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Proton and carbon ion therapy for skull base chordomas

Daniel M. Trifiletti and Paul D. Brown

Department of Radiation Oncology, Mayo Clinic, Jacksonville, Florida (D.M.T.); Department of Radiation Oncology, Mayo Clinic, Rochester, Minnesota (P.D.B.)

Corresponding Author: Daniel M. Trifiletti, MD, Department of Radiation Oncology, Mayo Clinic, 4500 San Pablo Road South, Jacksonville, FL, 32224 (trifiletti.daniel@mayo.edu).

See the article by Iannalfi et al., pp. 1348–1358, in this issue.

Chordomas of the base of skull represent a relatively rare and difficult disease to manage. Although considered slow-growing, these tumors often present with compression of the adjacent optic apparatus, brainstem, and cavernous sinus, making complete neurosurgical resection extraordinarily complex and, at times, of excessive risk to the patient. While promise exists in future systemic therapy options, to date there are no systemic agents approved in the treatment of chordoma. Moreover, while adjuvant radiotherapy has been shown to improve rates of long-term tumor control, chordomas are considered relatively radioresistant. Radiotherapy doses over 70 Gy are frequently utilized,[1] a dose that exceeds the typically acceptable dose tolerance of the immediately adjacent neurologic structures (ie, brainstem, optic apparatus, etc).

One opportunity for advancement in the field of radiotherapy for skull base chordomas is the utilization of particle therapy. Because of the location and dose required, there is fairly wide acceptance in the radiation oncology community that particle therapy should be strongly considered in the treatment of patients with chordoma. This is related to the physical properties and deposition of proton therapy (PT) energy in tissue (ie, Bragg peak) with little radiation deposited beyond the target (ie, exit dose) as opposed to X-ray radiation. Moreover, while carbon ion radiotherapy (CIRT) likewise allows for improved dose deposition, it also has been shown to have a clear increase in the radiobiologic effectiveness (RBE) compared with proton and X-ray radiotherapy.[2,3] Indeed, the biologic damage created by CIRT is more complex than PT and X-ray therapy for the same radiation dose (Gy), and the mechanisms of cell death vary between techniques. However, as there are differing mathematical models used to estimate the impact of CIRT on tissue, it can be difficult to compare CIRT plans across institutions. Compounding these issues, with a limited number of centers around the world, the published clinical data evaluating CIRT are relatively limited.

Iannalfi and colleagues[4] report on the prospective experience of the National Center for Oncological Hadrontherapy (CNAO) in Pavia, Italy in treating 135 patients with chordomas arising from the base of skull with either PT or CIRT. This is a critically important addition to the neuro-oncology scientific literature, as the outcomes of patients treated with CIRT in Japan[5,6] are corroborated and compared with those of other patients treated with PT.[4]

In this report, CNAO treated patients with particle therapy for skull base chordoma after maximum safe surgical resection and without previous irradiation. Patients were treated with either PT or CIRT based on physician discretion, but CIRT was usually chosen among patients who had recurrent disease, incomplete resections, visual defects, cranial nerve deficits, and larger tumor volumes (each $P < 0.05$), while other baseline characteristics were similar across groups.

With a median follow-up duration of 44 months, 5-year local control rate estimates of 84% with PT and 71% with CIRT were calculated (log rank $P = 0.15$). Severe (grades 3–4) toxicity was 12% overall and did not differ based on particle used. There was no brainstem or spinal cord injury reported in either group. Interestingly there were no reports of grades 3–4 radionecrosis in either group, despite the concern of radiation-induced brainstem or temporal lobe injury, particularly with CIRT.

On analysis for predictors of local control, patients with compression of the optic structures and brainstem were more likely to develop tumor progression, and on analysis of the patterns of failure, 87–92% of local failures occurred at the interface of the tumor and the brainstem/optic structures, suggesting that strict adherence to dose constraints on the brainstem and optic nerves resulted in "underdosing" of the adjacent tumor.

These results provide a critical additional piece of data to support further investigation in a patient population with a clear unmet clinical need for improved therapies. Taken as a whole, these data suggest that PT and CIRT should be strongly considered in patients with chordoma. Moreover, given the reported toxicity and patterns of failure, perhaps the commonly accepted brainstem dose constraints are too conservative among patients with chordoma where local

recurrence is the dominant mode of failure. Moving forward, there is a clear need for international consensus and refinement of RBE models in particle therapy, including CIRT as well as PT (especially along different points of the Bragg peak).

Indeed, the future of particle therapy is bright, as our biologic understanding matures, the costs associated with the technology decreases, combination therapy is explored (PT with CIRT, PT with immunotherapy, etc), and clinical experience continues to report. It is clear that an international, multidisciplinary, and coordinated effort is needed to rapidly meet the need of these patients, and through the effort of researchers like Iannalfi et al as well as several international particle therapy groups, we are confident that we are nearing this reality.

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References

1. Hug EB, Loredo LN, Slater JD, et al. Proton radiation therapy for chordomas and chondrosarcomas of the skull base. *J Neurosurg.* 1999;91(3):432–439.
2. Malouff TD, Mahajan A, Krishnan S, Beltran C, Seneviratne DS, Trifiletti DM. Carbon ion therapy: a modern review of an emerging technology. *Front Oncol.* 2020;10:82.
3. Mein S, Klein C, Kopp B, et al. Assessment of rbe-weighted dose models for carbon ion therapy towards modernization of clinical practice at HIT: in vitro, in vivo and in patients. *Int J Radiat Oncol Biol Phys* 2020.
4. Iannalfi A, D'Ippolito E, Riva G, et al. Proton and carbon ions radiotherapy in skull base chordomas: a prospective study based on a dual particle and a patient-customized treatment strategy. *Neuro Oncol.* 2020. Mar 20;noaa067. doi: 10.1093/neuonc/noaa067. Online ahead of print. https://www.sciencedirect.com/science/article/pii/S0360301620312074
5. Mizoe JE. Review of carbon ion radiotherapy for skull base tumors (especially chordomas). *Rep Pract Oncol Radiother.* 2016;21(4):356–360.
6. Mizoe JE, Hasegawa A, Takagi R, Bessho H, Onda T, Tsujii H. Carbon ion radiotherapy for skull base chordoma. *Skull Base.* 2009;19(3):219–224.