Skull Base Chondrosarcoma
Evidence-Based Treatment Paradigms

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KEYWORDS

• Chondrosarcoma • Skull base • Microsurgery • Radiotherapy

KEY POINTS

- Cranial chondrosarcomas are generally low-grade, indolent malignancies of bone that cause morbidity through compression of neurovascular structures at the skull base.
- The mainstay of treatment for chondrosarcoma is surgical resection followed by adjuvant radiation therapy. Although proton beam radiotherapy is often considered optimal management, multiple radiotherapy modalities demonstrate equivalent efficacy in long-term studies.
- Surgical approaches should be selected based on pattern of tumor growth and attachment, as well as preexisting neurologic deficits.
- Although chemotherapy is not currently part of the standard treatment regimen for chondrosarcoma, emerging molecular-targeted therapies may contribute to tumor control in the future.

INTRODUCTION

Chondrosarcoma is the second most common primary malignancy of bone, arising from cells of chondroid (cartilage) origin throughout the axial and appendicular skeleton.[1] Only 1% of chondrosarcomas arise in the skull base, and account for 6% of all skull-base tumors.[2] The vast majority of cranial tumors are low to intermediate grade with indolent growth and low metastatic potential.[3] However, their intimate association with critical neural and vascular structures at the skull base often results in significant morbidity from tumor growth and surgical intervention. The mainstay of therapy for chondrosarcoma is surgical resection, with fractionated radiation therapy used to limit recurrence. Recently, radiosurgery has been investigated as an alternative to fractionated radiotherapy. There has been little role for chemotherapy in the treatment of this disease.

This review examines the published literature on the management of cranial chondrosarcoma, including the importance of the extent of microsurgical resection and the multiple modalities of adjuvant radiation including radiosurgery, proton beam, and heavy-particle radiotherapy. The goal is to provide an evidence-based guideline for the management of this rare and complicated disease. In addition, laboratory evidence is presented for new molecular targets to improve emerging chemotherapies for chondrosarcoma.

PATHOLOGY

Cranial chondrosarcoma occurs primarily at the base of the skull, arising from rests of chondrocytes within the synchondroses of the basilar skull bones.[4] Tumors are found most often in the paraclival region arising from sphenopetrosal, petro-occipital, or spheno-occipital synchondroses.[5] The vast majority of lesions involve the bone of the clivus, and extend anteriorly into the parasellar sinuses or middle cranial fossa (30%–50%), or posteriorly into the posterior fossa (50%).[6] Although invasion through the dura is uncommon, compression of the brainstem or temporal lobe is frequent at presentation (**Fig. 1**).[6] Cranial chondrosarcoma occurs preferentially at the skull base,

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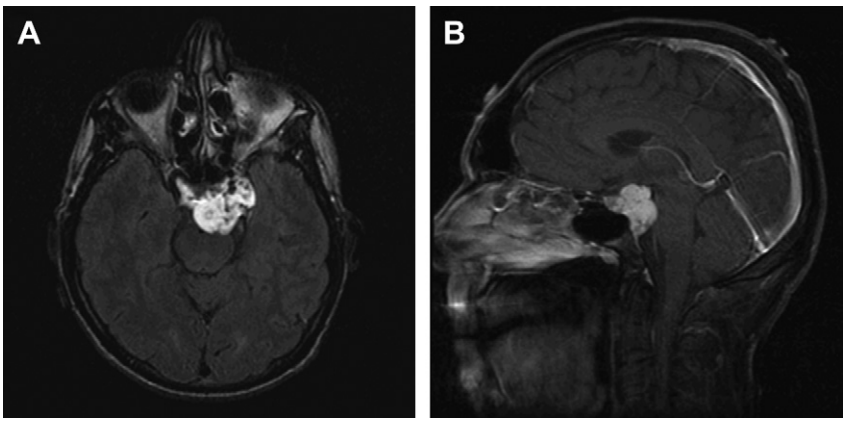

Fig. 1. T2-weighted axial FLAIR (*A*) and T1-weighted contrast enhanced sagittal (*B*) images of a patient with a skull-base chondrosarcoma centered at the left petroclival junction.

owing to differences in bone development between the cranial vault and the basilar structures. The cranial vault grows primarily by intramembranous ossification, whereas the basilar skull bones develop by endochondral ossification and retain rests of chondrocytes into maturity, which can undergo malignant degeneration.[7,8] Most chondrosarcomas develop sporadically, although tumor formation has been associated with diseases of endochondroma formation including Ollier disease and Maffucci syndrome.[9]

Chondrosarcoma manifests grossly as a destructive, mineralized mass that invades bone and extends into soft tissues. Lesions typically grow in bone with an infiltrative pattern, replacing normal marrow elements and spreading through Haversian canals.[10] Eventually lesions break through the cortex and invade surrounding soft tissue. Histopathologically, chondrosarcomas can be of the conventional, mesenchymal, clear-cell, or dedifferentiated type. Almost all skull-base tumors are the conventional type, with rare (<10%) mesenchymal lesions reported.[11] The clear cell and dedifferentiated types do not occur in the axial skeleton. Conventional chondrosarcoma can be composed of hyaline or myxoid cartilage, or a combination of the two (**Fig. 2**). Conventional lesions are graded according to the degree of cellularity, cytologic atypia, and mitotic activity on a 3- or 4-tiered scale, with the lowest grade representing well-differentiated tumors. In the 2 largest case series of skull-base chondrosarcoma reported in the literature, 50% of the lesions were low grade (grade 1) and nearly 90% were low to intermediate grade (grade 1–2).[11,12] High-grade, poorly differentiated lesions of the conventional subtype are rare in all anatomic locations, and identification of aggressively invasive, poorly differentiated cartilage should raise the possibility of chondroblastic osteosarcoma.

Chondrosarcomas, especially low-grade tumors, have relatively indolent growth compared with other sarcomas. Nonetheless, they are highly invasive and have the potential for distant metastasis. Approximately 7% of patients have distant metastasis, which is most commonly seen with high-grade conventional tumors and the mesenchymal subtype.[11]

CLINICAL PRESENTATION

Data from the national cancer database indicates that the median age at presentation for cranial chondrosarcoma is 51 years, with a slight male predominance (55% of cases).[11] Most cases (85%) occur in non-Hispanic white patients. As indicated previously, most cases demonstrate a conventional histologic subtype with low-grade pathology. Fewer than 10% of cases are of the mesenchymal subtype, and these patients tend

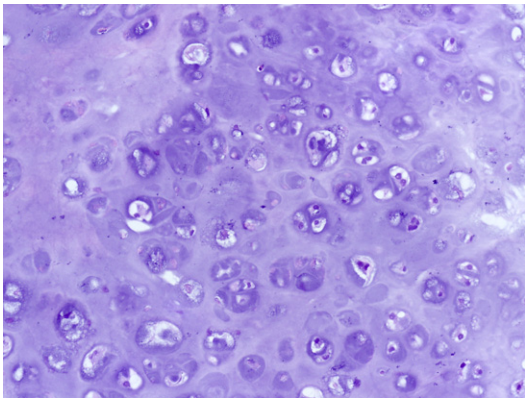

Fig. 2. Conventional chondrosarcoma, grade 1, demonstrating hyaline architecture (hematoxylin and eosin; original magnification ×200).

to be younger, with greater than 60% of cases occurring in patients younger than 30 years.[11]

Because of the location of most tumors in the skull base, along the spheno-petro-clival junction, the majority of patients present with symptoms of cranial nerve compression. In a series of 33 patients with cranial chondrosarcoma managed at the University of California, San Francisco, the most common presenting symptoms were headache and diplopia, with nearly 50% of patients presenting with palsy of the sixth cranial nerve.[13] A similar presentation was reported by groups from the Barrow Neurological Institute and the International Neuroscience Institute in Hannover, whose series contained mostly clivus-invading tumors causing sixth-nerve dysfunction from compression within the Dorello canal.[6,14] By contrast, the group from the House Clinic reported on 8 patients with a predominance of petrous apex tumors extending into the cerebellopontine angle who all presented with dysfunction of the lower cranial nerve.[15] The presence of particular cranial-nerve deficits at presentation can be an important factor in the selection of surgical approach, especially with regard to function of cranial nerve VIII and the feasibility of a transpetrosal approach.

The differential diagnosis for skull-base lesions in the typical location of a cranial chondrosarcoma includes chordoma, other primary bone tumors, skull-base metastases, meningiomas, schwannomas of the lower cranial nerve, neuroblastoma, and lymphoma. Although any of these expansile lesions may cause bony remodeling, erosive destruction of the petrous apex or clivus is not generally associated with lesions other than chondrosarcoma, chordoma, or metastases. Therefore, in addition to magnetic resonance imaging, computed tomography and plain radiographs may be useful in determining the diagnosis.

MANAGEMENT

Surgical Resection

The current standard for initial treatment of cranial chondrosarcoma is surgical resection to obtain a definitive tissue diagnosis and maximally cytoreduce the tumor. Selection of the approach to the skull base is principally determined by the primary direction of tumor growth and the involved cranial nerves.[6] Tumors involving the petrous apex and upper third of the clivus with extension anteriorly into the Meckel cave or the cavernous sinus are often addressed through a frontotemporal orbitozygomatic approach, or a pure middle-fossa craniotomy with subtemporal dissection. By contrast, posteriorly and inferiorly directed tumors extending below the internal acoustic canal are best treated through a retrosigmoid or transpetrosal approach. Large tumors may require a combined petrosal/middle-fossa approach or a staged procedure. Among a group of combined modern surgical case series for skull-base chondrosarcoma, approximately a third of tumors were resected via an anterior approach, a third via a posterolateral approach, and a third via alternative approaches including transfacial and transsphenoidal approaches.[5,6,13,14,16] Endoscopic transnasal approaches have also been reported with success for specific tumors.[17]

Preoperative cranial-nerve deficits are common in cranial chondrosarcoma patients, with the most common presenting symptom being diplopia secondary to dysfunction of cranial nerve VI. Given the invasive nature of chondrosarcoma and the difficult location of most tumors at the skull base, improvements in cranial nerve deficits after surgery are uncommon, and the potential for causing new deficits with surgery is significant. In their series of 18 patients, Samii and colleagues[6] found that 16 of 18 (89%) patients had at least a partial cranial neuropathy at presentation. After surgical resection 25% had new cranial nerve deficits, whereas 55% had no improvement in their preoperative symptoms. Similarly, Sekhar and colleagues[16] reported 41% new cranial neuropathies in their series of 22 chondrosarcoma patients. In addition to cranial neuropathies, modern surgical series also report an approximately 10% to 15% rate of vascular injury, 10% rate of cerebrospinal fluid leak, and up to 5% perioperative mortality.[14,16,18] Given the relatively high morbidity of such procedures, there is some controversy in the literature regarding the goals of operations. Some investigators have argued that the goal for initial intervention should be aggressive gross-total resection, as this offers the possibility for a surgical cure. The groups that advocate this approach report a complete resection achieved in 50% to 60% of patients.[5,6] By contrast, others have argued for an approach using maximal safe cytoreduction followed by radiotherapy to control residual tumor growth. In general, 5-year tumor-recurrence rates and overall survival were 70% to 80% and 80% to 90%, respectively, regardless of the approach used.[6,12,13,18] There is no direct evidence to suggest that extent of resection at the initial operation offers any recurrence or survival benefit when adjuvant radiation is given.

The authors previously performed a systemic analysis of the published literature on cranial chondrosarcoma, disaggregating the data from individual case series to statistically evaluate predictors of tumor recurrence[19] and overall

survival.[20] The cumulative data from all published series of cranial chondrosarcoma demonstrates a recurrence-free survival of 78% at 5 years and an overall survival of 88% at 5 years. The greatest predictor of outcome was tumor histology, with mesenchymal-type tumors showing nearly 5-fold greater 5-year mortality (**Fig. 3**A). Within conventional type tumors, tumor grade was associated with worsening survival (**Fig. 3**B). However, mesenchymal and high-grade conventional tumors were rare, representing fewer than 11% of all cases. For the majority of patients, outcome was significantly affected by the use of adjuvant radiation. The authors' analysis found that 5-year mortality was decreased from 25% to 9% with the addition of any form of radiation (**Fig. 3**C). A recent case series of 6 patients with cranial chondrosarcoma treated with surgical resection followed by fractionated radiotherapy found 100% tumor control at 5 years irrespective of the residual tumor volume after resection, which ranged from 0 to 28.7 cm^3.[21] Although this is a small series it supports the trend seen in the surgical data, which indicate that survival outcomes are approximately the same regardless of the extent of surgical resection. A robust analysis of the effect of extent of resection on a group of chondrosarcoma patients with equivalent adjuvant therapy has not been performed, leaving this issue open for debate.

Radiation Therapy

The use of adjuvant radiation following surgical resection for cranial chondrosarcoma has been shown to improve tumor control and overall survival in several case series.[12,13,18] As indicated, the authors' systematic analysis demonstrates decreased tumor recurrence and mortality at 5 years with the addition of radiation to surgical resection.[19,20] Radiotherapy for chondrosarcoma may be given by multiple modalities including fractionated photon radiotherapy, particle (proton, carbon ion) radiotherapy, or stereotactic radiosurgery. There are no class I data suggesting that the use of one radiation modality is preferable to any other. Support for the use of each radiation technique is based on individual case series.

Conventional fractionated radiotherapy has been used the longest as an adjuvant to surgical resection for cranial chondrosarcoma. Most case series report delivering a median total dose of 55 to 65 Gy.[18,22] Before the availability of the

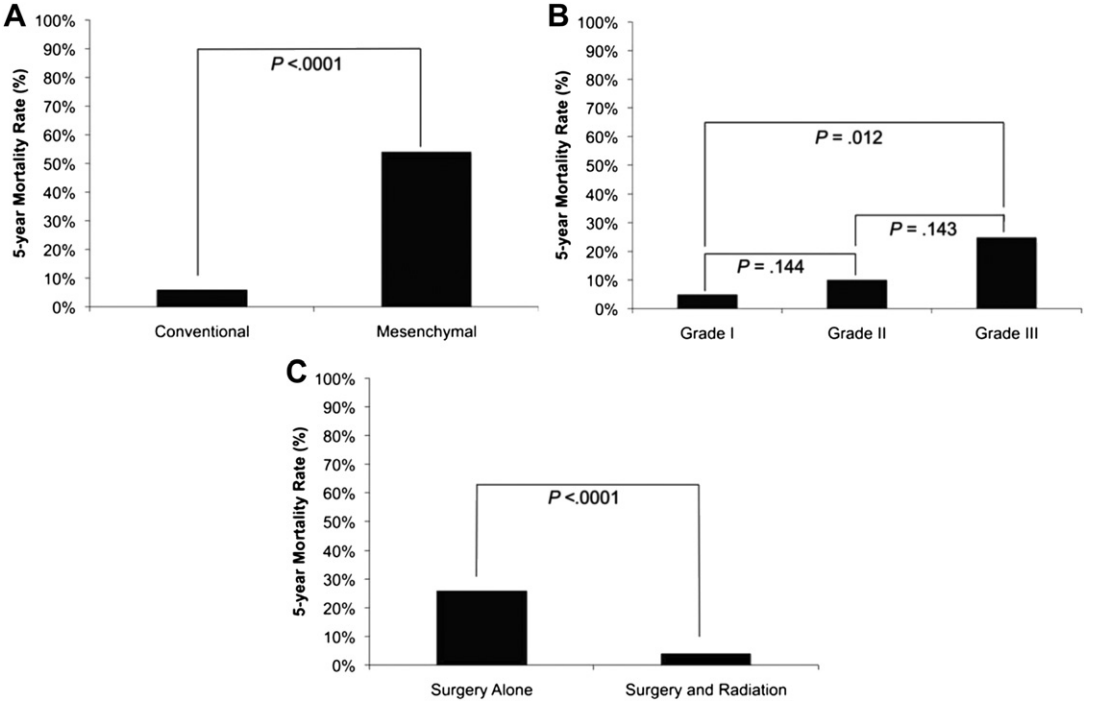

Fig. 3. Effects of tumor histology and treatment on overall survival. (*A*) The effect of histologic subtype on 5-year mortality demonstrates a nearly 5-fold increase in mortality associated with mesenchymal histology. (*B*) The effect of tumor grade on 5-year mortality in conventional type tumors demonstrates increased mortality with increasing tumor grade. (*C*) The effect of adjuvant radiation following surgery compared with surgery alone demonstrates a significant reduction in 5-year mortality with the addition of radiotherapy. (*From* Bloch O, Jian BJ, Yang I, et al. A systematic review of intracranial chondrosarcoma and survival. J Clin Neurosci 2009;16:1547–51; with permission.)

highly conformal techniques used today, such as intensity-modulated radiation therapy (IMRT), these doses were delivered using external beam radiotherapy with quantifiable dose distribution to the brainstem and other critical structures at the skull base. Using photon radiotherapy, most groups report 5-year progression-free survival rates of greater than 80%, and overall survival greater than 90%.[13,18,22] Little early or late radiation toxicity is reported with this technique.

Charged-particle radiotherapy, specifically proton beam therapy, has gained favor for the treatment of skull-base bony malignancies over the last 2 decades. Because of the sharp fall-off in ionizing energy at the target, known as the Bragg peak effect, protons can be used to deliver higher energy with high levels of conformality. In addition, there is a theorized radiobiological advantage to protons in comparison with photons. Proton therapy was first used at the skull base to treat chordomas, which are more radioresistant and have a greater tendency to recur, requiring higher doses of radiation than can safely be administered by conventional photon therapy. This technique has subsequently been applied to the treatment of cranial chondrosarcomas. Case series reporting proton beam as adjuvant therapy for chondrosarcoma administer substantially higher median doses than photon therapy, ranging from 60 to 79 cobalt Gray equivalents (CGE).[23,24] Similar to the results with photon radiotherapy, progression-free survival at 5 years for proton therapy ranges from 75% to 95% and overall survival ranges from 85% to 100%.[12,23–26] Although there are no studies directly comparing the efficacy of proton versus photon therapy, tumor control and overall survival rates reported in individual studies for both techniques are concordant. Studies on proton beam therapy do report a delayed radiation toxicity rate of 4% to 14% for grade 3 and 4 toxicities.[23–26]

In addition to protons, carbon-ion particle therapy has been used for the treatment of skull-base chondrosarcomas. Carbon ions have the same energy characteristics as protons, allowing high doses to be given to conformal fields, with a possible benefit of a greater radiobiological response to the carbon. The Radiation Oncology Group in Heidelberg has published their case series of 54 patients with skull-base chondrosarcomas treated with carbon ions, in which they report a tumor control rate of 89% and overall survival of 98% at 5 years.[27] These investigators treated patients to a median dose of 60 CGE in hypofractionated daily fractions of 3.0 CGE, and reported a delayed radiation toxicity rate of 10% for low-grade (1 and 2) toxicities and 2% for high-grade (3 and 4) toxicities.

An alternative adjuvant to fractionated radiotherapy with photons or protons is radiosurgery. Stereotactic radiosurgery (SRS) can deliver a highly conformal large radiation dose to a tumor in a single session, and has become the standard in radiotherapy for benign skull-base tumors. The use of SRS as adjuvant therapy for malignant skull-base tumors, including chondrosarcoma, has been increasing, with several published reports on outcomes. In 2007, the Pittsburgh group reported their series of 10 patients with skull-base chondrosarcomas who received adjuvant radiation with SRS with a median marginal dose of 16 Gy.[28] The investigators reported a 5-year tumor control rate of 80% and no acute or late radiation toxicity. In 2012, they updated their series of 22 chondrosarcoma patients treated with SRS, including 7 patients treated with SRS as primary therapy without surgery.[29] In the updated series, they reported a median marginal treatment dose of 15 Gy with a 22% rate of radiation toxicity. The tumor control rate and overall survival at 5 years were 70%. Similar tumor control and survival rates have been published by other groups in mixed studies of SRS for chordoma and chondrosacroma.[30–33] Although no direct comparisons of SRS with fractionated radiotherapy or proton beam therapy have been made in a controlled study, the reported outcomes for SRS as adjuvant or primary therapy for skull-base chondrosarcoma appear to be worse than those reported with other radiation modalities. The poor outcomes may be due, in part, to the mixed nature of the patients treated in the SRS studies, including patients who have had multiple resections and are receiving salvage therapy. Nonetheless, with the data available at this time, it is not possible to claim that SRS provides improved or even equivalent outcomes to fractionated radiotherapy for treatment following initial surgical resection.

Chemotherapy

Chemotherapy for chondrosarcoma in the skull base and throughout the axial skeleton has been largely ineffective and is, therefore, not part of the standard therapy for this tumor. Occasionally chemotherapy has been used as salvage therapy for multiply recurrent or metastatic disease. A review of the national cancer database demonstrated that less than 5% of patients with head and neck chondrosarcoma received any form of chemotherapy, usually in conjunction with surgical resection.[11] There is little evidence beyond individual case reports to suggest efficacy of any chemotherapeutic regimen. This area is one that requires further clinical research.

EMERGING THERAPIES

Although modern therapy for skull-base chondrosarcoma can achieve tumor control rates in excess of 80% at 5 years and overall survival in excess of 90% at 5 years, there remains significant room for improvement in long-term outcomes. Surgical resection is the standard of care for initial therapy, although the goals of therapy have been debated. Surgical morbidity for these tumors is significant, and despite improvements in skull-base surgical techniques, gross-total resection is only achievable in 50% of cases at best. Furthermore, there is no evidence that greater extent of resection improves outcome, as multiple studies have demonstrated equivalent survival regardless of the extent of resection when adjuvant radiation is given. Further improvements in surgical techniques are not likely to substantially improve outcomes for patients with skull-base chondrosarcoma. Radiation therapy, too, has seen substantial improvements in technique over the past 2 decades, but new modalities of radiation have not been shown to clearly improve outcome. With high-energy conformal techniques for photon therapy (IMRT) and particle therapy (proton beam), radiation can be delivered safely with minimal toxicity, but survival has not substantially improved. Further data, including controlled prospective trials of multiple radiation modalities, are necessary to determine the ideal method of adjuvant radiation for chondrosarcoma.

With limitations in the efficacy of surgery and radiation for control of skull-base chondrosarcomas, the future of treatment may be new molecular therapies targeted at chondrosarcoma cell proliferation and invasion. Unfortunately, in vitro and animal models of cranial chondrosarcoma are not readily available. Most of the studies on chondrosarcoma genetics and signaling come from appendicular specimens and cultures. The authors recently reviewed the literature on known signaling

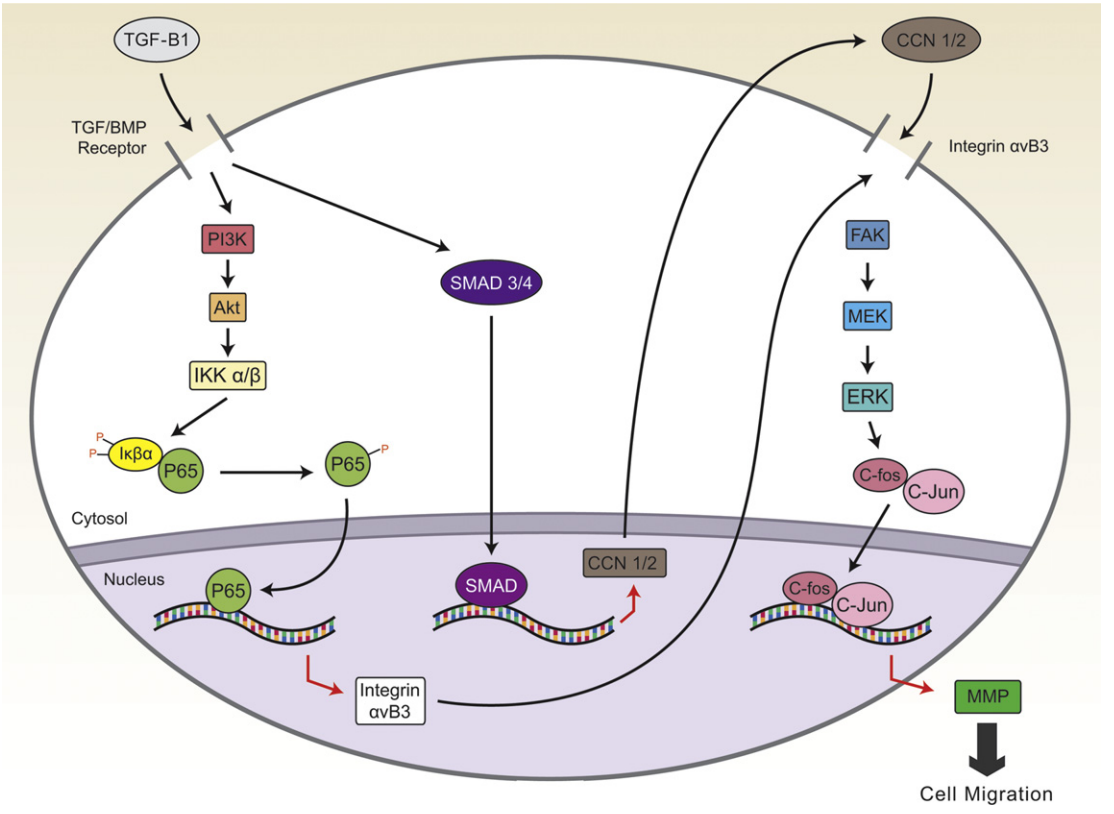

Fig. 4. Proposed interaction of chondrosarcoma with the extracellular environment. Inflammation results in transforming growth factor (TGF) receptor ligand formation, which binds to receptor and activated phosphoinositide 3-kinase (PI3K)/Akt activity and pathogenic upregulation of integrins and their ligands. When integrins bind ligands at the cell surface, the FAK-MEK-ERK pathway is activated, resulting in matrix metalloproteinase (MMP) expression and degradation of the extracellular matrix. BMP, bone morphogenetic protein; IKK, I-κB kinase. (*From* Bloch O, Sughrue ME, Mills SA, et al. Signaling pathways in cranial chondrosarcoma: potential molecular targets for directed chemotherapy. J Clin Neurosci 2011;18:881–5; with permission.)

pathways in chondrosarcoma that have been shown to functionally influence tumor-cell invasion and migration.[34] Chronic inflammation in rests of chondrocytes was found to result in activation of transforming growth factor receptors by inflammatory cytokines in the extracellular matrix of bone and cartilaginous tissue. Activation of these receptors leads to upregulation of integrins, specifically integrin $\alpha_v\beta_3$, through phosphoinositide (PI) 3-kinase signaling. When these integrins bind to constituents of the extracellular matrix at the cell surface, the FAK-MEK-ERK pathway is activated, leading to production of matrix metalloproteinases and degradation of the extracellular matrix, facilitating tumor invasion (**Fig. 4**). Small molecular inhibitors of the PI3-kinase and MEK pathways are currently in early-phase clinical trials as chemotherapeutic agents for other malignancies. This evidence suggests that these inhibitors may have some benefit in preventing tumor growth and invasion in skull-base chondrosarcoma. Further investigation, including coordinated multicentered clinical trials, will be necessary to study new interventions for this rare disease.

SUMMARY

Skull-base chondrosarcomas are indolent but invasive malignant tumors in locations that are often difficult to treat. Based on the available data, standard therapy should consist of maximal safe surgical resection with a goal of cytoreduction, followed by adjuvant fractionated radiotherapy with photons or protons. Further studies are necessary to determine whether one modality of radiotherapy has any advantage over the other. For conventional low-grade tumors, progression-free and overall survival at 5 years is high with this treatment paradigm. Negative predictors of outcome include mesenchymal tumor histology, high tumor grade, or a lack of appropriate adjuvant radiation. Chemotherapy is not currently a part of standard therapy, but new agents targeting specific molecular pathways may prove to be efficacious in the future.

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