radiosurgery and the progression manifestation in this patient was 16 months. The tumour control group showed two patterns of response: shrinkage in 20 patients (87%) and stable in one patient (4%). Five patients experienced transient progression after GK followed by shrinkage (Table I), (Figure 1).

Forward Stepwise Regression

Tumour volume at the last follow-up (dependent variable) showed no linear relationship with any of the predictor variables (age, sex, tumour location, volumes before and after surgery, interval between surgery and GK, and interval between GK and the last follow-up), except with the volume after GK. Volume after GK accounted for 41% of the variation in volume at the last follow-up, and the ANOVA test indicated that the model was significant ($p < 0.001$). This implies that overall, patients responded well to the surgical approach in combination with GK treatment.

Functional Preservation

Prior to surgery, all patients had a normal functioning FN (H-B Grade 1). These functions were maintained after surgery in all except one patient who had a temporary H-B Grade 3 that was resolved after four weeks. At the time of the last follow-up normal FN function was achieved in all patients.

Surgical Complications and Radiation-Induced Effects

In this cohort, no patient developed an infection, bleeding, or any surgical-related complication after surgery. However, one patient developed communicating hydrocephalus three years after the combined therapy and required a ventriculoperitoneal shunt. One patient underwent a second surgery due to tumour progression. Concerning early radiation-induced toxicities, only one patient suffered from a temporary paraesthesia in the trigeminal area. This developed six years later into a trigeminal neuralgia, which was treated with carbamazepine. No other late toxicities were seen in any of the patients.

DISCUSSION

The present study assessed the feasibility of managing Koos 4 VS more conservatively by utilizing the combined approach. All patients had a Koos 4 VS and suffered from complete hearing loss on the side of the tumour and had normal FN function. Therefore, the goal of

surgery was to reduce the mass effect and preserve FN functionality by leaving some rest tumour around the FN. After surgery, the mean tumour volume was reduced from 11.64 cm³ to 4.17 cm³. GK radiosurgery within 6 months after surgery resulted in tumour control in 91% of the patients with a mean follow-up of 100 months. This control is within the range of rates that have been published in studies reporting on the combined approach (79-100%) (7,15,22,23,39,40,41,53,58). These rates were pooled by a recent systematic review aiming at a better assessment of the efficacy of the combined approach in large VS. Two hundred and thirty patients with a tumour volume ranging from 1.16 to 9.35 cm³ (at the time of the SRS) were included in the analysis, and the estimated overall tumour control rate was 93.9% after 46 months (48).

To evaluate the tumour's response after treatment, all tumours were delineated manually to estimate a three-dimensional volume. Although this method takes more time than the traditional two-dimensional method, it is more accurate and has been found to be associated with a lower inter-observer error (27,52). At the last follow-up after GK irradiation, tumour stability was reported in one patient (4%), shrinkage in 20 patients (87%), and increase in volume in two patients (8%). Reducing the tumour volume allowed the GK radiosurgery to control residues in a comparable way to small-to-medium sized VS (<3 cm) when treated primarily by SRS, 92.7% after a mean follow-up of 51.24 months, reported by a meta analysis study (44). Interestingly, in our cohort five tumours demonstrated post-radiation growth followed by shrinkage. Okunaga stated that a true VS progression is only assured if the tumour growth continues for more than two years (37), and more recently, Fouard indicated that a minimum five years of follow-up is required (14).

Table I: Vestibular Schwannoma Volume Measurements in cm³ for All Patients at Four Time Points: (V_{T1}) Before Surgery, (V_{T2}) Before GK, (V_{T3}) After GK, and (V_{T4}) at the Last Follow-Up. Furthermore, the Disease Status and Follow-Up Duration are Displayed. *Case 2 underwent a second operation; the pre- and post-op volumes are presented.

Case	VT1	VT2	Amount of resection	VT3	VT4	Volume difference [VT2-VT4]	% of volume difference	Tumour control	Follow-up time (months)
1	7.12	2.14	70%	2.05	2.36	-0.22	+ 10%	Stable	79
2	4.59	1.74	62%	1.87	4.51/1.24*	-2.77	+ 159%	Progression	80
3	31.02	9.93	68%	6.35	3.06	6.87	- 69%	Shrinkage	106
4	17.66	8.23	53%	7.56	6.06	2.17	- 26%	Shrinkage	76
5	5.00	1.49	70%	1.30	0.15	1.34	- 90%	Shrinkage	72
6	10.9	2.28	79%	1.60	0.17	2.11	- 92%	Shrinkage	99
7	7.00	4.42	37%	3.55	1.88	2.54	- 57%	Shrinkage	72
8	4.91	2.92	40%	4.08	3.66	-0.74	+ 25%	Progression	75
9	11.00	4.88	56%	5.18	2.34	2.54	- 52%	Shrinkage	93
10	7.00	2.08	70%	1.44	0.44	1.64	- 79%	Shrinkage	42
11	8.62	4.24	51%	3.52	2.45	1.79	- 42%	Shrinkage	101
12	12.28	5.57	55%	5.88	2.28	3.29	- 59%	Shrinkage	66
13	9.35	3.27	65%	1.80	1.04	2.23	- 68%	Shrinkage	57
14	5.47	1.29	76%	1.00	0.34	0.95	- 74%	Shrinkage	119
15	10.57	5.60	47%	5.39	2.92	2.68	- 48%	Shrinkage	74
16	7.66	3.35	56%	2.74	1.92	1.43	- 43%	Shrinkage	139
17	20.00	3.86	81%	1.65	0.93	2.93	- 76%	Shrinkage	116
18	20.20	6.64	67%	3.76	1.13	5.51	- 83%	Shrinkage	125
19	5.40	1.76	67%	1.33	0.27	1.49	- 85%	Shrinkage	147
20	17.93	10.99	39%	9.40	2.62	8.37	- 76%	Shrinkage	141
21	22.02	3.45	84%	2.96	1.74	1.71	- 50%	Shrinkage	141
22	15.45	2.52	84%	2.69	1.01	1.51	- 60%	Shrinkage	104
23	6.54	3.17	51%	6.23	0.18	2.99	- 94%	Shrinkage	170

The challenge in VS management is that there is no specific method for identifying the growth rate or tumour behaviour. For example, a study that aimed to characterize the growth rate in 381 patients with small-to-medium-sized VS following a wait-and-scan policy reported that 32.5% had growth progression, 59.3% of the tumours remained stable, and 8.1% shrank after

a mean interval of 4.2 years between the first and last scans (34). Although no interventions were done, some tumours shrank. It is also known that VS may grow again, even after being macroscopically completely resected (36). Moreover, it is possible for patients undergoing radiation therapy to develop a late transient tumour enlargement (within four years after being irradiated) followed by shrinkage (14,32). Important to note is that many factors such as inflammation, and angiogenesis can influence the biological behaviour and volumetric growth of sporadic VS (8,9).

A key finding in the current study was the successful preservation of FN function in all patients (100%). This finding is in line with most of the previously published rates after the combined approach, which range from 85.7% to 100% (48). In literature, total resection of large VS as a treatment method takes up the largest number of previous publications and normally includes large sample sizes (49). This treatment preference is, mainly due to the excellent tumour control rates, reported in many articles (49). However, the FN preservation after total resection is highly dependent on the surgeon's experience (4,33). With an increase in VS volume, the FN will be stretched around the tumour and become thinner, making it more susceptible to injury during surgery (17). A dysfunction in the FN may significantly influence the patient's quality of life (39,43). Hence, a more conservative resection combined with GK radiosurgery may be considered beneficial for both the patient and the treating surgeon as it may ease the procedure for the surgeon and assure a high chance of functional preservation for the patient.

The absence of postsurgical and GK complications observed in the current study was in accordance with previous studies on the combined approach. Table II indicates that complications after partially resecting large VS are few and may resolve with time or medication. Major complications (non-neurological), such as wound infection, cerebral spinal fluid leakage, and meningitis, were more frequently reported after complete resection (2). A main objective of surgery in this combined approach is to achieve brain stem decompression and to reduce tumour volume to accommodate the radiosurgery, even though complete removal of the tumour would technically be feasible. The combined treatment reduces operation time as well as the degree of invasiveness, which is a plausible explanation for the decrease in complications. In 2011, Van de Langenberg noted a lower number of surgical complications after the combined approach by comparing their post-surgical outcomes with the literature (53). However, by gathering data from all the studies that reported the combined approach, this conclusion can be further strengthened. Nowadays, symptoms after GK radiosurgery do not constitute a major concern compared to early reports. Initially after the first use of GK to treat VS by Leksell (28), prescribed doses were commonly between 12–25 Gy (13,21,25). The high variation in the prescribed doses among early studies, with the most frequent being > 14 Gy, was because of the belief that VS can survive low doses. Although high control rates were achieved by these studies (90–100%), incidents of trigeminal neuropathy, reaching 81.7% in one study (13) and hearing deterioration were also high (21,25). The last two decades have

witnessed some consensus agreement on the dose range of 12–13 Gy. In the case of small-to-medium-sized VS treated primarily by radiosurgery, a marginal dose of 12–13 Gy has shown its efficacy in excellent control rates (>90%) and much lower incidents of toxicities (1,5,18). All studies of the combined approach (Table II), including the current study, consistently used this dosing scheme and showed similar results to those of small-to-medium-sized VS. One limitation of our study is that the number of patient with large VS treated between 2007 and 2018 in our department using the combined approach was larger, but due to incomplete data, the current study had a limited sample size of complete datasets. Additional limitations include the retrospective nature of the study design, which may have added some degree of bias to the results. Nevertheless, reporting volume change over time and functional outcomes of the combined approach for large VS neurosurgical treatment remains valuable.

Table II: Data Related to Surgical Complications and Radiation-Induced Effects Following the Subtotal Resection of Large VS and Subsequent GK Radiosurgery, respectively. These Data were Extracted from the 10 Studies That Followed the Combined Approach, Including the Current Study

Reference	Number of patients	Surgical approach	Surgical complications	Mean prescribed (marginal) dose, in Gy. (range)	Radiation-induced effects
Iwai et al. (23)	14	13 Retrosigmoid & 1 Transtentorial	No complications	12.1 (10–14.1)	No complications
Park et al. (40)	8	NR	-	12	No complications
Yang et al. (58)	61	Retrosigmoid	NR	11.8 (11-13)	No complications
Fuentes et al. (15)	8	NR	NR	12.5 (9-14)	No complications
Van de Langenberg et al. (53)	50		Minor complications include: hematoma in 2 patient, hydrocephalus in 2 patients, VP drainage in 1 patient, lumbar drainage in 1 patient, CN IX & X. Temporary dysfunction in 3 patients, CN IX & X persistent dysfunction 1 patient, temporary abducens paresis in 1 patient. Major complication (hemiparesis).	11 (9.4-11.9)	— H-B Grade II transient facial paresis in 2 patients. — Transient trigeminal hypaesthesia in 1 patient. — Persisting facial nerve spasms in 1 patient (improved with a botulinum toxin injections every 3 months).
		25 Retrosigmoid			
		25 Translabryrithine			

Table II: Data Related to Surgical Complications and Radiation-Induced Effects Following the Subtotal Resection of Large VS and Subsequent GK Radiosurgery, respectively. These Data were Extracted from the 10 Studies That Followed the Combined Approach, Including the Current Study (*continued*)

Reference	Number of patients	Surgical approach	Surgical complications	Mean prescribed (marginal) dose, in Gy. (range)	Radiation-induced effects
Pan et al. (39)	18	Retrosigmoid	Delayed hydrocephalus in 1 patient required a placement of a VP shunt.	12	No complications
Iwai et al. (22)	40	Retrosigmoid	Only minor complications: — Lung abscess due to aspiration pneumonia in 1 patient. — Aseptic meningitis in 1 patient (treated with steroids). — Pulmonary embolism in 1 patient.	12 (10-12)	— Transient facial spasms in 2 patients. — Transient trigeminal neuropathy in 2 patients. All symptoms were resolved spontaneously.
Radwan et al. (41)	22	NR	— Facial numbness in 4 patients (3 improved before radiosurgery). — Temporary dysphagia and dysarthria	12.5 (12-14)	Mild trigeminal neuropathy in 1 patient (last for 3 months).
Daniel et al. (7)	32	Retrosigmoid	— Transient facial hypoesthesia (resolved with time) — Transient vagus nerve deficit (resolved after 6 months)	12 (11-12)	No complications
Present study	23	Translabrynthine	No complications	12.9 (12-13)	Trigeminal paraesthesia/ neuralgia in one patient.

NR: Not reported, and the symbol “-“ indicates that there is no clear data.

CONCLUSION

Upfront planning for a partial resection followed by GK radiosurgery is an effective and safe treatment choice for patients with Koos 4 VS. The efficacy consists of good tumour control and a low number of complications, respectively.

REFERENCES

1. Apicella G, Paolini M, Deantonio L, Masini L, Krengli M: Radiotherapy for vestibular schwannoma: Review of recent literature results. *Rep Pract Oncol Radiother* 21:399-406, 2016. <https://doi.org/10.1016/j.rpor.2016.02.002>.
2. Betka J, Zvěřina E, Balogová Z, Profant O, Skřivan J, Kraus J, Lisý J, Syka J, Chovanec M: Complications of microsurgery of vestibular schwannoma. *BioMed Res Int* 2014:315952, 2014. <https://doi.org/10.1155/2014/315952>.
3. Bloch DC, Oghalai JS, Jackler RK, Osofsky M, Pitts LH: The fate of the tumor remnant after less-than-complete acoustic neuroma resection. *Otolaryngol Head Neck Surg* 130:1041-12, 2004. [https://doi.org/10.1016/s0194-5998\(03\)01598-5](https://doi.org/10.1016/s0194-5998(03)01598-5).
4. Bloch O, Sughrue ME, Kaur R, Kane AJ, Rutkowski MJ, Kaur G, Yang I, Pitts LH, Parsa AT: Factors associated with preservation of facial nerve function after surgical resection of vestibular schwannoma. *J Neurooncol* 102:281-286, 2011. <https://doi.org/10.1007/s11060-010-0315-5>.
5. Boari N, Bailo M, Gagliardi F, Franzin A, Gemma M, Vecchio AD, Bolognesi A, Picozzi P, Mortini P: Gamma knife radiosurgery for vestibular schwannoma: Clinical results at long-term follow-up in a series of 379 patients. *J Neurosurg* 121:123, 2014. <https://doi.org/10.3171/2014.8.GKS141506>.
6. Chung WY, Liu KD, Shiau CY, Wu HM, Wang LW, Guo WY, Ho DM, Pan DH: Gamma knife surgery for vestibular schwannoma: 10-year experience of 195 cases. *J Neurosurg* 102 Suppl:87-96, 2005
7. Daniel RT, Tuleasca C, George M, Pralong E, Schiappacasse L, Zeverino M, Maire R, Levivier M: Preserving normal facial nerve function and improving hearing outcome in large vestibular schwannomas with a combined approach: Planned subtotal resection followed by gamma knife radiosurgery. *Acta Neurochir* 159:1197-1211, 2017. <https://doi.org/10.1007/s00701-017-3194-0>.
8. De Vries M, Briaire-de Bruijn I, Malessy MJA, de Bruijne SFT, van der Mey AGL, Hogendoorn PCW: Tumor-associated macrophages are related to volumetric growth of vestibular schwannomas. *Otol Neurotol* 34:347-352, 2013. <https://doi.org/10.1097/MAO.0b013e31827c9fbf>.
9. De Vries M, Hogendoorn PCW, Briaire-de Bruyn I, Malessy MJA, van der Mey AGL: Intratumoral hemorrhage, vessel density, and the inflammatory reaction contribute to volume increase of sporadic vestibular schwannomas. *Virchows Arch* 460:629-636, 2012. <https://doi.org/10.1007/s00428-012-1236-9>.
10. El-Kashlan HK, Zeitoun H, Arts HA, Hoff JT, Telian SA: Recurrence of acoustic neuroma after incomplete resection. *Am J Otol* 21:389-392, 2000. [https://doi.org/10.1016/s01960709\(00\)80049-6](https://doi.org/10.1016/s01960709(00)80049-6).
11. Falcioni M, Fois P, Taibah A, Sanna M: Facial nerve function after vestibular schwannoma surgery. *J Neurosurg* 115:820826, 2011. <https://doi.org/10.3171/2011.5.JNS101597>.
12. Fedorov A, Beichel R, Kalpathy-Cramer J, Finet J, FillionRobin JC, Pujol S, Bauer C, Jennings D, Fennessy F, Sonka M, Buatti J, Aylward S, Miller JV, Pieper S, Kikinis R: 3D Slicer as an image computing platform for the Quantitative Imaging Network. *Magn Reson Imaging* 30:1323-1341, 2012. <https://doi.org/10.1016/j.mri.2012.05.001>.
13. Foote RL, Coffey RJ, Swanson JW, Harner SG, Beatty CW, Kline RW, Stevens LN, Hu TC: Stereotactic radiosurgery using the gamma knife for acoustic neuromas. *Int J of Radiat Oncol Biol Phys* 32:1153-1160, 1995. [https://doi.org/10.1016/03603016\(94\)00454-S](https://doi.org/10.1016/03603016(94)00454-S).
14. Fouard O, Daisne JF, Wanet M, Regnier M, Gustin T: Longterm volumetric analysis of vestibular schwannomas following stereotactic radiotherapy: Practical implications for followup. *Clin Transl Radiat Oncol* 33:1-6, 2022. <https://doi.org/10.1016/j.ctro.2021.12.003>.
15. Fuentes S, Arkha Y, Pech-Gourg G, Grisoli F, Dufour H, Regis J: Management of large vestibular schwannomas by combined surgical resection and gamma knife radiosurgery. *Prog Neurol Surg* 21:79-82, 2008. <https://doi.org/10.1159/000156709>.

16. Godefroy WP, van der Mey AGL, de Bruine FT, Hoekstra ER, Malessy MJA: Surgery for large vestibular schwannoma: residual tumor and outcome. *Otol Neurotol* 30:629-634, 2009. <https://doi.org/10.1097/MAO.0b013e3181a8651f>.
17. Gurgel RK, Dogru S, Amdur RL, Monfared A: Facial nerve outcomes after surgery for large vestibular schwannomas: Do surgical approach and extent of resection matter? *Neurosurgical Focus* 33:E16, 2012. <https://doi.org/10.3171/2012.7.Focus12199>.
18. Hasegawa T, Kida Y, Kato T, Iizuka H, Kuramitsu S, Yamamoto T: Long-term safety and efficacy of stereotactic radiosurgery for vestibular schwannomas: Evaluation of 440 patients more than 10 years after treatment with Gamma Knife surgery. *J Neurosurg* 118:557-565, 2013. <https://doi.org/10.3171/2012.10.Jns12523>.
19. Hayhurst C, Zadeh, G: Tumor pseudoprogression following radiosurgery for vestibular schwannoma. *Neuro Oncol* 14: 87-92, 2012. <https://doi.org/10.1093/neuonc/nor171>
20. Hitselberger WE, House WF: Classification of acoustic neuromas. *Arch Otolaryngol* 84:245-246, 1966.
21. Ito K, Kurita H, Sugawara K, Mizuno M, Sasaki T: Analyses of neuro-otological complications after radiosurgery for acoustic neurinomas. *Int J Radiat Oncol Biol Phys* 39:983-988, 1997. [https://doi.org/10.1016/s0360-3016\(97\)00507-5](https://doi.org/10.1016/s0360-3016(97)00507-5).
22. Iwai Y, Ishibashi K, Watanabe Y, Uemura G, Yamanaka K: Functional preservation after planned partial resection followed by gamma knife radiosurgery for large vestibular schwannomas. *World Neurosurg* 84:292-300, 2015. <https://doi.org/10.1016/j.wneu.2015.03.012>.
23. Iwai Y, Yamanaka K, Ishiguro T: Surgery combined with radiosurgery of large acoustic neuromas. *Surg Neurol* 59:283289, 2003. [https://doi.org/10.1016/S0090-3019\(03\)00025-9](https://doi.org/10.1016/S0090-3019(03)00025-9).
24. Jeyakumar A, Seth R, Brickman TM, Dutcher P: The prevalence and clinical course of patients with 'incidental' acoustic neuromas. *Acta Otolaryngol* 127:1051-1057, 2007. <https://doi.org/10.1080/00016480701200210>.
25. Kondziolka D, Lunsford LD, McLaughlin MR, Flickinger JC: Long-term outcomes after radiosurgery for acoustic neuromas. *New England J Med* 339:1426-1433, 1998. <https://doi.org/10.1056/nejm199811123392003>.
26. Lanman TH, Brackmann DE, Hitselberger WE, Subin B: Report of 190 consecutive cases of large acoustic tumors (vestibular schwannoma) removed via the translabyrinthine approach. *J Neurosurg* 90:617-623, 1999. <https://doi.org/10.3171/jns.1999.90.4.0617>.
27. Lawson McLean AC, McLean AL, Rosahl SK: Evaluating vestibular schwannoma size and volume on magnetic resonance imaging: An inter- and intra-rater agreement study. *Clin Neurol Neurosurg* 145:68-73, 2016. <https://doi.org/10.1016/j.clineuro.2016.04.010>.
28. Leksell L: A note on the treatment of acoustic tumours. *Acta Chir Scand* 137:763-765, 1971
29. Lunsford LD, Niranjan A, Flickinger JC, Maitz A, Kondziolka D: Radiosurgery of vestibular schwannomas: Summary of experience in 829 cases. *J Neurosurg* 102:195-199, 2005. https://doi.org/10.3171/sup.2005.102.s_supplement.0195.
30. Mamikoglu B, Wiet RJ, Esquivel CR: Translabyrinthine approach for the management of large and giant vestibular schwannomas. *Otol Neurotol* 23:224-227, 2002.
31. Marinelli JP, Lohse CM, Carlson ML: Incidence of vestibular schwannoma over the past half-century: A population-based study of olmsted county, Minnesota. *Otolaryngol Head Neck Surg* 159:717-723, 2018. <https://doi.org/10.1177/0194599818770629>.
32. Meijer OW, Weijmans EJ, Knol DL, Slotman BJ, Barkhof F, Vandertop WP, Castelijns JA: Tumor-volume changes after radiosurgery for vestibular schwannoma: Implications for follow-up MR imaging protocol. *AJNR Am J Neuroradiol* 29: 906-910, 2008. <https://doi.org/10.3174/ajnr.A0969>.
33. Moffat DA, Hardy DG, Grey PL, Baguley DM: The operative learning curve and its effect on facial nerve outcome in vestibular schwannoma surgery. *Am J Otol* 17:643-647, 1996

34. Moffat DA, Kasbekar A, Axon PR, Lloyd SKW: Growth characteristics of vestibular schwannomas. *Otol Neurotol* 33: 1053-1058, 2012. <https://doi.org/10.1097/MAO.0b013e3182595454>.
35. Myrseth E, Pedersen PH, Møller P, Lund-Johansen M: Treatment of vestibular schwannomas. Why, when and how? *Acta Neurochir* 149:647-660, 2007. <https://doi.org/10.1007/s00701-007-1179-0>.
36. Nakatomi H, Jacob JT, Carlson ML, Tanaka S, Tanaka M, Saito N, Lohse CM, Driscoll CLW, Link MJ: Long-term risk of recurrence and regrowth after gross-total and subtotal resection of sporadic vestibular schwannoma. *J Neurosurg* 133:1052-1058, 2017. <https://doi.org/10.3171/2016.11.Jns16498>.
37. Okunaga T, Matsuo T, Hayashi N, Hayashi Y, Shabani HK, Kaminogo M, Ochi M, Nagata I: Linear accelerator radiosurgery for vestibular schwannoma: Measuring tumor volume changes on serial three-dimensional spoiled gradientecho magnetic resonance images. *J Neurosurg* 103:53-58, 2005. <https://doi.org/10.3171/jns.2005.103.1.0053>.
38. Pan HC, Cheng FC, Sun MH, Chen CC, Sheehan J: Prediction of volumetric data errors in patients treated with gamma knife radiosurgery. *Stereotact Funct Neurosurg* 85:184-191, 2007. <https://doi.org/10.1159/000101297>.
39. Pan HC, Sheehan J, Sheu ML, Chiu WT, Yang DY: Intracapsular decompression or radical resection followed by Gamma Knife surgery for patients harboring a large vestibular schwannoma. *J Neurosurg* 117 Suppl:69-77, 2012. [doi:10.3171/2012.6.gks12697](https://doi.org/10.3171/2012.6.gks12697).
40. Park CK, Jung HW, Kim JE, Son YJ, Paek SH, Kim DG: Therapeutic strategy for large vestibular schwannomas. *J Neurooncol* 77:167-171, 2006. <https://doi.org/10.1007/s11060005-9015-y>.
41. Radwan H, Eisenberg MB, Sandberg Knisely JP, Ghaly MM, Schulder M: Outcomes in patients with vestibular schwannoma after subtotal resection and adjuvant radiosurgery. *Stereotact Funct Neurosurg* 94:216-224, 2016. <https://doi.org/10.1159/00047520>.
42. Ramina R, Coelho Neto M, Bordignon KC, Mattei T, Clemente R, Pires Aguiar PH: Treatment of large and giant residual and recurrent vestibular schwannomas. *Skull Base* 17:109-117, 2007. <https://doi.org/10.1055/s-2006-953510>.
43. Rosahl S, Bohr C, Lell M, Hamm K, Iro H: Diagnostics and therapy of vestibular schwannomas - an interdisciplinary challenge. *GMS Curr Top Otorhinolaryngol Head Neck Surg* 16:Doc03, 2017. <https://doi.org/10.3205/cto000142>.
44. Rykaczewski B, Zabek M: A meta-analysis of treatment of vestibular schwannoma using Gamma Knife radiosurgery. *Contemp Oncol* 18:60-66, 2014. <https://doi.org/10.5114/wo.2014.39840>.
45. Samii M, Gerganov VM, Samii A: Functional outcome after complete surgical removal of giant vestibular schwannomas. *J Neurosurg* 112:860-867, 2010. [doi:10.3171/2009.7.Jns0989](https://doi.org/10.3171/2009.7.Jns0989).
46. Schmidt RF, Boghani Z, Choudhry OJ, Eloy JA, Jyung RW, Liu JK: Incidental vestibular schwannomas: A review of prevalence, growth rate, and management challenges. *Neurosurg Focus* 33:E4, 2012. <https://doi.org/10.3171/2012.7.Focus12186>.
47. Stangerup SE, Caye-Thomasen P, Tos M, Thomsen J: The natural history of vestibular schwannoma. *Otol Neurotol* 27: 547-552, 2006. <https://doi.org/10.1097/01.mao.0000217356.73463.e7>.
48. Starnoni D, Daniel RT, Tuleasca C, George M, Levivier M, Messerer M: Systematic review and meta-analysis of the technique of subtotal resection and stereotactic radiosurgery for large vestibular schwannomas: A “nervecentered” approach. *Neurosurg Focus* 44:E4, 2018. <https://doi.org/10.3171/2017.12.Focus17669>.
49. Starnoni D, Giammattei L, Cossu G, Link MJ, Roche PH, Chacko AG, Ohata K, Samii M, Suri A, Bruneau M, Cornelius JF, Cavallo L, Meling TR, Froelich S, Tatagiba M, Sufianov A, Paraskevopoulos D, Zazpe I, Berhouma M, Jouanneau E, Verheul JB, Tuleasca C, George M, Levivier M, Messerer M, Daniel RT: Surgical management for large vestibular schwannomas: A systematic

- review, meta-analysis, and consensus statement on behalf of the EANS skull base section. *Acta Neurochir* 162:2595-2617, 2020. [https:// doi:10.1007/s00701-020-04491-7](https://doi.org/10.1007/s00701-020-04491-7).
50. Thomas C, Di Maio S, Ma R, Vollans E, Chu C, Clark B, Lee R, McKenzie M, Martin M, Toyota B: Hearing preservation following fractionated stereotactic radiotherapy for vestibular schwannomas: Prognostic implications of cochlear dose. *J Neurosurg* 107:917-926, 2007. [https:// doi:10.3171/jns07/11/0917](https://doi.org/10.3171/jns07/11/0917).
51. Vakilian S, Souhami L, Melançon D, Zeitouni A: Volumetric measurement of vestibular schwannoma tumour growth following partial resection: Predictors for recurrence. *J Neurol Surg Part B Skull Base* 73:117-120, 2012. [https:// doi:10.1055/s-0032-1301395](https://doi.org/10.1055/s-0032-1301395).
52. Van de Langenberg R, de Bondt BJ, Nelemans PJ, Baumert BG, Stokroos RJ: Follow-up assessment of vestibular schwannomas: Volume quantification versus two-dimensional measurements. *Neuroradiol* 51:517-524, 2009. [https:// doi:10.1007/s00234-009-0529-4](https://doi.org/10.1007/s00234-009-0529-4).
53. Van de Langenberg R, Hanssens PEJ, Van Overbeeke JJ, Verheul JB, Nelemans PJ, De Bondt BJ, Stokroos RJ: Management of large vestibular schwannoma. Part I. Planned subtotal resection followed by Gamma Knife surgery: Radiological and clinical aspects - Clinical article. *J Neurosurg* 115:875-884, 2011
54. Van de Langenberg R, Hanssens PEJ, Verheul JB, van Overbeeke JJ, Nelemans PJ, Dohmen AJ, de Bondt BJ, Stokroos RJ: Management of large vestibular schwannoma. Part II. Primary Gamma Knife surgery: Radiological and clinical aspects. *J Neurosurg* 115:885-893, 2011. [https:// doi:10.3171/2011.6.Jns101963](https://doi.org/10.3171/2011.6.Jns101963).
55. Weber DC, Chan AW, Bussiere MR, Harsh IVGR, Ancukiewicz M, Barker IIFG, Thornton AT, Martuza RL, Nadol JJB, Chapman PH, Loeffler JS: Proton beam radiosurgery for vestibular schwannoma: Tumor control and cranial nerve toxicity. *Neurosurgery* 53:577-588, 2003. [https:// doi:10.1227/01.NEU.0000079369.59219.C0](https://doi.org/10.1227/01.NEU.0000079369.59219.C0).
56. Whitmore RG, Urban C, Church E, Ruckenstein M, Stein SC, Lee JY: Decision analysis of treatment options for vestibular schwannoma. *J Neurosurg* 114:400-413, 2011. [https:// doi:10.3171/2010.3.jns091802](https://doi.org/10.3171/2010.3.jns091802).
57. Wiet RJ, Mamikoglu B, Odom L, Hoistad DL: Long-term results of the first 500 cases of acoustic neuroma surgery. *Otolaryngol Head Neck Surg* 124:645-651, 2001. [https:// doi:10.1177/019459980112400609](https://doi.org/10.1177/019459980112400609).
58. Yang SY, Kim DG, Chung HT, Park SH, Paek SH, Jung HW: Evaluation of tumor response after gamma knife radiosurgery for residual vestibular schwannomas based on MRI morphological features. *J Neurol Neurosurg Psychiatry* 79:431-436, 2008. [https://doi:10.1136/jnnp.2007.119602](https://doi.org/10.1136/jnnp.2007.119602).
59. Yao L, Alahmari M, Temel Y, Hovinga K: Therapy of sporadic and NF2-related vestibular schwannoma. *Cancers* 12:835, 2020. <https://doi.org/10.3390/cancers12040835>.
60. Zhang X, Fei Z, Chen YJ, Fu LA, Zhang JN, Liu WP, He XS, Jiang XF: Facial nerve function after excision of large acoustic neuromas via the suboccipital retrosigmoid approach. *J Clin Neurosci* 12:405-408, 2005. <https://doi.org/10.1016/j.jocn.2004.03.042>.
61. Zhang Z, Nguyen Y, De Seta D, Russo FY, Rey A, Kalamarides M, Sterkers O, Bernardeschi D: Surgical treatment of sporadic vestibular schwannoma in a series of 1006 patients. *Acta Otorhinolaryngol Ital* 36:408-414, 2016. [https:// doi:10.14639/0392-100X-1176](https://doi.org/10.14639/0392-100X-1176).

3

Sinonasal Tumors

Clinical outcome in patients with large sinonasal tumors with intracranial extension

Keizer ME, Hovinga KE, Lacko M, Eekers DBP, Baijens LWJ, Kremer B, Temel Y. Clinical Outcome in Patients with Large Sinonasal Tumors with Intracranial Extension. J Neurol Surg B Skull Base. 2023 May 24;85(4):347-357.

ABSTRACT

Malignant tumors of the sinonasal cavities with extension to the frontal skull base are rare and challenging pathologies. A combined-approach including frontobasal craniotomy, endoscopic sinus surgery with reconstruction of the anterior skull base, followed by adjuvant radiotherapy is our preferred treatment strategy in selected cases. Morbidity and mortality rates are high in this population. We performed a retrospective cross-sectional single center study of the long-term clinical outcome in our tertiary university referral hospital between 2010 and 2020. Patient, tumor, treatment, complications and survival characteristics of eighteen consecutive patients were extracted from the electronic health records. Descriptive statistics and frequency distributions were performed. Eighteen consecutive patients were included with a mean age of 61 (SD $\pm$ 10) years (range 38-80); ten males and eight females. Gross total resection was achieved in 14 (77%) patients. Eleven (61%) patients underwent local radiotherapy, one (5%) chemotherapy and three (17%) a combination of both. Mean follow-up duration was 49 months (range 3 – 138). Three (17%) patients died in the hospital due to post-operative complications. Six (33%) patients died during follow-up due to disease progression. Mean progression-free survival was 47 months (range 0 – 113). In conclusion, the overall survival was 50% for this group of patients with large sinonasal tumors. Progressive disease affects survival rate severely. Surgical complications were seen in five (28%) patients. Radiotherapy is associated with high complication rates. Radiation necrosis was a serious complication in two patients and could be treated with high dose steroids.

Keywords: Skull base, esthesioneuroblastoma, sinonasal carcinoma, inverted papilloma, squamous cell carcinoma, adenoid cystic carcinoma, radiotherapy, reconstruction, craniotomy

INTRODUCTION

Sinonasal tumors are rare and challenging pathologies, accounting for less than 1% of all malignancies¹. These lesions often present in an advanced stage, involving both paranasal sinuses and surrounding structures such as the anterior skull base, brain, and orbit¹. When the skull base is affected, the tumor may have invaded the dura and brain parenchyma worsening the prognosis². The treatment modality of these lesions depends on the extent of the lesion and histopathological diagnosis^{2,3}. Open approaches used to be the only surgical option, however in the last three decades endoscopic approaches are added as part of the surgical strategy. Current literature suggests a reduced complication rate in endoscopic approaches compared to open surgery while preserving comparable oncologic outcomes. The choice for specific surgical strategies also depends on preferences and experiences of the surgical team. Extensive invading tumors might be less suitable for endoscopic surgery alone. In tumors eligible for resection, surgical removal followed by skull base reconstruction is the first step⁴⁻⁶. Depending on the type of tumor and disease stage, post-operative chemo and/or radiation therapy is indicated⁷⁻¹⁵.

The most common tumor is the squamous cell carcinoma (SCC), accounting for up to 50% of all sinonasal malignancies, followed by adenocarcinoma (AC, 12.6%), melanoma (ML, 6.6%), esthesioneuroblastoma (ENB, 6.3%) adenoid cystic (ACC, 6.2%) and undifferentiated carcinoma (SNUC, 3.1%)¹. Most patients are diagnosed at an advanced stage where the cancer has invaded surrounding structures (54.5%) or show distant metastasis (14.9%)^{16,17}. A distinct minority presents in an early, local disease stage (30.6%)¹. Overall survival is poor with an average 5-years survival of 54.5%¹. However, subgroups of survival rates may be stratified according to histology and disease stage^{16,17}. A relatively good prognosis is seen in ENB and ACC with a 5-years overall survival of 71.0% and 69.5%, respectively, and in patients with only local disease (80.9%). Intermediate survival rates at 5 years are seen in SCC (53.0%) and AC (63.0%) and in patients with regionally advanced disease (48.6%). The poorest prognosis is observed in patients with ML and SNUC with only 34.7% survival after 5 years and patients with distant metastasis (28.2%)¹.

Surgical resection is the mainstay treatment for these tumors. Gross total resection is associated with better outcome compared to subtotal removal and to radiotherapy mono-treatment⁷. Radiotherapy can be applied as part of palliative treatment and as adjuvant therapy⁷. Surgery for tumor recurrence may be considered in selected cases but is associated with high morbidity and mortality². The benefit of induction or adjuvant chemoradiation is still unclear¹⁵.

Treatment of sinonasal cancer is associated with high rates of complications, both surgery and radiotherapy related. Post-operative mortality is around 4.7% and comorbidity is associated with a higher surgery related mortality¹⁸. Complications are seen in 36.3% of the

patients¹⁸. Wound related complications (infection, dehiscence, necrosis) occur in 19.8%, Central nervous system (CNS) related complications (cerebral spinal fluid leak, meningitis, pneumocephalus, neurological deficit) occur in 16.2%, systemic complications (cardiovascular, pulmonary, urinary tract infection) in 4.8% and orbital complications (blindness, diplopia, lacrimal duct obstruction) in 1.7%. The presence of medical comorbidity, induction radiotherapy, dural or brain invasion is associated with higher probability of complications¹⁸.

Radiotherapy associated complications are reported in up to 50% of patients. These include all five severity grades in accordance with the Common Terminology Criteria for Adverse Events¹⁹. Most common complications are visual deficits up to blindness, tear film imbalance, nasal mucosa inflammation, wound infection, bone flap necrosis, brain necrosis, pituitary deficit and pain^{11–14,18}.

The low incidence of these tumors and their heterogeneous aspect makes it difficult to execute large randomized controlled trials. Therefore, mostly papers reporting on small retrospective cohorts are available. We would like to add to the current literature by describing our single institute long-term outcome on the treatment of large sinonasal cancers with intracranial extension. The aim of this study is to evaluate tumor control, progression free and overall survival and therapy associated complications after a frontobasal craniotomy with endoscopic assistance and skull base reconstruction.

MATERIALS AND METHODS

Study design

We conducted a retrospective analysis of our cohort between January 2010 and December 2021. Data including medical history, neurological status, radiological examinations, operative details, surgical outcome, histopathology, adjuvant therapies, complications, and follow-up details were extracted from the electronic patient files. Tumor recurrence and clinical outcome data were collected at three and twelve months post-operative time-points and at the last follow-up time-point. The study protocol was approved by the medical ethics committee of Maastricht University Medical Centre+, and received the following reference number: 2021-2608.

Subjects

All consecutive patients with a sinonasal tumor with anterior skull base extension treated using a bifrontal (frontobasal) craniotomy by our multidisciplinary skull base team, were eligible to be included in this study. Case by case discussions took place and the best possible tailored therapy was proposed to the patient. Patients had to have a Karnofsky performance score above 60 to be eligible for resection and a gross total resection must be possible. In our institution, a bifrontal craniotomy is used in all cases with stage T4b carcinoma. Stage 4a

carcinoma can be treated by an endoscopic approach or a bifrontal craniotomy. The approach is selected based on anatomical location and whether the surgeon believes the local invasion can be removed and reconstructed by endoscopy, if not, a bifrontal craniotomy is indicated. The follow-up was performed by the multidisciplinary skull base team.

Surgical approach

The approach in all cases was the transcranial route (here referred as frontobasal craniotomy) to the paranasal sinuses and removal of tumor tissue along this route. Endoscopy was used through the transcranial opening and/or trans nasal to assist tumor removal. The details of the craniotomy were as follows. A bifrontal incision was performed with preservation of the periosteum to be used for the skull base reconstruction. When a second surgery was necessary, then the galea aponeurotica-layer was used for skull base reconstruction. After the bifrontal craniotomy, the dura was opened if there was intradural tumor. For the intradural approach, the most anterior part of the superior sagittal sinus was ligated and the falx cerebri was transected. The following step was to remove the posterior wall of the frontal sinus, drilling of the cribriform plate and drilling of the cranial part of the sphenoid plane to access the frontal, ethmoidal and sphenoid sinuses, respectively. Tumor tissue was removed using microsurgical techniques. The CUSA-aspirator was applied as well as the surgery-shaver, whenever applicable. When the intra orbital viscera were involved in the tumor process, an exenteration was performed and the craniofacial surgeon prepared the orbit for an ocular prosthetic. When gross total resection was achieved, reconstruction of the anterior skull base was performed. A split skull graft from the frontal craniotomy-bone was made and inserted at the frontal skull base opening, then the periosteum was used as cover supported by a fat graft from the para umbilical region. The wound was closed in a layered fashion. All patients received seven days of antibiotic prophylaxis post-operatively and two days of bed rest.

Adjuvant therapy

In our institution, all patients with T4 sinonasal carcinoma receive adjuvant local regional radiotherapy. In line with this, the patients in this series received photon radiation therapy, consisting of 30 to 35 fractions of 2.0 Gy to a total dose of 60 to 70 Gy using Volumetric Modulated Arc Therapy. The target volume consisted of the resection cavity and tumor remnant after resection with a margin according to local guidelines. Timing depended on wound healing and complications and varied between two to six weeks post-operatively.

Induction chemotherapy is not applied in our institution. Adjuvant systemic therapy is an option in patients with recurrent disease who are not eligible for re-resection or with distant metastases.

Clinical follow-up

Oncological follow-up was performed at three and six months post-operatively after which the standard interval remained six months. A standardized examination protocol, used in

daily clinical practice, was carried out. This protocol comprised a physical examination with endoscopic evaluation of the nasal cavity and opened paranasal sinuses. An MRI was performed to evaluate tumor recurrence. See figure 1 for an example. All cases who showed progressive disease or symptoms were discussed in our skull base board.

Statistics

A descriptive approach was used to display the data due to the small and heterogeneous nature of our cohort. All data were analyzed using Statistical Package for the Social Sciences version 27 software (SPSS, Chicago, IL, USA).

RESULTS

Demographics

In total 18 patients were identified for inclusion, 10 males and 8 females. Mean age at surgery was 61 years (range 38 – 80). Three (16%) patients were diagnosed with an esthesioneuroblastoma, three (16%) with an adenoid cystic sinonasal carcinoma, five (28%) with an adenocarcinoma, two (11%) with a squamous cell carcinoma, two with a sinonasal undifferentiated carcinoma, one (5%) with a melanoma, one with an inverted papilloma with squamous cell carcinoma differentiation and one patient with a sinonasal neuro-endocrine carcinoma. Most patients presented with complaints of nasal obstruction (n=10) and rhinorrhea (n=8). Two patients suffered from severe frontal lobe syndrome due to significant cytotoxic edema and mass effect on the frontal lobes. One patient had an epileptic seizure as her presenting symptom. Twelve patients had orbital involvement of the tumor process, six of which showed symptoms following this involvement. See table 1 for a more detailed description.

Clinical course and survival

Mean length of stay in hospital was 21 days (range 4 – 132). Gross total resection was achieved in 14 (77%) patients. Eleven patients (61%) had no complications during their hospital stay. Three (17%) patients died in the hospital due to post-operative complications consisting of subarachnoid hemorrhage (SAH), cardiac arrest, and ventriculitis, respectively.

Mean follow-up duration was 49 months (range 3 – 138). Six (33%) patients died during follow-up. Mean progression-free survival was 47 months (range 0 – 113).

The individual cases will be discussed per tumor type. See table 2 for a more detailed description.

Adenocarcinoma

Case 7 had no complications post-operatively and is now 58 months after surgery without signs of tumor recurrence. Case 11 showed at post-operative day two nasal liquorrhea, which

was resolved with an external lumbar drain and acetazolamide for 7 days. This patient is now 78 months in follow-up without tumor recurrence. Case 13 had no in-hospital complications, however showed distant cutaneous and osseous tumor recurrence after six months for which systemic therapy and loco regional radiotherapy were given. After 13 months, the patient died due to progressive disease. Case 14 experienced a delirium post-operatively, probably related to the pre-operative already present bifrontal edema. It resolved using antipsychotic medication. Six months post-operatively, the patient had distant leptomeningeal tumor recurrence. The patient refused chemo radiation and died shortly after. Case 17 had a severe per-operative complication, a SAH, from which the patient died three days post-operatively. More details are given in the next section.

Esthesioneuroblastoma

None of the patients diagnosed with esthesioneuroblastoma suffered from in-hospital complications. Case 1 is 20 months in follow-up in which there is no evidence for tumor recurrence.

Case 4 refused post-operative radiotherapy and showed tumor recurrence at 15 months after surgery. After discussions with the patient and parents, consent was given for re-resection with post-operative radiotherapy. The patient is now 51 months in follow-up with no sign of tumor recurrence.

Case 6 has died 64 months after surgery due to the late complications' effects of surgery and radiotherapy. The patient suffered from epilepsy and a frontal lobe syndrome with bifrontal radio necrosis and infection. Patient's condition deteriorated fast, without signs of tumor recurrence, and died

Adenoid cystic carcinoma

One case had an incomplete patient record. The other two cases had an uncomplicated hospital stay. Case 2 is now 66 months in follow-up without signs of tumor recurrence.

Case 5 has data available since 2012. The patient showed tumor recurrence 100 months post-operative for which re-resection with adjuvant radiotherapy was advised, however patient refused treatment. The patient was referred to an external oncologist for systemic therapy. Currently, the patient has shown minimal progressive disease after 138 months post-operative. Case 16 showed tumor recurrence at six months post-operatively for which the patient was referred to an external oncologist for systemic therapy. The patient is now in remission at 18 months follow-up.

Squamous cell carcinoma

Case 8 underwent an uncomplicated hospital stay and is now 113 months in follow-up without tumor recurrence. Case 12 had no complications in the first clinical period, however

only a subtotal resection was achieved; therefore, a second operation was needed to achieve curation. However, 4 months after the first operation patient showed pulmonary metastasis and refused further treatment. Patient died shortly after.

Sinonasal undifferentiated carcinoma

Case 15 had no in-hospital complications. After 7 months of follow-up, the patient showed loco-regional recurrence for which no curative treatments were available. Best supportive care protocol was applied and the patient died shortly after.

Case 18 had a major complicated clinical stay, for more details see the next section. The patient showed rapid disease progression after loco regional and systemic treatment. Best supportive care protocol was started and patient died shortly after.

Miscellaneous

Case 3 had a severely complicated hospital stay and died after more than four months of treatment, for more details see the next section.

Case 9 had an uncomplicated hospital stay and is now 94 months in follow-up without tumor recurrence.

Case 10 died from an in-hospital cardiac arrest, for more details see the next section.

Complications of surgery

We recorded surgical complications in 5 out of 18 patients (28%). Three (17%) patients died during the direct post-operative period. Five (28%) patients needed a re-operation due to a complication. See table 3 for a more detailed description of each individual case.

Wound infection

No patient suffered from direct post-operative wound infection. However, four patients got late post-radiotherapy wound problems requiring operative intervention.

Cases 1, 5 and 13: Post-radiation wound infection requiring wound revision and removal of the bone flap, 4 months, 72 months and 6 months, respectively. Case 6 also underwent wound revision for a chronic infection, in addition, a partial resection of the frontal lobe was performed to get histopathological samples excluding tumor recurrence and proving radio necrosis.

Liquorrhea

Three patients (17%) suffered from direct post-operative liquorrhea, all were treated successfully using an external lumbar drain, one with an addition of acetazolamide. We report one

late orbital liquorrhea following radiotherapy and a chronic infection requiring reconstructive surgery.

Case 11: nasal liquorrhea requiring 7 days external lumbar drainage and acetazolamide

Case 8: uncomplicated clinical period. 8 months post-operatively orbital liquorrhea with frontal lobe herniation and chronic infection. First, an external lumbar drain was placed; this did not resolve the liquorrhea. Therefore, a combined approach with the plastic surgeon was used to reconstruct the orbital region of the frontal skull base using a temporalis fascia and split skin graft. Post-operative wound healing was uneventful.

Case 18: Post-operative nasal liquorrhea and subsequent neurological deterioration based on pseudomonas meningitis occurred. Treatment with an external lumbar drain and antibiotics were given. On the ICU patient showed respiratory worsening based on a pneumonia and pulmonary embolism which were treated using antibiotics and low-molecular weight heparine in therapeutic dosages. Patient recovered and was discharged from hospital on day 21 postoperatively.

Case 10: Post-operative nasal liquorrhea occurred which was treated with an external lumbar drain. On post-operative day 13 the patient had a cardiac arrest, with unknown cause and unfortunately unsuccessful resuscitation. Family gave no permission for postmortem analysis.

Per-operative cerebral swelling

Case 17: Intra-operative severe cerebral swelling occurred necessitating premature ending of the procedure. Post-operative CT-scan demonstrated a subarachnoid hemorrhage with intraventricular expansion (fisher grade 4) without evidence of an aneurysm on the CT-angiogram. An external lumbar drain was placed to treat a hydrocephalus. The clinical status deteriorated and the lumbar drain was replaced by an external occipital catheter and removal of the bifrontal bone flap. Follow-up CT-scan showed further expansion of the SAH and an additional ICH in the right frontal lobe, see figure 2. The patient had a Glasgow Coma Score of E1M1Vtube without brainstem reflexes. No additional therapies were available, and patient died shortly after extubation. There was no approval for post-mortem analysis.

Post-infection hydrocephalus and refractory ventriculitis

Case 3: Patient presented with a severe frontal lobe syndrome based on a right frontal intraparenchymal streptococcus anginosus abscess and a sinonasal carcinoma. The abscess was aspirated and antibiotics were started. Patient improved rapidly, however follow-up MRI demonstrated growth of the abscess, possibly due to a defect of the anterior skull base. In the skull base board, it was decided to perform a combined approach to achieve maximal tumor and abscess resection and close the skull base defect. Post-operatively patient did

not regain normal consciousness due to massive bifrontal edema for which high dosage of dexamethasone and mannitol was administered. Patient slowly improved, however a second deterioration based on a hydrocephalus and ventriculitis lead to the placement of an external ventricular catheter. After over three months of treatment, including multiple drain revisions, a refractory ventriculitis was concluded. In combination with an ongoing oncological process, further medical treatment was considered obsolete. Best supportive care protocol was started, and patient died four days later.

Complications of radiation

Of 14 patients receiving post-operative radiotherapy, 7 (50%) had a complication linked to the radiotherapy. We report on each type of complication below. See table 4 for a more detailed description.

Wound infection

We observed five late wound infections (28%), in a range of 1 week to 65 months after radiotherapy, four of which needed re-operation.

Case 1: 4 months post-operative and 1 week after finishing radiotherapy patient reported a subcutaneous swelling and wound dehiscence. The wound was revised and the bone flap was removed after which the recovery was completed uneventful.

Case 6: 33 months post-radiotherapy, patient underwent re-operation for wound dehiscence and biopsy of suspected tumor recurrence/ radio necrosis, see figure 2. Analysis demonstrated no residual tumor.

Case 5: 65 months post-radiotherapy the patient got nasal liquorrhea and pneumocephaly, which recovered with a conservative approach. 72 months post-radiotherapy the patient got ocular pain and wound dehiscence based on a bone flap infection for which the wound was revised and the bone flap removed. Post-operative period was uneventful.

Case 13: 1-week post-radiotherapy wound infection. Three times antibiotic regime improved clinical status, however 6 months post-radiotherapy persistent wound infection, therefore the wound was revised, and the bone flap was removed. This case had an uneventful post-operative recovery.

Case 12: 1 week after start radiotherapy a wound infection of the orbit developed requiring antibiotics and recurrent nasal flushing, which led to full recovery.

Ocular symptoms

Case 6: The ophthalmologist diagnosed an instable tear film and asymmetrical cataract 6 months post-radiotherapy which was treated using supplementary tears.

Pituitary gland deficits

Case 6: 50 months post-radiotherapy patient was diagnosed with pituitary gland deficits needing supplementation.

Case 11: 36 months post-radiotherapy diagnosed with pituitary gland deficits requiring supplementation.

Radiation necrosis

We observed four (22%) patients with a radiological radio necrosis of the brain parenchyma; two were symptomatic (11%) requiring dexamethasone.

Case 6: 9 months post-radiotherapy patient had an epileptic seizure, presumably resulting from bifrontal radio necrosis, see figure 2. 16 months post-operative patient developed a severe frontal lobe syndrome due to bifrontal edema, which was treated with dexamethasone for three months and cognitive rehabilitation. The patient remained care dependent.

Case 8: 8 months post-op frontal lobe radio necrosis requiring dexamethasone for three months and cognitive rehabilitation. The patient remained care dependent.

Case 5: 24 months post-radiotherapy asymptomatic frontal radio necrosis, which required no treatment.

Case 11: 24 months post-radiotherapy asymptomatic frontal radio necrosis, which required no treatment.

Nasal symptoms

Case 8: 6 months post-radiation severe nasal synechiae with substantial nasal obstruction needing cleaving.

DISCUSSION

Sinonasal cancers are rare and challenging pathologies¹⁷. Often, they present in an advanced stage, making a gross total resection less probable¹⁷. Moreover, this group of tumors is histologically very heterogeneous, making comparisons difficult and interpretations more general. Additionally, the current treatment paradigm, which consists of surgical radical resection, possibly followed by adjuvant chemo and/or radiation, is associated with high rates of morbidity and mortality¹⁵⁻¹⁸. In our retrospective cohort study, we report on our own experience of 18 cases with sinonasal cancers with anterior fossa destruction treated by an endoscope assisted- frontobasal craniotomy followed by autologous skull base reconstruction. The cohort consists of eight different histological diagnoses. We achieved gross total resection in 14

patients (78%). Radiotherapy was given post-operatively to 14 patients, three of which were combined with chemotherapy. Half of the patients died; three patients died during the immediate post-operative period, and six patients died during a mean follow-up of 47 months. Five of those six patients showed disease progression within 7 months. We recorded surgical complications in five patients and radiotherapy related complications in seven patients.

Progression free and overall survival

Our cohort showed a mean progression free survival of 47 months. Overall survival was 50% at a mean follow-up of 49 months. These results are in line with reports in the literature^{7,8,16,17,20,21}. The most important predictor of survival is achieving gross total resection, while preserving quality of life²². We achieved complete resection in 14/18 patients; one partial resection was due to a per-operative complication. The other three patients with a subtotal tumor resection showed early recurrence between 3-6 months; one was treated with re-resection and systemic chemotherapy however the patient remained progressive. The other was given systemic chemotherapy and is in remission at 18 months. The third patient had a major complicated disease course and was progressive under chemoradiation.

A multi-modality management with a combination of surgery and chemoradiation is the preferred management strategy^{3,15-17}. The absence of large randomized controlled trials makes the evidence of low quality; however, in selected cohorts, a multi-modal treatment gives greater loco-regional tumor control and longer survival rates²³⁻²⁵. All patients eligible for adjuvant radiotherapy received fractionated loco-regional treatment (14/18). One patient with an esthesioneuroblastoma refused radiotherapy and had tumor recurrence at 15 months follow-up. After re-resection and radiotherapy, the patients remain recurrence free after 51 months. In general, the prognosis is positively affected by local tumor control and the absence of distant metastasis. In this cohort, eight patients had a tumor recurrence during follow-up. Two patients received a re-resection followed by adjuvant therapy, four were referred to the oncologist for systemic therapy and two were given palliative care. Five of these patients died shortly after diagnosis, one is without tumor recurrence, and two showed stable disease. Kaplan et al² reported on prognostic factors concerning resection of recurrent tumors. They state that histology grade, involvement of regional critical structures such as the orbit, carotid artery and skull base negatively affects the prognosis. This study only included grade 4 tumors with skull base involvement, which could explain the severe prognosis of our recurrent tumor group.

Complications

The treatment of high grade, locally advanced sinonasal cancers is accompanied by high rates of complications, morbidity and mortality¹⁸. Frequently reported complications are wound infections, liquorrhea, orbital deficits, radiation necrosis and systemic complications, in total up to 35%. Patients suffering from complications may no longer be eligible for adjuvant therapies, drastically diminishing their prognosis. Additionally, it negatively affects their

quality of life. In our study, we observed no early wound infection, one meningitis and five late wound infections. Three patients suffered from direct post-operative liquorrhea and one late liquorrhea, none with long-term sequela. Two patients suffered cardiovascular complications. Mortality was 3/18 patients; all complication rates are in line with reports from the literature¹⁸. We observed in 7/14 patients' complications following radiotherapy. All wound complications originated post-radiotherapy, most of them needing re-operation. Ganly et al¹⁸ reported on these surgery related complications and found that the addition of radiotherapy increases the rate of wound complications. Furthermore, intracranial invasion increases the risk of liquorrhea. In our cohort, all patients had intracranial expansion and were treated with adjuvant radiotherapy, which could explain the high numbers of complications.

Limitations

The retrospective nature of this study is subject to bias, which means we need to be careful of interpreting causality. Furthermore, the high variability in tumor histology in this cohort makes it difficult to compare the clinical course and outcomes between each pathology.

CONCLUSION

Patients with sinonasal cancers with skull base extension are a very rare and specific subgroup with a high recurrence rate. Due to an often late presentation, they present with advanced disease with growth into critical surrounding structures such as the orbit and brain parenchyma. This makes it more difficult to achieve a gross total resection, requiring radiation dosage to the surgical cavity resulting in high dose to nearby healthy tissue. In this study, which includes only stage four sinonasal cancers with skull base extension we report a survival of 50% with a mean follow-up of 49 months. This is comparable with other studies, which also include lower stages. Multimodal treatment complications are common and can be severe requiring readmission, reoperation and rehabilitation. This study aims to add to currently available cohorts in the literature.

REFERENCES

1. Turner, J. H. & Reh, D. D. Incidence and survival in patients with sinonasal cancer: A historical analysis of population-based data. *Head & Neck* **34**, 877–885 (2012).
2. Kaplan, D. J., Kim, J. H., Wang, E. & Snyderman, C. Prognostic Indicators for Salvage Surgery of Recurrent Sinonasal Malignancy. *Otolaryngology–Head and Neck Surgery* **154**, 104–112 (2016).
3. López, F. *et al.* The Impact of Histologic Phenotype in the Treatment of Sinonasal Cancer. *Adv Ther* **34**, 2181–2198 (2017).
4. Mendenhall, W. M. *et al.* Carcinoma of the nasal cavity and paranasal sinuses. *Laryngoscope* **119**, 899–906 (2009).
5. Komotar, R. J., Starke, R. M., Raper, D. M. S., Anand, V. K. & Schwartz, T. H. Endoscopic Endonasal Compared with Anterior Craniofacial and Combined Cranionasal Resection of Esthesioneuroblastomas. *World Neurosurgery* **80**, 148–159 (2013).
6. Hanna, E. *et al.* Endoscopic Resection of Sinonasal Cancers With and Without Craniotomy. *Archives of Otolaryngology–Head & Neck Surgery* **135**, 1219 (2009).
7. Guntinas-Lichius, O. *et al.* Single modality and multimodality treatment of nasal and paranasal sinuses cancer: A single institution experience of 229 patients. *European Journal of Surgical Oncology (EJSO)* **33**, 222–228 (2007).
8. Thorup, C. *et al.* Carcinoma of the nasal cavity and paranasal sinuses in Denmark 1995–2004. *Acta Oncologica* **49**, 389–394 (2010).
9. Dirix, P. *et al.* Malignancies of the Nasal Cavity and Paranasal Sinuses: Long-Term Outcome With Conventional or Three-Dimensional Conformal Radiotherapy. *International Journal of Radiation Oncology*Biophysics* **69**, 1042–1050 (2007).
10. Hoppe, B. S. *et al.* Treatment of nasal cavity and paranasal sinus cancer with modern radiotherapy techniques in the postoperative setting—the MSKCC experience. *International Journal of Radiation Oncology*Biophysics* **67**, 691–702 (2007).
11. Allen, M. W. *et al.* Long-Term Radiotherapy Outcomes for Nasal Cavity and Septal Cancers. *International Journal of Radiation Oncology*Biophysics* **71**, 401–406 (2008).
12. Chen, A. M. *et al.* Carcinomas of the Paranasal Sinuses and Nasal Cavity Treated With Radiotherapy at a Single Institution Over Five Decades: Are We Making Improvement? *International Journal of Radiation Oncology*Biophysics* **69**, 141–147 (2007).
13. Hoppe, B. S. *et al.* Postoperative intensity-modulated radiation therapy for cancers of the paranasal sinuses, nasal cavity, and lacrimal glands: Technique, early outcomes, and toxicity. *Head & Neck* **30**, 925–932 (2008).
14. Bath, S. S. *et al.* Clinical-dosimetric relationship between lacrimal gland dose and ocular toxicity after intensity-modulated radiotherapy for sinonasal tumours. *The British Journal of Radiology* **86**, 20130459 (2013).
15. Licitra, L., Resteghini, C. & Bossi, P. The Evolving Role of Systemic Therapy in the Primary Treatment of Sinonasal Cancer. *Adv Otorhinolaryngol* **84**, 78–86 (2020).
16. Haerle, S. K., Gullane, P. J., Witterick, I. J., Zweifel, C. & Gentili, F. Sinonasal Carcinomas. *Neurosurgery Clinics of North America* **24**, 39–49 (2013).
17. Taylor, M. A. & Saba, N. F. Cancer of the Paranasal Sinuses. *Hematology/Oncology Clinics of North America* **35**, 949–962 (2021).
18. Ganly, I. *et al.* Complications of craniofacial resection for malignant tumors of the skull base: Report of an International Collaborative Study. *Head & Neck* **27**, 445–451 (2005).
19. Freitas-Martinez, A., Santana, N., Arias-Santiago, S. & Viera, A. CTCAE versión 5.0. Evaluación de la gravedad de los eventos adversos dermatológicos de las terapias antineoplásicas. *Actas Dermo-Sifiliográficas* **112**, 90–92 (2021).

20. Mehta, G. U. *et al.* The neurosurgical management of sinonasal malignancies involving the anterior skull base: a 28-year experience at The MD Anderson Cancer Center. *J Neurosurg* 1–9 (2021) doi:10.3171/2021.5.JNS21772.
21. Xu, C. C., Dziegielewski, P. T., McGaw, W. T. & Seikaly, H. Sinonasal Undifferentiated Carcinoma (SNUC): the Alberta experience and literature review. *Journal of Otolaryngology - Head & Neck Surgery* **42**, 2 (2013).
22. Higgins, T. S., Thorp, B., Rawlings, B. A. & Han, J. K. Outcome results of endoscopic vs craniofacial resection of sinonasal malignancies: a systematic review and pooled-data analysis. *Int Forum Allergy Rhinol* **1**, 255–61.
23. Lee, M. Multimodality therapy in advanced paranasal sinus carcinoma: superior long-term results. *Cancer J Sci Am* 219–223 (1999).
24. Orlandi, E. *et al.* Locally advanced epithelial sinonasal tumors: The impact of multimodal approach. *Laryngoscope* **130**, 857–865 (2020).
25. Bossi, P. *et al.* The role of systemic therapy in the management of sinonasal cancer: A critical review. *Cancer Treatment Reviews* **41**, 836–843 (2015).

APPENDIX

Figure 1. Radiological imaging of sinonasal cancers

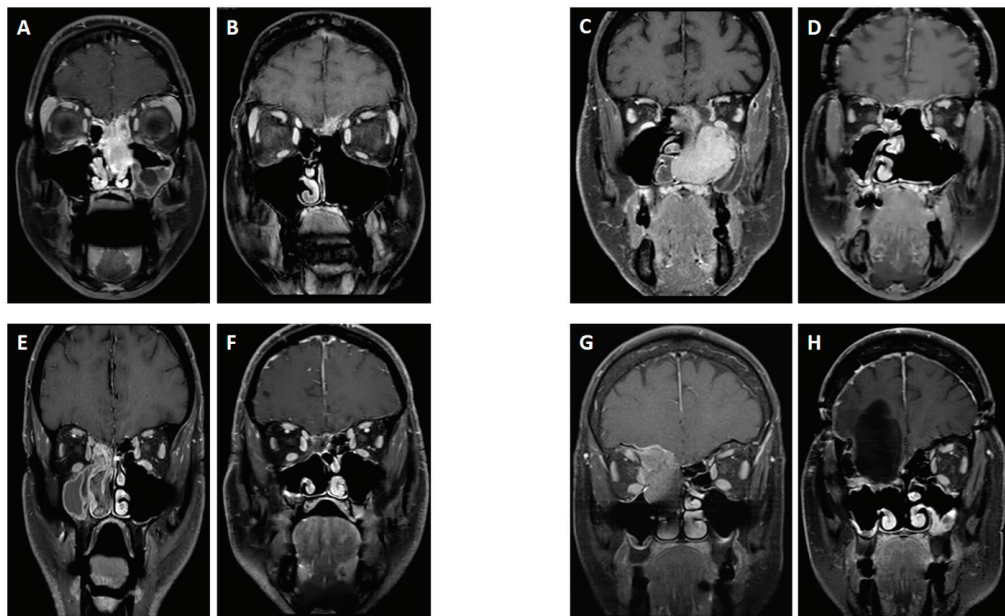


Figure 1. This figure demonstrates four cases with a pre- and post-operative contrast enhanced T1 MRI in the coronal plane. A-B: Case 4 with an esthesioneuroblastoma. C-D: Case 2 with an adenoid cystic carcinoma. E-F: Case 7 with an adenocarcinoma. G-H: Case 8 with a squamous cell carcinoma, an orbital exenteration has been performed to achieve gross total resection.

Figure 2. Radiological imaging of complications

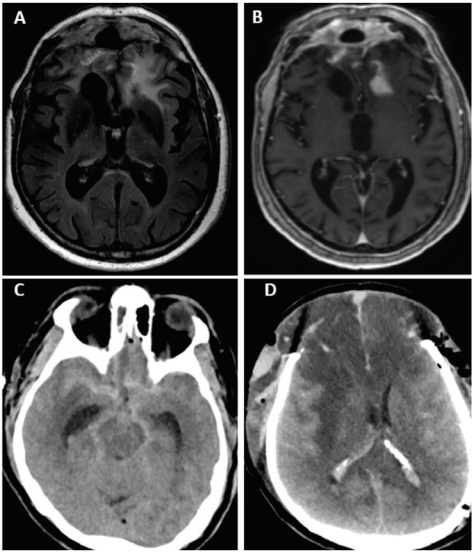


Figure 2. This figure demonstrates two cases with complications. A-B: Case 6 with bifrontal radio necrosis, A is a FLAIR T2 weighted axial image showing bifrontal hyperintense signal corresponding with subcortical edema. B is a T1 + gadolinium axial image demonstrating intraparenchymal and subcutaneous contrast enhancement suggestive of radio necrosis and/or infection. C-D: Case 17 with per-operative subarachnoid hemorrhage and cerebral swelling. C is a CT axial image direct post-operative demonstrating diffuse SAH in the basal cisterns and both sylvian fissures with enlarged temporal horns and diffuse swelling. D is a CT axial image after bone flap removal and occipital ventricular catheter placement. The image demonstrates large hypodense, ischaemic, areas bifrontal, herniating frontal lobes and diffuse swelling.

Table 1. Demographics

Case number	Sex	Age (year)	Presenting symptoms	Histopathology	Oncological staging	Radiological extension
1	F	74	Nasal obstruction, rhinorrhea	Esthesioneuroblastoma	cT4bN0M0	Nasal sinus, orbit
2	F	69	Nasal obstruction, rhinorrhea	Adenoid cystic carcinoma	cT4bN0M0	Nasal sinus, orbit, anterior fossa
3	M	59	Nasal obstruction, rhinorrhea	Inverted papilloma with squamous cell carcinoma	cT4bN0M0	Nasal sinus, orbit, anterior fossa
4	F	38	Nasal obstruction, rhinorrhea	Esthesioneuroblastoma	cT4bN0M0	Nasal sinus, anterior fossa
5	F	61	Epilepsy	Adenoid cystic carcinoma	cT4bN0M0	Nasal sinus, orbit, anterior fossa
6	M	69	Nasal obstruction, rhinorrhea, anosmia	Esthesioneuroblastoma	cT4bN0M0	Nasal sinus, anterior fossa

Table 1. Demographics (*continued*)

Case number	Sex	Age (year)	Presenting symptoms	Histopathology	Oncological staging	Radiological extension
7	M	55	Nasal obstruction, rhinorrhea, epistaxis	Adenocarcinoma	cT4bN0M0	Nasal sinus, anterior fossa
8	F	60	Visual deficit and diplopia	Squamous cell carcinoma	cT4bN0M0	Nasal sinus, orbit, anterior fossa
9	F	80	Nasal obstruction, epistaxis	Sinonasal neuro-endocrine carcinoma	cT4bN0M0	Nasal sinus, orbit, anterior fossa
10	F	73	Nasal obstruction, rhinorrhea, epistaxis	Melanoma	cT4aN0M0	Nasal sinus, orbit, anterior fossa
11	M	66	Frontal lobe syndrome	Adenocarcinoma	cT4bN0M0	Nasal sinus, anterior fossa
12	M	58	Nasal obstruction, diplopia, dacryorrhea	Squamous cell carcinoma	cT4aN0M0	Nasal sinus, orbit, anterior fossa
13	M	48	Nasal obstruction, epistaxis	Adenocarcinoma	cT4bN0M0	Nasal sinus, orbit, anterior fossa
14	M	56	Frontal lobe syndrome	Adenocarcinoma	cT4aN0M0	Nasal sinus, anterior fossa
15	M	64	Headache, anosmia, visual field deficit	Sinonasal undifferentiated carcinoma	cT4bN0M0	Nasal sinus, orbit, anterior fossa
16	F	50	Visual deficit, diplopia, anosmia	Adenoid cystic carcinoma	cT4bN0M0	Nasal sinus, orbit, anterior fossa
17	M	66	Epistaxis	Adenocarcinoma	cT4bN0M0	Nasal sinus, anterior fossa
18	M	52	Rhinorrhea, anosmia, diplopia	Sinonasal undifferentiated carcinoma	cT4bN0M0	Nasal sinus, orbit, anterior fossa

Table 1. This table shows demographic data consisting of case nr, sex, age at surgery, presenting symptoms at diagnosis, the histological diagnosis, oncological staging and the extension of the tumor borders. F (female), M (male).

Table 2. Clinical course and survival stratified towards tumor type

Case number	Histopathology	Hospital length of stay (days)	Complications in hospital	Progression free survival (months)	Total survival (months)
1	Esthesioneuroblastoma	11	No	20	20
4	Esthesioneuroblastoma	10	No	15	51
6	Esthesioneuroblastoma	8	No	64	64†
2	Adenoid cystic carcinoma	9	No	66	66
5	Adenoid cystic carcinoma	-	-	100	138
16	Adenoid cystic carcinoma	17	No	6	18

Table 2. Clinical course and survival stratified towards tumor type (*continued*)

Case number	Histopathology	Hospital length of stay (days)	Complications in hospital	Progression free survival (months)	Total survival (months)
7	Adenocarcinoma	7	No	58	58
11	Adenocarcinoma	22	Liquorrhea	78	78
13	Adenocarcinoma	13	No	6	13 †
14	Adenocarcinoma	26	Delirium	6	7 †
17	Adenocarcinoma	4	SAH, HCP	-	- †
8	Squamous cell carcinoma	15	No	113	113
12	Squamous cell carcinoma	8	No	0	4 †
15	Sinonasal undifferentiated carcinoma	9	No	7	8 †
18	Sinonasal undifferentiated carcinoma	21	Liquorrhea, meningitis, pulmonary embolism	-	3 †
3	Inverted papilloma with squamous cell carcinoma	136	Hydrocephalus, ventriculitis, pneumonia,	-	- †
9	Sinonasal neuro-endocrine carcinoma	28	No	94	94
10	Melanoma	13	Liquorrhea, cardiac arrest	-	- †

Table 2. Cases are categorized in accordance to their histopathology; hospital stay is presented in days, progression free and overall survival is presented in months. SAH: subarachnoid hemorrhage, HCP: hydrocephalus, †: deceased

Table 3. Details on surgery stratified towards tumor type

Case number	Histopathology	Procedure	Extent of resection	Complication	Reoperation
1	Esthesioneuroblastoma	Bifrontal + endoscopy	Gross total	Late wound infection after RTx	Wound revision with bone flap removal
4	Esthesioneuroblastoma	Bifrontal + endoscopy	Gross total	-	Re-resection regrowth
6	Esthesioneuroblastoma	Bifrontal + endoscopy	Gross total	Late wound infection after RTx, pneumocephaly, epilepsy	Wound revision with bone flap removal and resection radio necrosis
2	Adenoid cystic carcinoma	Bifrontal + endoscopy	Gross total	-	-
5	Adenoid cystic carcinoma	Bifrontal	Gross total	Late wound infection after RTx, pneumocephaly	Wound revision with bone flap removal

Table 3. Details on surgery stratified towards tumor type (*continued*)

Case number	Histopathology	Procedure	Extent of resection	Complication	Reoperation
16	Adenoid cystic carcinoma	Bifrontal + endoscopy	Subtotal	-	-
7	Adenocarcinoma	Bifrontal + endoscopy	Gross total	-	-
11	Adenocarcinoma	Bifrontal	Gross total	Liquorrhea	External lumbar drainage 7 days + acetazolamide
13	Adenocarcinoma	Bifrontal + endoscopy	Gross total	Late wound infection after RTx	Wound revision with bone flap removal
14	Adenocarcinoma	Bifrontal + endoscopy	Gross total	-	-
17	Adenocarcinoma	Bifrontal	Partial	SAH, hydrocephalus	External lumbar drain, external ventricular drain, craniectomy
8	Squamous cell carcinoma	Bifrontal + endoscopy + exenteration	Gross total	Late orbital liquorrhea after RTx	External lumbar drain and combined reconstruction orbit
12	Squamous cell carcinoma	Bifrontal + endoscopy	Subtotal	-	Orbit exenteration and lat rhinotomy for remnant tumor
15	Sinonasal undifferentiated carcinoma	Bifrontal + endoscopy	Gross total	-	-
18	Sinonasal undifferentiated carcinoma	Bifrontal + endoscopy	Subtotal	Nasal liquorrhea, meningitis,	External lumbar drain
3	Inverted papilloma with squamous cell carcinoma	Bifrontal + endoscopy	Gross total	Hydrocephalus, ventriculitis, cerebral edema	Multiple external and internal shunt revisions
9	Sinonasal neuro-endocrine carcinoma	Bifrontal + endoscopy	Gross total	-	-
10	Melanoma	Bifrontal + lat rhinotomy + exenteration	Gross total	Liquorrhea, cardiac arrest	External lumbar drain for 5 days

Table 3: Cases are organized according to tumor type. We report of the operation strategy; bifrontal craniotomy, lateral rhinotomy, endoscopic assistance and orbital exenteration. Additionally, we provide the degree of resection; gross total >90%, subtotal 80-90% and partial <80%. Finally, the treatment related complication is described and the concurrent treatment. RTx: radiotherapy, SAH: subarachnoid hemorrhage.

Table 4. Radiotherapy complications according CTCAE version 5.

Case number	Histopathology	Prescribed radiation dose	Complications	Grade & timing
1	Esthesioneuroblastoma	33 x 2 Gy	Wound dehiscence and infection, tear film instability	4, late; 3, early
4	Esthesioneuroblastoma	Post re-resection 33 x 2 Gy	-	
6	Esthesioneuroblastoma	33 x 2 Gy	Radio necrosis, frontal lobe syndrome, epilepsy, pituitary deficit	4, late
2	Adenoid cystic carcinoma	33 x 2 Gy	-	
5	Adenoid cystic carcinoma	33 x 2 Gy	Radio necrosis, nasal liquorrhea, wound infection	4, late
16	Adenoid cystic carcinoma	35 x 2 Gy	-	
7	Adenocarcinoma	33 x 2 Gy	-	
11	Adenocarcinoma	33 x 2 Gy	Radio necrosis, pituitary deficit	4, late
13	Adenocarcinoma	33 x 2 Gy	Wound infection	4, early
14	Adenocarcinoma	33 x 2 Gy	-	
17	Adenocarcinoma	-	-	
8	Squamous cell carcinoma	33 x 2 Gy	Nasal synechiae, radio necrosis	4, late
12	Squamous cell carcinoma	35 x 2 Gy	Wound dehiscence orbit	4, early
15	Sinonasal undifferentiated carcinoma	35 x 2 Gy	-	
18	Sinonasal undifferentiated carcinoma	-	-	
3	Inverted papilloma with squamous cell carcinoma	-	-	
9	Sinonasal neuro-endocrine carcinoma	33 x 2 Gy	-	
10	Melanoma	-	-	

Table 4: Cases are organized according to tumor type. We report on the radiotherapy scheme; the first number is the amount of fractions, the second is the fractionated dosage in grey. Finally, we describe the radiotherapy related complications and their severity grade according to the current guidelines¹⁹. We differentiate between early and late occurrence.

4

Chordoma

Clinical outcomes in skull base chordoma, a single-center experience

Keizer M, Ravindran PK, Yang C, Kunst D, Eekers D, Compter I, Hovinga K, van Aalst J, Temel Y (submitted to Acta Neurochirurgica)

ABSTRACT

Objectives: To describe the outcome of our center's experience treating skull base chordoma.

Design: A retrospective cohort study.

Setting: Tertiary university medical center.

Participants: Adult patients diagnosed with and treated for primary skull base chordoma.

Main Outcome Measures: Primary outcome measures are progression – and overall survival rates using the Kaplan Meier method. Secondary outcomes are treatment complication rate and improvement of clinical symptoms.

Results: A total of 29 patients were eligible for inclusion. The main presenting symptom is diplopia. In total 67 surgeries were performed. In the first decade, midfacial degloving was the most frequent technique utilized and in the last decade, the technique of choice became the extended endoscopic trans nasal approach. Symptoms improved in 34% of the patients and worsened in 10%. The mean follow-up was 116 months (range 16-308). The 5-year and 10-year progression free survival was 42% and 18%, respectively. The 5-year and 10-year overall survival was 75% and 55%, respectively. Surgical complications occurred in 38%, mostly being nasal CSF leakage and (transient) cranial nerve palsies. Adjuvant radiotherapy was administered in 23 (79%) patients, of which 13 received proton beam therapy, eight received photon therapy and two patients received either Gamma Knife or Carbon Ion therapy. Radiotherapy-induced complications occurred in 14 (61%) patients, predominantly radiation necrosis (n=8).

Conclusions: Skull base chordoma are rare and complex tumors. Treatment consists of maximal safe resection followed by adjuvant radiotherapy. The development of endoscopic surgical approaches and advanced radiotherapy administration techniques have improved overall survival and reduced morbidity.

Keywords: Skull base, chordoma, clinical outcome, endoscopic, craniotomy, complications

INTRODUCTION

Chordoma is a malignant tumor arising from remnants of the fetal notochord cells¹. These tumors occur along the vertebral column but are most commonly found at the clivus and sacrum. The incidence is estimated to be 0.05 to 0.08 per 100,000 persons per year^{2,3}. The mean age at presentation is between 40-60 years, with patients presenting with skull base chordomas typically being younger than those with spinal chordomas². Surgical resection is the primary treatment modality with adjuvant radiotherapy being increasingly applied in the last decades^{4,5}. There is some consensus on the optimal treatment strategy⁶. Systemic therapies have gained traction in recent years, however, remain limited in effect. Several therapies are being actively investigated, with some showing promising efficacy⁷. This is partly due to the difficulties being faced understanding the molecular and pathogenic pathways in the formation of a chordoma^{8,9}. Recurrence rates after 5- and 10 years are 52.9% and 88.3%, respectively. Overall survival at 5- and 10 years follow-up is 67.6% and 39.9%, respectively¹⁰. Macroscopic complete resection has a positive effect on the survival rates¹¹. However, due to close proximity or involvement of critical neurovascular structures such as the carotid artery, cranial nerves and the brainstem this is often difficult or not feasible. Advancements in microsurgery, neuro-navigation and endoscopic trans nasal approaches have made chordoma operations safer and increased the likelihood of complete tumor removal while minimizing patient harm¹².

The rarity of this tumor and the tailored treatment approach make conducting randomized trials or large prospective studies logistically challenging and currently underrepresented in the literature. Our current understanding of chordoma treatment outcome is primarily based on case series and systematic reviews. With this study we aim to add our single center experience of treating skull base chordoma patients to the existing literature.

MATERIALS AND METHODS

Study design

This is a retrospective, single center cohort study of patients with skull base chordoma treated mainly in the last two decades at Maastricht University Medical Center +. Data on clinical presentation, radiological characteristics, surgical details, adjuvant therapies, tumor control, survival and complications were retrieved from available medical records. The final date of data extraction is March 1st, 2025. The primary outcomes are overall- and progression free survival, where disease progression is considered local tumor recurrence or regrowth or distant metastases. Secondary outcomes include treatment-related complication rates and improvement of clinical symptoms. The study protocol was approved by the medical ethics committee of Maastricht University Medical Center + with reference number: 2021-2608.

Subjects

All consecutive patients with a histopathological diagnosis of chordoma in the skull base treated with surgical resection were eligible for inclusion. We decided to include incomplete records to create a real-world database with as many patients as possible. Incomplete records were left out of each specific analysis on which no information could be retrieved. This is reported as not available (n.a.) in table 1. Exclusion criteria are patients who did not receive surgical treatment or received surgical treatment elsewhere. Macroscopic complete resection was regarded as no residual tumor remnant visible on the post-operative MRI. Symptoms outcome was assessed at the first post-operative follow-up. This was a combination of patient reports and neurological examination, ranging from improved to stable and worsened.

Clinical workflow

All cases were evaluated in the multidisciplinary skull base tumor board and regional sarcoma board. Patients who were operated on during the first decades underwent surgical approaches including lateral rhinotomy, midfacial degloving, craniotomy or a combined approach. In the recent decade, the advancement of endoscopic techniques led to a shift towards trans nasal extended endoscopic approaches. Post-operative radiological assessment was applied to evaluate the presence of residual tumor. In the case of operable tumor remnant, a re-operation was proposed. Adjuvant radiotherapy, either particle- or photon or gamma therapy was administered after maximal surgical resection was achieved. Clinical target volumes were delineated following the ESTRO guideline¹³. In 2019 our proton therapy center was established, prior to that time all our patients were referred to centers abroad for particle therapy.

Follow-up consisted of a baseline post-operative MRI scan, followed by regular MRI-scans at 6 months interval. In the event of disease recurrence, cases were discussed in the tumor board and tailored treatment plans were made, consisting of re-operation, re-irradiation, systemic therapy or combined modalities.

Statistics

Descriptive statistics were used to summarize the data given the small sample size and heterogeneity of the cohort. Inferential statistics were not conducted due to the limited sample size. Survival analyses were analyzed using the Kaplan Meier method. All analyses were performed using IBM SPSS Statistics for Windows, version 27.0 software (IBM Corp. Armonk, NY, USA).

RESULTS

Demographics

Thirty-three consecutive patients with skull base chordoma could be retrieved from the medical archives. Two patients declined surgical treatment, and two patients received their complete treatment in a different hospital; these four patients were excluded from the analysis.

The remaining 29 patients consist of 15 males and 14 females with a mean age at presentation of 49 years (range 24 - 76). See table 1 for all demographic details. The most common presenting symptom was diplopia caused by abducens nerve involvement (n=17, 59%) followed by vision loss due to optic nerve compression (n=6, 21%) and headache (n=5, 17%). The clivus was the most prominent tumor location, with possible extension into the petroclival fissure, cavernous sinus or sellar region. The cavernous sinus was involved in 19 (66%) cases and 14 (48%) patients showed evidence of brainstem compression, see figure 1 for exemplary cases.

Figure 1

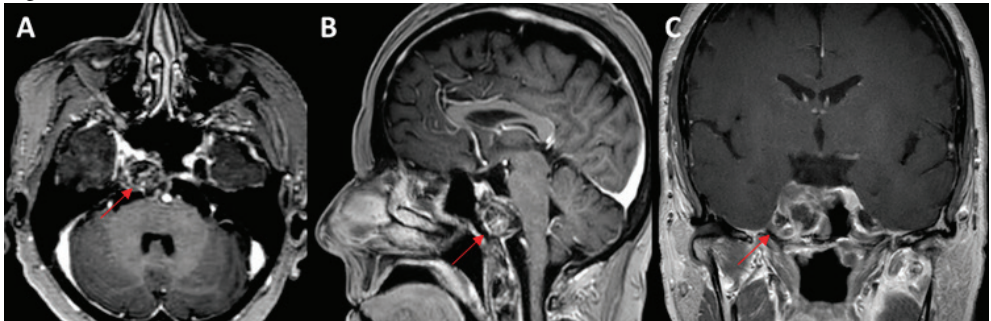


Figure 1: All images are T1-weighted, gadolinium enhanced MRI scans. The top row portrays the axial (A), sagittal (B) and coronal (C) MRI of case 1. The chordoma is located primarily in the right petroclival fissure with extension towards the right cavernous sinus and the pre-pontine cistern. The red arrows mark the location of the chordoma and its invasion in the cavernous sinus, explaining the abducens nerve palsy. The middle row demonstrates the pre-operative axial (D), sagittal (E) and coronal (F) MRI of case 8. This chordoma is predominantly located in the upper clivus with cisternal extension and brainstem compression. The bottom row shows the post-operative axial (G), sagittal (H) and coronal (I) MRI of case 8. The images show the abdominal fat graft, marked by the red arrows, to seal off the clival defect.

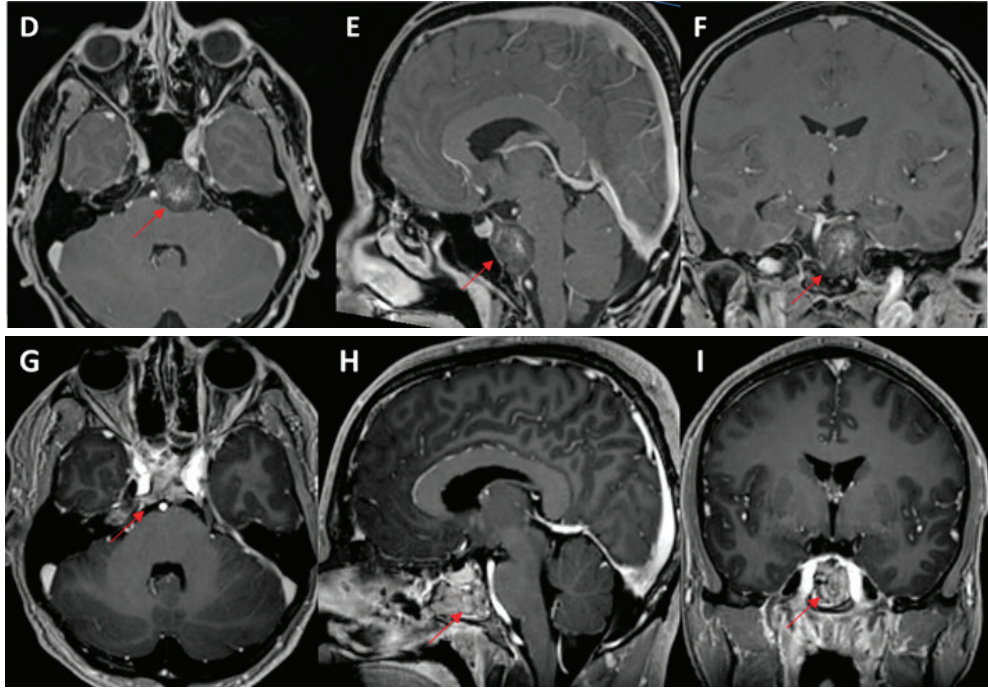
Figure 1 (*continued*)

Figure 1: All images are T1-weighted, gadolinium enhanced MRI scans. The top row portrays the axial (A), sagittal (B) and coronal (C) MRI of case 1. The chordoma is located primarily in the right petro-clival fissure with extension towards the right cavernous sinus and the pre-pontine cistern. The red arrows mark the location of the chordoma and its invasion in the cavernous sinus, explaining the abducens nerve palsy. The middle row demonstrates the pre-operative axial (D), sagittal (E) and coronal (F) MRI of case 8. This chordoma is predominantly located in the upper clivus with cisternal extension and brainstem compression. The bottom row shows the post-operative axial (G), sagittal (H) and coronal (I) MRI of case 8. The images show the abdominal fat graft, marked by the red arrows, to seal off the clival defect.

Surgical outcomes

A total of 67 surgical procedures were performed, ranging from one to six operations per patient, see table 1. The main surgical approach was midface degloving (n=20, 30%), followed by endoscopic transsphenoidal approach (n=6, 9%). This difference is explained by the introduction of endoscopic approaches in our center in 2017. Notably, four operations were performed for subcutaneous seeding metastases, and two patients underwent a cranio-cervical fixation following resection of chordoma at the atlanto-occipital junction. Macroscopic complete resection was achieved in nine patients (31%). Pre-operative symptoms improved in ten patients (34%), worsened in three (10%) and remained stable in seven (24%). In the remaining patients the symptom outcomes were not documented.

Eighteen patients experienced no post-operative complications. Four patients developed post-operative CSF leakage (three midfacial degloving, one endoscopic trans nasal approach), which was resolved by external lumbar drainage for 5-7 days. Four patients experienced cranial nerve deficits (one accessory (transient), one hypoglossal (transient), one facial(permanent) and one trigeminal neuralgia). One patient had an asymptomatic hemorrhage. One patient suffered from a post-operative transient partial thoracic paraplegia due to a vascular hypoperfusion. Two patients (7%) died due to post-operative complications: one brainstem infarction and one due to meningitis, ventriculitis and refractory hydrocephalus.

Radiotherapy outcomes

Post-operative adjuvant radiotherapy was administered in 23 patients (79%), of which 13 received proton therapy (range 48-80 Gy), 8 received photon therapy (range 59-74Gy) and two patients received either Gamma Knife (range 13-22Gy) or carbon ion therapy (60Gy). Ten patients underwent multiple irradiation sessions either for local recurrence or for distant (seeding) metastases. Two patients experienced spinal drop metastases for which post-operative local photon therapy was administered. Two patients received multiple post-resection Gamma Knife sessions on subcutaneous seeding metastases. One patient underwent carbon ion therapy following proton therapy for a locally aggressive chordoma recurrence.

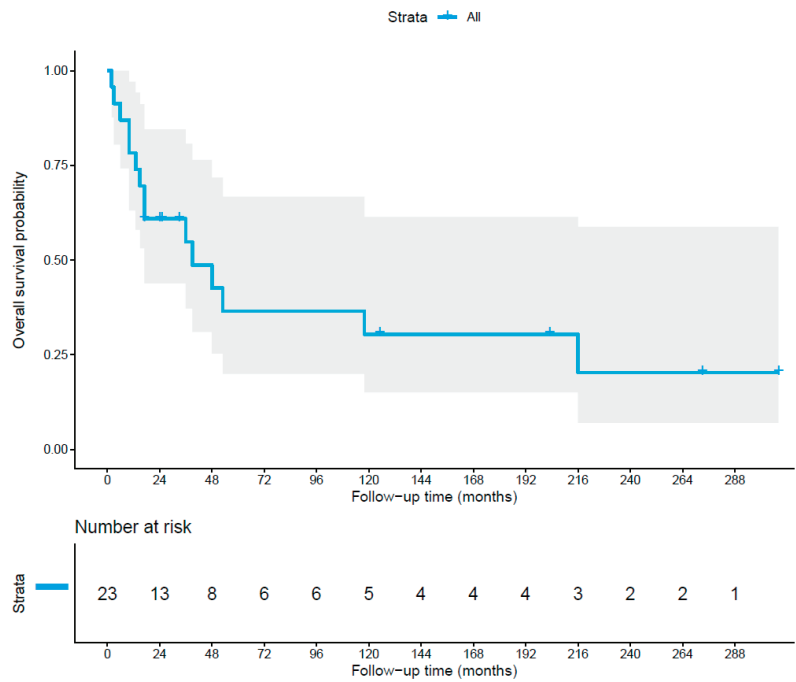
Fourteen patients (61%) experienced complications after radiotherapy. Radiation necrosis (n=8) was the most common complication, predominantly affecting the temporal lobe, followed by the brain stem, all patients received proton therapy. One patient required a re-operation for temporal lobe necrosis due to uncertainty about possible recurrence. Two patients developed epilepsy due to temporal lobe necrosis. Additionally, cranial nerve neuropathies were observed in three patients (facial nerve, trigeminal nerve, glossopharyngeal and vagal nerve). Furthermore, five patients developed panhypopituitarism. For more details see table 1.

Survival outcomes

Six patients were lost to follow-up and were therefore excluded from survival analyses. In the remaining cohort, the mean follow-up was 116 months (range 16-308). The 5-year and 10-year progression free survival were 42% and 18%, respectively. The 5-year and 10-year overall survival were 75% and 55%, respectively. The Kaplan-Meier curves of the progression free – and overall survival and the presence of brainstem compression and cavernous sinus invasion are presented in figure 2.

Figure 2

A



B

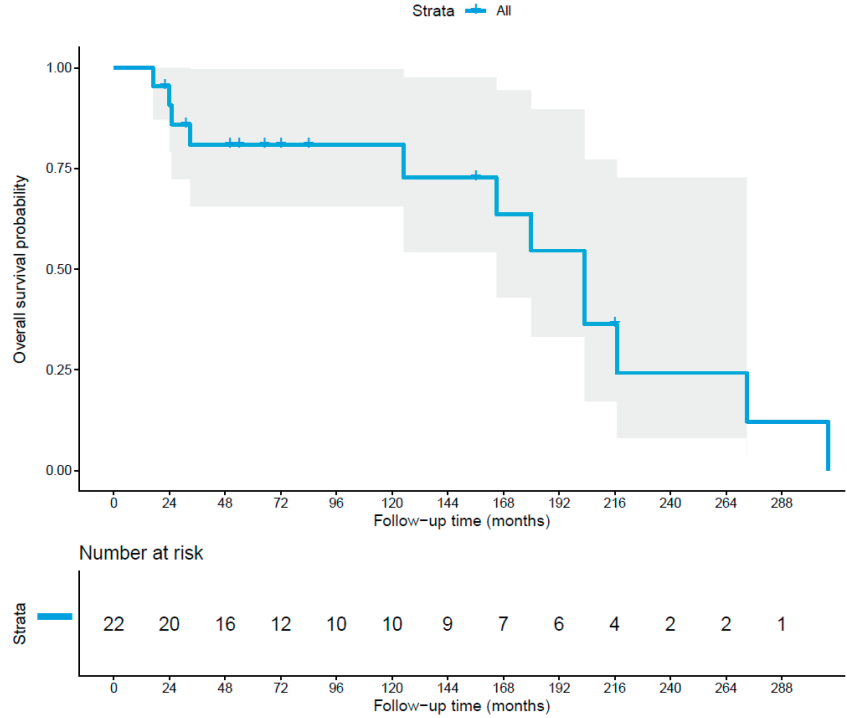
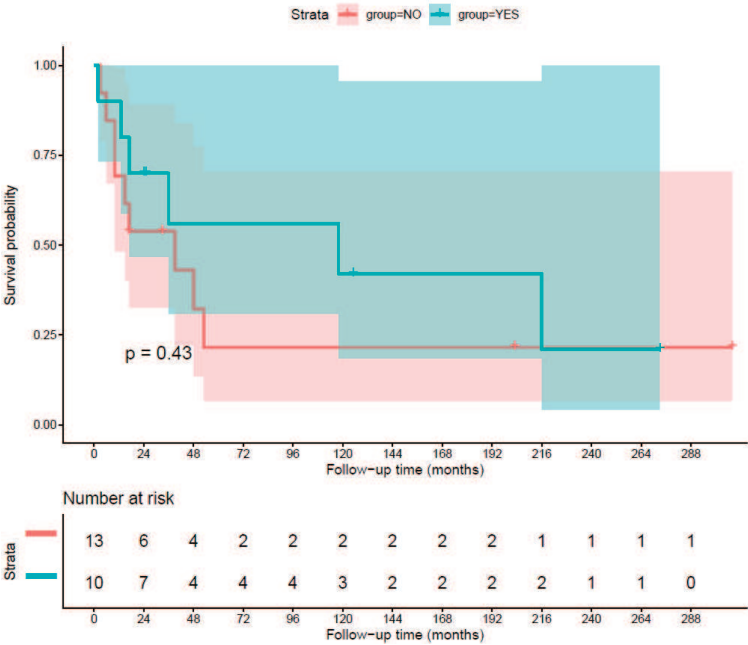


Figure 2 (continued)

C



D

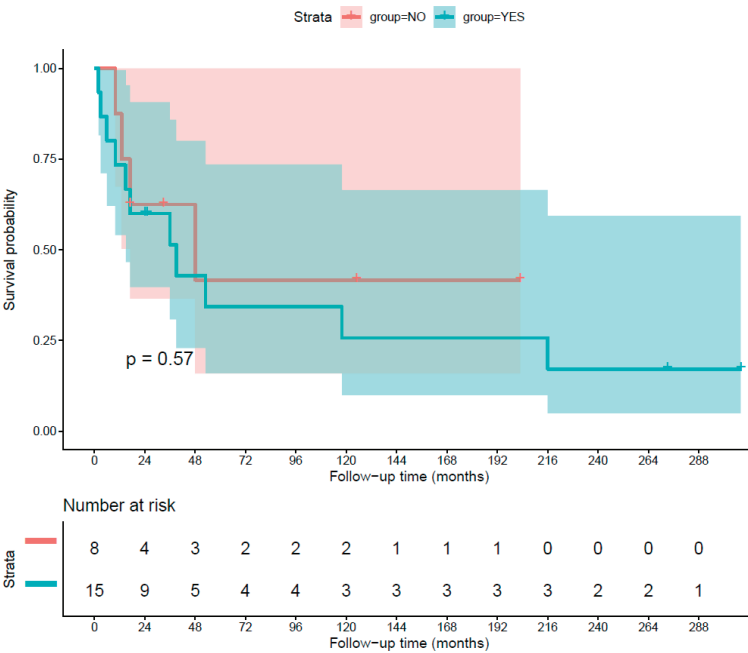


Figure 2. Kaplan Meier survival curves of the (A) progression free survival, (B) overall survival, (C) presence of brainstem compression and (D) cavernous sinus invasion.

Table 1 Patient characteristics

Case	Sex	Age	Presenting symptom	Neurological deficit	Location	Cavernous sinus invasion	Brain stem compression	Surgical approach	Post-op symptoms	Surgical complication (CTCAE grade)	Radiotherapy	Radiotherapy complication (CTCAE grade)
1	F	68	Headache and diplopia	CN VI	Clivus	Right	Yes	Endoscopic endonasal	Improved	No	Photon (74Gy)	No
2	M	63	None	No	Clivus	No	No	Endoscopic endonasal	Unchanged	CSF leakage Gr 3	Photon (74Gy)	No
3	F	30	Diplopia	CN VI	Clivus	Left	No	Sublabial transphenoidal	Unchanged	CSF leakage Gr 3	Proton(80GyE)	Bilateral otitis media Gr 2, Pituitary dysfunction Gr 3, cerebral cyst Gr 1
4	F	24	Diplopia	CN VI	Petroclival	No	No	Endoscopic endonasal, Re-endoscopic 3x	Improved	No	Photon (74Gy)	No
5	F	26	Diplopia, headache and panhypopituitarism	CN VI	Clivus	Both	Yes	Midfacial deglovement, Retrosigmoid	Unchanged	CSF leakage Gr 3	Photon (66Gy)	N.A.

Table 1 Patient characteristics (continued)

Case	Sex	Age	Presenting symptom	Neurological deficit	Location	Cavernous sinus invasion	Brain stem compression	Surgical approach	Post-op symptoms	Surgical complication (CTCAE grade)	Radiotherapy complication (CTCAE grade)
6	M	62	Diplopia, headache and panhypopituitarism	CN VI	Clivus	Left	Yes	Open transphenoidal, Midface deglovement	N.A.	N.A.	Temporal lobe radiation necrosis Gr 2
7	F	70	Diplopia	CN III, VI	Clivus	Both	Yes	Transsphenoidal	N.A.	N.A.	No
8	M	25	Headache	No	Clivus	Left	Yes	Endoscopic transphenoidal	Unchanged	No	Photon (74Gy) N.A.
9	F	69	Vision loss, diplopia	CN II, III, V, VI	Sella, clivus	Both	N.A.	Open transphenoidal, Retrosigmoid	N.A.	Hemorrhage Gr 2	Proton(74GyE), GK (13Gy) on recurrence
10	M	53	Nasal obstruction	No	Clivus	No	No	Midface deglovement, Pterional, Bifrontal	N.A.	N.A.	Proton(48GyE)/Photon boost (20Gy), (SRT 55.8Gy) on recurrence

Table 1 Patient characteristics (*continued*)

Case	Sex	Age	Presenting symptom	Neurological deficit	Location	Cavernous sinus invasion	Brain stem compression	Surgical approach	Post-op symptoms	Surgical complication (CTCAE grade)	Radiotherapy complication (CTCAE grade)
11	M	76	Diplopia, visual deficit	CN II, III, VI	Sella, clivus	Left	No	Endoscopic endonasal	Improved	No	Photon (70Gy) No
12	M	47	Dysarthria, neck pain	CN XII	Lower clivus, occ condyle, C2	No	Yes	Suboccipital, Far lateral, Transcondylar, Anterior cervical, Posterior cervical	Worsened (transient)	Accessory palsy Gr 3 (transient)	Proton (76 GyE), Photon boost (14 Gy), Proton (64 GyE) on recurrence, GK 22 Gy on seeding metastasis No
13	F	53	Diplopia	CN VI	Clivus	Left	No	Endoscopic endonasal, Lat rhinotomy	Improved	No	Proton 74GyE, carbon-ion 51GyE Trigeminal neuropathy Gr 3
14	F	39	Diplopia	CN VI	Clivus	No	No	Midface deglovement	Improved	No	Proton 74GyE Perceptive hearing loss Gr 3, Panhypopituitarism Gr 3, Radiation necrosis Gr 3

Table 1 Patient characteristics (continued)

Case	Sex	Age	Presenting symptom	Neurological deficit	Location	Cavernous sinus invasion	Brain stem compression	Surgical approach	Post-op symptoms	Surgical complication (CTCAE grade)	Radiotherapy complication (CTCAE grade)	Radiotherapy complication (CTCAE grade)
15	F	32	Altered mental status	No	Petroclival	Left	Yes	Subtemporal, Translabryrithine/Trans-	N.A.	N.A.	GK (unknown dosage), Spinal axis (unknown modality), GK on seeding metastasis (unknown dosage)	N.A.
								tentorial, Thoracic				
								laminectomy on spinal metastasis, Subcutaneous seeding metastasis				
16	M	51	Facial pain, diplopia	CN III, V, VI	Cavernous sinus	Right	No	Pterional, Re-pterional, Temporal lobectomy, Subcutaneous seeding metastasis	Improved	No	Proton (78GyE), Proton (56GyE) recurrence	Radiation necrosis Gr 3, Vocal cord paralysis Gr 4, n IX and X palsy Gr 4

Table 1 Patient characteristics (*continued*)

Case	Sex	Age	Presenting symptom	Neurological deficit	Location	Cavernous sinus invasion	Brain stem compression	Surgical approach	Post-op symptoms	Surgical complication (CTCAE grade)	Radiotherapy complication (CTCAE grade)
17	F	27	Visual deficit	Hemianopsia left	Clivus, Sella	Left	Yes	Open transnasal, Subfrontal right, Bifrontal	Improved	No	Photon (59Gy), Photon (24Gy) lumbar metastasis
18	M	45	Diplopia, vision loss	CN II, VI	Clivus, Sella	N.A.	N.A.	Open transphenoidal, Midfacial deglovement C0-C3 fixation, Far lateral transcondylar left; right, retroauricular right seeding metastasis, re-metastectomy right	N.A.	N.A.	N.A.
19	F	43	Cervicalgia	No	Lower clivus	No	No	Hypoglossal palsy Gr 3 (transient), Wound dehiscence Gr 3	Improved		Proton (74GyE), second radiotherapy terminated early
20	M	39	Headache	No	Clivus	Right	No	Lateral rhinotomy	N.A.	N.A.	Brain stem necrosis with hemiplegia and diplopia Gr 4

Table 1 Patient characteristics (continued)

Case	Sex	Age	Presenting symptom	Neurological deficit	Location	Cavernous sinus invasion	Brain stem compression	Surgical approach	Post-op symptoms	Surgical complication (CTCAE grade)	Radiotherapy complication (CTCAE grade)
21	F	40	Visual deficit	Bitemporal hemianopsia	Clivus, sella	Both	Yes	Open transphenoidal biopsy		Partial thoracic paraplegia, vascular origin, complete recovery Gr 3	Photon (54 Gy), 25.2 Gy, 25.2 Gy) two recurrences
								Bifrontal craniotomy, Lateral rhinotomy	Improved		Otitis externa Gr 2
22	F	27	Asymptomatic	No	clivus	N.A.	N.A.	Midface deglovement	N.A.	No	Radiation necrosis Gr 2, Panhypopituitarism Gr 3, Pontine infarction Gr 4
23	M	75	Diplopia	CN VI	Clivus	Both	No	Lateral rhinotomy	Unchanged	Trigeminal neuralgia Gr 3	Carbon ion 60GyE
24	M	54	Vision loss	CN II	Clivus	Both	No	Lateral rhinotomy, Pterional right, Lateral rhinotomy	Improved	No	Radiation necrosis Gr 3

Table 1 Patient characteristics (*continued*)

Case	Sex	Age	Presenting symptom	Neurological deficit	Location	Cavernous sinus invasion	Brain stem compression	Surgical approach	Post-op symptoms	Surgical complication (CTCAE grade)	Radiotherapy complication (CTCAE grade)
25	F	53	Diplopia	CN VI	Clivus	Left	Yes	Midfacial deglovement, Lateral rhinotomy, Remy, Rhinotomy	Unchanged	No	Proton (74GyE), 2x GK on recurrence (unknown dosage) Radiation necrosis Gr 3, Facial nerve palsy Gr 3, Left facial hypoaesthesia Gr 2
26	M	66	Diplopia and gait disturbance	CN VI, corticospinal tract	Clivus	Both	Yes	Lateral rhinotomy	Worsened	Brainstem infarction Gr 5 Hydrocephalus Gr 5,	No
27	M	39	Diplopia	CN VI	Clivus	N.A.	Yes	Petrosectomy	Worsened	Right facial nerve palsy Gr 3	Radiation necrosis Gr 3, Epilepsy Gr 3, Panhypopituitarism Gr 3
28	M	52	Diplopia	CN VI	Clivus	No	Yes	Lateral rhinotomy	Unchanged	No	Radiation necrosis Gr 3, Epilepsy Gr 3
29	M	72	Gait disturbance, dysphagia	Cerebrospinal tract	Clivus	Both	Yes	Lateral rhinotomy	Worsened	CSF leakage Gr 5, Meningitis Gr 5, Hydrocephalus Gr 5,	No

Table 1: This table displays the details on demographic, symptoms, tumor, treatment and complication of each individual patient. CSF = Cerebrospinal fluid. N.A = not available. GK = Gamma Knife. Gy = Gray. GyE = Gy equivalent.

DISCUSSION

This study presents the treatment experience of skull base chordoma at our institute over the past decades. Several factors have influenced the management of chordoma patients at our center. In this paper we address these factors and give our insights into overcoming these challenges.

Current literature on skull base chordoma is mainly based on retrospective case series and systematic reviews. In oncologic surgery achieving clear margins significantly improves local control and survival rates¹¹. However, the proximity of critical neurological and vascular structures in skull base chordoma makes en bloc resection virtually impossible¹⁴. Still, a macroscopic complete resection improves the progression free -and overall survival rates compared to subtotal resection and biopsy^{10,11}. The addition of adjuvant radiotherapy seems to further improve the outcome¹⁵. Therefore, a maximum safe resection followed by high-dose radiotherapy is the current standard of care^{4,16}. There is considerable debate regarding the optimal radiotherapy modality^{15,17}. Particle therapies such as proton- and carbon ion beam therapy have been applied the most in worldwide literature due to its unique high Bragg's peak, delivering high dose radiation on target with a quick drop-off to protect surrounding structures¹⁸.

Survival outcome

Skull base chordoma have a high recurrence rate and survival outcome is mainly affected by age and resection rate^{19,20}. A meta-analysis from Amit et al²⁰ showed an average 5-year progression free survival of 65.7% and overall survival of 86%. The 5-year overall survival of surgery followed by adjuvant radiotherapy was 87% compared with 69% of those treated by surgery alone $p = 0.12$. In subgroup analyses for patients undergoing gross total resection without radiotherapy, the 5-year overall survival was 92%, and for those receiving adjuvant radiotherapy overall survival was 100%. In patients undergoing partial resection without adjuvant radiotherapy the 5-year overall survival was 41%, with adjuvant radiotherapy the 5-year overall survival was 84% $p < 0.001$.

In this cohort the mean follow-up was 116 months (range 16-308). The 5-year and 10-year progression free survival were 42% and 18%, respectively. The 5-year and 10-year overall survival were 75% and 55%, respectively. Seven patients in this cohort are long survivors (>10 years). Two of them had a local recurrence within 13 and 17 months but were successfully treated with re-operation only and remained recurrence free thereafter. This suggests that not all early local recurrences mean that the tumor is uncontrollable after primary surgical and radiotherapeutic therapy, and salvage therapy can offer long term control.

A notable finding was that neither brainstem compression nor cavernous sinus invasion demonstrated a significant association with long-term progression-free survival. Previous

literature has consistently identified both features as adverse prognostic markers for progression²¹. These characteristics likely reflect more locally advanced disease and increased tumor burden, as larger tumors are more commonly associated with brainstem compression and/or cavernous sinus extension. Indeed, tumor size and volume themselves have repeatedly been shown to negatively influence progression-free survival²². In the present cohort, however, log-rank analysis failed to demonstrate a significant effect of either variable, likely owing to the limited sample size and corresponding reduction in statistical power.

Surgical approach

Another key development was the introduction of endoscopic skull base surgery in 2017 at our center. Previously, patients underwent extensive trans facial or trans cranial approaches, which were associated with greater morbidity and longer hospitalization¹⁹. In this series the most recent six cases were operated using an endoscopic approach; therefore, they have a shorter follow-up, warranting caution to compare the survival outcomes with the other surgical approaches. Gross total resection was achieved in 9 patients (31%), of which 4 underwent endoscopic resection. Three of the GTR subgroup demonstrated a local recurrence (33%). Post-operative CSF leakage was comparable between the endoscopic and trans facial and transcranial approaches; one patient (17%) after endoscopic surgery in comparison with three (15%) after midfacial degloving. Our team developed a dural closure technique for small defects, which is faster and does not require the use of tissue flaps. It incorporates a specific cone shaped surgical cavity in which shards of autologous abdominal fat is applied in layers to cover the defect. This method will be assessed in the future but shows promising results in our practice to prevent post-operative CSF leakage. Larger defects are closed in a standard multilayer technique involving tissue flaps²³.

Several papers have been published on the difference between endoscopic and open microsurgical surgery for skull base chordoma^{19,24-29}. Both approaches have statistically similar recurrence rates: open 31.8% (99% CI 14-52.8) and endoscopic 19.4% (99% CI 5.4-39.2), however a trend favoring endoscopic surgery has been shown¹⁹. This is more evident in the post-operative complications; open approaches demonstrate significantly higher cranial nerve deficits 17.2% (99% CI 3.8-37.5) vs endoscopic 4.8% (99% CI 1.4-10) and comparable CSF leakage: open 9.5% (99% CI 5.1-16.6) vs endoscopic 10.3% (99% CI 5-17.3). This cohort demonstrates a similar pattern with all cranial nerve complications being in the open surgery group.

Adjuvant radiotherapy

A major challenge was the unavailability of proton beam therapy in The Netherlands up to 2019. As a result, each patient was referred to centers abroad e.g. Paris (France), Boston (USA) and Heidelberg (Germany) imposing significant logistical, emotional, and financial burdens on patients and their families. The establishment of a proton therapy in the Netherlands in 2018 markedly improved treatment timelines and patient comfort. Our current

practice is to compare clinical target volumes for photon and proton therapy for each patient to determine the optimum balance between high-dose radiation to the target and minimal dosage to nearby neural structures³⁰. In our cohort 60% experienced side effects from radiotherapy. These primarily constitute of radiation necrosis, pituitary gland deficits and cranial nerve neuropathies. In particular, temporal lobe necrosis had a significant impact on quality of life, with two patients developing epilepsy and one requiring a re-operation to clarify the difference between tumor progression and necrosis. Chordoma are radiation resistant tumors, requiring high-dose radiotherapy to achieve tumor control. At the edge of the Bragg peak, the linear energy transfer is much higher, resulting in an increased relative biological effectiveness³¹. In skull base tumors this often means adjacent neural structures receive toxic dosages leading to significant percentages of late radiotherapy effects. Several papers report on the adverse effects of particle therapy in skull base chordoma^{18,32-39}. Koto et al reports on the long-term outcomes of carbon ion radiotherapy and 9% of patients developed temporal lobe necrosis^{17,40}. A meta-analysis by Palavani et al reported a pooled incidence of 16% complication rate in proton and carbon ion therapy¹⁵. They do, however, see notable heterogeneity among the studies in reporting complications. Reported rates of symptomatic cerebral necrosis after proton therapy vary between 3-12%^{38,41,42}. Presently, approximately 90 proton therapy centers are located globally, with the majority in the western world. Additionally, it is an expensive therapy with extensive production costs. This implies that it remains a largely unavailable treatment option for patients in lesser developed countries. Future studies should focus on the difference in tumor control and toxicity profile between particle and photon radiotherapy.

Limitations

The retrospective nature of this cohort inherently leads to bias in data availability and interpretation. Several patients record files, mainly from the previous century, were incomplete due to non-digitized documentation. In addition, most patients were treated in multiple institutions, resulting in incomplete records. The digitalization of hospital records will aid in diminishing incomplete records and further standardize the registration process. Furthermore, the rarity of skull base chordoma and the individualized treatment plans in single institute cohorts limit the generalizability of findings and complicate statistical comparisons across studies. Multicenter prospective collaborations may help overcome these limitations in the future.

CONCLUSION

Skull base chordoma is an extremely rare and poorly understood malignancy. Current practice consists of maximum safe resection followed by high dose radiotherapy to optimize recurrence and survival rates. The development of endoscopic approaches has increased macroscopic complete resection rates while decreasing the surgical complications. The avail-

ability of an advanced radiotherapy institution is essential for optimal patient care. Advances in photon therapy allow for radiating safely at a high dose. Tumor recurrence is often associated with increased mortality; however, salvage therapy i.e. surgery, re-irradiation, adding carbon-ion after photon/proton therapy, may offer prolonged survival rates in specific cases, predominantly in seeding metastases.

REFERENCES

1. Kyriakos M, Totty WG, Lenke LG. Giant vertebral notochordal rest: a lesion distinct from chordoma: discussion of an evolving concept. *Am J Surg Pathol*. Mar 2003;27(3):396-406. doi:10.1097/00000478-200303000-00015
2. McMaster ML, Goldstein AM, Bromley CM, Ishibe N, Parry DM. Chordoma: incidence and survival patterns in the United States, 1973-1995. *Cancer Causes Control*. Jan 2001;12(1):1-11. doi:10.1023/a:1008947301735
3. Frezza AM, Botta L, Trama A, Dei Tos AP, Stacchiotti S. Chordoma: update on disease, epidemiology, biology and medical therapies. *Curr Opin Oncol*. Mar 2019;31(2):114-120. doi:10.1097/CCO.0000000000000502
4. Alahmari M, Temel Y. Skull base chordoma treated with proton therapy: A systematic review. *Surg Neurol Int*. 2019;10:96. doi:10.25259/SNI-213-2019
5. Koutourousiou M, Snyderman CH, Fernandez-Miranda J, Gardner PA. Skull base chordomas. *Otolaryngol Clin North Am*. Oct 2011;44(5):1155-71. doi:10.1016/j.otc.2011.06.002
6. Di Maio S, Temkin N, Ramanathan D, Sekhar LN. Current comprehensive management of cranial base chordomas: 10-year meta-analysis of observational studies. *Journal of neurosurgery*. Dec 2011;115(6):1094-105. doi:10.3171/2011.7.JNS11355
7. Banu MA, Raza SM, Amini M, et al. The role of systemic therapy in advanced skull base chordomas: overview of the current state and the MD Anderson protocol. *Neurosurg Focus*. May 2024;56(5):E15. doi:10.3171/2024.2.Focus2416
8. Yakkoui Y, van Overbeeke JJ, Santegoeds R, van Engeland M, Temel Y. Chordoma: the entity. *Biochim Biophys Acta*. Dec 2014;1846(2):655-69. doi:10.1016/j.bbcan.2014.07.012
9. Bai J, Shi J, Li C, et al. Whole genome sequencing of skull-base chordoma reveals genomic alterations associated with recurrence and chordoma-specific survival. *Nat Commun*. Feb 3 2021;12(1):757. doi:10.1038/s41467-021-21026-5
10. Barber SM, Sadrameli SS, Lee JJ, et al. Chordoma-Current Understanding and Modern Treatment Paradigms. *J Clin Med*. Mar 4 2021;10(5)doi:10.3390/jcm10051054
11. Perez-Vega C, Akinduro OO, Ruiz-Garcia HJ, et al. Extent of Surgical Resection as a Predictor of Tumor Progression in Skull Base Chordomas: A Multicenter Volumetric Analysis. *World Neurosurg*. Jan 2024;181:e620-e627. doi:10.1016/j.wneu.2023.10.101
12. Yaniv D, Soudry E, Strenov Y, Cohen MA, Mizrahi A. Skull base chordomas review of current treatment paradigms. *World J Otorhinolaryngol Head Neck Surg*. Jun 2020;6(2):125-131. doi:10.1016/j.wjorl.2020.01.008
13. Offersen BV, Boersma LJ, Kirkove C, et al. ESTRO consensus guideline on target volume delineation for elective radiation therapy of early stage breast cancer, version 1.1. *Radiother Oncol*. Jan 2016;118(1):205-8. doi:10.1016/j.radonc.2015.12.027
14. Rychen J, Constanzo F, Xu Y, et al. Supramarginal resection of skull base chordomas: proof of concept and preliminary outcomes. *Neurosurgical focus*. May 2024;56(5):E3. doi:10.3171/2024.2.FOCUS23909
15. Palavani LB, Borges P, Andreao FF, et al. Optimizing radiotherapy strategies for skull base chordoma: a comprehensive meta-analysis and systematic review of treatment modalities and outcomes. *Neurosurgical focus*. May 2024;56(5):E11. doi:10.3171/2024.2.FOCUS2413
16. Stacchiotti S, Sommer J, Chordoma Global Consensus G. Building a global consensus approach to chordoma: a position paper from the medical and patient community. *Lancet Oncol*. Feb 2015;16(2):e71-83. doi:10.1016/S1470-2045(14)71190-8

17. Koto M, Ikawa H, Kaneko T, Hagiwara Y, Hayashi K, Tsuji H. Long-term outcomes of skull base chordoma treated with high-dose carbon-ion radiotherapy. *Head Neck*. Sep 2020;42(9):2607-2613. doi:10.1002/hed.26307
18. Rodrigues A, Tos SM, Shaaban A, Mantziaris G, Trifiletti DM, Sheehan J. Proton beam and carbon ion radiotherapy in skull base chordoma: a systematic review, meta-analysis and meta-regression with trial sequential analysis. *Neurosurg Rev*. Dec 7 2024;47(1):893. doi:10.1007/s10143-024-03117-1
19. Cannizzaro D, Tropeano MP, Milani D, et al. Microsurgical versus endoscopic transphenoidal approaches for clivus chordoma: a pooled and meta-analysis. *Neurosurg Rev*. Jun 2021;44(3):1217-1225. doi:10.1007/s10143-020-01318-y
20. Amit M, Na'ara S, Binenbaum Y, et al. Treatment and Outcome of Patients with Skull Base Chordoma: A Meta-analysis. *J Neurol Surg B Skull Base*. Dec 2014;75(6):383-90. doi:10.1055/s-0034-1376197
21. Bakker SH, Jacobs WCH, Pondaag W, et al. Chordoma: a systematic review of the epidemiology and clinical prognostic factors predicting progression-free and overall survival. *Eur Spine J*. Dec 2018;27(12):3043-3058. doi:10.1007/s00586-018-5764-0
22. Teng C, Yang Q, Xiong Z, Ye N, Li X. Multivariate Analysis and Validation of the Prognostic Factors for Skull Base Chordoma. Original Research. *Frontiers in Surgery*. 2021-November-23 2021;Volume 8 - 2021doi:10.3389/fsurg.2021.764329
23. Soneru CP, Riley CA, Tabaei A, Kacker A, Anand VK, Schwartz TH. The Challenge of Skull Base Closure: Methods for Reducing Postoperative Cerebrospinal Fluid Leak. *World Neurosurg*. Apr 2019;124:502-512. doi:10.1016/j.wneu.2019.01.121
24. Stippler M, Gardner PA, Snyderman CH, Carrau RL, Prevedello DM, Kassam AB. Endoscopic endonasal approach for clival chordomas. *Neurosurgery*. Feb 2009;64(2):268-77; discussion 277-8. doi:10.1227/01.NEU.0000338071.01241.E2
25. Baig Mirza A, Ravindran V, Okasha M, et al. Systematic Review Comparing Open versus Endoscopic Surgery in Clival Chordomas and a 10-Year Single-Center Experience. *J Neurol Surg B Skull Base*. Jun 2022;83(Suppl 2):e113-e125. doi:10.1055/s-0041-1722933
26. Rahme RJ, Arnaout OM, Sanusi OR, Kesavabhotla K, Chandler JP. Endoscopic Approach to Clival Chordomas: The Northwestern Experience. *World Neurosurg*. Feb 2018;110:e231-e238. doi:10.1016/j.wneu.2017.10.146
27. Cavallo LM, Mazzatenta D, d'Avella E, et al. The management of clival chordomas: an Italian multicentric study. *Journal of neurosurgery*. Jul 1 2021;135(1):93-102. doi:10.3171/2020.5.JNS20925
28. Shimony N, Gonen L, Shofty B, Abergel A, Fliss DM, Margalit N. Surgical resection of skull-base chordomas: experience in case selection for surgical approach according to anatomical compartments and review of the literature. *Acta neurochirurgica*. Oct 2017;159(10):1835-1845. doi:10.1007/s00701-016-3032-9
29. Komotar RJ, Starke RM, Raper DM, Anand VK, Schwartz TH. The endoscope-assisted ventral approach compared with open microscope-assisted surgery for clival chordomas. *World Neurosurg*. Sep-Oct 2011;76(3-4):318-27; discussion 259-62. doi:10.1016/j.wneu.2011.02.026
30. Wagenaar D, Habraken SJM, Rinaldi I, et al. Evaluating and reporting LET and RBE-weighted dose in proton therapy for glioma - The Dutch approach. *Radiother Oncol*. Jan 2025;202:110653. doi:10.1016/j.radonc.2024.110653
31. Lambrecht M, Eekers DBP, Alapetite C, et al. Radiation dose constraints for organs at risk in neuro-oncology; the European Particle Therapy Network consensus. *Radiother Oncol*. Jul 2018;128(1):26-36. doi:10.1016/j.radonc.2018.05.001

32. Dong M, Liu R, Zhang Q, et al. Efficacy and safety of carbon ion radiotherapy for chordomas: a systematic review and meta-analysis. *Radiat Oncol*. Sep 13 2023;18(1):152. doi:10.1186/s13014-023-02337-x
33. Lu VM, O'Connor KP, Mahajan A, Carlson ML, Van Gompel JJ. Carbon ion radiotherapy for skull base chordomas and chondrosarcomas: a systematic review and meta-analysis of local control, survival, and toxicity outcomes. *Journal of neuro-oncology*. May 2020;147(3):503-513. doi:10.1007/s11060-020-03464-1
34. Chhabra AM, Rice SR, Holtzman A, et al. Clinical outcomes and toxicities of 100 patients treated with proton therapy for chordoma on the proton collaborative group prospective registry. *Radiother Oncol*. Jun 2023;183:109551. doi:10.1016/j.radonc.2023.109551
35. Iannalfi A, D'Ippolito E, Riva G, et al. Proton and carbon ion radiotherapy in skull base chordomas: a prospective study based on a dual particle and a patient-customized treatment strategy. *Neuro Oncol*. Sep 29 2020;22(9):1348-1358. doi:10.1093/neuonc/noaa067
36. Mattke M, Ohlinger M, Bougattf N, et al. Proton and carbon ion beam treatment with active raster scanning method in 147 patients with skull base chordoma at the Heidelberg Ion Beam Therapy Center-a single-center experience. *Strahlenther Onkol*. Feb 2023;199(2):160-168. doi:10.1007/s00066-022-02002-4
37. Pehlivan B, Ares C, Lomax AJ, et al. Temporal lobe toxicity analysis after proton radiation therapy for skull base tumors. *International journal of radiation oncology, biology, physics*. Aug 1 2012;83(5):1432-40. doi:10.1016/j.ijrobp.2011.10.042
38. Deraniyagala RL, Yeung D, Mendenhall WM, et al. Proton therapy for skull base chordomas: an outcome study from the university of Florida proton therapy institute. *J Neurol Surg B Skull Base*. Feb 2014;75(1):53-7. doi:10.1055/s-0033-1354579
39. Gendreau JL, Hameed NUF, Jimenez A, Chakravarti S, Mehkri Y, Mukherjee D. Fractionated Radiotherapy After Gross Total Resection of Clival Chordoma: A Systematic Review of Survival Outcomes. *Neurosurgery*. Aug 1 2023;93(2):257-266. doi:10.1227/neu.0000000000002418
40. Koto M, Hasegawa A, Takagi R, et al. Risk factors for brain injury after carbon ion radiotherapy for skull base tumors. *Radiother Oncol*. Apr 2014;111(1):25-9. doi:10.1016/j.radonc.2013.11.005
41. Weber DC, Malyapa R, Albertini F, et al. Long term outcomes of patients with skull-base low-grade chondrosarcoma and chordoma patients treated with pencil beam scanning proton therapy. *Radiother Oncol*. Jul 2016;120(1):169-74. doi:10.1016/j.radonc.2016.05.011
42. Fung V, Calugaru V, Bolle S, et al. Proton beam therapy for skull base chordomas in 106 patients: A dose adaptive radiation protocol. *Radiother Oncol*. Aug 2018;128(2):198-202. doi:10.1016/j.radonc.2017.12.017

5

Chondrosarcoma

Skull Base Chondrosarcoma: A Systematic Review of The Role of Postoperative Radiotherapy

*Keizer ME, *Ravindran PK, Kunst HPM, Compter I, Van Aalst J, Eekers DBP, Temel Y. Skull-Base Chondrosarcoma: A Systematic Review of the Role of Postoperative Radiotherapy. *Cancers (Basel)*. 2024 Feb 21;16(5):856.

*Both authors contributed equally.

Simple Summary: Currently, there is no global consensus regarding the treatment of skull-base chondrosarcoma. Some believe surgery is sufficient, others administer adjuvant radiotherapy regardless of the extent of surgical resection. This review aims to gather the latest available evidence regarding the treatment of skull base chondrosarcoma and to analyze the long-term prognosis to ascertain the potential added value of adjuvant radiotherapy and its application.

Abstract: Surgery and radiotherapy are key elements to the treatment of skull base chondrosarcomas, however currently there is no consensus regarding whether adjuvant radiotherapy has to be administered. This study searched EMBASE, Cochrane and PubMed databases for clinical studies evaluating the long-term prognosis of surgery with or without adjuvant radiotherapy. After reviewing the search results, a total of 22 articles were selected for this review. A total of 1388 patients were included in this cohort, of which 168 received surgery only. With mean follow-up periods ranging from 39.1 to 86 months, surgical treatment provided a PFS ranging from 83.7% - 92.9% at 3 years, 64.0% - 99.0% at 5 years, and 42.3% - 98.0% at 10 years. Post-operative radiotherapy provides a PFS ranging between 87-96.2% at 3-years, 57.1%-100% at 5-years, and 67%-100% at 10-years. Recurrence rate varied from 5.3% and 39.0% in the surgery only approach, and between 1.5% and 42.80% for the postoperative radiotherapy group. When considering prognostic variables, higher age, brainstem/optic apparatus compression, and larger tumor volume prior to radiotherapy were found to be significant factors for local recurrence. Further research is required to statistically prove the possible superiority of one treatment option over the other.

Keywords: skull-base, chondrosarcoma, low-grade, radiotherapy, surgery

INTRODUCTION

Chondrosarcomas are a prominent group of sarcomas, second to osteosarcomas in frequency. The term ‘chondrosarcoma’ encapsulates a diverse group of malignant tumors stemming from chondroid cells in the appendicular and axial skeleton. It accounts for approximately 11% of primary malignant bone tumors, with an estimated incidence of 1 in 200,000 in the United States [1,2]. Cases of chondrosarcoma primarily affect the cartilaginous cells of the arms, shoulders, legs, spine, and pelvis. Chondrosarcomas of the skull base account for approximately 1% of these cases and mostly arise *de novo* [2]. Inversely, skull base chondrosarcomas account for approximately 6% of all skull-base tumors and 0.15% of all intracranial neoplasms [3,4].

Current literature suggests that most primary skull base chondrosarcomas occur in the middle fossa, with the petrous bone, the clivus, and/or the petroclival synchondrosis holding the most common locations [2]. Macroscopically, chondrosarcomas are often bigger than 2 cm in diameter, and are characterized by being hard, smooth, and lobulated [3]. Chondrosarcomas typically have: (1) an abundant hyaline-type cartilaginous stroma and (2) neoplastic chondrocytes. There also may be myxoid or mucoid material and cystic changes seen macroscopically. Malignancy is characterized by the infiltration into the bony trabeculae [4]. Microscopically, chondrosarcomas house irregularly shaped cartilage lobules, separated by fibrous bands. The chondrocytes are usually atypical and variable in size. Myxoid changes and matrix liquefaction can also be seen microscopically [5].

Histological analysis categorizes chondrosarcomas into four subgroups: conventional, mesenchymal, clear cell, and dedifferentiated chondrosarcoma. Additionally, chondrosarcomas can be grouped into three grades as per the cell differentiation – as introduced by the World Health Organization: Grade I (well differentiated), Grade II (intermediately differentiated), and grade III (poorly differentiated) [4]. Grade I is characterized by low cellularity, low to no myxoid, and abundant chondroid matrix. A conventional chondrosarcoma would, for example, fall in this category of grade I. Grade II is recognized by its increased cellularity, low chondroid matrix, and more prominent myxoid [6]. Examples of histological subtypes that fall into this grade include conventional and myxoid chondrosarcoma [6]. Lastly, grade III is identified by its high cellularity, the presence of nuclear pleomorphism, no chondroid matrix, and myxoid stroma. Examples of histological subtypes that fall into this grade include conventional, mesenchymal, and dedifferentiated [6]. Conventional chondrosarcomas are the most common histopathological subtype; likewise, grade I comprise the majority, and less commonly, grade II [3]. Histologically, the clear-cell and conventional tumor types are associated with the highest overall survival, whereas the dedifferentiated and mesenchymal types were found to be associated with the lowest overall survival [7]. Similarly, grade I and II tumors are associated with a better prognosis than grade III [7].

Patients usually present at a median age of 42.5 years with symptoms dependent on the tumor size and location [2]. Aside from headaches, mostly located in the occipital or retro-orbital region, neuro-ophthalmological symptoms are the most reported signs [4]. Visual symptoms include blurred or loss of vision, ptosis, diplopia, and visual field defects. Other signs are often consistent with the consequences of brainstem compression and cranial nerve palsy [4]. Furthermore, this tumor can have endocrinological implications leading to hypopituitarism and diabetes insipidus because of involvement of the sellar and/or suprasellar structures [4]. Bigger tumors may compress the brainstem.

The role of chemotherapy is limited in chondrosarcoma; thus, surgery and radiation therapy remain as the two keystones for the treatment of chondrosarcomas [8]. Chemotherapy however is a viable option in locally advanced disease or on metastases [8]. Surgery is conducted for two reasons: to obtain tissue for diagnosis and to reduce tumor volume. The open, transcranial, transfacial and transpetrous, infratemporal, and the endoscopic/microscopic endonasal approaches are all commonly used and efficacious options for surgical treatment of chondrosarcomas [3]. Albeit complete resection is favored, the anatomical constraints and proximity to critical neurovascular structures often makes this an unrealistic philosophy. Despite these tumors being slow growing, they show a high local recurrence with metastasis occurring in approximately 10% of cases [3]. Common complications of surgery include cerebrospinal fluid leak, transient neurological complications such as cranial nerve neuropathies, meningitis/brain abscesses, and persistent neurological complications, due to, for instance, an intracranial hemorrhage. Adjuvant radiotherapy is often given, to treat the tumor bed because of postoperative micro/macrosopic remnants [3,4,7]. Commonly used adjuvant radiotherapy includes linear accelerator (LINAC) based intensity modulated radiotherapy (IMRT), Stereotactic radiotherapy (SRT) with LINAC or Gamma Knife, and CyberKnife all using photons and particle radiotherapy using e.g. protons or carbon ions [3,4]. Complications are associated with damage to the surrounding 'organs at risk' (OARs).

Despite these treatment options being available, each with their own benefits and caveats, no randomized clinical trials or large prospective series exist to define the ideal treatment. Furthermore, there are no studies comparing radiotherapy modalities (e.g., particles versus photons). This systematic review aims to discuss the current literature and describe the effect of adjuvant radiotherapy on long-term prognosis in patients with skull base chondrosarcoma.

METHODS

Search Strategy and Study Eligibility

This systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. PubMed, EMBASE (OVID) and Cochrane databases were searched using the following search input: ((skull base) OR

((intracranial)) AND ((chondrosarcoma) OR (skull base chondrosarcoma)) AND ((proton therapy) OR (radiotherapy) OR (proton beam therapy) OR (gamma knife) OR (carbon ion therapy) OR (surgery) OR (photon therapy)) AND ((local control) OR (survival) OR (progression) OR (prognosis)). Studies published after 1999 were screened for inclusion, no other limits/filters were used. The search was conducted up to date with the last search being performed on January 5, 2024. Three authors (P.K.R, M.K, and Y.T) went through the search results to identify clinical trial and observational studies conforming with our inclusion criteria. This was accomplished by firstly exporting the database searches to EndNote (Clarivate Analytics), after which duplicates were removed. Thereafter, the one author (P.K.R) independently 1) screened the title and abstracts and excluded the articles not suitable to the goal of our review; and 2) of the remaining articles, the full text was analyzed and was included if eligible. This was confirmed by two other authors (M.K. and Y.T). If the full article was not available, the authors were contacted to obtain access. Disagreements between authors were solved by consensus. This review protocol was registered on PROSPERO, ID: CRD42024496554.

Inclusion and exclusion criteria were defined prior to the search. Studies were included if they were: (1) peer-reviewed original articles in patients with skull base chondrosarcomas who have undergone surgery alone or received postoperative adjuvant radiation therapy, (2) studies reporting the prognostic values (e.g., overall survival, local control, disease-specific survival), and (3) written in English. Studies were excluded if they were: (1) literature or systematic reviews, meta-analyses, case-reports, comments, books, information pages, animal, or phantom studies, (2) histological studies, and (3) written in a foreign language.

Data Extraction and Quality Assessment

Data was extracted from the search inputs by one author (P.K.R) and confirmed independently by two additional authors (Y.T. and M.K.). The extracted data included: (1) study information, including research design, authors, year of publishing, (2) characteristics of patients, including sex, mean age, mean follow up time, tumor size, type of intervention, type of surgical approach, mean dose of radiotherapy, type of radiotherapy, and (3) outcomes, including progression-free survival (PFS), overall survival rates (OS), disease free survival (DFS), complications or adverse events, and recurrence rates. For simplification purposes, local control and recurrence-free survival was considered as identical to progression-free survival. Thus, local control will be used from studies where progression-free survival is not available, and when local control is not available, recurrence-free survival was used if provided. The scale used to measure acute and late adverse events is mentioned in the results if reported by the original study. The study authors were contacted once when the studies did not report enough data to compute the effect size.

In order to assess the quality of the included study, the Cochrane Library guidelines were consulted and the Risk of Bias in Nonrandomized Studies – of Interventions (ROBINS-I)

tool was used. This tool assesses the confounding, selection bias, classification of interventions, deviations from intended interventions, missing data, measurement of outcomes, and reporting bias. Each study was assessed in terms of these categories and were rated as low, high, or unclear level of bias.

Reporting bias assessment

The quality of the included studies was primarily assessed using the Cochrane Risk of Bias in Nonrandomized Studies- of Interventions (ROBINS-I) tool. For studies that used a format conforming to a case series, as opposed to a cohort study, the JBI quality assessment tool for case series was used. The domains in this review using the two tools include: confounding, selection bias, reporting bias, and information bias. The studies assessed using the ROBINS-I were assessed on a scale of risk: low-risk, moderate risk, serious risk, critical risk, or no information.

Statistical Analysis

The primary outcome for this review was to assess the prognosis (i.e., OS, PFS, DFS, LC) of the intervention, i.e., surgery with or without postoperative radiotherapy. The data on patient characteristics and clinical information from all the studies was pooled to obtain the mean baseline characteristics. This was done using SPSS V.28 (IBM SPSS Statistics, IBM Corp, Armonk, New York, NY, USA). After consulting with a professor in statistics, it was deemed impossible to pool the data from the survival of all the studies as majority of the studies did not report the number at risk of the Kaplan Meier curve, the effect size (i.e. hazard ratio), or the confidence intervals. As a result, we resorted to report a systematic review without a meta-analysis.

RESULTS

Literature search

The literature search identified 830 results from PubMed, EMBASE (OVID), and Cochrane Library of which 56 were selected based on the study design, title, and abstract (see Figure 1). Further assessment of the full text resulted in 32 papers being excluded and eventually 22 papers were included in this review; more information is shown in Figure 1.

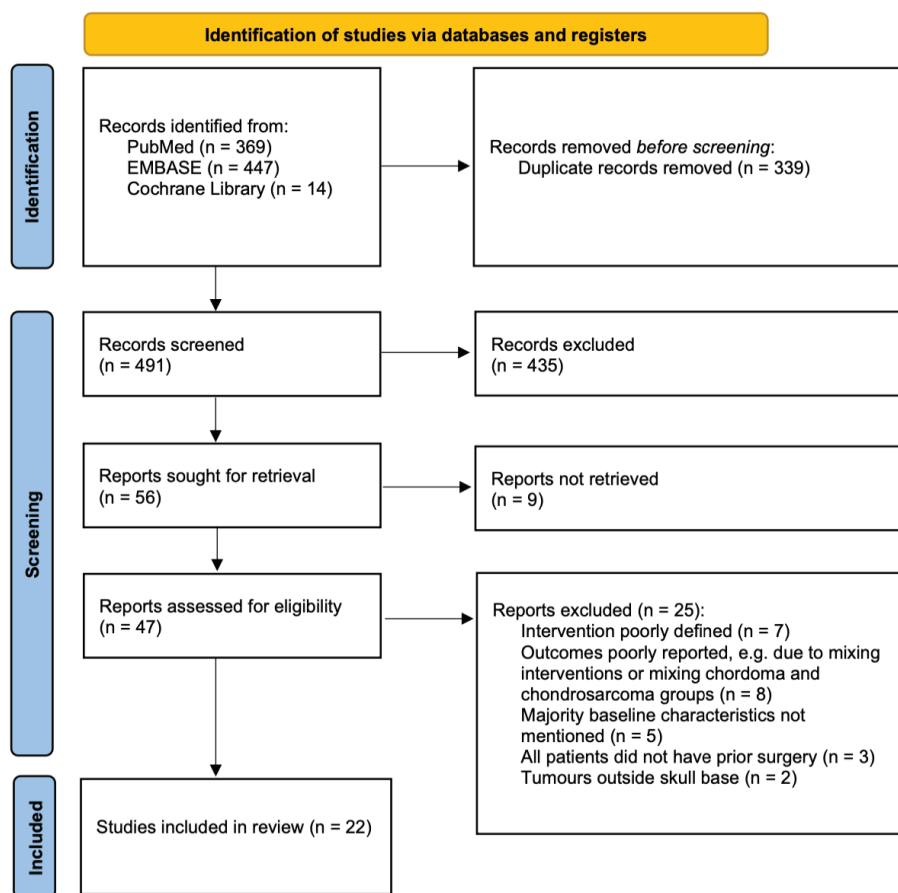


Figure 2: PRISMA flow diagram showing inclusion process.

Risk of Bias Assessment

As per the ROBINS-I tool, the following confounding domains were identified in the protocol phase of the study: age, sex, extent of resection, tumor size, tumor pathology/grade, radiotherapy dose, and type of radiotherapy. No co-interventions were determined to be relevant for this risk of bias assessment. Studies of a case-series design were assessed using the JBI's quality measurement tool for case series. The risk of bias assessment of all articles ranged from moderate risk to critical risk, portrayed in Table 1 of the Supplementary Appendix.

Table 1: Pooled baseline patient characteristics

Characteristic	Total number of patients
Sex	
Male	631 (45.5%)
Female	757 (54.5%)
Mean Age $\pm$ SD (range)	41.81 $\pm$ 4.2 (32-52)
Presenting Symptoms	
Diplopia	185 (59.3%)
Headaches	86 (27.6%)
Hearing deficit	64 (20.5%)
Visual field deficit	37 (11.9%)
Nasal issues	20 (6.4%)
Dizziness	18 (5.7%)
Coordination problems	11 (3.5%)
Facial weakness	11 (3.5%)
Facial sensory problems	9 (2.9%)
Swallowing difficulties	7 (2.2%)
Hoarseness/dysphagia	6 (1.9%)
Facial pain	6 (1.9%)
Tinnitus	6 (1.9%)
Hemiparesis/amaurosis	6 (1.9%)
Miscellaneous	25 (8.0%)
Tumor Location	
Petrous bone	169 (16.6%)
Clivus	154 (15.1%)
Temporo-occipital junction	137 (13.4%)
Cavernous sinus	123 (12.1%)
Petroclival	117 (11.5%)
Sphenoid bone	45 (4.4%)
Anterior skull base	35 (3.4%)
Parasellar	29 (2.8%)
Sphenopetrosal	22 (2.2%)
Suprasellar	22 (2.2%)
Ethmoid	20 (1.9%)
Posterior fossa	19 (1.9%)
Paranasal sinuses	14 (1.4%)
Meckel's cave	14 (1.4%)
Sphenoethmoid complex	12 (1.2%)
Middle fossa	12 (1.2%)
Petrous bone + cavernous sinus $\pm$ occipital bone	11 (1.1%)
Jugular foramen	11 (1.1%)
Skull base	11 (1.1%)

Table 1: Pooled baseline patient characteristics (continued)

Characteristic	Total number of patients
Craniocervical junction	2 (0.2%)
Miscellaneous	40 (3.9%)
Surgical Approach	
Endonasal	101 (32.9%)
Subtemporal-infratemporal	44 (14.3%)
Pteronial	28 (9.1%)
Retrosigmoid	18 (5.8%)
Extended sub- frontal	18 (5.8%)
Frontotemporal-transzygomatic	11 (3.6%)
Epidural anterior petrosectomy	10 (3.3%)
Lateral rhinotomy	7 (2.3%)
Transethmoid	6 (1.9%)
Posterior sigmoid	5 (1.6%)
Infratemporal fossa	5 (1.6%)
Extreme lateral transcondylar	3 (0.9%)
Subtemporal	3 (0.9%)
Transcranial-transnasal	3 (0.9%)
Transcranial	24 (7.8%)
Miscellaneous	21 (6.8%)
Cranial Nerve Palsies	
Abducens	204 (30.7%)
Trigeminal	70 (10.6%)
Facial	52 (7.8%)
Vestibulocochlear	46 (6.9%)
Oculomotor	44 (6.6%)
Hypoglossus	26 (3.9%)
Vagus	22 (3.3%)
Glossopharyngeal	20 (3.0%)
Optic	14 (2.1%)
Accessory	11 (1.7%)
Trochlear	11 (1.7%)
Olfactory	3 (0.4%)
Unmentioned	140 (21.1%)
Total CN palsies	663

Table 1: This table depicts the sex, mean age, baseline presenting symptoms, tumor location, surgical approach used, and lastly the preoperative cranial nerve palsies. Frequencies of less than 1% were grouped into the respective categories as Miscellaneous. In the presenting symptoms, examples of symptoms that fell into the Miscellaneous group include fatigue, proptosis, and cognitive impairment. In tumor location, examples of locations that fell into the Miscellaneous group include the orbital apex, infratemporal fossa, and cervical spine. Lastly, in the surgical approach group, examples of approaches that fell into the Miscellaneous group include: maxillectomy, presigmoid, and transoral transmandibular approach.

Overview of Results

Table 1 shows the pooled characteristics of the patients from all the included studies, with reference to, sex, mean age, presenting symptoms, tumor location, surgical approach, and preoperative cranial nerve palsies. To summarize, this review includes a total of 1388 patients, with a mean age of 41.81. There were 631 (45.5%) male and 757 female (54.5%) participants in this review. The median age was approximated as being the mean, because in studies where both median and mean age were reported, little difference was present between the two. Patients typically harbored a low-grade chondrosarcoma (98.9%), located primarily in the petroclival area, and usually presented with diplopia, headaches, and visual field/hearing deficits. When considering the cranial nerve palsies, abducens palsy is most common, possibly accounting for the diplopia. Table 2 shows the characteristics of the included studies with respect to, sample size, intervention, extent of resection, grade of chondrosarcoma, tumor size, mean dose, follow-up time, progression-free survival, overall survival, and disease-specific survival.

The included studies were conducted from across the world, primarily at specialized hospitals. Of the 23 articles all were retrospective in design and majority of which were single-arm cohort studies. Hasegawa et al., Tzortidis et al., and Simon et al., were the only studies to set up a two-arm retrospective cohort study comparing the surgery-only approach to giving postoperative radiotherapy. Overall, the surgical approaches used to remove these tumors have developed over the years, as acknowledged by several of the included studies; when pooling the reported approaches, we find that the endonasal, subtemporal-infratemporal, and pterional approach are most popular. This reflects the most suitable technique for the patients as well as the familiarity of the technique for the operating surgeons.

Surgery only

Out of the 23 included studies, 8 investigated the long-term prognosis of patients treated with surgery only. A total of 168 patients underwent surgery only, with salvage therapy upon recurrence. Excluding the study by Tzortidis et al. [12], (due to a lack of baseline characteristics specific to the surgery only group), there were 72 (45.9%) males and 85 (54.1%) females, and average tumor size of 35.94 cm³. The proportion of patients, per study, undergoing gross tumor resection is shown in Table 2. The tumors resected were primarily of low-grade (99.4%). With mean follow-up periods ranging from 39.1 to 86 months, surgical treatment provided a PFS ranging from 83.7% - 92.9% at 3 years, 64.0% - 99.0% at 5 years, and 42.3% - 98.0% at 10 years. Similarly, when considering the OS, we find it ranging from 68.0%-95.0% at 5 years; based on two studies. As no more than one study was available at the 3- and 10-years, no range of overall survival could be provided at these timepoints. Despite all studies reporting the surgical approaches, the details regarding the surgery are not consistently reported in all 8 studies.

The study by Al Shaibibi et al. [29], adopts the surgical aim to safely resect as much of the tumor as possible whilst preserving the internal carotid artery and the cranial nerves V, VI, VII, and VIII. All patients in this study were operated using an epidural anterior petrosectomy approach as described by Kawase et al. The surgical resection began with identifying the upper pole of the tumor, whereafter piecemeal resection of the tumor ensued, this was followed by the careful use of ring curettes to allow for additional resection. Parts of the dura was opened and resected if the tumor mass infiltrated the meningeal layers, despite the tumors all being epidural. The petrous cavity was filled with abdominal fat and the temporal bone flap was secured with titanium plates and screws. Limited data is available regarding the surgical removal of the tumor in patients from the Simon et al. study. The surgical approach included pterional, infratemporal fossa, retrosigmoid, lateral rhinotomy, and endonasal in the surgery only group.

The intention of Tzortidis et al. [12], was to obtain a complete tumor resection if possible. A second, or rarely third, operation was staged and was conducted with extensive tumors or when large tumor residue was seen on postoperative MRI. Radiotherapy was given when patients underwent subtotal resection. Different types of cranial base approaches were used. Internal carotid artery resection and grafting was necessary in 6 cases. Various vascularized flaps were used for reconstruction including, temporalis muscle flap, pericranial flap, and rectus abdominis free flap, supplemented by free fat grafts. In Samii et al., the operative approaches were chosen on the basis of the predominant direction of tumor extension. When there was brainstem and/or optic apparatus compression, the primary goal was to relieve this pressure, and only secondarily excise the tumor. The most common approaches were retrosigmoid (in 12 surgeries), pterional approach (in 9 surgeries), and transthemoid approach (in 6 cases). In case of dural penetration/opening, a fat graft was used, and a lumbar drain was placed to reduce the chance of CSF leak. The reconstruction technique is not described.

The patients in the study by Hasegawa et al. [21] all underwent endoscopic transnasal surgery for their skull base chondrosarcomas. Tumors were approached either via the transsphenoidal route, transpterygoid approach, or the transmaxillary approach. Tumors located in the lower clivus, craniovertebral junction, and the nasopharynx was approached via the upper pharynx. Tumors in the anterior skull base was approached directly through the ethmoidal sinus. The aim was to attain maximal retention, in the case of remnant tumor component – adjuvant SRS was advised at 3-6 months after surgery. Reconstruction technique is not reported.

In the study by Vaz-Guimaraes et al. [20], the patients underwent endoscopic endonasal surgery for their chondrosarcoma. The aim of the surgery was complete removal of the tumor, except for 3 patients (due to extensive disease and poor condition). For extensive disease, staged and combined operations were used. The choice of approach was dependent on tumor location. The common approaches used upon tumor extension included the anterolateral ap-

proach, transpetrous and far-lateral approach, and transcervical approach. Intradural tumor resection, dural opening, or extensive skull base drilling was followed by a multilayer reconstruction. The techniques used varied, including the pedicled vascularized flaps (e.g. pedicled nasoseptal flap), inferior turbinate, pericranial, and temporoparietal fascial flaps. Where no dural opening and limited cranial base drilling was done, reconstruction was conducted with tissue glue only.

Liu et al. [30] included patients whose tumors were removed by craniotomy ($n = 20$) and by endoscopic endonasal transsphenoidal approach ($n = 4$). The craniotomy approach included the pterional or expanded pterional approach, posterior sigmoid sinus approach, orbitozygomatic approach, paramedian approach, posterior median extension approach, and combined supratentorial and infratentorial approach. The reconstruction technique was not reported.

Radiotherapy

A total of 17 studies reports the long-term prognosis of patients treated with postoperative radiotherapy. A total of 1202 patients underwent postoperative radiotherapy, of which 530 (44.8%) were male and 654 (55.2%) were female, excluding Tzortidis et al. for the aforementioned reason [12]. The extent of resection is reported per study in Table 2, the tumors receiving radiotherapy were primarily low-grade (98.9%). The mean/median tumor volume and radiation dose are provided in Table 2. This review reports several forms of radiotherapy: namely, proton therapy, photon therapy, carbon ion therapy, and gamma knife radiosurgery. It should be noted that the study by Tzortidis et al., splits the study sample into two groups: those that underwent gross total resection, and the other who received subtotal resection (STR) alongside radiotherapy [12]. Despite majority of patients receiving subtotal resection followed by radiotherapy in this review, the long-term recurrence free survival of patients undergoing STR with postoperative radiotherapy in the study is somewhat of an outlier (e.g. a 10-year recurrence free survival of 13.8%). This may be explained due to a delayed time between the subtotal resection and subsequent radiotherapy – as the time between surgery and postoperative radiotherapy is not reported in the study. Furthermore, there is no standardization in the radiotherapy received: proton therapy was given to 15.6%, radiosurgery (gamma knife or CyberKnife) in 68%, and fractionated radiation in 15.6%. Due to these discrepancies, we have excluded this study in consideration when providing the ranges of PFS and OS.

The follow period reported in each study is shown in Table 2. Post-operative radiotherapy provides a PFS ranging between 87-96.2% at 3-years, 57.1%-100% at 5-years, and 67%-100% at 10-years. As for the OS, the following ranges are seen: 87.8%-100% at 3 years, 84.1%-100% at 5 years, and 78.1% - 87% at 10 years. Specific to proton therapy, the following PFS ranges are seen; 90-100% at 2-years, 75%-100% at 5-years, and 84.2%-100% at 10-years. The results are similar to the overall OS when analyzing the OS of patients undergoing proton therapy at the aforementioned timepoints. Carbon-ion radiotherapy was evaluated by three studies [13, 16, 23], from which a PFS between 95.9% and 97.2% and OS between 96.1% and 98.5% are seen at 3 years. Two studies report the long-term prognosis of postoperative GKRS [27, 28], however contain methodological differences as to when the GKRS was given and how the PFS was measured.

Table 2: Raw data of selected articles. GTR: gross tumor resection, STR: subtotal resection, PR: partial resection, P.O. = postoperative, R.T = Radiotherapy, N.M: not mentioned, N/A = not applicable. See appendix for assessment of study 4 and 21.

Study Number	Author, Year	Number of Patients (No. Males)	Intervention	Extent of Resection (%)	Tumor Pathology
1	Tzortzidis et al., 2006 [11]	47 (24)	Surgery only (n = 29) Adjuvant RT (proton, radiosurgery, fractionated radiation) (n = 18)	GTR in 29 (62) STR in 18 (38)	Low grade, n = 45 High grade, n = 2
2	Simon et al., 2018 [12] Moderate Risk	Surgery only: 24 (10) Surgery + RT: 23 (13)	Surgery only (n = 24) P.O proton RT (n = 23)	Surgery only: GTR in 13 (54) PR in 11 (46) Surgery + RT: GTR in 3 (13) PR in 20 (87)	Low grade, n = 47
3	Hasegawa et al., 2021 [13] Moderate Risk	Surgery only: 18 (6) Surgery + RT: 14 (9)	Surgery + proton RT (n = 11) Surgery only (n = 18) P.O photon RT (n = 1) P.O photon + proton therapy (n = 2)	Surgery only: GTR in 10 (56) Non-GTR in 8 (44) P.O RT: GTR in 1 (7) Non-GTR in 13 (93)	Low grade, n = 32
4	Samii et al., 2008 [14] Critical Risk	25 (18)	Surgery only (n = 25)	N.M	Low grade, n = 25
5	Vaz-Guimaraes et al., 2017 [15] Moderate Risk	35 (14)	Surgery only (n = 35)	GTR in 22 (63) NTR in 11 (31) STR in 2 (6)	Low grade, n = 35
6	Hasegawa et al., 2018 [16] Critical Risk	19 (10)	Surgery only (n = 19)	GTR in 15 (79) STR in 2 (10.5) PR in 2 (10.5)	Low grade, n = 18 High grade, n = 1
7	Al-Shaibibi et al., 2023 [17]	10 (4)	Surgery only (n = 10)	STR in 10 (100)	Low grade, n = 10
8	Liu et al., 2023 [18] Moderate Risk	26 (10)	Surgery only (n = 26)	GTR in 14 (54) STR in 10 (38) PR in 2 (8)	Low grade, n = 26
9	Schulz et al., 2007 [19] Critical risk	54 (27)	P.O. carbon-ion RT (n = 54)	N.M	Low grade, n = 54
10	Uhl et al., 2014 [20] Moderate risk	79 (39)	P.O carbon RT (n = 79)	PR in 62 Biopsy in 17	Low grade, n = 78 High grade, n = 1
11	Mattke et al., 2018 [21] Moderate risk	101 (54)	P.O carbon RT (n = 79) P.O proton RT (n = 22)	P.O carbon RT PR in 75 (95) Biopsy in 4 (5) P.O proton RT: PR in 18 (82) Biopsy in 4 (18)	Low grade, n = 101
12	Hug et al., 1999 [22] Moderate risk	25 (9)	P.O proton RT (n = 25)	N.M	Low grade, n = 25
13	Rosenberg et al., 1999 [23] Critical risk	200 (67)	P.O photon and proton RT (n = 200)	GTR in 10 (5) STR in 148 (74) PR in 42 (21)	Low grade, n = 200

Tumor Size	Mean Dose	Follow Up	Progression-Free Survival	Overall Survival	Disease-Specific Survival
N.M	N.M	Mean: 86 months	GTR: 3y: 92% 5y: 78.3% 10y: 42.3% STR + RT: 3y: 78% 5y: 41% 10y: 13.8%	N.M	N.M
Mean (surgery only) = 39 cm ³ Mean (P.O. proton therapy = 33 cm ³	Mean: 70 GyE	Mean: 91 months	Surgery only: 5y: 67.8% 10y: 58.2% P.O proton radiotherapy: 5y: 100% 10y: 87.5%	N.M	Surgery only: 5y: 89.8% 10y: 89.8% P.O proton radiotherapy: 5y: 100% 10y: 100%
Mean diameter in Surgery + RT group = 35 mm Mean diameter in Surgery group = 34 mm	70 GyE	Surgery + RT, median: 44 months Surgery only, median: 154 months	Surgery + RT 5y, 10y: 100% 15y: 67% Surgery only: 5y, 10y, 15y: 64%	N.M	Overall DSS: 5y: 100% 10y, 15y: 95%
Mean = 16.9 cm ³	N/A	Mean: 80 months	N.M	5y, 10y: 95%	N.M
Mean = 31.9 cm ³	N.M	Mean: 44.6 months Median: 44 months	3y: 83.7% 5y: 80.8%	N.M	3y: 91.1% 5y: 90.5%
Mean = 14.5 cm ³	N/A	Median: 47 months	3y, 5y: 92.9%	N.M	N.M
N.M	N/A	Median: 70 months	1y: 90% 2y: 80% 5y: 60%	N.M	N.M
Mean: 65.13 cm ³	N/A	Mean: 39.12 months	N.M	1y: 100% 3y: 81.8% 5y: 68%	N.M
Median: 20 cm ³	Median: 60 CGE	Median: 33 months	3y: 96.2% 4y: 89.8%	3y, 4y: 98.2%	N.M
Mean boost volume = 60.5 cm ³	Median: 60 GyE	Median: 91 months	3y: 95.9% 5y, 10y: 88%	3y, 5y: 96.1% 10y: 78.9%	N.M
Mean carbon RT boost volume = 34.9 cm ³ Mean proton RT boost volume = 38.2 cm ³	Carbon: 60 GyE Proton: 70 GyE	Carbon (median): 43.7 months Proton (median): 30.7 months	Carbon 1y: 98.6% 2y: 97.2% 4y: 90.5% Proton 1y, 2y, 4y: 100%	Carbon 1y: 100% 3y: 98.5% 4y: 92.9% Proton: 1y, 3y, 4y: 100%	N.M
N.M	Mean: 70.7 GyE	Mean: 33.2 months	3y: 94% 5y: 75%	3y, 5y: 100%	N.M
N.M	Median: 72.1 GyE	Mean: 65.3 months	5y: 99% 10y: 98%	N.M	5y, 10y: 99%

Table 2: Raw data of selected articles. GTR: gross tumor resection, STR: subtotal resection, PR: partial resection, P.O. = postoperative, R.T = Radiotherapy, N.M: not mentioned, N/A = not applicable. See appendix for assessment of study 4 and 21. (continued)

Study Number	Author, Year	Number of Patients (No. Males)	Intervention	Extent of Resection (%)	Tumor Pathology
14	Noel et al., 2001 [24] Moderate risk	11 (5)	P.O proton RT (n = 11)	N.M	Low grade, n = 11
15	Sahgal et al., 2014 [25] Serious risk	18 (10)	IG-IMRT photon RT (n = 18)	GTR in 7 (39) STR in 9 (50) Biopsy in 2 (11)	Low grade, n = 18
16	Feuvret et al., 2016 [26] Moderate risk	159 (72)	P.O proton RT or proton and photon RT (n = 159)	Complete in 13 (8) Incomplete in 133 (84) Biopsy 13 (8)	Low grade, n = 159
17	Weber et al., 2016 [27] Moderate risk	71 (31)	P.O proton RT (n = 71)	GTR in 3 (4) STR in 68 (96)	Low grade, n = 71
18	Weber et al., 2016 [28] Moderate risk	77 (35)	P.O proton RT (n = 77)	N.M	Low grade, n = 73 High grade, n = 4
19	Weber et al., 2018 [29] Moderate to serious risk	251 (109)	P.O. proton (n=116) P.O proton ± photons (n = 135)	N.M.	N.M.
20	Holtzman et al., 2019 [30] Critical risk	43 (18)	P.O proton RT (n = 43)	N.M	Low grade, n =41 High grade, n = 2
21	Kawashima et al., 2022 [31] Serious bias	51 (25)	Surgery with postoperative GKRS (n = 30) Surgery + GKRS as salvage therapy (n = 21)	GTR in 1 (2) STR in 18 (35) PR in 24 (47)	Low grade, n = 31 High grade, n = 2 Dedifferentiated subtype of nonconventional SBC, n = 1 Unknown, n = 17
22	Pattankar et al., 2022 [32] Critical risk	7 (1)	P.O adjuvant GKRS (n = 7)	STR in 6 (86) PR in 1 (14)	N.M

Table 2: This table shows the raw data of 22 included studies. It shows the number of patients included per study, the intervention used to treat the patient, the extent of resection (stated as gross-total resection, subtotal resection, partial resection, or biopsy), grade of the chondrosarcoma (low or high grade), mean/median tumor size (in cm³), mean/median dose (in GyE/CGE), and mean/median follow-up time (in months). Furthermore, it also shows the progression-free survival, overall survival, and disease-specific survival reported in each study. When PFS was not available, local control was used instead, and when that was not available, recurrence-free survival was used. *GTR: gross tumor resection, STR: subtotal resection, PR: partial resection, P.O. = postoperative, R.T = Radiotherapy, N.M: not mentioned, N/A = not applicable, y = years.*

Tumor Size	Mean Dose	Follow Up	Progression-Free Survival	Overall Survival	Disease-Specific Survival
Mean = 28 cm ³	Photon median: 45Gy Proton median: 22 GyE Overall Mean: 66.7 GyCGE	Mean: 30.5 months	2y, 3y: 90%	3y: 90% 4y: 60%	N.M
Mean = 24.6 cm ³	Median: 70 GyE	Median: 66.5 months	5y: 88.1%	3y: 87.8% 5y: 84.1%	N.M
Mean = 23.1 cm ³	Median total dose: 70.2 GyE Median proton: 36.6 GyE Median photon: 34.2 Gy	Clinical: 77 months Radiologic: 65 months	5y: 93.2% 10y: 84.2%	5y: 94.9% 10y: 87%	N.M
Mean = 36.1 cm ³	Mean: 72.5 GyE	Mean: 50 months	5, 7y: 93.6%	N.M	N.M
Median = 25.9 cm ³	Median: 70 GyE	Mean: 69.2 months	5y: 94.2% 8y: 89.7%	5y, 8y: 93.5%	N.M
P.O. proton = 35.53 cm ³ P.O proton ± photons = 22.22cm ³	P.O. proton = 69.67 GyE P.O proton ± photons = 69.86 GyE	All patients (median): 87.3 months Surviving patients (median): 88.0 months	7y: 93.1%	7y: 93.6%	N.M
Mean = 18 cm ³	Median: 73.8 GyE	Median: 44.4 months	2y: 100% 3y: 93% 4y: 89%	2y: 98% 3y, 4y: 95%	2y, 3y, 4y: 100%
Median: 8 cm ³	Median: 16 Gy	Median: 62 months	3y: 87% 5y: 78% 10y: 67%	N.M	After GKRS: 3y: 96% 10y: 83% After disease diagnosis: 3y: 98% 5y, 15y: 90%
Mean: 4.16 cm ³	Mean: 18.29 Gy	Mean: 72 months Median: 60 months	5y: 57.1%	5y: 100%	N.M

Recurrence & Prognosis

The recurrences, salvage treatment given, and prognostic factors reported from the included studies are depicted in Table 3. The percentages given in this table were calculated based on the number of recurrences divided by the total sample size. In the articles assessing the surgery only approach, a tumor recurrence rate between 5.3% and 39.0% was seen. In these cases, salvage therapy was given which consisted of primarily surgery ± radiotherapy (commonly proton therapy or gamma knife radiosurgery), which provided sufficient tumor control in most cases. As for the radiotherapy group, the recurrence rate ranged from 1.5% -42.80%.

Table 3: Reported recurrences, salvage treatment(s), and prognostic factors for tumor control and/or overall survival

Author, Year	Intervention	Number of Recurrences	Time to Recurrence (months). Given as mean/median (range)	Salvage Treatment	Prognostic Factors
Hug et al., 1999 [9]	P.O. proton therapy	2 (8.0%)	Mean: 33	Not specific to chordosarcoma	LC: Tumor volume, brainstem involvement
Rosenberg et al., 1999 [10]	P.O. proton therapy	3 (1.5%)	Mean: 65.3 (2.1-222.2)	N.M	N.M
Noel et al., 2001 [11]	P.O. proton +/- photon therapy	2 (18.2%)	N.M	N.M	LC + OS: age, number of surgical resections prior, time to SRS
Tzortidis et al., 2006 [12]	Surgery ± radiotherapy	15 (32.0%)	86 (2-255)	N.M	N.M
Schulz-Ertner et al., 2007 [13]	P.O. Carbon ion therapy	2 (3.7%)	Patient 1: 36 Patient 2: 48	Patient 1: photon radiation therapy (45 Gy) Patient 2: partial resection and post-operative reirradiation with carbon ion radiation therapy (60 CGE)	N.M
Sahgal et al., 2014 [15]	P.O. IGMRT Photon therapy	2 (11.0%)	Median: 15.6 (14.4 – 16.8)	N.M	LC: age
Uhl et al., 2014 [16]	P.O. carbon ion therapy	10 (12.6%)	Median: 91 (3 – 175)	N.M	LC: age, GTV OS: age, sex
Feuvret et al., 2016 [17]	P.O. proton therapy	6 (3.8%)	Median: 39.1	N.M	LC/OS/PFS: age, GTV, primary disease status, controlled tumor status
Weber et al., 2016 [18]	P.O. proton therapy	5 (7.0%)	Mean: 50 (4 – 176)	N.M	Prognostic variables assessed together with chordoma

Table 3: Reported recurrences, salvage treatment(s), and prognostic factors for tumor control and/or overall survival (continued)

Author, Year	Intervention	Number of Recurrences	Time to Recurrence (months). Given as mean/median (range)	Salvage Treatment	Prognostic Factors
Weber et al., 2016 [19]	P.O. proton therapy	6 (7.8%)	Median: 28.4 (11. – 140.8)	N.M	LC: tumor volume, brainstem and/or optic apparatus compression, age
Vaz-Guimaraes et al., 2017 [20]	Surgery only	7 (20.0%)	23.5 (14 – 58)	3 surgery and P.O. proton therapy 2 developed lung metastasis and underwent chemotherapy 2 not reported	N.M
Hasegawa et al., 2018 [21]	Surgery only	1 (5.3%)	12	Surgery	N.M
Simon et al., 2018 [22]	Surgery only P.O. Proton RT	Surgery only: 8 (33.3%) P.O. proton RT: 1 (4.0%)	Mean: 51 (9 – 142)	Surgery in 8 Secondary proton therapy in 5	N.M
Mattke et al., 2018 [23]	Proton therapy Carbon ion therapy	5 (5.0%)	Median: 29.8 (8.1 – 47.3)	N.M	LC: age
Weber et al., 2018 [24]	Proton +/- photon radiotherapy	15 (5.9%)	Median: 43.6 (5.2-140.8)	N.M	FFS: tumor volume, optic pathway compression OS: tumor volume, age, number of surgeries, brainstem/optic apparatus compression
Holtzman et al., 2019 [25]	P.O. proton therapy	3 (6.9%)	Median: 44.4	Surgery only in all 3	N.M
Hasegawa et al., 2021 [26]	Surgery only P.O. radiotherapy (proton, GKRS)	Surgery only: 7 (39%) P.O. RT: 1 (7.0%)	Median: 38 (16 – 225) in surgery only group Median: 33 in surgery + RT group	Surgery only: Radiotherapy alone in 3 Surgery alone in 3 Surgery + RT in 1 P.O. RT: 1 treated with proton RT	N.M

Table 3: Reported recurrences, salvage treatment(s), and prognostic factors for tumor control and/or overall survival (continued)

Author, Year	Intervention	Number of Recurrences	Time to Recurrence (months). Given as mean/median (range)	Salvage Treatment	Prognostic Factors
Kawashima et al., 2022 [27]	P.O. GKRS Surgery only with GKRS as salvage	Progression in 12 (23.5%), of which 7 (13.7%) recurrences	Median time between initial GKRS and additional treatment = 47	2 – repeated GKRS - Tumor control achieved. 3 – surgery only (transcranial/endoscopic) 6 – surgery + RT (incl GKRS) 1 – conservative management due to age	LC: repeated recurrences, prescription doses $\geq 15\text{Gy}$ and 14Gy. Multivariate analysis showed higher prescription dose, and no history of repeated recurrences were significant factors for better local control
Pattankar et al., 2022 [28]	P.O. adjuvant GKRS	3 (42.9%)	Mean: 32.76	2 – redosurgery alone 1 – redosurgery + conventional EBRT	N.M
Al-Shaibibi et al., 2023 [29]	Surgery only	3 (30.0%)	Mean: 101	One patient treated with salvage GK twice. Stability for 6 years after second GK. One patient treated with proton therapy. Stability for 3 years after therapy. No adjuvant therapy for third patient. Stability for 11 years after surgery.	N.M
Liu et al., 2023 [30]	Surgery only	7 (26.9%)	N.M	1 – surgery and radiotherapy 2 – surgery alone 3 – radiotherapy alone	OS: tumor excision (HR 5.7, 95% CI 1.5–22), tumor volume (HR 7, 95% CI 1.3 – 39), and pathological grading (HR 42, 95% CI 3.5 – 500). Protective factors: extent of tumor resection (HR 21.74, 95% CI 1.25 – 376.6) and pathological grading (HR 131.99, 95% CI 4.05 – 4300.5)

Table 3: This table reports the recurrences and its prognostic factors. It depicts the number of recurrences, mean/median follow-up to recurrence (in months), salvage therapy used, and the prognostic variables associated with poor prognosis.

Complications

The patients of the selected articles were pooled together and a summary of the surgical and radiation induced adverse effects are reported in Table 4 and 5, respectively. There were 59 reported deaths due to the tumor, and 36 deaths due to intercurrent disease amongst the selected articles. Radiation induced adverse effects are split into acute and late adverse effects. Articles that did not grade the complications as per the CTCAE classification [31] were listed as 'n.m': not mentioned'.

Table 4. Cumulated surgical complications.

Complication	No. of patients (%)
Cranial nerve palsy	68 (45.0%)
Subcutaneous hydrops	4 (2.6%)
Dysphagia	3 (1.9%)
Facial numbness	2 (1.3%)
Cerebrospinal fluid leak	23 (15.2%)
Hearing loss	15 (9.9%)
Meningitis	8 (5.3%)
PE/DVT	5 (3.3%)
Cerebral ischemia	4 (2.6%)
Diabetes insipidus	3 (1.9%)
Cerebrovascular events	2 (1.3%)
ICA damage	2 (1.3%)
Hydrocephalus	2 (1.3%)
Miscellaneous	10 (6.6%)

Table 4: This table shows the complications faced postoperatively reported in the 22 studies. Complications that had a frequency of less than 1% were grouped into the category 'Miscellaneous'. Examples of complications that fell into this category include ataxia, temporal epilepsy, and cerebral abscess.

Complications that fell under 'miscellaneous' include bleeding, seizure meningitidis, arachnoid cyst, ataxia, hemiparesis and aphasia, visual field defect, and temporal epilepsy.

Table 5. Cumulated acute radiation induced adverse events. Grading as per CTCAE v4.0 [16].

Complication	Grade	No. of patients (%)
Alopecia	1-2	202 (16.8%)
Middle ear effusion	1-2	159 (13.2%)
Asthenia	1-2	159 (13.2%)
Erythema	1-2	159 (13.2%)
Nausea/vomiting	1-2	159 (13.2%)
Fatigue	1-2	43 (3.5%)
Radiation dermatitis	1-2	43 (3.5%)

Table 5. Cumulated acute radiation induced adverse events. Grading as per CTCAE v4.0 [16]. (continued)

Complication	Grade	No. of patients (%)
Mucositis	1-3	46 (3.8%)
Erythema	n.m.	36 (2.9%)
Headaches	n.m.	36 (2.9%)
Alopecia	n.m.	32 (2.7%)
Loss of appetite	n.m.	25 (2.1%)
Fatigue	n.m.	25 (2.1%)
Nausea/vomiting	n.m.	25 (2.1%)
Dysgeusia	n.m.	15 (1.2%)
Xerostomia	n.m.	15 (1.2%)
Mucositis	n.m.	15 (1.2%)
External/middle ear otitis	n.m.	11 (0.9%)
Acute parotitis	n.m.	1 (0.08%)

Table 5: This table shows the total acute radiation induced adverse events reported in the 18 studies. The definition used for ‘acute’ varies in the 18 studies, and most do not define it. The complications are defined as per the common terminology criteria for adverse events (CTCAE) v4.0.

Table 6. Cumulated late radiation induced adverse events. Grading as per CTCAE v4.0 [16].

Characteristic	Grade	No. of patients (%)
Pituitary dysfunction	1-2	97 (38.8%)
Hearing loss	3-4	29 (11.6%)
Hearing loss	n.m.	21 (8.4%)
Unspecified Grade 3+	3+	14 (5.6%)
Brain necrosis	3+	9 (3.6%)
Temporal lobe necrosis/lesions	1-2	9 (3.6%)
Hearing loss	1-2	5 (2.0%)
Bone necrosis	3	5 (2.0%)
Hypopituitarism	n.m.	5 (2.0%)
Temporal lobe necrosis/lesions	n.m.	5 (2.0%)
Dizziness	n.m.	4 (1.6%)
Memory loss	2	4 (1.6%)
Visual field deficits	n.m.	4 (1.6%)
Spinal cord necrosis	3	3 (1.2%)
CN palsy	1-2	3 (1.2%)
CN palsy	n.m.	3 (1.2%)
Miscellaneous		30 (12.0%)

Table 6: This table shows the total late radiation induced adverse events reported in the 18 studies. The grade of the complication is also mentioned, as per the common terminology criteria for adverse events (CTCAE) v4.0, when reported. When not reported, it is reported as not mentioned, n.m’. Complications with a frequency of under 1% were all grouped into the ‘Miscellaneous’ category, examples of complications that fell under this category include: cerebellum necrosis, spinal cord necrosis, stroke, hyperprolactinemia, serous otitis, and temporal lobe edema.

DISCUSSION

Due to the rarity of skull base chondrosarcomas, the number of studies investigating the efficacy of therapeutic options have been limited. This systematic review included 23 studies investigating the long-term efficacy of surgical therapy and postoperative radiotherapy, encompassing a total of 1388 patients. Majority of the skull base chondrosarcomas were low-grade, and there was no predilection to the sex of the patient. The studies provide a broad range of long-term measures of survival primarily due to the heterogeneity in the data included and the lack of detail in the Kaplan-Meier survival analysis provided. Majority of the articles assess patients up to the 5-year mark, most up to the 10-year mark, and seldom to 15 years.

The treatment of skull base chondrosarcoma requires a multidisciplinary approach, with involvement of the neurosurgeon, ENT surgeon, neuro-radiologist, neuropathologist, radiotherapist and medical oncologist. Surgical resection of the chondrosarcoma is considered the first line therapy; however it also provides the opportunity to obtain histological and molecular diagnosis. Radical resection is often not possible, and instead a maximal, safe resection approach is undertaken to spare the surrounding critical structures and decrease iatrogenic morbidity. The overall prognosis in the surgery only group ranges widely, especially as the follow-up time increases. However, one constant observation is the steeper decline in the lower limit of the prognostic ranges from 1 year to 10 years, (-41.4%) when compared to the postoperative radiotherapy group (-20.0%) during the same time period. This contrasts with the upper limit which remains constant in both intervention groups. Unlike the surgery only group, the P.O. radiotherapy group does not see a steady decline in the lower limit – as seen in the increase in the lower limit of survival outcomes at 10 years. We believe that this is rather due to a methodological issue of survival estimates, as the number at risk is not reported it is unclear whether: 1) there was loss to follow up, and 2) whether the loss to follow up were specific to a group of patients (e.g. those that showed better recovery). This would result in a different composition of the remaining cohort – resulting in an altered prognosis. This would suggest better long-term control with adjuvant radiotherapy, however this was not reflected in a systematic review conducted in 2009, where the surgery only group had better 5-year prognostic outcomes. This discrepancy might possibly be explained by the fact that newer studies became available, further elucidating the true prognostic differences between the two intervention groups.

When analyzing the surgery only group, it is important to recognize that data was extracted from only eight studies. Majority of the patients in this group underwent a gross total resection (61.2%), with patients undergoing multiple staged surgeries if needed. Furthermore, the most common surgical approaches were endonasal, subtemporal-infratemporal, and pterional. The endonasal approach has taken the spotlight in recent literature, showing good prognostic outcomes. Endoscopic surgery provides a better route to tumor than the transcra-

nial approach considering most originate in the petroclival area. As reported by Schwartz et al., the transcranial approach is more likely to traverse cranial nerves than the endoscopic approach. The gross total resection rates are reported to be around 66.7%-80.0% with good tumor control as opposed to a GTR rate of 50%-100% in the transcranial approach [33]. Moreover, endoscopic nasal approaches allow for shorter hospitalization, decreased complications, and decreased mortality [34]. With the development of new approaches, such as the transmaxillary approach, the use of endoscopic skull base surgery is only increasing. The reconstruction method is also vital to evaluate, reported in 3 of the 8 studies, with vascularized flaps being the most common (2/3 studies). The decision between the use of abdominal fat or vascularized flaps for reconstruction is fueled by the indication alongside surgical expertise [35]. Complications in skull base surgery for tumor resection, reported in literature include intracranial bleeding, blindness, CSF leak, osteonecrosis, cerebral abscess, meningitis, cranial nerve neuropathies, and cosmetic deformities [34]. Many overlaps with the complications seen in this review. Studies indicate that CSF leak rates are reduced when the reconstruction is done with vascularized local tissue, particularly in patients with history of radiotherapy. Furthermore, multilayered reconstruction is reported to be superior to single layer. There is more to explore regarding the skull base reconstruction techniques, however, falls beyond the scope of this paper.

When considering the postoperative radiotherapy group, 17 studies investigated the efficacy of this intervention; with proton therapy being most commonly investigated. Contrary to the surgery only group, only 6.3% of the reported cases were gross total resections. The remaining patients underwent either a partial resection (44.8%), sub-total resection, or biopsy (4.9%) prior irradiation. According to the studies included, proton and carbon therapy provide a better tumor control than gamma knife radiosurgery. These promising results for proton therapy obtained in this review are also reflected in current literature. For example, in the review by Noel et al. assessing the role of proton therapy in various intracranial tumors, an overall local control between 85%-100% is found at 3-years and 75%-95% at 5-years for chondrosarcomas [36]. Similarly, the carbon ion group, despite only having 3 studies in this review, shows promise with high control rates. These results are further confirmed in the systematic review by Holtzman et al., which includes the articles selected for this review, from which a 1-, 3-, and 5-year control rates of 99%, 89%, and 88% [37]. We see a significant improvement in the long-term prognosis when administering postoperative proton therapy, with the lowest reported PFS being 75% at 5 years, as opposed to 64.0% with surgery only at 5 years. The literature review by Kano et al., provides a better overview of the long-term efficacy of gamma knife SRS for skull base chondrosarcoma. This review compiles 46 patients from 5 studies, of which one is included in this review, who underwent postoperative GKRS. Without prior radiotherapy, the PFS rates were 92%, 88%, and 81% at 1-, 3-, and 5-years [32]. Although not as effective as particle therapy, it provides the clinician with an alternative option for primary or salvage treatment.

Although radiotherapy offers an improvement in the treatment of skull base cancers, it also comes with complications. The complications listed in Table 5 overlap with the ones reported in current literature [36]. The same applies for the reported late radiation induced adverse events in this review, with literature reporting pituitary gland insufficiency, ocular pathway damage, sensorineural hearing loss and temporal lobe necrosis being the most common complications [1]. These complications are of utmost importance to consider considering the close proximity of critical organs to the chondrosarcoma. A particular advantage that particle therapy offers is a steeper dose gradient to the organs at risk adjacent to the gross tumor volume compared to non-particle radiotherapy. This is related to the physical properties of particle itself, more specifically the Braggs peak and cure, which depicts the deposition of energy as the particle travels through matter. Promising control of the Braggs curve is shown with the pencil beam system. The rate of complications was far higher in the studies investigating the efficacy of adjuvant radiotherapy. We expect two possible explanations for this difference: 1) This reflects the true difference in the complication rate between the surgery only approach and giving postoperative radiotherapy, or 2) the surgical complications are underreported, as not all studies did so. However, findings consistent with the former explanation were found in the review by Palmisciano et al [2].

Albeit the rate of recurrences provided were broad, it is evident that the recurrences were more frequent in the surgery only group. This can be elucidated when the upper limit of the recurrence rate in the radiotherapy group is properly evaluated. Due to the small sample size in the study by Pattankar et al., which only included 7 patients, any recurrence was bound to be high in percentage. Realistically, when considering this study as an outlier, one obtains a recurrence range between 1.5% and 18.4% in the postoperative radiotherapy group. This lower recurrence rate is also supported in recent literature [38]. When considering the prognostic variables, the risk factors that increase the likelihood for poor tumor control and overall survival include high tumor volume, brainstem/optic apparatus involvement, high age, increased number of prior surgeries. These factors are also reported in previous literature, for example in Kremenevski et al., albeit most reviews combine data from chordoma and chondrosarcoma studies [4].

There are certain limitations to consider for this review. Although the search input was well generated, abiding by the PICOT structure, the articles obtained were dubious in terms of bias. All studies were retrospective observational studies, dating back to 1999. With several articles not accounting for potential confounding factors specific to their analysis, the development of surgical and radiotherapy techniques/protocols between 1999 and current times plays a confounding role. As a result of the former point, the risk of the included articles ranges from moderate to critical bias as per the ROBINS-I tool. Furthermore, the articles included do not further detail their Kaplan-Meier curves, restricting us from creating a meta-analysis. This limits this review to be merely descriptive in nature and restrains us from providing a statistical answer to prove the superiority of one intervention over the other.

Furthermore, some studies included were limited by the small sample size, in these cases the percentages reported might simply be inflated. In these cases, an open access database where the prognostic outcomes alongside baseline data of patients with skull base chondrosarcoma are included seems ideal, considering its rarity and as it would allow for robust statistical analysis. Another limitation that this review faced was the short follow-up period of maximally 10 years in most studies. Although not surprising considering the rarity of this condition. Additionally, several excluded and some included articles grouped chordoma and chondrosarcoma patients together impairing our ability to extract data specific to the latter group. Future research can perhaps elaborate on the prognostic outcomes at a longer follow-up period specific to the chondrosarcoma patient. Another limitation revolves around the prognostic outcomes used, as it only assesses tumor control. Measuring patient-oriented outcomes, such as quality of life, to properly ascertain the impact of radiation related complications and long-term prognosis would provide a more patient-oriented answer to integration of radiotherapy into their care. Lastly, majority of the patients were diagnosed with low-grade chondrosarcoma, therefore leaving the treatment of high-grade cases an unexplored terrain for future research.

Future research comparing the local control provided by different surgical techniques on a longer term would be beneficial. It would allow clinicians to understand the best operative route specific to tumor location, whilst giving them an idea of the expected control rate. Furthermore, nuances in the endoscopic technique can further be explored thereby further substantiating its efficacy as a surgical option. As for radiotherapy, we suggest further investigation of the different forms of radiation delivery, for example investigating the long-term prognosis of patients treated with image-guided radiotherapy, intensity-modulated radiotherapy, or pencil beam scanning. Such techniques allow for better control of the dosage of radiation delivered to the tumor whilst sparing the nearby critical organs. Such research was slowly introduced since 2016, with papers such as Sahgal et al. and Weber et al., and show promising results. Furthermore, assessing the use of hypo-fractionated versus hyper-fractionated radiotherapy in terms of tumor control can be another point of focus. Recent studies, such as in Sallabanda et al., have shown promising results for a hypo-fractionated schedule for proton therapy in providing good tumor control [39].

Furthermore, investigating other forms of particle therapy than proton therapy is another potential focus. More specifically, this review has shown the potential for carbon ion radiotherapy. Although the dose distribution of charged particles is similar, there exist discrepancies between different particles – as seen in carbon ion vs proton therapy []. With carbon ions there is a sharper dose falloff at both the distal and lateral beam edges, essentially targeting the tumor in a more precise fashion [40]. Moreover, when analyzing the amount of radiation energy deposited along a particle's trajectory in a particular medium (quantified by the linear energy transfer, LET), we find that carbon has a higher LET than protons. The high-LET in carbon ions is theoretically, more optimal tumor control, and spares tissues upstream of the

target [40]. Considering these potential advantages, we believe that carbon ion radiotherapy might be an important option to investigate.

Further research can also focus on the logistics behind the treatment of patients with chondrosarcoma. For example, analyzing the cost-effectiveness of particle therapy and its implementation in healthcare.

CONCLUSION

Skull base chondrosarcomas remain a challenge to treat, due to their location and close proximity to vital structures. Surgery has been the primary treatment option chosen for patients harboring a skull base chondrosarcoma, with recent literature supporting the use of an endoscopic approach. However, the recurrence rate is still high and usually some form of salvage therapy is used to treat for recurrence. This review shows promising results in terms of long-term prognosis and recurrence rate favoring the use of particle therapy as postoperative radiotherapy.

REFERENCES

1. Gazendam A, Popovic S, Parasu N, Ghert M. Chondrosarcoma: A Clinical Review. *J Clin Med*. 2023 Mar 26;12(7):2506. doi: 10.3390/jcm12072506. PMID: 37048590; PMCID: PMC10095313.
2. Palmisciano P, Haider AS, Sabahi M, Nwagwu CD, Bin Alamer O, Scalia G, Umana GE, Cohen-Gadol AA, El Ahmadi TY, Yu K, Pathmanaban ON. Primary Skull Base Chondrosarcomas: A Systematic Review. *Cancers (Basel)*. 2021 Nov 26;13(23):5960. doi: 10.3390/cancers13235960. PMID: 34885071; PMCID: PMC8656924.
3. Snyderman C. Chordoma and chondrosarcoma of the skull base [Internet]. 2022. Available from: https://www.uptodate.com/contents/chordoma-and-chondrosarcoma-of-the-skull-base?search=Chordoma+and+chondrosarcoma+of+the+skull+base&source=search_result&selectedTitle=1~95&usage_type=default&display_rank=1
4. Kremenevski N, Schlaffer SM, Coras R, Kinfe TM, Graillon T, Buchfelder M. Skull Base Chordomas and Chondrosarcomas. *Neuroendocrinology*. 2020;110(9-10):836-847. doi: 10.1159/000509386. Epub 2020 Jun 15. PMID: 32541136.
5. Limaïem F, Davis DD, Sticco KL. Chondrosarcoma. [Updated 2023 Aug 14]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK538132/>
6. 1. Murphy A. Chondrosarcoma grading: Radiology reference article [Internet]. Radiopaedia.org; 2022. Available from: <https://radiopaedia.org/articles/chondrosarcoma-grading>
7. Coşkun HS, Erdoğan F, Büyükceran İ, Dabak N. Evaluation of prognostic factors affecting survival in chondrosarcoma treatment and comparison with literature. *Jt Dis Relat Surg*. 2022;33(2):440-448. doi: 10.52312/jdrs.2022.526. Epub 2022 Jul 6. PMID: 35852206; PMCID: PMC9361089.
8. Colia V, Provenzano S, Hindi N, Casali PG, Stacchiotti S. Systemic therapy for selected skull base sarcomas: Chondrosarcoma, chordoma, giant cell tumour and solitary fibrous tumour/hemangiopericytoma. *Rep Pract Oncol Radiother*. 2016 Jul-Aug;21(4):361-9. doi: 10.1016/j.rpor.2015.12.005. Epub 2016 Jan 13. PMID: 27330421; PMCID: PMC4899415.
9. Hug EB, Loredó LN, Slater JD, DeVries A, Grove RI, Schaefer RA, Rosenberg AE, Slater JM. Proton radiation therapy for chordomas and chondrosarcomas of the skull base. *J Neurosurg*. 1999 Sep;91(3):432-9. doi: 10.3171/jns.1999.91.3.0432. PMID: 10470818.
10. Rosenberg AE, Nielsen GP, Keel SB, Renard LG, Fitzek MM, Munzenrider JE, Liebsch NJ. Chondrosarcoma of the base of the skull: a clinicopathologic study of 200 cases with emphasis on its distinction from chordoma. *Am J Surg Pathol*. 1999 Nov;23(11):1370-8. doi: 10.1097/00000478-199911000-00007. PMID: 10555005.
11. Noël G, Habrand JL, Mammar H, Pontvert D, Haie-Méder C, Hasboun D, Moisson P, Ferrand R, Beaudré A, Boissérie G, Gaboriaud G, Mazal A, Kérody K, Schlienger M, Mazon JJ. Combination of photon and proton radiation therapy for chordomas and chondrosarcomas of the skull base: the Centre de Protonthérapie D'Orsay experience. *Int J Radiat Oncol Biol Phys*. 2001 Oct 1;51(2):392-8. doi: 10.1016/s0360-3016(01)01634-0. PMID: 11567813.
12. Tzortzidis F, Elahi F, Wright DC, Temkin N, Natarajan SK, Sekhar LN. Patient outcome at long-term follow-up after aggressive microsurgical resection of cranial base chondrosarcomas. *Neurosurgery*. 2006 Jun;58(6):1090-8; discussion 1090-8. doi: 10.1227/01.NEU.0000215892.65663.54. PMID: 16723888.
13. Schulz-Ertner D, Nikoghosyan A, Hof H, Didinger B, Combs SE, Jäkel O, Karger CP, Edler L, Debus J. Carbon ion radiotherapy of skull base chondrosarcomas. *Int J Radiat Oncol Biol Phys*. 2007 Jan 1;67(1):171-7. doi: 10.1016/j.ijrobp.2006.08.027. Epub 2006 Oct 23. PMID: 17056193.

14. Samii A, Gerganov V, Herold C, Gharabaghi A, Hayashi N, Samii M. Surgical treatment of skull base chondrosarcomas. *Neurosurg Rev.* 2009 Jan;32(1):67-75; discussion 75. doi: 10.1007/s10143-008-0170-4. Epub 2008 Sep 26. PMID: 18818961.
15. Sahgal A, Chan MW, Atenafu EG, Masson-Cote L, Bahl G, Yu E, Millar BA, Chung C, Catton C, O'Sullivan B, Irish JC, Gilbert R, Zadeh G, Cusimano M, Gentili F, Laperriere NJ. Image-guided, intensity-modulated radiation therapy (IG-IMRT) for skull base chordoma and chondrosarcoma: preliminary outcomes. *Neuro Oncol.* 2015 Jun;17(6):889-94. doi: 10.1093/neuonc/nou347. Epub 2014 Dec 27. PMID: 25543126; PMCID: PMC4483121.
16. Uhl M, Mattke M, Welzel T, Oelmann J, Habl G, Jensen AD, Ellerbrock M, Haberer T, Herfarth KK, Debus J. High control rate in patients with chondrosarcoma of the skull base after carbon ion therapy: first report of long-term results. *Cancer.* 2014 May 15;120(10):1579-85. doi: 10.1002/cncr.28606. Epub 2014 Feb 5. PMID: 24500784.
17. Feuvret L, Bracci S, Calugaru V, Bolle S, Mammar H, De Marzi L, Bresson D, Habrand JL, Mazeron JJ, Dendale R, Noël G. Efficacy and Safety of Adjuvant Proton Therapy Combined With Surgery for Chondrosarcoma of the Skull Base: A Retrospective, Population-Based Study. *Int J Radiat Oncol Biol Phys.* 2016 May 1;95(1):312-321. doi: 10.1016/j.ijrobp.2015.12.016. Epub 2015 Dec 17. PMID: 26883563.
18. Weber DC, Malyapa R, Albertini F, Bolsi A, Kliebsch U, Walser M, Pica A, Combescure C, Lomax AJ, Schneider R. Long term outcomes of patients with skull-base low-grade chondrosarcoma and chordoma patients treated with pencil beam scanning proton therapy. *Radiother Oncol.* 2016 Jul;120(1):169-74. doi: 10.1016/j.radonc.2016.05.011. Epub 2016 May 28. PMID: 27247057.
19. Weber DC, Badiyan S, Malyapa R, Albertini F, Bolsi A, Lomax AJ, Schneider R. Long-term outcomes and prognostic factors of skull-base chondrosarcoma patients treated with pencil-beam scanning proton therapy at the Paul Scherrer Institute. *Neuro Oncol.* 2016 Feb;18(2):236-43. doi: 10.1093/neuonc/nov154. Epub 2015 Aug 30. PMID: 26323608; PMCID: PMC4724177.
20. Vaz-Guimaraes F, Fernandez-Miranda JC, Koutourousiou M, Hamilton RL, Wang EW, Snyderman CH, Gardner PA. Endoscopic Endonasal Surgery for Cranial Base Chondrosarcomas. *Oper Neurosurg (Hagerstown).* 2017 Aug 1;13(4):421-434. doi: 10.1093/ons/oxp020. PMID: 28838112.
21. Hasegawa H, Shin M, Kondo K, Hanakita S, Mukasa A, Kin T, Saito N. Role of endoscopic transnasal surgery for skull base chondrosarcoma: a retrospective analysis of 19 cases at a single institution. *J Neurosurg.* 2018 May;128(5):1438-1447. doi: 10.3171/2017.1.JNS162000. Epub 2017 Jul 7. PMID: 28686110.
22. Simon F, Feuvret L, Bresson D, Guichard JP, El Zein S, Bernat AL, Labidi M, Calugaru V, Froelich S, Herman P, Verillaud B. Surgery and protontherapy in Grade I and II skull base chondrosarcoma: A comparative retrospective study. *PLoS One.* 2018 Dec 17;13(12):e0208786. doi: 10.1371/journal.pone.0208786. PMID: 30557382; PMCID: PMC6296545.
22. Mattke M, Vogt K, Bougatf N, Welzel T, Oelmann-Avendano J, Hauswald H, Jensen A, Ellerbrock M, Jäkel O, Haberer T, Herfarth K, Debus J, Uhl M. High control rates of proton- and carbon-ion-beam treatment with intensity-modulated active raster scanning in 101 patients with skull base chondrosarcoma at the Heidelberg Ion Beam Therapy Center. *Cancer.* 2018 May 1;124(9):2036-2044. doi: 10.1002/cncr.31298. Epub 2018 Feb 22. PMID: 29469932.
24. Weber DC, Murray F, Combescure C, Calugaru V, Alapetite C, Albertini F, Bolle S, Goudjil F, Pica A, Walser M, Mammar H, Bachtary B, Lomax T, Noël G, Dendale R, Feuvret L. Long term outcome of skull-base chondrosarcoma patients treated with high-dose proton therapy with or without conventional radiation therapy. *Radiother Oncol.* 2018 Dec;129(3):520-526. doi: 10.1016/j.radonc.2018.06.040. Epub 2018 Jul 17. PMID: 30021697.

25. Holtzman AL, Rotondo RL, Rutenberg MS, Indelicato DJ, Mercado CE, Rao D, Tavanaiepour D, Morris CG, Louis D, Flampouri S, Mendenhall WM. Proton therapy for skull-base chondrosarcoma, a single-institution outcomes study. *J Neurooncol*. 2019 May;142(3):557-563. doi: 10.1007/s11060-019-03129-8. Epub 2019 Mar 2. PMID: 30827010.
26. Hasegawa H, Vakharia K, Graffeo CS, Carlson ML, Pollock BE, Brown PD, Perry A, Van Gompel JJ, Driscoll CLW, Link MJ. Long-term outcomes of grade I/II skull base chondrosarcoma: an insight into the role of surgery and upfront radiotherapy. *J Neurooncol*. 2021 Jun;153(2):273-281. doi: 10.1007/s11060-021-03764-0. Epub 2021 Apr 27. PMID: 33907967.
27. Kawashima M, Shin M, Jokura H, Hasegawa T, Yamanaka K, Yamamoto M, Matsunaga S, Akabane A, Yomo S, Onoue S, Kondoh T, Hasegawa H, Shinya Y, Saito N. Outcomes of Gamma Knife radiosurgery for skull base chondrosarcomas: a multi-institutional retrospective study. *J Neurosurg*. 2022 Feb 18:1-8. doi: 10.3171/2022.1.JNS212703. Epub ahead of print. PMID: 35180704.
28. Pattankar S, Warade A, Misra BK, Deshpande RB. Long-term outcome of adjunctive Gamma Knife radiosurgery in skull-base chordomas and chondrosarcomas: An Indian experience. *J Clin Neurosci*. 2022 Feb;96:90-100. doi: 10.1016/j.jocn.2021.12.018. Epub 2022 Jan 11. PMID: 35030499.
29. Al-Shabibi T, Troude L, Hamdi H, Baucher G, Boucekine M, Régis J, Roche PH. Functional and oncological outcome of petroclival chondrosarcoma operated on through an extradural anterior petrosectomy approach. A single center experience. *Neurochirurgie*. 2023 Jul;69(4):101430. doi: 10.1016/j.neuchi.2023.101430. Epub 2023 Apr 28. PMID: 37121214.
30. Liu H, Li Z, Xue Y, Zhao T, Wu Y. A multicenter retrospective analysis of clinical outcomes of intracranial chondrosarcoma in 26 patients. *Sci Rep*. 2023 Sep 5;13(1):14647. doi: 10.1038/s41598-023-41378-w. PMID: 37669996; PMCID: PMC10480207.
31. National Cancer Institute (U.S). Common terminology criteria for adverse events (CTCAE). Bethesda, MD: U.S. Dept. of Health and Human Services, National Institutes of Health, National Cancer Institute; 2009.
32. Kano H, Iyer A, Lunsford LD. Skull base chondrosarcoma radiosurgery: a literature review. *Neurosurgery*. 2014 Aug;61 Suppl 1:155-8. doi: 10.1227/NEU.0000000000000382. PMID: 25032544.
33. Schwartz TH, Morgenstern PF, Anand VK. Lessons learned in the evolution of endoscopic skull base surgery. *J Neurosurg*. 2019 Feb 1;130(2):337-346. doi: 10.3171/2018.10.JNS182154. PMID: 30717035.
34. Wang W, Shokri T, Manolidis S, Ducic Y. Complications in Skull Base Surgery and Subsequent Repair. *Semin Plast Surg*. 2020 Nov;34(4):286-292. doi: 10.1055/s-0040-1721765. Epub 2020 Dec 24. PMID: 33380915; PMCID: PMC7759428.
35. Bell EB, Cohen ER, Sargi Z, Leibowitz J. Free tissue reconstruction of the anterior skull base: A review. *World J Otorhinolaryngol Head Neck Surg*. 2020 Apr 17;6(2):132-136. doi: 10.1016/j.wjorl.2020.01.004. PMID: 32596659; PMCID: PMC7296482.
36. Noel G, Gondi V. Proton therapy for tumors of the base of the skull. *Chin Clin Oncol*. 2016 Aug;5(4):51. doi: 10.21037/cco.2016.07.05. PMID: 27558252.
37. Holtzman AL, Seidensaal K, Iannalfi A, Kim KH, Koto M, Yang WC, Shiao CY, Mahajan A, Ahmed SK, Trifiletti DM, Peterson JL, Koffler DM, Vallow LA, Hoppe BS, Rutenberg MS. Carbon Ion Radiotherapy: An Evidence-Based Review and Summary Recommendations of Clinical Outcomes for Skull-Base Chordomas and Chondrosarcomas. *Cancers (Basel)*. 2023 Oct 17;15(20):5021. doi: 10.3390/cancers15205021. PMID: 37894388; PMCID: PMC10605639.
38. Folbe AJ, Svider PF, Liu JK, Eloy JA. Endoscopic Resection of Clival Malignancies. *Otolaryngol Clin North Am*. 2017 Apr;50(2):315-329. doi: 10.1016/j.otc.2016.12.008. PMID: 28314400.

39. Sallabanda M, Vera JA, Pérez JM, Matute R, Montero M, de Pablo A, Cerrón F, Valero M, Castro J, Mazal A, Miralbell R. Five-Fraction Proton Therapy for the Treatment of Skull Base Chordomas and Chondrosarcomas: Early Results of a Prospective Series and Description of a Clinical Trial. *Cancers (Basel)*. 2023 Nov 25;15(23):5579. doi: 10.3390/cancers15235579. PMID: 38067283; PMCID: PMC10705113.
40. Rutenberg MS, Beltran C. Future Perspective: Carbon Ion Radiotherapy for Head and Neck and Skull Base Malignancies. *Oral Maxillofac Surg Clin North Am*. 2023 Aug;35(3):485-492. doi: 10.1016/j.coms.2023.02.009. Epub 2023 Apr 26. PMID: 37117091.

6

Shrinking & Growing Chordoma

Spontaneous shrinking and growing skull base chordoma

*Keizer ME, *Bosman EM, van Aalst J, Broen MPG, Postma AA, Vernemmen AIP, Kunst HPM, Temel Y. Spontaneous Shrinking and Growing Skull Base Chordoma. J Neurol Surg Rep. 2025 May 9;86(2):e107-e111.

*Both authors contributed equally

ABSTRACT

Background: Chordomas are rare slow-growing tumors occurring in the axial skeleton and can demonstrate local aggressive behavior, typically extending from the median axis compressing surrounding tissue. Complete surgical resection and adjuvant radiotherapy are the preferred treatments. We present an unusual case of a spontaneously shrinking and growing off-midline petroclival chordoma.

Case description: A 23-year-old female presented with right abducens nerve palsy. Computed tomography (CT) and magnetic resonance imaging (MRI) revealed an off-midline petroclival lesion compressing the abducens nerve with characteristics of a chondrosarcoma. Pre-operative MRI indicated spontaneous lesion regression and the abducens nerve showed clinical improvement. Hence, the planned surgery was canceled. During the wait-and-scan period, abducens nerve palsy recurred. MRI confirmed lesion growth and showed an intratumoral linear structure indicative of blood. Even though pre-operative MRI again demonstrated shrinkage, the lesion was surgically removed. Despite the unusual presentation, histopathological examination diagnosed a conventional chordoma. A second surgery was required to remove the residual tumor after which the patient received high-dose photon beam therapy.

Conclusion: This article discusses the uncommon presentation and behavior of a petroclival chordoma showing fluctuating cycles of off-midline growth and spontaneous regression. While intratumoral hemorrhage is hypothesized to explain this tumor behavior, the exact etiology needs further investigation. The case presented here emphasizes the importance of considering chordoma in the differential diagnosis despite an atypical disease course

Keywords

Skull base chordoma, chondrosarcoma, spontaneous shrinkage, hemorrhage, endoscopic, skull base surgery

INTRODUCTION

Chordomas are rare malignant bone tumors originating from primitive notochordal remnants¹⁻³. This malignancy can arise anywhere along the craniospinal axis: skull base (32%), mobile spine (32.8%), and sacral (29.2%)⁴. Skull base chordomas show an annual incidence of 1 case per 2,000,000 individuals, constituting less than 0.2% of all intracranial neoplasms^{1,5}. Clival chordomas typically show slow growth from the clival midline but can demonstrate locally osteolytic, aggressive behavior, and may compress surrounding neurovascular structures⁶. The long-term prognosis of skull base chordomas is unfavorable, with 5- and 10-year recurrent rates of 52.9% and 88.3%⁷, respectively, and 5-, 10-, and 20-year survival rates dropping to 67.6%, 39.9%, and 13.1%, respectively⁴. While chordomas are often not metastatic on presentation, 5 to 30% show metastatic potential⁸⁻¹². Gross total surgical resection of the tumor followed by high-dose radiotherapy is considered the gold standard treatment⁶. Here, we describe an unusual disease course of an off-midline, petroclival chordoma.

Case presentation

A 23-year-old female patient presented with horizontal diplopia due to progressive right abducens nerve palsy. A dull headache with fluctuating intensity and nausea accompanied the diplopia development but gradually decreased after a few days. The patient did not suffer from other neurological deficits, complaints, or comorbidities. A computed tomography (CT) scan demonstrated an intraosseous lytic lesion at the right petroclival fissure and posterior clivus. Magnetic resonance imaging (MRI) revealed a T2 hyperintense lesion with faint peripheral contrast-enhancing and hyperintense signal at FLAIR, measuring 9mm x 14mm x 17mm (L; W; H) with abducens nerve compression at the location of the right canal of Dorello, and intradural expansion in the posterior fossa without brain stem compression (Figure 1). The differential diagnosis included chondrosarcoma, epidermoid, ecchordosis physaliphora, benign notochordal cell tumor, and off-midline chordoma. Endoscopic trans-sphenoidal resection was planned. The pre-operative navigation MRI showed spontaneous regression of the lesion with dissociation from the abducens nerve (Figure 2), and the patient experienced abduction improvement of the right eye. The differential diagnosis was reconsidered, and a simple bone cyst was added. While simple bone cysts in the skull base are rare¹³⁻¹⁵, their spontaneous resolution has been reported in long bones and the mandible^{16,17}. Therefore, the procedure was cancelled, and a conservative wait-and-scan policy with a 6-month interval was chosen.

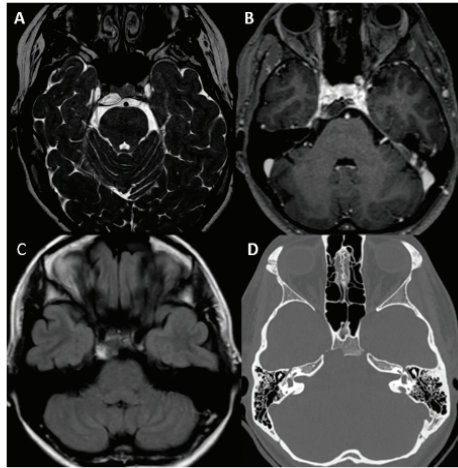


Figure 1. Imaging at presentation demonstrating a right petroclival fissure lesion (orange arrows), hyperintense at T2-W (A), hypointense with only subtle rim enhancement at contrast-enhanced T1-W (CE-T1-W) (B) slight hyperintense at FLAIR (C) and lytic at CT with sclerosis of the rim (D).

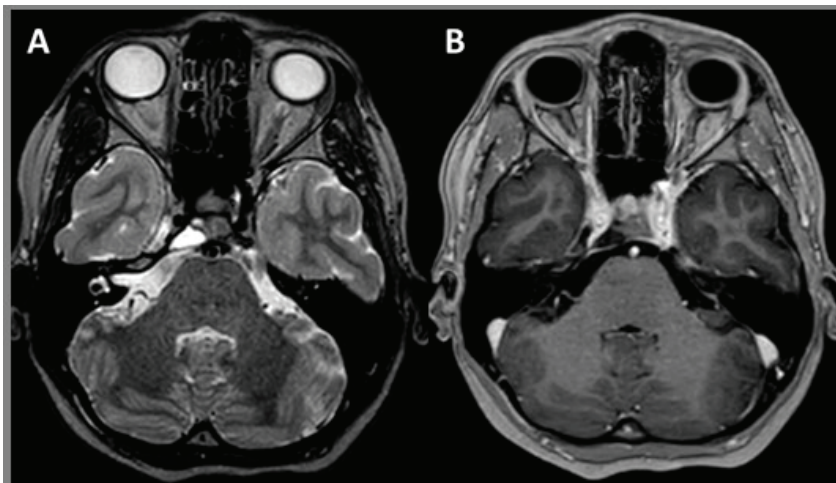


Figure 2. Pre-operative neuronavigation imaging demonstrates decreased antero-posterior dimensions and increased space between the lesion and the pons at T2-W (A) and CE-T1-W (B).

At next follow-up, MRI showed a slight enlargement of the petroclival lesion towards the right abducens nerve without clinical changes and a shorter time interval wait-and-scan was scheduled. During the waiting period, the right abducens nerve palsy recurred. MRI demonstrated significant lesion growth, affecting the abducens nerve. A hypointense linear structure traversing the lesion was recognized in contrast-enhanced T2-weighted (T2-W) images, which could indicate blood (Figure 3). At this moment, hemangioma, simple bone cyst, and chondrosarcoma constituted the differential diagnosis. Surgery was scheduled.

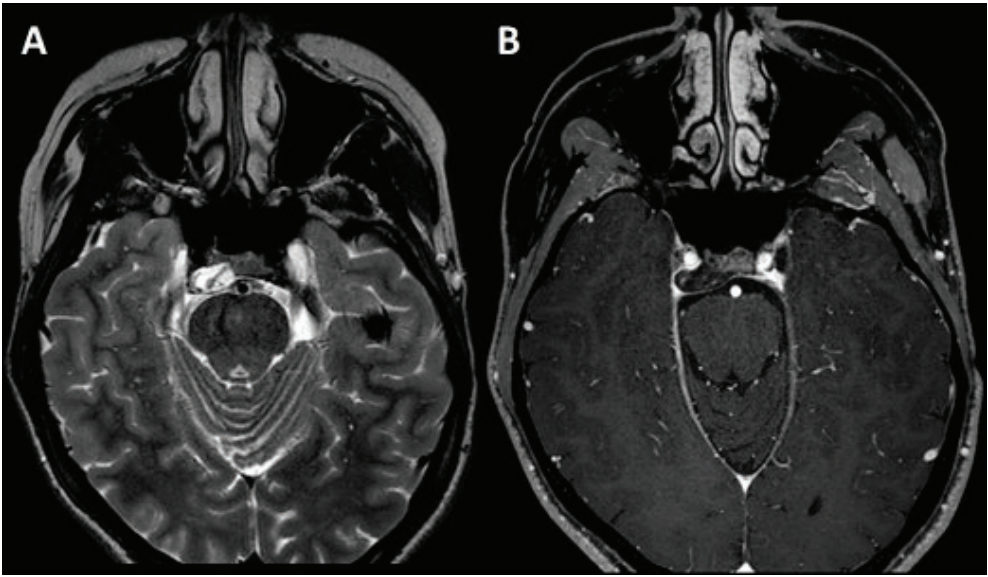
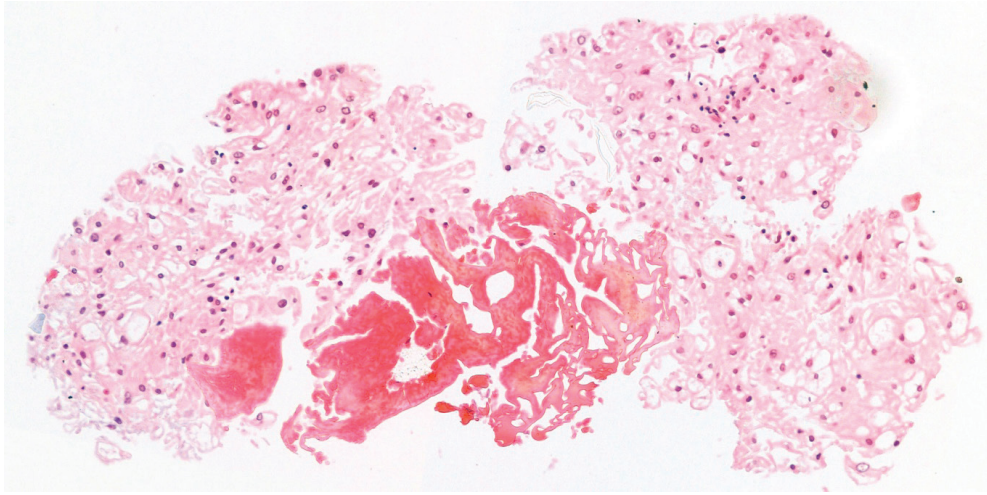


Figure 3. T2-W (A) and CE-T1-W (B) imaging at 9 months demonstrates lesion progression with a hypointense structure traversing the lesion (orange arrow).

Interestingly, pre-operative MRI again showed lesion regression, consistent with the diplopia improvement experienced by the patient. Nevertheless, the patient underwent an uncomplicated endoscopic endonasal skull base surgery to decompress the abducens nerve further and remove the tumor. Histopathology revealed a population of disorganized physaliphorous cells (Figure 4A). The cell nuclei displayed some anisokaryosis and were normochromic to bright in appearance. Immunohistochemical analysis revealed positive cell staining for cytokeratin AE1/AE3, and a dubiously weak S100 staining for a subset of cells. Additional positive staining for brachyury expression confirmed the diagnosis of a conventional chordoma (Figure 4B). Next to the tumor was a small focus of degenerated erythrocytes; yet pre- versus intra-operative hemorrhage could not be distinguished histologically with certainty.

A



B

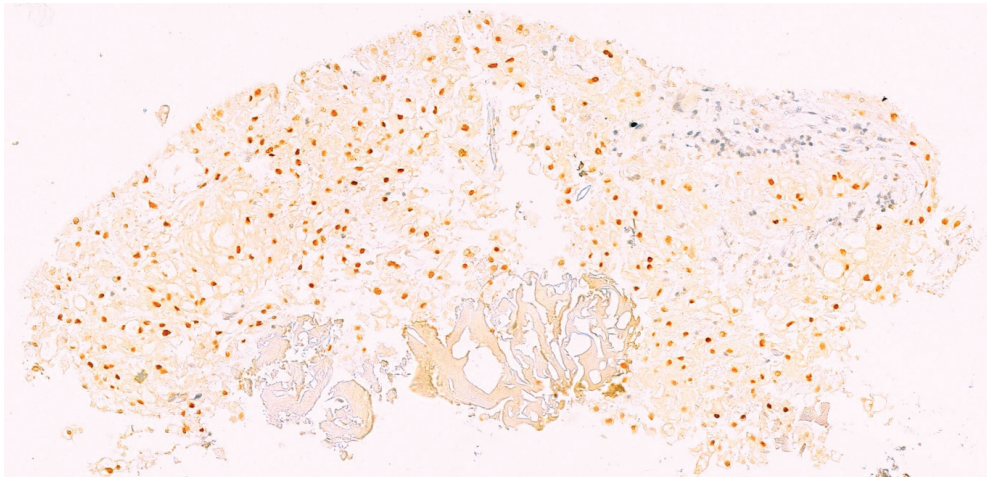


Figure 4. Immunohistochemical staining of the chordoma. A) Hematoxylin and eosin (H&E) staining (magnification x20) demonstrates disorganized physaliphorous cells. B) Brachyury nuclear expression (magnification x20).

While post-operative MRI showed an evident size reduction of the petroclival lesion, a minor residual persisted dorsal to the right internal carotid artery. A second endoscopic endonasal surgery was performed for maximal, though safe, resection of the residual lesion. Postoperative MRI indicated no macroscopically evident lesion remnants. Subsequently, the patient received photon beam therapy with a dose of 74 Gy in 37 sessions. Abducens nerve function largely recovered. At one year follow-up the patient is recurrence-free.

DISCUSSION

Chordomas are rare neoplasms that typically show progressive growth and locally aggressive behavior. Here we describe an unusual disease course of a skull base chordoma showing off-midline growth, spontaneous shrinkage without intervention, and signs of a small bleeding. While lesion growth induced abducens nerve palsy, shrinkage led to abducens and diplopia recovery.

Clival chordoma diagnosis depends on clinical presentation, histopathology, and imaging characteristics associated with the tumor location and invasion¹⁸. CT and MRI are the preferred imaging modalities to assess bone involvement and evaluate the proximity of the lesion to critical soft-tissue structures. On non-contrast CT, clival chordomas often appear as osteolytic lesions that are well-circumscribed, hypo-attenuated, and heterogeneous^{19,20}. The tumor bulk generally has increased density compared to surrounding neural structures¹⁹. Sometimes CT shows intratumoral calcifications or areas of low attenuation representing mucinous content within the tumor^{19,20}. On MRI, chordomas appear hypointense on T1- and hyperintense on T2-W images. This signal intensity may vary with foci of hyper- or hypo-intensity on the respective MRI sequences, resembling a heterogeneous honeycomb enhancement pattern related to mucus, hemorrhage, or calcification^{20,21}. Gadolinium administration usually leads to mild heterogeneous contrast enhancement, with restricted diffusion-weighted imaging (DWI)⁷. These CT and MRI features are in line with the presented case.

However, chondrosarcomas share similar characteristics in both imaging modalities, complicating their distinction from chordomas on pre-operative imaging^{20,22}. The location of the tumor origin is often used as a differentiation direction. Skull base chordomas usually grow in the clival midline, while a lateral clival origin, in and next to the petroclival fissure would favor chondrosarcoma^{20,23}. Yet, chordomas growing laterally in the petrous bone have previously been described²⁴. As for the presented case, immunohistochemical detection of brachyury is currently required to confirm the diagnosis of chordoma.

Only a few cases of spontaneous chordoma regression are known: two in the skull base^{25,26}, one in the cervical region²⁷, one in the sacrococcygeal region²⁸, and pulmonary metastases of a sacral chordoma²⁹. Bander *et al.*²⁵ described a case of spontaneous clival chordoma regression without surgical intervention or radiotherapy. Herbal supplements and animal oils consumed by the 75-year-old female patient were hypothesized to exert anti-tumoral effects and contribute to tumor shrinkage²⁵. Radl *et al.*²⁷ reported a case of chordoma disappearance in the C2 vertebral body after non-operative treatment in a 24-year-old male patient. The patient received dexamethasone and antibiotic treatment, of which the immune-mediated mechanisms were proposed to contribute to chordoma disappearance²⁷. However, similar to the case presented here, the remaining cases do not share these inflammatory or

immunological factors^{26,28,29}. Instead, González *et al.*²⁸ related the spontaneous regression of a sacrococcygeal chordoma to intratumoral hemorrhage resorption. Intratumoral foci of hemorrhage can be confirmed by hypo-intensity on susceptibility-weighted imaging (SWI)¹⁸.

Hemorrhagic chordoma are uncommon but have previously been documented, mainly in clival chordomas^{18,25}. While the underlying etiology remains elusive, some mechanisms have been suggested. Rapid tumor growth could lead to an inadequately matched blood supply and rupture of fragile vessels¹⁸. Similarly, small vessel occlusion after vascular proliferation can result in areas of ischemic necrosis and hemorrhage^{18,30}. Moreover, chordomas may induce neovascularization, resulting in increased vessel permeability and fragility, and, consequently, spontaneous hemorrhage³¹. These phenomena seem to correlate with vascular endothelial growth factor (VEGF) overexpression occurring in chordomas^{31,32}. VEGF is known for inducing tumor angiogenesis and is often hypoxia-driven^{32,33}. Indeed, the presence of hypoxic areas in chordomas has been presented by [18F]-fluoromisonidazole positron emission tomography/computed tomography (FMISO-PET/CT)^{34,35}. Hypoxic tumor areas are generally radioresistant and may be an indicator of poor prognosis¹⁹.

For the case presented here, cycles of intratumoral hemorrhage and partial hemorrhage resolution are hypothesized to explain the fluctuating tumor growth and shrinkage. The hyperintensity of the first FLAIR MRI and the linear structure observed on MRI may have indicated the occurrence of intratumoral bleeding that led to temporally increased tumor size. The linear structure was only observed after tumor growth but disappeared after shrinkage. Yet, the underlying mechanism driving these processes remains unknown. Various factors may be involved in this odd disease course, and further research is required to evaluate the etiology.

CONCLUSION

To conclude, we present an unusual case of chordoma growth and spontaneous regression. While no consensus has yet been achieved on the underlying mechanisms of growth reversibility, this odd disease course should increase awareness and warrant further investigation of chordoma behavior. Off-midline presentation, intratumoral hemorrhage, and spontaneous regression should not exclude chordoma from the differential diagnosis or change the treatment. Hence, histological conformation is mandatory in such cases.

REFERENCES

1. Koutourousiou M, Snyderman CH, Fernandez-Miranda J, Gardner PA. Skull Base Chordomas. *Otolaryngol Clin North Am.* 2011;44(5):1155-1171. doi:10.1016/j.otc.2011.06.002
2. Kyriakos M, Totty WG, Lenke LG. Giant Vertebral Notochordal Rest: A Lesion Distinct From Chordoma: Discussion of an Evolving Concept. *Am J Surg Pathol.* 2003;27(3):396.
3. Vujovic S, Henderson S, Presneau N, et al. Brachyury, a crucial regulator of notochordal development, is a novel biomarker for chordomas. *J Pathol.* 2006;209(2):157-165. doi:10.1002/path.1969
4. McMaster ML, Goldstein AM, Bromley CM, Ishibe N, Parry DM. Chordoma: incidence and survival patterns in the United States, 1973–1995. *Cancer Causes Control.* 2001;12(1):1-11. doi:10.1023/A:1008947301735
5. Crockard HA, Steel T, Plowman N, et al. A multidisciplinary team approach to skull base chordomas. *J Neurosurg.* 2001;95(2):175-183. doi:10.3171/jns.2001.95.2.0175
6. Almefty K, Pravdenkova S, Colli BO, Al-Mefty O, Gokden M. Chordoma and chondrosarcoma: Similar, but quite different, skull base tumors. *Cancer.* 2007;110(11):2467-2477. doi:10.1002/cncr.23073
7. Wu Z, Zhang J, Zhang L, et al. Prognostic factors for long-term outcome of patients with surgical resection of skull base chordomas—106 cases review in one institution. *Neurosurg Rev.* 2010;33(4):451-456. doi:10.1007/s10143-010-0273-6
8. Kishimoto R, Omatsu T, Hasegawa A, Imai R, Kandatsu S, Kamada T. Imaging characteristics of metastatic chordoma. *Jpn J Radiol.* 2012;30(6):509-516. doi:10.1007/s11604-012-0086-3
9. Chambers PW, Schwinn CP. Chordoma: A Clinicopathologic Study of Metastasis. *Am J Clin Pathol.* 1979;72(5):765-776. doi:10.1093/ajcp/72.5.765
10. Stacchiotti S, Casali PG, Lo Vullo S, et al. Chordoma of the Mobile Spine and Sacrum: A Retrospective Analysis of a Series of Patients Surgically Treated at Two Referral Centers. *Ann Surg Oncol.* 2010;17(1):211-219. doi:10.1245/s10434-009-0740-x
11. Fagundes MA, Hug EB, Liebsch NJ, Daly W, Efrid J, Munzenrider JE. Radiation therapy for chordomas of the base of skull and cervical spine: Patterns of failure and outcome after relapse. *Int J Radiat Oncol.* 1995;33(3):579-584. doi:10.1016/0360-3016(95)02014-3
12. Bjornsson J, Wold LE, Ebersold MJ, Laws ER. Chordoma of the mobile spine. A clinicopathologic analysis of 40 patients. *Cancer.* 1993;71(3):735-740. doi:10.1002/1097-0142(19930201)71:3<735::AID-CNCR2820710314>3.0.CO;2-8
13. Fatani JA, Arab A, Alkhalidi H, Ajlan A. Clival simple bone cyst: Rare pathological entity (case report). *Surg Neurol Int.* 2020;11:427. doi:10.25259/SNI_478_2020
14. Shkarubo A, Kuleshov A, Semenova L, et al. Surgical Treatment of Clival and Axial Bone Cysts. *Neurosurg.* Published online 2016:73.
15. Gunawat P, Shaikh ST, Karmarkar V, Deopujari C, Shah N. Endoscopic Excision of Symptomatic Simple Bone Cyst at Skull Base. *J Clin Diagn Res JCDR.* 2016;10(10):PD03-PD04. doi:10.7860/JCDR/2016/20684.8646
16. Damante JH, Da S Guerra EN, Ferreira Jr O. Spontaneous resolution of simple bone cysts. *Dentomaxillofacial Radiol.* 2002;31(3):182-186. doi:10.1038/sj/dmfr/4600696
17. Wilkins RM. Unicameral bone cysts. *JAAOS-J Am Acad Orthop Surg.* 2000;8(4):217-224.
18. Uysal E, Cohen MA, Abou-Al-Shaar H, Palmer C, Couldwell W. Hemorrhagic skull base chordoma presenting as chordoma apoplexy. *Cureus.* 2021;13(11).
19. Santegoeds RGC, Temel Y, Beckervordersandforth JC, Van Overbeeke JJ, Hoeberigs CM. State-of-the-Art Imaging in Human Chordoma of the Skull Base. *Curr Radiol Rep.* 2018;6(5):16. doi:10.1007/s40134-018-0275-7

20. Erdem E, Angtuaco EC, Van Hemert R, Park JS, Al-Mefty O. Comprehensive review of intracranial chordoma. *Radiographics*. 2003;23(4):995-1009.
21. Meyers SP, Hirsch WL, Curtin HD, Barnes L, Sekhar LN, Sen C. Chordomas of the skull base: MR features. *Am J Neuroradiol*. 1992;13(6):1627-1636.
22. Pamir MN, Özduman K. Analysis of radiological features relative to histopathology in 42 skull-base chordomas and chondrosarcomas. *Eur J Radiol*. 2006;58(3):461-470.
23. Vuong HG, Dunn IF. Chondrosarcoma and Chordoma of the Skull Base and Spine: Implication of Tumor Location on Patient Survival. *World Neurosurg*. 2022;162:e635-e639. doi:10.1016/j.wneu.2022.03.088
24. Brown RV, Sage MR, Brophy BP. CT and MR findings in patients with chordomas of the petrous apex. *Am J Neuroradiol*. 1990;11(1):121-124.
25. Bander ED, Kocharian G, Liechty B, Tsiouris AJ, Schwartz TH. Spontaneous regression of a clival chordoma. Case report. *Acta Neurochir (Wien)*. 2020;162(2):433-436. doi:10.1007/s00701-019-04107-9
26. Vellutini E de AS, Stamm AEC, Oliveira MF de. Spontaneous Regression of a Clival Chordoma: An Unusual Case Report. *J Neurol Surg Part Cent Eur Neurosurg*. 2022;83(4):388-390. doi:10.1055/s-0040-1720990
27. Radl R, Leithner A, Kastner N, Bodo K, Nader A, Windhager R. Disappearance of a Cervical Spine Chordoma After Nonoperative Treatment: A Case Report. *JBJS*. 2005;87(8):1822. doi:10.2106/JBJS.D.02408
28. González TMC, Lam SW, van der Wal R, Navas A, van Langevelde K. Sacrococcygeal chordoma with spontaneous regression due to a large hemorrhagic component. *Skeletal Radiol*. Published online May 13, 2024. doi:10.1007/s00256-024-04700-9
29. Takagi K, Nagano A, Tsugita M, Nishimoto Y, Miyazaki T, Akiyama H. Spontaneous Regression of Multiple Pulmonary Metastasis of Sacral Chordoma: A Case Report. *JBJS Case Connect*. 2021;11(4):e21.00227. doi:10.2106/JBJS.CC.21.00227
30. Lee HJ, Kalnin AJ, Holodny AI, Schulder M, Grigorian A, Sharer LR. Hemorrhagic chondroid chordoma mimicking pituitary apoplexy. *Neuroradiology*. 1998;40(11):720-723. doi:10.1007/s002340050671
31. Vilela MD, Pedrosa HAS, Dias Filho MA. A Hemorrhagic Clival Chordoma with a Long Progression-Free Survival. *World Neurosurg*. 2017;105:1042.e1-1042.e4. doi:10.1016/j.wneu.2017.06.169
32. Tauziède-Espariat A, Bresson D, Polivka M, et al. Prognostic and Therapeutic Markers in Chordomas: A Study of 287 Tumors. *J Neuropathol Exp Neurol*. 2016;75(2):111-120. doi:10.1093/jnen/nlv010
33. Li X, Ji Z, Ma Y, Qiu X, Fan Q, Ma B. Expression of hypoxia-inducible factor-1 α , vascular endothelial growth factor and matrix metalloproteinase-2 in sacral chordomas. *Oncol Lett*. 2012;3(6):1268-1274. doi:10.3892/ol.2012.645
34. Cheney MD, Chen YL, Lim R, et al. [18F]-Fluoromisonidazole Positron Emission Tomography/Computed Tomography Visualization of Tumor Hypoxia in Patients With Chordoma of the Mobile and Sacrococcygeal Spine. *Int J Radiat Oncol Biol Phys*. 2014;90(5):1030-1036. doi:10.1016/j.ijrobp.2014.08.016
35. Mammar H, Kerrou K, Nataf V, et al. Positron Emission Tomography/Computed Tomography Imaging of Residual Skull Base Chordoma Before Radiotherapy Using Fluoromisonidazole and Fluorodeoxyglucose: Potential Consequences for Dose Painting. *Int J Radiat Oncol*. 2012;84(3):681-687. doi:10.1016/j.ijrobp.2011.12.047

7

Skull Base Reconstruction

A simple and rapid skull base reconstruction after endoscopic clival surgery: a technical note

Genc B, Keizer M, van Aalst J, Kunst H, Temel Y (submitted to British Journal of Neurosurgery)

ABSTRACT

Skull base chordomas, challenging due to their proximity to critical structures, have seen treatment advancements, notably the trans nasal endoscopic approach. Traditionally, closure after tumor removal involved complex techniques. Our report presents three cases diverging from tradition, utilizing a simplified closure method employing autologous fat tissue alone after modified bony resection. All three cases underwent successful endoscopic resection, followed by fat tissue placement to cover defects. Although one case experienced a transient cerebrospinal fluid (CSF) leak 4 days after the surgery, the other two cases showed no complications during the 24-month and 3-month follow-ups after surgery, respectively. These cases demonstrate the efficacy of the simplified closure technique, including bony resection, prompting its integration into our surgical approach for skull base chordomas.

Keywords: Clivus, Chordoma, Clival tumors, Skull base reconstruction, Cerebrospinal fluid (CSF) fistulas

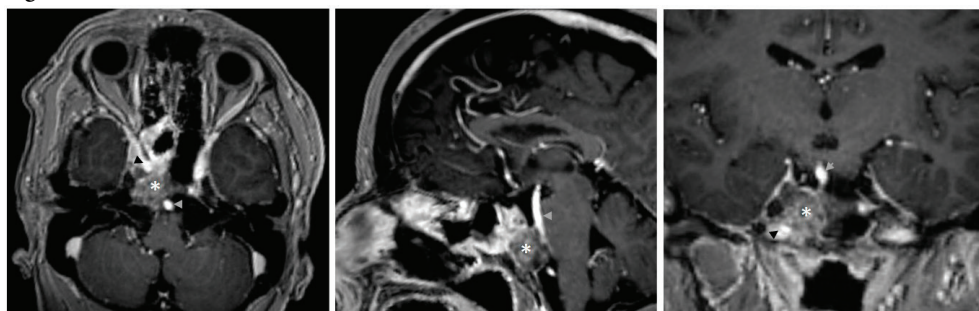
INTRODUCTION

Skull base chordoma is a challenging surgical pathology due to its proximity to critical structures such as the brainstem, cranial nerves, and vascular structures. In the last two decades advances in endoscopic techniques and radiation therapy have changed this field [1]. We are able to remove more tumor and irradiate relatively safely with a high dose (up to approx. 75Gy). Nowadays, the preferred surgical approach is the trans nasal endoscopic approach. After tumor removal, closing the defect can be challenging as well. While different closure techniques exist [2], an often-applied closure technique is using a vascularized nasoseptal flap in combination with a multi-layer reconstruction. External lumbar drainage may aid in preventing CSF leakage [3]. Preventing the leakage of cerebral spinal fluid (CSF) is essential, since it can cause serious morbidity including infection, pneumocephalus, and hydrocephalus. Between 2000 and 2024, 33 cases with clival tumors were treated in our center. Traditionally, skull base reconstruction was performed using a vascularized nasoseptal flap in combination with a multi-layer reconstruction. However, in our most recent three cases, closure of the dural defect was performed using a “simple” and “fast” method, with autologous fat tissue only. Here, we discuss these cases and describe the closure technique.

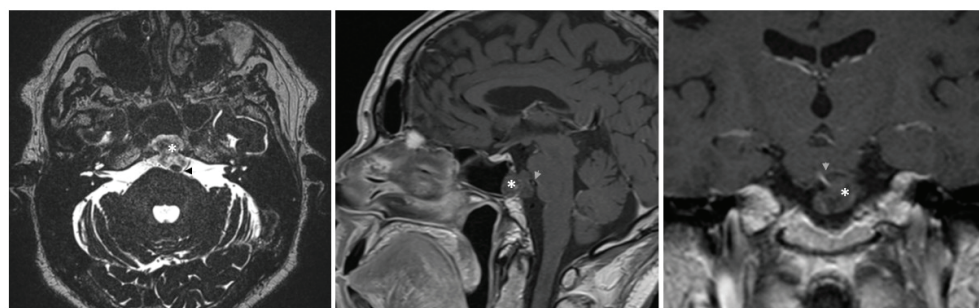
CASE DESCRIPTIONS

In the first case, a 68 year old female presented with right abducens nerve palsy and a burning sensation in her nose that had started 2 weeks earlier. Subsequent radiological examinations revealed a paramedian clival tumor compressing on the brainstem and extending to the right of the petroclival fissure (Fig. 1A). The second case was a 65-year old male patient who was incidentally diagnosed during medical evaluation for a hearing deficit that included a MRI scan. A left paramedian clival tumor was found, compressing the posterior brainstem and extending into the sphenoid sinus (Fig. 1B). And the third case was a 24-year old male patient who was diagnosed with headache and occasional nausea. The subsequent MRI shows a lesion located in the left paramedian clival area, compressing on the brainstem (Fig.1C).

Figure 1A



1B



1C

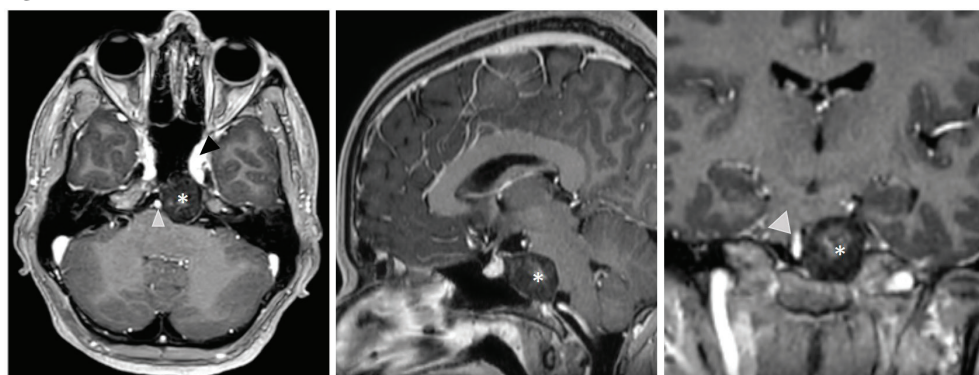


Fig1A. Preoperative axial, sagittal and coronal T1 weighted with Gadolinium magnetic resonance imaging (from case 1)

black arrow tip; internal carotid artery, grey arrow tip; basilar artery, *, tumor

Fig1B. Preoperative axial spin echo (Space sequence), preoperative sagittal and coronal T1 weighted with Gadolinium magnetic resonance imaging (from case2)

black arrow tip; internal carotid artery, grey arrow tip; basilar artery, *, tumor

Fig1C. Preoperative axial, sagittal and coronal T1 weighted with Gadolinium magnetic resonance imaging (from case 3)

black arrow tip; internal carotid artery, grey arrow tip; basilar artery, *, tumor

We performed an endonasal endoscopic approach using electromagnetic neuronavigation in all cases. The middle turbinates were retracted bilaterally, and a binostril transsphenoidal approach was performed. After excising the mucosal tissues surrounding the sphenoid ostium, a diamond burr was used to drill the ostium and the sphenoid sinus was opened. The anterior wall of the sphenoid sinus and septum were drilled out to expose the boundaries of the carotid prominences laterally, the sellar floor superiorly, and the defect created by the mass inferiorly. In all three cases, the tumor capsule was opened using microdissecting-scissors. The chordoma was removed using curettes, microsurgical dissectors and gentle suction. Components extending towards the brainstem and basilar artery were dissected and removed (Figure 2)

Figure 2

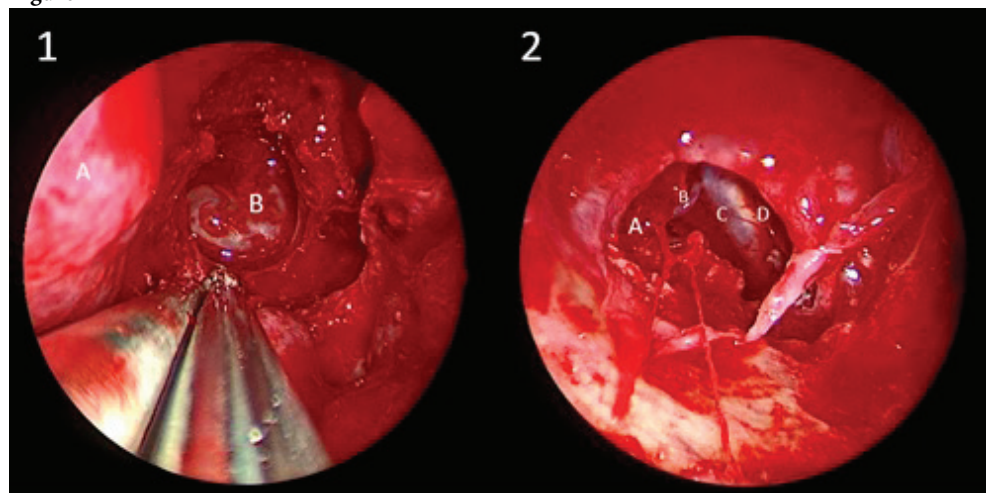


Fig2. Endonasal endoscopic approach (From case 2)

1 Before tumor excision; A. Middle Turbinate, B. Tumor

2 After excision; A. Dura Mater B. Anterior inferior cerebellar artery, C. Basilar artery, D. Brain stem

Fig3. Schematic sagittal view of the surgical corridor, sagittal section of computerized Tomography (From case 2)

A Clivus, B Fat tissue, C Basilar artery, D brainstem

After the surgical removal was completed, the clival bone and the sphenoid sinus were carefully shaped by drilling, to create a ridge that descends from the nasal cavity down to the dural defect and the brainstem (Figure 3). Subsequently, fat tissue harvested from the abdomen was shaped into French fries-like strips, approximately 20x5 mm in size. The fat tissue was then consecutively placed from the periphery of the defect towards the center until the defect was completely covered. (Figure 4). A second layer of fat tissue was placed in the sphenoid sinus and tissue glue was applied to the fatgraft.

Figure 3

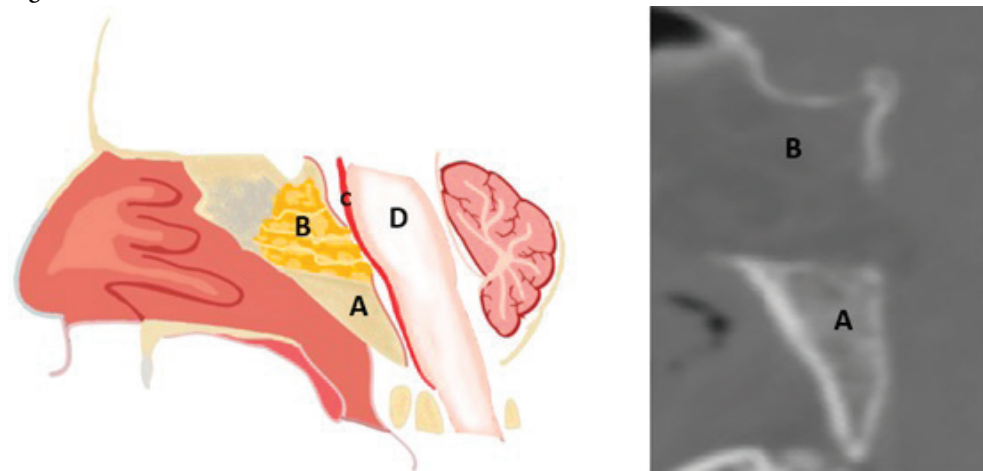


Figure 4

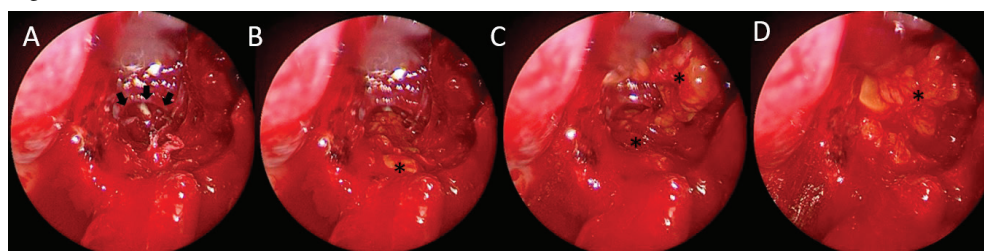


Fig4. Endoscopic view of the clival closure (From case 2)

Arrow tip; dural defect, *; French fries shaped fat tissue

A) After the excision, the surgical route was prepared for fat graft placement through clival drilling.

B) The extracted fat tissue is formed into a shape resembling French fries and placed so that it extends inward from the edges of the defect.

C) The prepared French fries shaped fat grafts are meticulously positioned in multiple orientations, ensuring longitudinal anteroposterior placement.

D) The procedure is repeated until the defect is completely closed.

No intraoperative complications were observed during the surgery in all three cases. The abducens nerve palsy of the first case was resolved in the early postoperative period. In the second case, a CSF leak occurred 4 days after surgery. We applied external lumbar drainage for a short period of time and resolved the leakage. Other than this, all patients had uneventful postoperative recoveries. Postoperative imaging showed no residual tumor. Subsequently, all patients underwent photon radiotherapy, with case 1 and 3 receiving treatment after 3 months and case 2 after 9 months. During the follow-up period of 21 months there were no tumor recurrences or complications requiring reoperation (Figure 5). The total dose of photon therapy was 74 Gy in 37 sessions.

Figure 5

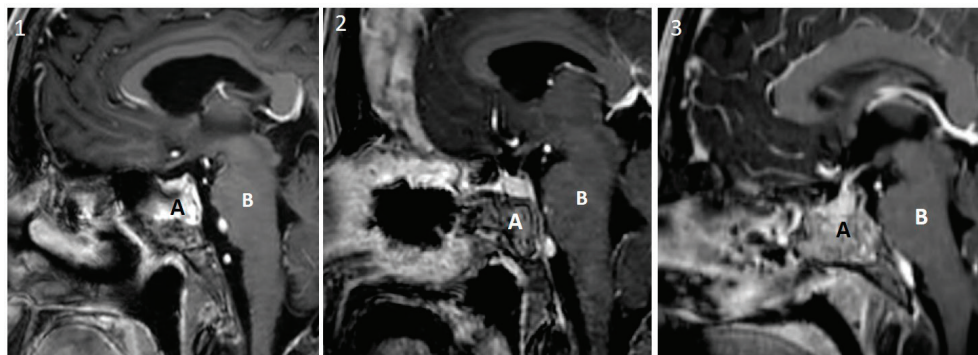


Fig5. 1; Case 1, Post operative 4th month T1 weighted with Gadolinium post-operative magnetic resonance imaging; A) Fat graft, B) Pons

2; Case 2, Post operative 9th month T1 weighted with Gadolinium magnetic resonance imaging; A) Fat graft, B) Pons

3; Case 3, Post operative 2th month T1 weighted with Gadolinium magnetic resonance imaging; A) Fat graft, B) Pons

CONCLUSION

Here, we describe three cases of skull base chordoma surgery in which we applied a rather “simple” and “rapid” method of dural closure using autologous fat tissue only. In our experience, this closure technique was successful, and we decided to implement this approach in our surgical technique for limited defects.

REFERENCES

- 1 Kassam AB, Gardner P, Snyderman C, Mintz A, Carrau R. Expanded endonasal approach: fully endoscopic, completely transnasal approach to the middle third of the clivus, petrous bone, middle cranial fossa, and infratemporal fossa. *Neurosurg Focus*. 2005 Jul;19(1):E6.
- 2 Hadad G, Bassagasteguy L, Carrau RL, Mataza JC, Kassam A, Snyderman CH, et al. A Novel Reconstructive Technique After Endoscopic Expanded Endonasal Approaches: Vascular Pedicle Nasoseptal Flap. *The Laryngoscope*. 2006;116(10):1882–6.
- 3 Zwagerman NT, Wang EW, Shin SS, Chang Y-F, Fernandez-Miranda JC, Snyderman CH, et al. Does lumbar drainage reduce postoperative cerebrospinal fluid leak after endoscopic endonasal skull base surgery? A prospective, randomized controlled trial. *J Neurosurg*. 2018 Oct;1–7.

8

Discussion

DISCUSSION

Skull base surgery has changed over time like other fields in neurosurgery such as functional and vascular neurosurgery due to advances in neurotechnology (i.e. neuroimaging, neuro-monitoring), microscopic and endoscopic surgery and radiation therapy. We have incorporated all these advances in our neurosurgical center including a proton therapy facility. This thesis is a collection of our institutional experience with managing skull base tumors, and this variety in pathologies is also reflected in our management style – a multidisciplinary nature. The previous articles place the described findings into the context of the greater understanding, in this section I will briefly recapitulate the key concepts and discuss future directions that may further advance the field in accordance with current literature and our institutional philosophy.

VESTIBULAR SCHWANNOMA

Upfront planning for a partial resection followed by GK radiosurgery is an effective and safe treatment choice for patients with Koos 4 VS. The efficacy consists of good tumor control and a low number of complications, respectively. Previous large meta-analyses reporting an overall tumor control rate of 93.9% in 248 patients treated with this approach(1). In our series, tumor stability was reported in one patient (4%), shrinkage in 20 patients (87%), and increase in volume in two patients (8%). Interestingly, in our cohort five tumors demonstrated post-radiation growth followed by shrinkage. This means that longer follow-ups may be required. The critical reflection here is whether postoperative radiotherapy should be applied to all residual VS. The answer is no. Wait and scan after surgery and apply radiotherapy when residual tumor shows growth, is nowadays the way to go.

Another key finding in our study was the successful preservation of FN function in all patients. Partial resection of a large VS results in preservation of FN function (even not a HB grade 2 deficit) in most of the patients but leaves a residual tumor (ca. 30% residual tumor). The critical question here is what is worse? A minimal residual tumor but in 10-30% of the patients a FN deficit, or a larger residual tumor and no deficit. My answer is clear; I advise my patients on the second scenario. Residual tumor can be managed effectively by radiation therapy and if necessary, another surgery after several years. But the FN deficit has an immediate and large impact on quality of life.

Future studies should focus on identifying which residual tumors are likely to grow and therefore require early radiosurgery. Specific clinical factors, growth kinetics, and radiomics may help individualize postoperative management (2, 3) . Longer follow-up is also essential to distinguish true progression from temporary post-radiation enlargement. Overall, our findings support a function-preserving, staged treatment philosophy for Koos grade 4 ves-

tibular schwannoma, in which tumor control remains important, but not at the expense of facial nerve function.

SINONASAL CARCINOMA

Patients with sinonasal cancers with skull base extension are a very rare and specific subgroup with a high recurrence rate. Due to an often-late presentation, they present with advanced disease with growth into critical surrounding structures such as the orbit and brain parenchyma. This makes it more difficult to achieve a gross total resection, requiring radiation dosage to the surgical cavity resulting in high dose to nearby healthy tissue. In our study, which includes only stage four sinonasal cancers with skull base extension we report a survival of 50% with a mean follow-up of 49 months. This is comparable with other studies, which also include lower stages (4). Multimodal treatment complications are common and can be severe requiring readmission, reoperation and rehabilitation. We added to currently available cohorts in the literature. The critical reflection here is the retrospective nature of our study. Our study is subject to bias, which means we need to be careful of interpreting causality. Furthermore, the high variability in tumor histology in this cohort makes it difficult to compare the clinical course and outcomes between each pathology.

Another critical reflection is the vulnerability of these patients and as a result being prone to complications. The treatment of high grade, locally advanced sinonasal cancers is accompanied by high rates of complications, morbidity and mortality. In our study, we observed no early wound infection, one meningitis and five late wound infections. Three patients suffered from direct post-operative liquorrhea and one late liquorrhea, none with long-term sequela. Two patients suffered cardiovascular complications. Mortality was 3/18 patients, all complication rates are in line with reports from the literature (5). We observed in 7/14 patients complications following radiotherapy. All wound complications originated post-radiotherapy, most of them needing re-operation. Furthermore, intracranial invasion increases the risk of liquorrhea. In our cohort, all patients had intracranial expansion and were treated with adjuvant radiotherapy, which could explain the high numbers of complications.

Future research should focus on multicentre collaboration to overcome the rarity and heterogeneity of sinonasal cancers with skull base extension. Prospective registries with standardised reporting of tumor histology, radiotherapy dose, complications and patient-reported outcomes are needed. Ultimately, treatment should move towards a more individualized strategy, balancing radical resections with potential complications, postoperative functional status and quality of life.

CHORDOMA

Skull base chordomas comprise one of the rarest pathologies we manage within our institution. Chapter 4 highlights our experience. A notable observation is the poor local control of this tumor, primarily due to the inability to obtain a gross total resection without violating the tumor capsule. This aim is attainable within sacral chordomas, where the surgical corridor is wide enough to maneuver the critical neurovascular structures around the tumor safely in order to remove the tumor *en bloc*. However, due to this challenge, recurrence rates remain common, upward of 50%.

One notable observation is the timing of the recurrences, with our data supporting the concept that early recurrences do not mean uncontrollable tumor. Seven patients in our cohort were long survivors (>10 years). Two of them had a local recurrence within 13 and 17 months but were successfully treated with re-operation only and remained recurrence free thereafter. This suggests that not all early local recurrences mean that the tumor is uncontrollable after primary surgical and radiotherapeutic therapy, and salvage therapy can offer long term control. Here, the importance of close follow-up and multidisciplinary input is vital.

In the attempt of achieving a maximal safe resection, postoperative CSF leakage can be frequently encountered. In our cohort, postoperative CSF leakage was comparable between the endoscopic and trans facial and transcranial approaches; one patient (17%) after endoscopic surgery in comparison with three (15%) after midfacial degloving. Our team developed a dural closure technique for small defects, which is faster and does not require the use of tissue flaps. It incorporates a specific cone shaped surgical cavity in which shards of autologous abdominal fat is applied in layers to cover the defect. This method will be assessed in the future but shows promising results in our practice to prevent post-operative CSF leakage. Larger defects are closed in a standard multilayer technique involving tissue flaps.

The main concern within the management of chordoma is the high recurrences, as seen in the multiple recurrences that our institution has faced. Systemic therapy is extremely limited in chordoma, with the most promising therapy modality being receptor tyrosine kinase pathway inhibitors and immunotherapy, particularly immune checkpoint inhibitors (6, 7). Furthermore, investigation into tumor biology will also improve risk stratification, prognostication, and overall management. Collectively, these developments reflect a broader transition toward biologically driven and personalized multimodal management strategies aimed at improving long-term tumor control and patient outcomes in this challenging disease.

CHONDROSARCOMA

Similar to skull base chordomas, chondrosarcomas remain challenging to treat due to the location and proximity to critical neurovascular structures. As aforementioned in this thesis, chondrosarcomas often originate from the petroclival synchondrosis and are locally invasive and often erode into adjacent bones, including middle fossa, cervical area, and towards the cerebellopontine angle. Recent literature advocates the use of endoscopic endonasal surgical management as it provides an adequate surgical corridor to access these lesions (8). Regardless of the optimization of the surgical management, recurrence rates remain high, as illustrated in chapter 5.

Historically, radical gross total resection was prioritized and seen as the gold standard for managing skull base lesions. However, in the contemporary period, neurological preservation and quality of life have been increasingly prioritized, requiring a multidisciplinary approach. The increasing use of postoperative radiotherapy reflects a broader paradigm shift in skull base oncology toward maximal safe resection combined with adjuvant therapies. Our review favors its use, particularly particle therapy. High-dose particle therapy offers theoretical and practical advantages due to the Bragg peak phenomenon, allowing improved dose conformity and escalation, and limits the radiation exposure to surrounding tissue. However, recent developments in the delivery techniques of photon therapy have made it a viable alternative, certainly for institutes that lack proton therapy facilities.

Beyond surgery and radiotherapy, tumor behavior is also vital to consider in terms of management. Recent studies suggest that histological stratification is important in considering management for conventional skull base chondrosarcomas. Rubino et al. emphasized the importance of avoiding the frequent grouping of grade I and grade II chondrosarcomas, as grade II lesions generally demonstrate a more aggressive biological behavior and significantly higher recurrence risk (9). Similarly, molecular and genetic profiling is increasingly recognized as a promising avenue for refining prognostication and guiding individualized treatment strategies. Key oncogenic pathways implicated in the pathophysiology of skull base chondrosarcoma include IDH1/IDH2 and COL2A1 (10). Agosti et al. conducted a systematic review specifically evaluating targeted therapies for skull base chondrosarcomas, identifying IDH1 inhibitors and PD-1/PD-L1 immune checkpoint inhibitors as the most frequently investigated therapeutic strategies across ongoing clinical trials (11).

Molecularly targeted agents and immunotherapies, including agents such as ivosidenib, pembrolizumab, and pazopanib, have demonstrated favorable antitumoral activity in clinical studies of advanced chondrosarcoma, with median progression-free survival ranging from 5.5 to 19.9 months (11). While these results remain preliminary and largely derived from small or heterogeneous cohorts, they underscore a broader shift toward personalized, molecularly driven treatment strategies. Continued translational research integrating tumor

molecular profiling with clinical outcomes will be essential to refine patient selection and establish targeted therapy as a meaningful component of the multimodal management of skull base chondrosarcoma.

Collectively, surgery remains the cornerstone for treatment, with adjuvant therapy playing a crucial role in preserving neurological and functional status and quality of life. Future research focusing on tumor biology will highlight further dependencies that we can target to improve tumor control.

REFERENCES

1. Starnoni D, Daniel RT, Tuleasca C, George M, Levivier M, Messerer M. Systematic review and meta-analysis of the technique of subtotal resection and stereotactic radiosurgery for large vestibular schwannomas: a “nerve-centered” approach. *Neurosurg Focus*. 2018;44(3):E4.
2. Egiz A, Nautiyal H, Alalade AF, Gurusinghe N, Roberts G. Evaluating growth trends of residual sporadic vestibular schwannomas: a systematic review and meta-analysis. *J Neurooncol*. 2022;159(1):135-50.
3. Gill T, Hamilton D, Rajgor A. The application of radiomics in vestibular schwannomas. *J Laryngol Otol*. 2025;139(8):647-54.
4. Chen MY, Wen X, Wei Y, Chen L, Huang ZX, Lu T, et al. Oncologic outcome of multimodality treatment for sinonasal malignancies: An 18-year experience. *Front Oncol*. 2022;12:958142.
5. Dodhia S, Fitzgerald CWR, McLean AT, Yuan A, Valero Mayor C, Adilbay D, et al. Predictors of surgical complications in patients with sinonasal malignancy. *J Surg Oncol*. 2021;124(5):731-9.
6. Golding R, Abuqubo R, Pansa CJ, Bhatta M, Shankar V, Mani K, et al. Immunologic and Targeted Molecular Therapies for Chordomas: A Narrative Review. *J Clin Med*. 2024;13(19).
7. Banu MA, Raza SM, Amini M, Seaman S, Rubino F, Snyder R, et al. The role of systemic therapy in advanced skull base chordomas: overview of the current state and the MD Anderson protocol. *Neurosurg Focus*. 2024;56(5):E15.
8. Mesquita Filho PM, Ditzel Filho LF, Prevedello DM, Martinez CA, Fiore ME, Dolci RL, et al. Endoscopic endonasal surgical management of chondrosarcomas with cerebellopontine angle extension. *Neurosurg Focus*. 2014;37(4):E13.
9. Rubino F, Zenonos GA, Algattas H, Gardner PA, Fernandez-Miranda JC, Vigo V, et al. Impact of adjuvant radiation therapy on outcomes in grade 2 conventional chondrosarcoma. *J Neurosurg*. 2025;143(5):1406-18.
10. Vuong HG, Ngo TNM, Dunn IF. Prognostic importance of IDH mutations in chondrosarcoma: An individual patient data meta-analysis. *Cancer Med*. 2021;10(13):4415-23.
11. Agosti E, Zeppieri M, Antonietti S, Ius T, Fontanella MM, Panciani PP. Advancing the Management of Skull Base Chondrosarcomas: A Systematic Review of Targeted Therapies. *J Pers Med*. 2024;14(3).

9

Summary

SUMMARY

This thesis describes the experience of our center regarding the treatment of skull base tumors. Skull base tumors are complex, often involved in critical neurovascular structures and leading to substantial health and psychosocial related burden. Treatment is often multidisciplinary and requires experienced skull base dedicated teams to offer optimized management. Treatment may consist of surgical resection, radiotherapy, systemic therapies or a combination. Tumors may be benign or highly malignant and treatment goals may differ between pathologies and patients. This thesis addresses the challenges faced in the treatment of chordoma, vestibular schwannoma, chondrosarcoma and sinonasal cancer.

In **chapter 2** I present our results on the combined approach to treating large Koos IV vestibular schwannoma. It combines a planned partial resection followed by Gamma Knife radiotherapy. Primary outcome is local tumor control and secondly; treatment toleration. This chapter describes excellent tumor control and functional outcome after a combined surgical and radiotherapeutic treatment for large vestibular schwannoma.

In **chapter 3** I present the treatment outcome of patients with cranially extended sinonasal carcinoma. These rare tumors are typically treated using radical resection followed by high dose radiotherapy. It portrays the results of this treatment on tumor control and adverse effects. The chapter concludes that aggressive treatment may lead to prolonged survival, but it often comes at a cost regarding complications and decrease in functional outcome.

Chapter 4 depicts our experience of treating skull base chordoma. This rare and locally aggressive malignancy proves a fierce opponent in many skull base practices. The goal of this study was to evaluate the survival rates in our cohort and compare open vs endoscopic approaches. It additionally describes treatment complications and results of salvage therapies. The chapter concludes that long term survival may not be dependent on early local tumor control failure and salvage therapy may adequately prolong overall survival.

Chapter 5 presents the current evidence on the added value of radiotherapy in the treatment of skull base chondrosarcoma. It depicts the lack of high-quality data, but it may indicate a positive effect on progression free survival when applying particle therapy. This review may guide future decision making for clinicians and demonstrates knowledge gaps for future research endeavors.

Chapter 6 describes a patient with a clival lesion presenting with paroxysmal abducens palsy. The tumor demonstrates growth and regression coupled with the patient's symptoms. Histo-pathology shows a chordoma. This case illustrates the importance of pathological confirmation in uncertain radiological cases, which could aid colleagues in decision making.

The evolution of skull base surgery, as is elaborated on in the previous paragraph, is a continuous process. The goal of decreased morbidity and improved recovery after surgery is always demanding. In our center we developed a simple and rapid technique to close small clival defects without the need for vascularized flaps. In **chapter 7** this is presented in a case series. The aim is to provide surgeons with different options for skull base closure techniques.

In conclusion this thesis describes the various challenges faced in treating complex skull base tumors. Delineating the fine line between curation and neurological preservation and portraying the evolution the specialty has underwent in the last few decades. Future endeavors must focus on further improving individual patient care and exploring tumor behavior both biologically and radiologically.

10

Samenvatting

SAMENVATTING

Dit proefschrift beschrijft de ervaring van ons centrum met betrekking tot de behandeling van schedelbasistumoren. Schedelbasistumoren zijn complex, vaak betrokken bij kritieke neurovasculaire structuren en leiden tot een aanzienlijke gezondheids- en psychosociale belasting. De behandeling is vaak multidisciplinair en vereist ervaren schedelbasis pathologie gespecialiseerde teams om een optimale behandeling te kunnen bieden. De behandeling kan bestaan uit chirurgische resectie, radiotherapie, systemische therapieën of een combinatie hiervan. Tumoren kunnen goedaardig of hooggradig kwaadaardig zijn, en de behandeldoelen kunnen verschillen per pathologie en patiënt. Dit proefschrift behandelt de uitdagingen die gepaard gaan met de behandeling van chordoom, vestibulair schwannoom, chondrosarcom en sinonasale kanker.

In **hoofdstuk 2** presenteer ik onze resultaten van de gecombineerde aanpak voor de behandeling van grote Koos IV vestibulaire schwannomen. Deze aanpak combineert een geplande partiële resectie gevolgd door Gamma Knife-radiotherapie. De primaire uitkomstmaat is lokale tumorcontrole en secundair de behandelverdraagzaamheid. Dit hoofdstuk beschrijft uitstekende tumorcontrole en functionele uitkomsten na een gecombineerde chirurgische en radiotherapeutische behandeling van grote vestibulaire schwannomen.

In **hoofdstuk 3** presenteer ik de behandeluitkomsten van patiënten met craniaal uitgebreide sinonasale carcinomen. Deze zeldzame tumoren worden doorgaans behandeld met radicale resectie gevolgd door hoog gedoseerde radiotherapie. Het hoofdstuk beschrijft de resultaten van deze behandeling op het gebied van tumorcontrole en bijwerkingen. De conclusie luidt dat een agressieve behandeling kan leiden tot verlengde overleving, maar vaak gepaard gaat met complicaties en een afname van functionele uitkomsten.

Hoofdstuk 4 beschrijft onze ervaring met de behandeling van schedelbasis chordomen. Deze zeldzame en lokaal agressieve maligniteit vormt een geduchte uitdaging binnen veel schedelbasiscentra. Het doel van deze studie was het evalueren van de overlevingspercentages binnen ons cohort en het vergelijken van open versus endoscopische benaderingen. Daarnaast worden behandelingscomplicaties en de resultaten van recidief therapieën beschreven. Het hoofdstuk concludeert dat langetermijnoverleving mogelijk niet afhankelijk is van vroegtijdig falen van lokale tumorcontrole en dat recidief therapie de algehele overleving adequaat kan verlengen.

Hoofdstuk 5 presenteert het huidige bewijs voor de toegevoegde waarde van radiotherapie bij de behandeling van schedelbasis chondrosarcomen. Het beschrijft het gebrek aan hoogwaardige gegevens in de huidige literatuur, maar suggereert mogelijk een positief effect op progressievrije overleving bij toepassing van partikeltherapie. Dit review kan toekomstige

besluitvorming door clinici ondersteunen en geeft de kennislacunes weer voor toekomstig onderzoek.

Hoofdstuk 6 beschrijft een patiënt met een clivus laesie die zich presenteerde met paroxismale abducens parese. De tumor vertoont groei en regressie gekoppeld aan de symptomen van de patiënt. Histopathologisch onderzoek toont een chordoom aan. Deze casus illustreert het belang van pathologische bevestiging bij onzekere radiologische bevindingen, wat collega's kan ondersteunen in de besluitvorming.

De evolutie van schedelbasischirurgie, zoals beschreven in de voorgaande paragrafen, is een continu proces. Het streven naar minder morbiditeit en een verbeterd herstel na chirurgie blijft een voortdurende uitdaging. In ons centrum hebben wij een eenvoudige en snelle techniek ontwikkeld om kleine clivus defecten te sluiten zonder gebruik te maken van gevasculariseerde flappen. In **hoofdstuk 7** wordt deze techniek gepresenteerd in een casusreeks. Het doel is chirurgen verschillende opties te bieden voor technieken ter sluiting van schedelbasisdefecten.

Concluderend beschrijft dit proefschrift de uiteenlopende uitdagingen bij de behandeling van complexe schedelbasistumoren. Het schetst het dunne koord tussen curatie en neurologische preservatie en toont de evolutie die het vakgebied in de afgelopen decennia heeft doorgemaakt. Toekomstige inspanningen moeten gericht zijn op verdere verbetering van gepersonaliseerde patiëntenzorg en op het beter begrijpen van tumorgedrag, zowel biologisch als radiologisch.

11

Impact & Valorization

“If I have seen further, it is standing on the shoulders of giants”

– Isaac Newton

Skull base pathologies represent only a small subset of the broader spectrum of neurosurgical diseases encountered in daily clinical practice. Nevertheless, this thesis aims to provide a platform for patients afflicted by these rare and challenging pathologies, who equally deserve optimal long-term oncological outcomes, preservation of neurological function, and quality of life. Despite its rarity, skull base tumors have substantial clinical impact due to their proximity to critical neurovascular structures. Even small lesions may cause impairing symptoms, including visual, hearing-related, swallowing-related and cranial nerve function related problems. The management of skull base tumors therefore extends beyond achieving oncological control alone and requires careful consideration of long-term functional outcomes and patient well-being. This thesis highlights the complexity of treating these rare pathologies and reflects the broader evolution within skull base oncology toward multidisciplinary, technologically advanced, and increasingly individualized treatment strategies aimed at preserving neurological function while optimizing long-term tumor control.

This thesis reflects the importance of multidisciplinary collaboration within modern skull base oncology. The management of complex skull base tumors at the Maastricht University Medical Center+ relies on close cooperation between neurosurgery, otorhinolaryngology, radiation oncology, neuroradiology, pathology, ophthalmology, rehabilitation specialists, and specialized nursing teams. Such collaboration is vital considering the anatomical and pathophysiological complexity of these lesions. Furthermore, the integration of advanced technologies, including endoscopic skull base surgery, stereotactic radiosurgery, modern photon radiotherapy techniques, and proton therapy, has expanded the therapeutic possibilities available to patients within our institution. This thesis also contributes to institutional innovation through the evaluation of novel surgical and reconstructive techniques aimed at reducing treatment-related morbidity, improving recovery, and optimizing long-term functional outcomes. This philosophy was shaped in part by our research efforts depicted in this thesis and the efforts of those that came before me; and will likely be shaped by those that come after me.

The articles published within this thesis will likely also have meaningful scientific impact. Given the rarity and heterogeneity of skull base tumors, high-quality evidence is often limited to small retrospective cohorts and experiences from specialized tertiary referral centers. Consequently, the contribution of institutional experiences remains highly valuable in advancing the collective understanding of these challenging pathologies. The studies presented in this thesis provide long-term follow-up data, analyses of multimodal treatment strategies, complication profiles, and systematic review data, all of which may assist other skull base centers in clinical decision-making and patient counseling. Furthermore, the thesis highlights both the benefits and limitations of contemporary management paradigms, including maximal safe resection, adjuvant radiotherapy, and multidisciplinary care. By critically evaluating treatment outcomes and functional morbidity in rare skull base tumors, this work

contributes to the ongoing international discussion regarding optimization of oncological control while preserving neurological function and quality of life.

Beyond scientific and clinical relevance, this thesis also carries societal value, namely it emphasizes the idea of putting the patient first. Skull base tumors and their treatment can profoundly affect a patient's daily functioning, independence, employability, and overall quality of life. Neurological deficits involving hearing, balance, vision, swallowing, facial nerve function, cognition, and endocrine regulation may result in long-term physical and psychosocial burden. The findings presented throughout this thesis emphasize the growing importance of treatment strategies aimed not only at maximizing oncological control, but also at preserving neurological function and minimizing treatment-related morbidity. This is particularly the case for slow-growing pathologies such as chondrosarcomas and vestibular schwannomas. Furthermore, the recognition of treatment-related complications, rehabilitation needs, and long-term survivorship highlights the necessity of comprehensive multidisciplinary follow-up and patient counseling.

Lastly, this thesis also provides a platform for future research to build further upon. The findings in this thesis have answered some questions and opened up many more. This involves both clinical and translational questions, which, once answered, may impact several facets of skull base tumor management. On the clinical side, focus should be placed on optimizing multimodal treatment strategies, improving complication prevention, and refining long-term functional outcomes. The focus on translational neuro-oncology is steadily increasing within our institution, as many treatment responses and tumor behaviors observed in clinical practices can be attributed to the underexplored biology of these tumors. Continued advances in molecular profiling, targeted therapies, and immunotherapy may contribute to more individualized and biologically driven treatment strategies in the future.

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Dankwoord

DANKWOORD

De totstandkoming van dit proefschrift was niet mogelijk geweest zonder de steun en toewijding van talloze vrienden, familie en collega's. Hieronder volgt een lijst van de meest betrokken personen, maar mijn dank gaat minstens net zo veel uit naar alle anderen die niet bij naam genoemd zijn. Met het slechte nieuws over mijn gezondheid is tot ver boven mijn verwachting steun en liefde mijn kant opgekomen en prijs ik mij zeer gelukkig met al deze fijne mensen om mij heen. Het feit dat ik binnenkort toch dit proefschrift mag verdedigen is alleen maar mogelijk geweest door de hulp van mijn fantastische onderzoeksteam.

Ik kijk uit naar een toekomst waarin mijn gezondheid het toelaat om het leven naar eigen invulling te leven waarin ik zowel privé als professioneel mijn doelen kan bereiken.

Geachte Prof. Dr. Y. Temel, beste Yasin. Mijn eerste kennismaking met jou was op de TV via het programma Topdokters, dit was nog voor ik besloot te solliciteren voor de ANIOS-positie in 2020. Die aflevering heeft mij en vele anderen een indrukwekkend inzicht gegeven in jou als mens en dokter. Je wekte bij mij direct de indruk dat ik mij thuis zou voelen in jouw team. Ik was dus ook zeer verheugd dat ik werd aangenomen als arts-assistent. Nadat ik in 2022 werd aangenomen voor de opleiding, gingen we het avontuur samen aan van een klinisch promotietraject op schedelbasistumoren. Een avontuur met vele hoogtepunten en nog meer leermomenten. Ik heb het voorrecht jou mijn mentor te kunnen noemen, op professioneel, academisch, maar ook persoonlijk vlak. Max, ben je in balans? Vroeg je dikwijls, terwijl ik weer met een vermoeid hoofd de ochtendoverdracht presenteer. Jouw vermogen om individuen te inspireren, een groep te laten floreren en toch zelf betrokken te blijven is ongeëvenaard. Nu dit jaar het promotietraject afgerond mag worden kijk ik terug op hele mooie, bijzondere jaren in onze onderzoeksgroep. Yasin, dat jij in mij jouw opvolger ziet is het grootste compliment dat je mij kan geven. Ik ben je zeer dankbaar voor al je steun, mentorschap en vriendschap in voor- en tegenspoed.

Geachte Dr. K.E. Hovinga, beste Koos. Onze relatie heeft zich over de afgelopen jaren sterk ontwikkeld. Vooral de afgelopen 2 jaar ben jij een steunpilaar geweest in mijn persoonlijke begeleiding. Ik waardeer onze wandelingen en gesprekken enorm, en deze hebben mij dikwijls door moeilijke periodes geholpen. Ik complimenteer je nuchtere nuances in lastige situaties en je eerlijkheid in de kwetsbare. Je zou een fantastische opleider kunnen zijn als je het zou willen! Koos ik dank je zeer voor al je hulp en mentorschap de afgelopen jaren.

Geachte Prof. Dr. H.P.M. Kunst, beste Dirk. Hoogleraar in de verbinding zou een goede tweede leerstoel kunnen zijn. Inspirerend hoe jij groepen kan motiveren de samenwerking op te zoeken en verder te groeien. Jouw inzet voor de Europese schedelbasisvereniging is ongeëvenaard en heeft de groei van de afgelopen jaren kunnen bewerkstelligen. Ik waardeer de rust en nuancering in onze discussies over onderzoek ideeën en hoe we onze patiëntenzorg

moeten optimaliseren. Ik ben heel dankbaar voor jouw begeleiding en jouw voorbeeldrol als verbinder de afgelopen jaren.

Geachte leden van de beoordelingscommissie: Prof. Dr. H. van Santbrink, Prof. Dr. M. Bruneau, Prof. Dr. C.M.F. Dirven, Dr. P.C.M. Ackermans. Ik dank u voor uw tijd en inzet om dit proefschrift te beoordelen en deel te nemen in mijn oppositie. Ik kijk uit naar een inspirerende dialoog.

Aan mijn opleiders: dr M. Ter Laak-Poort, dr. J. van Aalst, beste Mariel, beste Jasper. Ik vind het moeilijk om de juiste woorden te vinden in z'n korte paragraaf om mijn dank uit te spreken richting jullie. De relatie tussen opleiders en AIOS is er bij jullie altijd één geweest met de diepte van een ouder met zijn kinderen. Jullie betrokkenheid voor ons welzijn en ontwikkeling is denk ik ongeëvenaard binnen de neurochirurgie. Ik ben heel blij dat wij elkaar ook op meer persoonlijk vlak hebben mogen leren kennen en dat er zoveel meer buiten het werkleven belangrijk is. Jullie liefde en support nu het met mijn gezondheid minder gaat is heel waardevol en helpt mij erdoorheen. Ik kijk uit naar verbetering en het vervolmaken van de opleiding.

Aan de voltallige vakgroep neurochirurgie: Toen ik in 2020 tijdens COVID voor het eerst kennis mocht maken met jullie, viel mij op hoe saamhorig en zorgzaam jullie waren. De ontvangst was uitstekend, ik voelde me gelijk thuis. Het was pas een hele tijd later dat ik leerde hoezeer jullie geïnvesteerd hebben in de vakgroep om tot dit resultaat te komen na een zware periode. Jullie fundament is robuust omdat het uitstraalt naar alle andere werknemers die jullie cultuur verder uitdragen. Ik ben jullie gaan beschouwen als mijn tweede familie en nu in deze periode is dat alleen maar versterkt en bevestigd. Ik dank jullie allen voor het vertrouwen in mij als persoon en de liefde die ik van jullie mag ontvangen als mens.

Aan mijn paranimfen: Rick en Lars. Mijn partners in crime sinds het eerste uur in het MUMC+ en nu aan mijn zijde tijdens het hoogtepunt van mijn carrière, daar ben ik zeer dankbaar voor. Rick, je was de allereerste assistent die ik mocht ontmoeten, je zat in je stage jaar bij de neurologie en had derhalve voldoende tijd om een kop koffie met me te kunnen drinken en mij de afdelingen te laten zien;). Toch was dat gebaar al voldoende om mij te laten inzien dat je een mens bent met een groot sociaal hart en altijd je wil inzetten voor je medemens. Ik ben van je gaan houden als een broer en nu we allebei een jonge dochter hebben is deze band alleen maar versterkt. Ik haal inspiratie uit je liefde voor de neurochirurgie en ik wens jou en je gezin al het goeds voor de toekomst. Lars, wij waren chef Heerlen in jouw 3^e opleidingsjaar en dat klikte direct, hoe kan het ook anders met jouw sprankelende karakter. Je hebt me op sleeptouw genomen en mij thuis voelen begon direct. De heerlijke BBQ's bij jullie thuis, LEGO sets discussiëren en samen met Rick Age of Empires spelen kenmerken die eerste jaren. Ik ben heel blij dat we nog steeds veel in contact zijn en dat we elkaars gezinnen zien opgroeien. Ook jij bent een grote broer van me geworden waar ik van houd. Je onver-

moeibaarheid en enthousiasme voor alle mooie dingen in het leven zijn een heerlijkheid. Ik hoop van harte dat jij en je prachtige gezin een gezonde en gelukkige toekomst gaan hebben. Lieve Rick en Lars, jullie aanwezigheid op mijn vrijgezellenfeest en nu op mijn promotie zijn herinneringen die ik koester en met veel geluk op terugkijk. Dank voor alles.

Aan mijn mede assistenten: Inge, Valérie, Maarten, Roos, Hanna, Caspar, Shabnam, Bianca, Celine, Camille, Hicham, Chiara.

Hier begint het moeilijkste gedeelte, want er kan een heel 2^e proefschrift geschreven worden over alle avonturen waar we samen op terug kunnen blikken. Ik ga het dus maar bij een korte samenvatting houden, voor de details moet je me maar komen opzoeken. Allerliefste collega's, jullie zijn mijn vrienden. Ik dank jullie voor alle inzet, moeite en energie die jullie gestoken hebben om dit kleine team draaiende te houden in rumoerige tijden. Het was vaak uitdagend en meestal onmogelijk, maar toch op de een of andere manier weten jullie het altijd weer op te lossen. Dat is een groot goed. Ik kijk terug op fantastische AIOS dagen, assistentenweekenden en skireizen. Herinneringen voor het leven. Lieve vrienden, blijf in contact met elkaar, blijf elkaar helpen en geniet ook onderweg van de rit. Dank voor alles.

Aan de PA's Luc en Rick: Mijn steun en toeverlaat en mijn grootste uitlaatkleppen. Ieder in zijn eigen toko vormen jullie de kern van de afdeling. De routine waar we op terug kunnen vallen. Er zijn veel ouwe mannen gesprekken geweest de afgelopen jaren, over de zin en onzin van het leven. Hier ben ik zeer dankbaar voor. Lieve Rick, dank voor alle steun en gezelligheid de afgelopen jaren, geniet van je prachtige gezin en ik wens jullie al het goeds in de toekomst. Lieve Luc, in al je complexiteit ben je gelukkig heel eenvoudig, namelijk een puur mens met een groot hart. Ik waardeer je eerlijkheid en kwetsbaarheid. Blijf trouw aan jezelf en heb vertrouwen in de groep. Super dat je een plant naar me hebt vernoemd, oprecht ontroerend! Dank voor alles en ik wens jou en gezin al het goeds voor de toekomst.

Aan de leden van The Group: Pawan, Cheng, Denzel, Esmée, Daniel.

Lieve vrienden van de wetenschap. In de loop der jaren zijn we steeds groter en hechter geworden en gegroeid tot een volwaardige onderzoeksgroep en vriendengroep. Special shoutout to Cheng and his famous hotpot! Ik weet zeker dat dit proefschrift er zonder jullie niet zou zijn geweest. Jullie steun en hulp is onvoorwaardelijk gebleken en daar ben ik zeer dankbaar voor. Ik kijk terug op prachtige congressen en publicaties en gezellige avonden. Dank voor alles.

親愛的程，謝謝你的友誼和愛。祝你未來一切順利。

Aan de secretariaten van het MUMC+ en het Zuyderland.

Lieve dames en heer, jullie zijn de definitie van een secretariaat. Altijd opzoek naar de oplossing, onvermoeibaar en immer goed gemutst. Jullie hebben mij dikwijls door de problemen heen gesleept en daar ben ik jullie zeer dankbaar voor. Speciale dank aan Monique van Tillo, onze lieve tante van de opleiding, heel veel dank voor al je hulp de afgelopen jaren, je bent onmisbaar.

Aan de verpleegafdelingen D5, C5, MC5, afdeling 11 en de BCU

Voor onze zorghelden aan het front. Dank voor jullie tomeloze inzet, onvermoeibare glimlach voor onze patiënten en het ondergaan van mijn nachtelijk chagrijn (sorry daarvoor). Zonder jullie zijn wij allemaal nergens. Dank voor alles.

Aan de operatieverpleegkundigen MUMC en Zuyderland

Het hart van onze chirurgische tak. Jullie expertise, hulp en geduld zijn allemaal van essentieel belang geweest voor mijn opleiding de afgelopen jaren. Daarnaast zijn jullie ook allemaal ontzettend lieve en betrokken mensen. Ik waardeer het enorm dat ondanks dat er soms maanden tussen wederzien zitten, jullie blijven onthouden wat er speelt en mij op persoonlijk vlak blijven kennen. Op de OK zijn met jullie voelt als thuiskomen. Dank voor alles.

Aan mijn maatjes van het Heerendispuut de NUL en in het bijzonder lichting '13: Timo, Arnout, Rik, Ruben. Ik heb dit dispuut vanaf de grond opgebouwd mogen zien worden en in de loop van 15 jaar is het uitgegroeid tot een groot succes. Het dispuut leeft, organiseert prachtige activiteiten en waardeert de historie. Dank voor jullie broederschap en steun.

Mannen van het 13^e. Te lang hebben we elkaar niet meer gezien en gesproken, meegesleurd door de tsunami van het leven. Toch koester ik onze vriendschap nog altijd en kijk ik terug op mooie jaren met jullie als student. Lieve Timo, gelukkig zijn wij nog altijd close, meer waarschijnlijk nog dan tijdens onze studententijd. We zijn wijs geworden;). Nu met een prachtige vrouw en 2 dochters lacht het leven jullie toe. Ik hou van je en ik dank je voor je vriendschap.

Aan mijn oud collega's van het Schneyzael Genootschap en in het bijzonder Prof. Dr. G-J Kleinrensink, beste Gert-Jan, mijn surrogaat vader.

Lieve maatjes, in 2013 trad ik toe tot het studentensnijzaalteam. Een beslissing die zonder twijfel de grootste persoonlijke ontwikkeling in mijn leven teweeg heeft gebracht. Bij jullie voel ik me thuis en dat deed mij opbloeien. Er ontstond een kameraadschap die maar zelden in teams gevormd wordt. Niet lullen, maar poetsen, handen uit de mouwen, geen woorden maar daden. Ze kwamen allemaal langs. Het leven raast verder en het contact verminderde, maar door recente gebeurtenissen word ik herinnert aan onze vriendschap en jullie liefde

en steun bleek onverminderd. Heel veel dank voor alles. Lieve Gert-Jan, jouw rol als pater Anatomicus voor onze groep en mij in het bijzonder is een heel speciale. Jouw vermogen om van een groep individuen een collectief te maken met onvermoeibaar enthousiasme en passie is ongeëvenaard. Je brede glimlach onder een nog bredere snor straalde immer vertrouwen uit. Deze band koester ik ten zeerste, en vele met mij. Ik ben dankbaar dat na al die jaren, die band minstens zo warm is gebleven en ik kijk uit naar ons wederzien op de verdediging. Gert-Jan ik hou van jou als een vader, heel veel dank voor alles.

Mijn oud collega's uit Rotterdam: Wouter, Marit, Oscar, Kennedy, Bibi, Anne, Jasper, Victor, John, Rutger, Dafna, Nadine, Sandra en alle stafleden. Ik kijk met veel plezier terug aan mijn eerste voetstappen binnen dit prachtige vak in het Erasmus MC. De leercurve was stijl en de dagen lang. Maar dankzij jullie hulp heb ik die 1,5 jaar toch overleefd. De bemoedigende woorden van Oscar: "enjoy the ride" voor mijn eerste nachtdienst blijven ronddwalen ergens in de donkere gangen richting de piketkamer. Dank voor jullie vriendschap en steun.

Aan de geneeskunde vrienden van het eerste uur, Joppe, Milan en Calvin. Het is spijtig dat de jaren en afstand ons uit elkaar heeft doen groeien, toch wil ik bij deze mijlpaal stilstaan bij het allereerste begin: eurekaweeke 2011. Genesis. Zonder baard en met een alcoholtolerantie van 1,5 biertje begonnen we samen aan ons studentenavontuur. Dat eerste jaar bestond uit barcommissie, ME-gala, BEEST-feesten en af en toe een tentamen. Het was magistraal. We hebben samen enorm veel avonturen meegemaakt; met baldadige Joppe en de achtervolging door een Ford Fiesta door de binnenstad van Rotterdam als hoogte- of dieptepunt afhankelijk van het perspectief. Maatjes, ik dank jullie voor jullie vriendschap en ik wens jullie al het goeds voor de toekomst.

Aan mijn schoonfamilie: Lieve Jur en Esther, sinds dag 1 zijn jullie mijn nieuwe broer en zus gebleken, ik waardeer jullie nuchterheid, liefde voor spelletjesavond en droge humor. We zien elkaar wat weinig in dit hectische leven, maar ik kijk jaarlijks uit naar de immer gezellige kerstavonden samen. Ik wens jullie al het goeds voor de toekomst.

Lieve Herman en Anja, lieve paps en moeders. Ik ben zeer dankbaar met jullie als schoonouders, lief, betrokken, zorgzaam en gewoon normaal. De energie die jullie de afgelopen jaren in ons gezin hebben gestoken om ons te helpen waar nodig ben ik eeuwig dankbaar voor. Ik hou ontzettend veel van jullie en ik wens jullie al het goeds in de toekomst.

Mijn lieve broers Redmer, Arthur, Pim. Zo verschillend als dat we zijn zo goed kunnen we op elkaar lijken. Juist deze dynamiek vind ik onze grote kracht. Jullie zijn allemaal succesvol geworden in jullie dromen en daar kan ik ontzettend van genieten. De afgelopen jaren zijn we tot mijn grote vreugde nog verder naar elkaar gegroeid. De wintersporten, game avonden en borrels bij de Kaasbar en Gouverneur zijn graag geziene activiteiten en ik ben blij dat jullie

te allen tijde aanwezig waren op de hoogtepunten van mijn leven. Ik hou zielsveel van jullie en ik wens jullie al het geluk en gezondheid voor de toekomst.

Mijn lieve ouders Koos en Astrid. Onvoorwaardelijk, zo blijkt maar weer de liefde tussen ouder en kind. Tijdens de beste en de slechtste momenten, jullie staan altijd naast mij. Ik ben jullie eeuwig dankbaar voor de kansen die jullie mij geschonken hebben om mijn leven te maken zoals hij nu is. Volmaakt. Al mijn dromen zijn uitgekomen, opleiding, carrière, relatie, dochter, dankzij jullie hulp. En nu de toekomst zwartgallig is veranderd, staan jullie daar weer, aan mijn zijde tot het bitterzoete einde. Lieve papa en mama, ik hou van jullie met heel mijn hart, voor altijd.

Mijn allerliefste vrouw Isa. Geen woorden in deze paragraaf kunnen de diepgang van onze relatie en mijn liefde voor jou beschrijven. Inmiddels kennen we elkaar 10 jaar en ik ga elk jaar meer van jou houden. Het begin van onze studenten kalverliefde tot aan het ouderschap met onze prachtige Mila, het was allemaal perfect. We hebben veel mooie en emotionele momenten samen mogen delen en ik had met niemand anders dit pad willen bewandelen. Hoogtepunten zoals onze trouwdag, de reis naar Canada, de geboorte van Mila zijn de gelukkigste momenten uit mijn leven en jij was er telkens bij. Ik ben beretrots op jou; je doorzettingsvermogen, je onuitputtelijke liefde, zorgzaamheid en geduld voor Mila en mij en dat allemaal verpakt in een wonderschone vrouw. Ik prijs mij de gelukkigste man op aarde met jou aan mijn zijde, voor altijd. Lieve Isa, ik hou van jou met heel mijn hart.

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Curriculum Vitae

Curriculum Vitae

Max Keizer is geboren op 12 oktober 1993 te Eindhoven. Gedurende zijn jeugd heeft hij met veel plezier gehockeyd en viool gespeeld. Max heeft zijn tweetalig vwo-diploma behaald in 2011 aan het Stedelijk College te Eindhoven. Hij is hierna geneeskunde gaan studeren aan de Erasmus Universiteit in Rotterdam, waar hij in 2018 afstudeerde met een dubbel master geneeskunde en neurowetenschappen. Naast zijn studie is Max actief geweest in verschillende commissies binnen de geneeskunde faculteit en is hij betrokken geweest bij de oprichting van een geneeskundig Heerendispuut. Zijn interesse voor de (neuro)anatomie kwam tot leven toen hij toetrad tot het studenten snijzaalteam onder de bezielende begeleiding van Prof. Dr G-J Kleinrensink in 2013. Hier heeft hij in de jaren daaropvolgend zich ontwikkeld in het geven en ontwikkelen van anatomieonderwijs en het prepareren van hoofd-hals anatomie preparaten. Zodoende is de interesse in de neurochirurgie ontstaan en na een succesvol oudste coschap op de afdeling neurochirurgie is Max arts-assistent geworden bij het neurochirurgisch team in het Erasmus MC. Na anderhalf jaar met veel plezier daar gewerkt te hebben heeft hij de stap gemaakt naar het MUMC+ te Maastricht in 2020. In 2022 is hij aldaar begonnen aan een gecombineerd opleidingstraject tot neurochirurg en een promotietraject met het onderwerp schedelbasistumoren. Dit onderzoek is afgerond in 2026 en zal op 23 juni verdedigd worden. De opleiding tot neurochirurg is op het moment van schrijven tot nader order stilgezet vanwege ziekteverlof en wordt hopelijk spoedig hervat.

Naast zijn professionele leven is Max zeer gelukkig met zijn fantastische vrouw Isa Zuiderduijn-Keizer waarmee hij op 5 september 2024 is getrouwd. Zij hebben het geluk gehad om een jaar later op 15 september 2025 hun mooiste cadeau te mogen verwelkomen; een gezonde, vrolijke en karaktervolle dochter Mila. Naast het vaderschap speelt Max fanatiek golf en kan hij genieten van een mooi Lego pakket en een prachtige wintersport afgesloten met een biertje op een zonnig terras.

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List of publications

LIST OF PUBLICATIONS

Gravesteyn BY, Keizer ME, Vincent AJPE, Schouten JW, Stolker RJ, Klimek M. Awake craniotomy versus craniotomy under general anesthesia for the surgical treatment of insular glioma: choices and outcomes. *Neurol Res.* 2018 Feb;40(2):87-96. doi: 10.1080/01616412.2017.1402147. Epub 2017 Nov 23. PMID: 29168669.

Keizer ME, Kunst HPM, Temel Y. Skull Base Tumors: The Equilibrium between Curation and Preservation. *Cancers (Basel).* 2023 May 19;15(10):2829. doi: 10.3390/cancers15102829. PMID: 37345166; PMCID: PMC10216195.

Keizer ME, Hovinga KE, Lacko M, Eekers DBP, Baijens LWJ, Kremer B, Temel Y. Clinical Outcome in Patients with Large Sinonasal Tumors with Intracranial Extension. *J Neurol Surg B Skull Base.* 2023 May 24;85(4):347-357. doi: 10.1055/a-2082-4951. PMID: 38966298; PMCID: PMC11221902.

Ravindran PK, Keizer ME, Kunst HPM, Compter I, Van Aalst J, Eekers DBP, Temel Y. Skull-Base Chondrosarcoma: A Systematic Review of the Role of Postoperative Radiotherapy. *Cancers (Basel).* 2024 Feb 21;16(5):856. doi: 10.3390/cancers16050856. PMID: 38473218; PMCID: PMC10931115.

Van Lanen RHGJ, Keizer ME, Ter Laak-Poort MP, Herrler A, Poort LJ, Schijns OEMG. 3D printed headholder for use in neurosurgical cadaver training: Technical note. *Brain Spine.* 2024 Aug 6;4:102906. doi: 10.1016/j.bas.2024.102906. PMID: 39220412; PMCID: PMC11365292.

Yang C, Alvarado D, Ravindran PK, Keizer ME, Hovinga K, Broen MPG, Kunst HPM, Temel Y. Untreated Vestibular Schwannoma: Analysis of the Determinants of Growth. *Cancers (Basel).* 2024 Nov 4;16(21):3718. doi: 10.3390/cancers16213718. PMID: 39518155; PMCID: PMC11545831.

Bosman EM, Keizer ME, van Aalst J, Broen MPG, Postma AA, Vernemmen AIP, Kunst HPM, Temel Y. Spontaneous Shrinking and Growing Skull Base Chordoma. *J Neurol Surg Rep.* 2025 May 9;86(2):e107-e111. doi: 10.1055/a-2587-6573. PMID: 40352577; PMCID: PMC12064314.

Yang C, Alvarado D, Ravindran PK, Keizer ME, Hovinga K, Broen MPG, Eekers D, Compter I, Kunst HPM, Temel Y. Predictors of Growth of Vestibular Schwannoma After Gamma Knife Treatment: A Systematic Review. *Cancers (Basel).* 2025 Jun 14;17(12):1993. doi: 10.3390/cancers17121993. PMID: 40563642; PMCID: PMC12191170.

Al-Ahmari M, Keizer M, Al-Dhafery B, Eekers D, Hovinga K, Kunst H, Temel Y. Tumour Shrinkage and Good Facial Nerve Function After Planned Partial Resection and Gamma Knife Radiosurgery in Koos 4 Vestibular Schwannoma. *Turk Neurosurg.* 2025;35(2):265-273. doi: 10.5137/1019-5149.JTN.46381-24.1. PMID: 40129205.

Yang C, Alvarado D, Ravindran PK, Keizer ME, Hovinga K, Broen MPG, Kunst HPM, Temel Y. MRI-Based Prediction of Vestibular Schwannoma: Systematic Review. *Cancers (Basel).* 2026 Jan 17;18(2):289. doi: 10.3390/cancers18020289. PMID: 41595208; PMCID: PMC12838792.

Keizer ME, Ravindran PK, Yang C, Kunst D, Eekers D, Compter I, Hovinga K, van Aalst J, Temel Y. Clinical Outcomes in Skull Base Chordoma, a Single-Center Experience (submitted 2026)

Genc B, Keizer ME, van Aalst J, Kunst H, Temel Y. A Simple and Rapid Skull Base Reconstruction After Endoscopic Clival Surgery: A Technical Note. (submitted 2026)

Cheng Yang, Hengjian Liu, Daniel Alvarado, Pawan Kishore Ravindran, Max E. Keizer, Koos Hovinga, Henricus P. M. Kunst and Yasin Temel. A Voxel-Wise Spatial Analysis of Tumor Locations in Skull Base Meningiomas: Association with Long-term Tumor Control Rates (submitted 2026)

Pawan Kishore Ravindran, Govert Hoogland, Max E. Keizer, Jasper van Aalst, Henricus P.M. Kunst, Koos Hovinga, Yasin Temel. Chordoma biology: genetic alterations, signaling pathways and the tumor microenvironment – a narrative review (submitted 2026)

Pawan Kishore Ravindran, Max E. Keizer, Zeynep Erdem, Henricus P.M. Kunst, Koos E. Hovinga, Jasper van Aalst, Yasin Temel. Recurrent dedifferentiated clival chondrosarcoma: a case report (submitted 2026)

