REVIEW

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Postsurgical management strategies in patients with skull base chondrosarcomas

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Practice Points

- The current standard of care for intracranial chondrosarcomas is initial maximal safe surgical resection followed by either adjuvant radiation therapy and/or early radiosurgery.
- Overall survival and progression-free survival range between 70 and 100% at 5 years when multimodality approaches are used.
- Overall survival may be increased for patients who have a shorter interval (<6 months) between diagnosis and stereotactic radiosurgery, an older age, and either a single or no prior resection.
- Progression-free survival may be increased for patients older than 40 years of age, who have not had prior radiation therapy, and for those with smaller tumors that do not compress the brainstem.

SUMMARY Chondrosarcomas of the skull base are rare, slow-growing tumors that are often lethal and remain a management quandary. A systematic review was performed to understand postsurgical management options for patients with these tumors. The current standard of care includes surgical resection followed by either adjuvant radiation therapy and/or early radiosurgery. The role of chemotherapy has been limited, but remains under investigation. Overall survival and progression-free survival range between 70 and 100% at 5 years when multimodality approaches are used. Overall survival may be greater for patients who have a shorter interval (<6 months) between diagnosis and radiosurgery, an older age, and either a single or no prior resection. Progression-free survival may be increased for patients older than 40 years of age, who have not had prior radiation therapy, and for those with smaller tumors that do not compress the brainstem.

Intracranial chondrosarcomas overview

Chondrosarcomas of the skull base are rare, slow-growing tumors. They were first reported by Mott in 1899 and comprise approximately 0.1% of all intracranial neoplasms and 6% of all skull base lesions [1]. Although the majority

of chondrosarcomas arise *de novo*, they may be associated with Paget's disease, Ollier's disease, Maffucci syndrome and osteochondromas [2]. The typical sites of skull base lesions are synchondroses of the clivus, the sphenoid–ethmoid region, the parasellar area and

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the temporal–occipital junction [3,4]. The differential diagnosis of chondrosarcoma includes chordoma, chondromyxoid fibroma, plasmacytoma, nasopharyngeal carcinoma and other metastatic tumors [5]. The most commonly presenting symptom is diplopia, secondary to an abducens nerve palsy (11%) and closely followed by headache (9%) [2].

The main subtypes of chondrosarcomas include a conventional/classic type that comprises 80% of cases and clear cell, mesenchymal and dedifferentiated variants that comprise the remaining 20% [6]. The conventional/classic type is further divided into WHO grades 1–3 tumors based on the degree of cellularity and atypia. The mesenchymal type exhibits the most aggressive growth behavior and poorest prognosis [7].

Owing to their location deep within the skull base and the relationship to cranial nerves and vessels, chondrosarcomas can rarely be gross totally resected. Accordingly, most patients undergo initial skull base microsurgery, but require additional adjuvant treatment. Lower-grade tumors may have a relatively indolent course, which generally requires long-term follow-up in order to detect tumor progression or recurrence after initial management.

Distinction from chordomas

The ability to distinguish chondrosarcomas from chordomas by imaging alone is often difficult but important, since the prognosis is generally considered better for chondrosarcomas [8,9]. The majority of studies that have evaluated the role of radiosurgery in the management of skull base tumors have grouped chordomas together with chondrosarcomas, despite their differences in histology as well as therapeutic response [10–14]. Differentiating chordomas from chondrosarcomas requires specific immunohistochemical staining [15]. Both chordomas and chondrosarcomas can be positive for S-100 and vimentin. However, chordomas are generally immunopositive for epithelial markers, such as cytokeratin and endothelial membrane antigen, whereas chondrosarcomas are negative for both [15,16]. Anatomically, chordomas tend to develop in more midline skull base structures.

Skull base microsurgery

Maximal safe microsurgical resection is considered the first-line management for intracranial chondrosarcomas [16,17] in order to confirm the

histological analysis and achieve maximal safe resection. The ability to obtain a gross total resection has improved as microsurgical skull base access techniques have matured. Korten *et al.* reviewed a series of patients with intracranial chondrosarcomas in The Netherlands [18]. They found that surgery alone was associated with a 53% local recurrence rate and the mean time to recurrence was 32 months. Wanebo *et al.* reported 23 patients who underwent a total of 43 surgical resections of skull base chondrosarcomas [19]. The 5- and 10-year overall survival rates were 93% at 5 years and 71% at 10 years. Ten patients underwent adjuvant radiation therapy.

Gay *et al.* reported a 90% overall survival at 5 years for 14 patients who underwent either skull base surgery or surgery followed by radiation therapy [20,21]. Crockard *et al.* reported a 93% 5-year survival rate for 17 patients who underwent surgery alone [22]. Bloch *et al.* found a recurrence rate of 44% in patients who underwent surgical resection alone, compared with 9% in patients who had surgery followed by radiation therapy [7]. Interestingly, the recurrence rate in patients who underwent radiation alone was significantly lower than the recurrence rate of patients who underwent surgery alone (19 vs 44%) [2].

The surgical approach may also influence the tumor control rate. Brackmann and Teufert followed eight patients who underwent resection via various surgical approaches to the skull base [23]. Seven patients underwent surgery via the infratemporal fossa approach and one patient underwent surgery via the transcochlear approach. Six of those patients had gross total resection and all six had no evidence of recurrence at the time of the last imaging follow-up. One patient with residual tumor identified at 1 year had no further treatment. The single patient who underwent surgery via the transcochlear approach had a recurrence by 3 months [23]. The choice of surgical approach is determined by experience, specialty training, and tumor location and volume. The small number of patients in many series does not allow clear descriptions of advantages of one approach versus another. Bloch *et al.* suggested that gross total resection does not improve recurrence-free survival if adjuvant radiation therapy is given [2].

A recent review of the literature demonstrated that for 560 patients with intracranial chondrosarcomas (median follow-up time of 60 months),

the 5-year mortality was 11.5% with a median survival of 24 months. Mortality at 5 years was significantly greater for patients with the mesenchymal subtype and for patients who had received surgical resection without adjuvant radiation. There was also no association between the rate of recurrence and the histological grade of the tumor [7].

Chemotherapy

The role of chemotherapy has generally been limited in the management of intracranial chondrosarcomas [24]. Several experiments have shown that chondrosarcoma tumorigenesis is dependent on decreased PPAR- γ expression, and that migration is dependent on integrin activation and ERK signaling [25]. Additionally, studies have correlated the lack of response to chemotherapy with the expression of P-glycoprotein [26]. *In vivo* studies have demonstrated the use of antiangiogenic SU6668 in controlling tumor growth [27]. However, targeted therapies are still under investigation for human subjects. There was a case reported of ifosfamide and doxorubicin controlling tumor recurrence in an adult patient [28] and successful chemoradiation (cisplatin and adriamycin) for a pediatric patient [29]. Yet, despite several reported cases, the role of chemotherapy in managing intracranial chondrosarcomas needs to be further elucidated.

Proton beam therapy

Reports of the use of fractionated proton beam radiation therapy have increased in the past decade. The technology was first developed in the late 1940s but has enjoyed expanded application in the years after 2000. Owing to its initial high costs and infrastructure needs, it remains an option only at relatively few centers internationally. Over the past 30 years, dependable proton dose constraints

for normal tissues at the skull base were studied and doses have been escalated to improve biological response while maintaining a reasonable toxicity profile [10,11,30,31]. Most proton facilities rely on the use of the Bragg peak effect, which facilitates energy deposition at the target with a sharp medial exit dose fall off, thereby reducing the potential for brain stem injury. Depending on the skull base location, dose plans must carefully assess the entrance dose in structures such as the temporal lobe. Proton radiation therapy is typically fractionated over multiple treatments. For patients who have undergone initial resection, the target volume during fractionated radiation therapy techniques probably includes the tumor bed as well as any residual tumor identified by post-operative MRI. Fractionation is performed to reduce toxicity risks to adjacent CNS structures. There is limited data to demonstrate any substantive radiobiological advantage of protons over fractionated photon radiation delivered by linear accelerators.

Fuji *et al.* studied eight patients with chondrosarcomas and eight patients with chordomas of the skull base who underwent proton radiation therapy; they reported a local control rate at 3 years of 86% and a median follow-up of 42 months [11]. A median dose of 63 Gy was used for tumors that had a median size of 40 cm³, which included chordomas. Weber *et al.* [32] and Ares *et al.* [33] published a series of 64 patients, 22 of whom had chondrosarcomas. Delivery of a median target fractionated dose of 68.4 Gy resulted in a 3-year actuarial overall survival rate of 91%. The 3- and 5-year local control rates were 100 and 94%, respectively. Other studies have also reported local control rates and overall patient survival at 5 years to be above 90% [4,18].

Hug *et al.* reported 58 patients with chondrosarcomas and chordomas of the skull base,

Table 1. Studies and patient characteristics in published series of chondrosarcoma patients treated with stereotactic radiosurgery.

Study (year)	Patients (n)	Median age (years)	Radiation type	Median dose (Gy)	Median tumor volume (cm ³)	PFS (%)		OS (%)		Ref.
						5-year	10-year	5-year	10-year	
Krishnan <i>et al.</i> (2005)	4	45	GKS	15	14.4	100	NA	NA	NA	[40]
Hasegawa <i>et al.</i> (2007)	7	47	GKS	14 [†]	19.7 [†]	76	67	90	53	[39]
Cho <i>et al.</i> (2008)	11	38	GKS + EBRT	18.5 (GKS) 58.2 (EBRT)	3.7	89	80	100	100	[41]
Koga <i>et al.</i> (2010)	4	43	GKS	15.6	NA	100	NA	NA	NA	[38]
Iyer <i>et al.</i> (2012)	22	42	GKS	15	8.0	72	54	70	56	[36]

[†]Mean.

EBRT: Conventional external beam radiation therapy; GKS: Gamma Knife® radiosurgery; NA: Not available; OS: Overall survival; PFS: Progression-free survival.

22 of whom had chondrosarcomas [34]. The overall patient survival was 100% at 5 years for chondrosarcoma patients. For the entire series, patients who did not have brainstem involvement and had tumors less than 25 ml in volume, had better local control compared with patients with brainstem involvement or larger volumes (94 vs 53% and 100 vs 56%, respectively). Brainstem involvement was associated with a worse prognosis, possibly related to the need to restrict radiation effects in the adjacent brainstem. Since chordomas and chondrosarcomas have different biological responses and survivals, the tendency to include both chondrosarcomas and chordomas in the same outcome analysis limits the value of these retrospective studies.

Stereotactic radiosurgery

Stereotactic radiosurgery (SRS) is a surgical technique that delivers a highly focused dose of ionizing radiation in a single procedure, guided by high-definition imaging of the tumor. SRS encompasses various technologies, including the Gamma Knife® (Elekta, Stockholm, Sweden), CyberKnife® (Accuray, CA, USA) and various other linear accelerator platforms. The Gamma Knife utilizes a radioactive cobalt source and requires the patient to wear a frame that is fixed to the skull, which ensures immobilization of the tumor. The CyberKnife is a frameless system that relies on a small linear accelerator mounted on a moving arm to deliver x-rays to a localized region that is visible on fluoroscopy. Similar to other linear accelerators, the CyberKnife emits x-rays and does not rely on a radioisotope source.

SRS has been shown to result in less toxicity to surrounding structures and have fewer complications than fractionated radiation therapy in the management of chordomas and chondrosarcomas (Table 1) [12,31,34–37].

Koga *et al.* reported the results of four patients who had surgical resection followed by SRS (median follow-up of 99 months; range 45–145) [38]. Three of the four patients (margin doses: 15, 16 and 20 Gy) had no change in tumor size during follow-up. One patient who received a lower tumor margin dose of 12 Gy developed tumor recurrence 100 months after SRS. Hasegawa *et al.* studied 30 patients with chordomas and seven patients with chondrosarcomas who underwent SRS [39]. The actuarial 5-year progression-free survival rate in patients with low-grade chondrosarcomas was 76%. A tumor volume of less than 20 ml significantly improved progression-free survival. Krishnan *et al.* studied 25 patients with chordomas and four patients with chondrosarcomas who were treated by SRS [40]. All four patients with chondrosarcomas had tumor control at 5 years. No prognostic factors were identified in these early studies.

Iyer *et al.* studied 22 patients who underwent Gamma Knife SRS for residual or recurrent intracranial chondrosarcomas [36]. The overall patient survival after SRS was 95, 70 and 56% at 1, 5 and 10 years, respectively. Factors associated with longer survival after SRS included a shorter interval (<6 months) between diagnosis and SRS, age greater than 40 years, and either a single or no prior resection. Treated tumor control rates were 91% at 1 year, 72% at 5 years and 54% at 10 years. Factors associated with longer

Figure 1. A 52-year-old female patient who underwent two surgical resections for a chondrosarcoma. (A) T₁-weighted contrast-enhanced axial MRI of residual tumor involving the cavernous sinus, showing the radiosurgery target with a marginal dose of 10.5 Gy. **(B)** T₂-weighted axial MRI showing residual tumor involving the cavernous sinus at the time of stereotactic radiosurgery. **(C)** Axial T₁-weighted contrast-enhanced MRI obtained 7 years after stereotactic radiosurgery showing regression of enhancing lesion. **(D)** Axial T₂-weighted MRI obtained 7 years after stereotactic radiosurgery showing regression of the enhancing lesion.

progression-free survival after SRS included patient age greater than 40 years and no prior radiation therapy. It is possible that older age is a positive prognostic factor, because such tumors may have a lower mitotic rate than those that are diagnosed at a younger age. **Figure 1** illustrates the long-term effect of stereotactic surgery for a 52-year-old patient with residual tumor in the cavernous sinus following surgical resection.

Conclusion

The deep location and diverse histopathology of intracranial chondrosarcomas makes this tumor a management quandary. Given the often prolonged survival of chondrosarcoma patients, it is difficult to determine consistent prognostic factors or define an evidence-based treatment algorithm. Initial maximal safe resection should be attempted in most patients. Multiple operations over several years may be required. Overall patient survival and progression-free survival have increased with the addition of postoperative radiation therapy and/or adjuvant radiosurgery. The most effective technology and the necessary treatment paradigm (fractionated radiation therapy, proton radiation therapy or SRS) require further study. Owing to the rarity of such tumors, a multicenter experience will certainly be necessary to gain a greater understanding of the best combination of surgical and radiation modalities. Studies evaluating the role of radiosurgery in the management of intracranial chondrosarcomas have found that overall survival may be increased in patients who undergo SRS earlier (<6 months) after initial

resection, in older patients, and in patients who have undergone either a single or no prior resection [36]. Longer progression-free survival may be associated with patient age greater than 40 years, patients who had not undergone prior fractionated radiation therapy and patients with smaller tumor volumes without brainstem compression [34,36,39].

Future perspective

Based on the potential improved therapeutic profile of radiosurgery in the management of skull base chondrosarcomas, especially smaller volume residual or recurrent tumors, additional outcome studies are needed. Such studies will need to further analyze important prognostic factors [34,36,38,39]. The North American Gamma Knife Consortium currently has 17 medical centers as members and is gathering multicenter data from these centers in order to better understand the various management strategies necessary to improve outcomes in this rare tumor.

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