

Skull base chondrosarcoma

Review Article

William M. Mendenhall^{1,*}, Stephen B. Lewis², Douglas B. Villaret³, and Nancy P. Mendenhall¹

¹Radiation Oncology Department

²Neurosurgery Department

³Otolaryngology Department, University of Florida College of Medicine, Gainesville, Florida

***Correspondence:** William M. Mendenhall, M.D., Department of Radiation Oncology, University of Florida Health Science Center, P.O. Box 100385, Gainesville, FL 32610-0385; Telephone: (352) 265-0287; Fax: (352) 265-0759; e-mail: mendewil@shands.ufl.edu

Key words: Chondrosarcomas, Base of skull, Radiotherapy, Proton radiotherapy, Treatment outcomes

Abbreviations: American Joint Committee on Cancer, (AJCC); cobalt gray equivalents, (CGE); Computed tomography, (CT); epithelial membrane antigen, (EMA); loss of heterozygosity, (LOH); magnetic resonance imaging, (MRI); radiotherapy, (RT); retinoblastoma, (Rb)

Received: 18 November 2004; revised: 6 December 2004

Accepted: 7 December 2004; electronically published: January 2005

Summary

The purpose of this paper is to discuss the natural history, optimal treatment, and outcomes for skull base chondrosarcomas. The pertinent literature was reviewed. The majority of skull base chondrosarcomas are low grade and exhibit an indolent growth pattern. A small subset of patients present with mesenchymal or dedifferentiated chondrosarcomas and have a poor prognosis. Although extensive skull base resections may result in long disease-free survival, the likelihood of a complete resection with negative margins is low, and the permanent morbidity of these operations is significant. Proton radiotherapy after subtotal resection or biopsy results in a high rate of cure with a relatively low probability of late complications. The preferred treatment for skull base chondrosarcomas is proton radiotherapy alone or combined with less aggressive surgical procedures.

I. Introduction

Chondrosarcoma is a relatively rare tumor that may arise in any bone that is preformed by cartilage (Brown et al, 1994). It accounts for 11% to 19% of all primary bone tumors and may arise de novo or in preexisting conditions including Paget's disease, enchondromas, osteo-cartilaginous exostoses, Ollier's disease, and osteochondromas (Brown et al, 1994). Skull base chondrosarcomas usually arise de novo and account for approximately 0.15% of all intracranial tumors (Brown et al, 1994; Crockard et al, 2001). Approximately 75% of chondrosarcomas occur in the trunk, femur, or humerus, 5% to 12% arise in the head and neck, and roughly 1% are found in the skull base (Brown et al, 1994). The majority of skull base chondrosarcomas arise in synchondroses near the temporooccipital junction (Rosenberg et al, 1999; Raghu et al, 2004). Rosenberg et al, (1999) reported on 200 patients treated at the Massachusetts General Hospital (Boston) for skull base chondrosarcomas and observed the following site distribution: temporooccipital, 66%; clivus, 28%; and sphenothmoid complex, 6%.

Skull base chondrosarcomas exhibit a roughly equal gender distribution and a wide age range. (Korten et al,

1998; Hug et al, 1999; Rosenberg et al, 1999). Rosenberg et al, (1999) observed a 1:1.3 male to female ratio and an age range of 10 to 79 years (mean, 39 years). Korten et al, (1998) reported on 15 patients with skull base chondrosarcomas treated in the Netherlands, and 177 patients reported in the literature and observed a 1:1.1 male to female ratio and an age range of 3 months to 76 years (mean, 37 years).

Patients often present with cranial nerve deficits (usually the abducens nerve), headaches, and symptoms related to temporal bone invasion (Volpe et al, 1993; Korten et al, 1998; Crockard et al, 2001; Raghu et al, 2004). Korten et al, (1998) reported the following presenting symptoms: oculomotor dysfunction, 51%; headaches, 31%; and diminished hearing, dizziness, and tinnitus, 21%. Volpe et al, (1993) evaluated the neuroophthalmologic findings in 48 patients with skull base chordomas and 49 patients with skull base chondrosarcomas and observed abnormal visual examinations in 67% and 94%, respectively. The duration of symptoms before presentation is variable. Korten et al, (1998) observed a range of 1 month to 12 years (mean, 27 months; median, 15 months).

II. Pathology

Chondrosarcomas may be stratified as conventional, mesenchymal, and dedifferentiated and are graded based on cellularity, nuclear pleomorphism, and mitotic activity (Brown et al, 1994). In contrast to conventional chondrosarcomas, mesenchymal, and dedifferentiated chondrosarcomas exhibit aggressive behavior and portend a poor prognosis (Brown et al, 1994).

Conventional chondrosarcomas are composed of round or oval cartilaginous cells with single or multiple nuclei and may contain myxoid changes, calcifications, and/or ossification (Brown et al, 1994; Rosenberg et al, 1999). Mesenchymal chondrosarcomas are composed of islands of cartilage and sheets of undifferentiated small stromal cells with hyperchromatic nuclei (Brown et al, 1994). Differentiated chondrosarcomas exhibit anaplastic foci within a low-grade cartilaginous matrix (Brown et al, 1994).

Korten et al, (1998) observed the following histologic distribution: grade 1, 51%; grade 2, 11%; mesenchymal, 30%; and myxoid, 8%. The following grade distribution was reported by Rosenberg et al, (1999) in 200 patients with conventional chondrosarcomas: grade 1, 50.5%; mixed grade 1 and grade 2, 28.5%; and grade 2, 21%.

Chondrosarcomas must be distinguished from chondroid chordomas that tend to behave more aggressively and have a worse prognosis. Rosenberg et al, (1999) observed that 96 of 97 chondrosarcomas (99%) stained positively for S-100; none exhibited keratin positivity. Seven of 88 patients (8%) stained faintly for epithelial membrane antigen (EMA) (Rosenberg et al, 1999). Ishida and Dorfman, (1994) analyzed 9 patients with skull base chondrosarcomas and 7 patients with skull base chondroid chordomas and found that chondrosarcomas did not stain for cytokeratin or EMA,

whereas chondroid chordomas stained positively for both. Eisenberg et al, (1997) analyzed loss of heterozygosity (LOH) of the retinoblastoma (Rb) gene (a tumor suppressor gene found in a number of malignancies) in 7 patients with skull base chordomas and 2 patients with skull base chondrosarcomas. Two of 7 chordomas exhibited LOH compared with 0 of 2 chondrosarcomas; both chordomas with LOH behaved very aggressively (Eisenberg et al, 1997).

III. Diagnostic evaluation

Computed tomography (CT) and magnetic resonance imaging (MRI) are employed to evaluate the primary tumor; chest CT should be obtained in patients with poorly differentiated tumors.

CT generally demonstrates a lytic lesion and is used to demonstrate the extent of bone invasion and tumor mineralization (Brown et al, 1994; Crockard et al, 2001; Maleuz et al, 1996). Contrast-enhanced CT often shows moderate enhancement (Maleuz et al, 1996).

MRI is useful to demonstrate the soft tissue extent of the tumor. T1-weighted gadolinium DTPA enhanced MRI shows a hyperintense mass in the portions of the tumor that are non-calcified; the calcified part of the tumor exhibits a mixture of hypo- and hyperintensity (Maleuz et al, 1996). T2-weighted contrast-enhanced MRI reveals a hyperintense tumor with areas of inhomogeneity corresponding to the calcified portions of the mass (Maleuz et al, 1996).

IV. Staging

Patients are staged according to the recommendations of the American Joint Committee on Cancer (AJCC) (2002) staging system (**Table 1**).

Table 1. American Joint Committee on Cancer Staging System, 2002

DEFINITION OF TNM

Primary Tumor (T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor 8 cm or less in greatest dimension
T2	Tumor more than 8 cm in the greatest dimension
T3	Discontinuous tumors in the primary bone site

Regional Lymph Nodes (N)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis

Distant Metastasis (M)

MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis
M1a	Lung
M1b	Other distant sites

Stage Grouping

Stage 1A	T1	N0	M0	G1, 2 Low grade
Stage 1B	T2	N0	M0	G1, 2 Low grade
Stage IIA	T1	N0	M0	G3, 4 High grade
Stage IIB	T2	N0	M0	G3, 4 High grade
Stage III	T3	N0	M0	Any G
Stage IVA	Any T	N0	M1a	Any G
Stage IVB	Any T	N1	Any M	Any G
	Any T	Any N	M1b	Any G

Histologic Grade (G)

GX	Grade cannot be assessed
G1	Well differentiated - Low grade
G2	Moderately differentiated - Low grade
G3	Poorly differentiated - High grade
G4	Undifferentiated - High grade

V. Treatment

The treatment of skull base chondrosarcoma is controversial and varies from skull base resection alone or combined with conventional radiotherapy (RT) or charged particle RT to less aggressive operations combined with proton RT (Ruark et al, 1992; Stapleton et al, 1993; Gay et al, 1995; Berson et al, 1988; Hug et al, 1999; Rosenberg et al, 1999; Crockard et al, 2001). There are few data pertaining to the efficacy of stereotactic radiosurgery (Muthukumar et al, 1998). It is difficult to compare the outcomes of various treatment strategies because skull base chondrosarcomas are uncommon, the majority are low grade and exhibit an indolent growth pattern, and the outcomes data are sometimes combined with those of chordomas which have a more unfavorable prognosis.

VI. Local-regional control and survival**A. Surgery**

Stapleton et al, (1993) reported on 8 patients with skull base chondrosarcomas treated surgically at Atkinson Morley's Hospital (London) between 1985 and 1991. Two patients were operated on after treatment failures from previous RT (1 patient) or surgery (1 patient). No patient received proton RT. One patient underwent an operation; the remaining 7 patients underwent 2 operations (4 patients), 4 operations (2 patients), and 5 operations (1 patient), respectively. One patient received postoperative RT. Three patients were alive and disease-free at 7, 9, and 10 years, respectively. One patient was alive with the disease at 4.8 years, 2 patients died with disease at 2 and 8 years, 1 patient was lost to follow-up at 1 year, and 1

patient died postoperatively after a fourth resection 3 years after the first surgical procedure.

Crockard et al, (2001) reported on 17 patients with low-grade (15 patients) or mesenchymal (2 patients) skull base chondrosarcomas treated surgically at St. Bartholomew's Hospital (London) between 1986 and 1998. Two patients had previous surgery, 3 patients had previous surgery and RT, and 2 patients had previous surgery and chemotherapy. Survival was calculated from the time of tissue diagnosis, leading to significant lead-time bias in the 7 previously treated patients. All 17 patients underwent resection; none of the resections resulted in complete tumor removal. The 2 patients with mesenchymal chondrosarcomas died at 1.7 and 3 years, respectively. The 5-year overall survival rate for the 15 patients with low-grade chondrosarcomas was 93%. However, some of those patients were previously treated and, as previously stated, the method of outcomes analysis resulted in significant lead-time bias.

Gay et al, (1995) reported on 60 patients with skull base chondrosarcomas (14 patients) and chordomas (46 patients) treated surgically at the University of Pittsburgh (PA) between 1984 and 1993. Thirty of 60 patients (50%) were previously treated. Sixty-seven percent of the 60 patients had a total or near total resection and 20% received postoperative RT. The 5-year recurrence-free survival rate for the 14 patients with chondrosarcomas was 90%.

Raghu et al, (2004) reported on 3 patients with temporal bone chondrosarcomas treated with surgery and postoperative RT at Addenbrookes Hospital (Cambridge, UK). All 3 patients were alive and disease-free at 5, 6, and 8 years, respectively.

B. Radiotherapy

Berson et al, (1988) reported on 13 patients with chondrosarcomas of the skull base or cervical spine treated with subtotal resection and charged particle RT alone or combined with photons at the University of California Lawrence Berkeley Laboratory between 1977 and 1986. The 5-year local control and survival rates were approximately 77% and 72%, respectively. Three patients (23%) developed distant metastases; all 3 had grade 2 chondrosarcomas. Castro and co-workers, (1994) reported an update of their experience that included 27 patients with skull base chondrosarcomas: the 5-year local control and survival rates were 78% and 83%, respectively.

Hug et al, (1999) reported on 25 patients treated with proton RT at Loma Linda University Medical Center (CA) between 1992 and 1998 for skull base chondrosarcomas. Two of 25 patients (8%) were previously treated, 9 patients (36%) had brainstem invasion, and 21 patients (84%) had gross tumor present at the time of proton RT. Twenty-three of 25 patients (92%) were locally controlled and remained disease-free after treatment.

Noël et al, (2003) reported on 67 patients treated with proton RT for skull base or cervical spine chondrosarcomas (18 patients) or chordomas (49 patients) between 1995 and 2000 at the Centre de Protonthérapie d'Orsay (Orsay, France). Median follow-up was 20 months. Two-thirds of the treatment was delivered with photons and one-third with protons. Four of 18 patients with chondrosarcomas underwent gross total resection, 11 had a subtotal resection, and 3 had a biopsy before proton RT. Thirteen patients had no previous therapy and 5 patients were treated for locally recurrent disease. The 3-year local control and survival rates after proton RT were 85% and 75%, respectively.

Rosenberg et al, (1999) reported on 200 patients with grade 1 and 2 skull base chondrosarcomas treated at the Massachusetts General Hospital and Harvard Cyclotron (Boston, MA) between 1978 and 1997. Five percent of patients had a gross total resection, 74% had a subtotal resection, and 21% had a partial resection or biopsy before proton RT. Follow-up ranged from 2 months to 18.5 years (mean, 65 months). Patients received a median dose of 72.1 cobalt gray equivalents (CGE) in 38 fractions (range, 64.2 to 79.6 CGE). The 10-year local control and cause-specific survival rates were 98% and 99%, respectively. No patient experienced hematogenous dissemination. Austin et al, (1993) analyzed the cause of failure in 3 patients treated with proton RT at the Massachusetts General Hospital; two recurrences were marginal and likely due to low doses in regions where the dose was constrained because of the risk of normal tissue toxicity, and one recurrence was within the high-dose volume.

VII. Complications

A. Surgery

Gay et al, (1995) reported on 60 patients treated surgically at the University of Pittsburgh (PA) for skull base chondrosarcomas (14 patients) and chordomas (46 patients). Postoperative complications for the overall group of 60 patients included cerebrospinal fluid leak, 18

patients (3%); meningitis, 6 patients (10%); brain infarct, 2 patients (3%); and death, 2 patients (3%). Forty-eight patients (80%) had a new cranial nerve deficit (usually the 6th cranial nerve) after the operation, 15% had hearing loss (usually partial), 8% had 7th cranial nerve paralysis or paresis, and 8% had visual loss or decline. Overall, 24 of 60 patients (40%) had a permanent functional decline after the operation, usually 10 points on the Karnofsky performance scale.

Raghu et al, (2004) reported on 3 patients treated with surgery and postoperative RT for temporal bone chondrosarcomas; all 3 had cranial nerve injuries after the operation.

B. Radiotherapy

Hug et al, (1999) reported on 58 patients treated with proton RT for skull base chondrosarcomas (25 patients) and chordomas (33 patients); 3 patients (5%) experienced late symptomatic complications including severe unilateral hearing loss (1 patient), a single focal seizure (1 patient) and significant bilateral loss of hearing and vision (1 patient).

Noël et al, (2003) reported on 67 patients treated with proton RT for skull base and cervical spine chondrosarcomas (18 patients) and chordomas (49 patients). Sixteen patients (24%) experienced total (14 patients) or partial (2 patients) hypopituitarism, 12 patients (18%) had mild hearing loss, and 4 patients (6%) experienced severe late complications including oculomotor impairment (2 patients), severe hearing loss (1 patient), and near complete bilateral visual loss (1 patient).

VIII. Conclusion

Skull base chondrosarcoma is rare, usually low grade, and exhibits an indolent growth pattern. Although patients can be treated with aggressive resection, the probability of complete resection with negative margins is low and the permanent morbidity of these procedures is often significant. Charged particle RT (such as protons or carbon ions) alone or combined with subtotal resection results in a high probability of cure and relatively low risk of toxicity.

References

- American Joint Committee on Cancer (2002) Bone. In: American Joint Committee on Cancer. **AJCC Cancer Staging Manual**. New York: Springer, 187-92
- Austin JP, Urie MM, Gardenosa G, Munzenrider JE (1993) Probable causes of recurrence in patients with chordoma and chondrosarcoma of the base of skull and cervical spine. **Int J Radiat Oncol Biol Phys** 25, 439-44
- Berson AM, Castro JR, Petti P, Phillips TL, Gauger GE, Gutin P, Collier JM, Henderson SD, Baken K (1988) Charged particle irradiation of chordoma and chondrosarcoma of the base of skull and cervical spine: The Lawrence Berkeley laboratory experience. **Int J Radiat Oncol Biol Phys** 15, 559-65
- Brown E, Hug EB, Weber AL (1994) Chondrosarcoma of the skull base. **Neuroimaging Clin N Am** 4, 529-41
- Castro JR, Linstadt DE, Bahary JP, Petti PL, Daftari I, Collier JM, Gutin PH, Gauger G, Phillips TL (1994) Experience in

- charged particle irradiation of tumors of the skull base: 1977-1992. **Int J Radiat Oncol Biol Phys** 29, 647-55.
- Crockard HA, Cheeseman A, Steel T, Revesz T, Holton JL, Plowman N, Singh A, Crossman J (2001) A multidisciplinary team approach to skull base chondrosarcomas. **J Neurosurg** 95, 184-9
- Eisenberg MB, Woloschak M, Sen C, Wolfe D (1997) Loss of heterozygosity in the rhinoblastoma tumor suppressor gene in skull base chordomas and chondrosarcomas. **Surg Neurol** 47, 156-61
- Gay E, Sekhar LN, Rubinstein E, Wright DC, Sen C, Janecka IP, Snyderman CH (1995) Chordomas and chondrosarcomas of the cranial base: Results and follow-up of 60 patients. **Neurosurgery** 36, 887-97
- Hug EB, Loredó LN, Slater JD, DeVries A, Grove RI, Schaefer RA, Rosenberg AE, Slater JM (1999) Proton radiation therapy for chordomas and chondrosarcomas of the skull base. **J Neurosurg** 91, 432-9
- Ishida T, Dorfman HD (1994) Chondroid chordoma versus low-grade chondrosarcoma of the base of the skull: Can immunohistochemistry resolve the controversy? **J Neuro-Oncol** 18, 199-206
- Korten AGGC, ter Berg HJW, Spincemaille GH, van der Laan RT, Van de Wel AM (1998) Intracranial chondrosarcoma: Review of the literature and report of 15 cases. **J Neurol Neurosurg Psychiatry** 65, 88-92
- Maleux G, Demaerel P, Vanslambrouck K, Aerts P, Brijs S, Tanghe W (1996) Chondrosarcoma of the skull base: CT, MR and pathological features. **ROFO (or Fortschr Rontgenstr)** 165, 599-601
- Muthukumar N, Kondziolka D, Lunsford LD, Flickinger JC (1998) Stereotactic radiosurgery for chordoma and chondrosarcoma: Further experiences. **Int J Radiat Oncol Biol Phys** 41, 387-92
- Noël G, Habrand JL, Jauffret E, de Crevoisier R, Dederke S, Mammari H, Haie-Meder C, Pontvert D, Hasboun D, Ferrand R, Boisserie G, Beaudre A, Gaboriaud G, Guedea F, Petriz L, Mazon JJ (2003) Radiation therapy for chordoma and chondrosarcoma of the skull base and cervical spine. Prognostic factors and patterns of failure. **Strahlenther Onkol** 179, 241-8
- Raghu M, Moumoulidis I, De R, Moffat D (2004) Chondrosarcomas of the temporal bone: Presentation and management. **J Laryngol Otol** 118, 551-5
- Rosenberg AE, Nielsen GP, Keel SB, Renard LG, Fitzek MM, Munzenrider JE, Liebsch NJ (1999) Chondrosarcoma of the base of the skull. A clinicopathologic study of 200 cases with emphasis on its distinction from chordoma. **Am J Surg Pathol** 23, 1370-8
- Ruark DS, Schlehaider UK, Shah JP (1992) Chondrosarcomas of the head and neck. **World J Surg** 16, 1010-5
- Stapleton SR, Wilkins PR, Archer DJ, Uttley D (1993) Chondrosarcoma of the skull base: A series of eight cases. **Neurosurgery** 32, 348-56
- Volpe NJ, Liebsch NJ, Munzenrider JE, Lessell S (1993) Neuro-ophthalmologic findings in chordoma and chondrosarcoma of the skull base. **Am J Ophthalmol** 115, 97-104



William M. Mendenhall

