Proton Radiation Therapy for Local Control in a Case of Osteosarcoma of the Neck

Stanley I. Gutiontov, MD1,2; Zachary S. Zumsteg, MD2,3; Benjamin H. Lok, MD2; Sean Berry, PhD2; Chiaojung J. Tsai, MD, PhD2; Sean M. McBride, MD, MPH2; Nadeem Riaz, MD2; Oren Cahlon, MD2; and Nancy Y. Lee, MD2

1Northwestern University Feinberg School of Medicine, Chicago, IL, USA
2Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York, NY, USA
3Cedars Sinai Samuel Oschin Comprehensive Cancer Center, Los Angeles, CA, USA

Abstract

A 33-year-old man with symptomatic, unresectable osteosarcoma of the neck experienced disease progression despite treatment with multiple systemic agents. Given the tumor location, adjacent to the spinal cord and encasing the brachial plexus, proton beam therapy was recommended instead of conventional photon radiation therapy. The treatment was delivered in 3 weekly 10 cobalt-gray equivalents fractions, and there was minimal associated toxicity. There has been significant improvement in the patient’s presenting symptoms as well as radiologically stable disease at 1 year. A photon intensity–modulated radiation therapy plan was created retrospectively for dosimetric comparison and demonstrated noninferiority, thereby highlighting the need for judicious use of proton therapy in certain cases.

Keywords: head and neck, hypofractionation, osteosarcoma, outcomes, proton therapy

Introduction

Osteosarcoma of the head and neck is a rare malignancy without prospective evidence to guide management decisions. Prognosis is relatively poor [1, 2], and patterns of failure differ from those found in osteosarcomas arising in other regions. Distant metastasis rates are lower, and rates of local failure are high [2, 3]. Following imaging workup and pathologic diagnosis [4], the mainstay of treatment is adequate surgical resection [1, 5–7]. However, obtaining widely negative margins in the head and neck can be challenging, and patients with borderline resectable or unresectable disease often undergo neoadjuvant chemotherapy with various combinations of methotrexate, doxorubicin, cisplatin, and ifosfamide [8].

Osteosarcoma has traditionally been considered a radiation-resistant disease [9], and photon therapy has been used primarily in the setting of unresectable or incompletely resected disease. Meanwhile, the available data for particle therapy in osteosarcoma has been promising, but limited, and will be reviewed below. In this case, we used hypofractionated proton radiation therapy to take advantage of the biology of high dose per fraction radiation; such an approach has been demonstrated to be safe in photon therapy of head and neck squamous cell carcinomas in several prospective studies [10–12]. A comparison photon intensity–modulated radiation therapy plan was created posttreatment, which demonstrated dosimetric noninferiority to the executed proton plan. To our knowledge, this is the first case of a cervical osteosarcoma treated with
hypofractionated proton therapy in the literature and an excellent example of the importance of both comparative dosimetry and the judicious use of proton therapy.

Case Report

A 33-year old man with medical history significant for severe psoriasis, treated with adalimumab, presented to an outside hospital with neck pain and right upper-extremity discomfort of approximately 2 years’ duration, as well as progressive, work-limiting, right upper-extremity weakness during the past several months. Physical therapy had not improved his symptoms, and a prior nerve-conduction study had demonstrated a right C6 radiculopathy. On examination, there was torticollis, a palpable right-sided soft tissue neck mass, and decreased right upper-extremity strength and sensation, proximal greater than distal.

Magnetic resonance imaging of the cervical spine was performed and demonstrated a poorly defined, nonenhancing, densely calcified, paraspinal mass extending from C2 to T1, inseparable from the adjacent vertebral bodies’ bony matrix and invading the right anterior scalene and longus colli muscles, with adjacent soft tissue reaction. There was obliteration of the right internal jugular vein, encasement of the right carotid and vertebral arteries, and abutment and invasion of the right brachial plexus (Figure 1). A computed tomography (CT)–guided biopsy was performed. Pathology showed a fibrous and spindle cell lesion that could not be further classified. Immunohistochemistry showed focal positivity for smooth muscle actin and CD34, but was negative for β-catenin, desmin, S100, TLE-1, and ERG. A positron emission tomography (PET)/CT demonstrated a hypermetabolic, right, paraspinal mass (standardized uptake value, 8.3) and indeterminate, mildly hypermetabolic, bilateral cervical and mediastinal lymph nodes. An open surgical biopsy was subsequently performed. Pathology from this procedure demonstrated high-grade osteosarcoma, with Ki-67 staining up to 15% of the cells in some areas. None of 12 excised supraclavicular nodes contained evidence of metastatic disease.

Given the unresectable nature of the mass, a multidisciplinary tumor board recommended neoadjuvant chemotherapy to attempt to shrink the mass sufficiently to allow for resection. The patient, therefore, received one cycle of cisplatin and doxorubicin followed by 2 cycles of high-dose methotrexate, but mild, local progression was noted on his first restaging magnetic resonance imaging. The patient then underwent 2 cycles of ifosfamide and etoposide with stabilization of disease but discontinued this regimen secondary to neurotoxicity and delirium. Concurrent chemoradiation was recommended, but the patient chose to pursue additional systemic therapy.
He subsequently received 7 cycles of gemcitabine and docetaxel. There was a slight decrease in the neck mass following treatment, and a 3-month treatment break was initiated at the patient’s request. After this treatment break, interval imaging showed stable, local disease. However, an increase of several subcentimeter lung nodules was noted and thought to be suspicious for metastases. He was then enrolled in a clinical trial using alisertib, an Aurora kinase inhibitor. Interval imaging again demonstrated stable disease, but the patient came off the study after 3 months for financial reasons.

The patient then received sorafenib for 8 months and had significant improvement in his neck pain and a mild decrease in his neck mass radiographically. However, the patient decided to stop sorafenib for the next 4 months due to fatigue. The patient restarted sorafenib for an additional 2 months but was found to have radiographic local progression. He then received 2 cycles of liposomal doxorubicin but again progressed locally.

After that, radiation oncology was consulted. Given that the patient’s paraspinal osteosarcoma was infiltrating the right brachial plexus as well as the adjacent neural foramina, hypofractionated radiation therapy was recommended to provide local control and symptomatic relief. To minimize radiation dose to the adjacent spinal cord and esophagus, proton beam therapy was used. The patient was treated with a 4-field technique using thermoplastic immobilization devices and daily stereoscopic kilovolt image guidance (Figures 2 and 3). A 0.3-cm planning margin for setup uncertainty was added to the clinical target volume. The patient received 3 fractions of 10 cobalt gray equivalent (CGE) delivered once weekly, for a total dose of 30 CGE, with a resulting biologically equivalent dose of 115.7 Gy assuming an $\alpha/\beta$ of 3.5 [13]. The visible spinal cord was contoured with a generous planning organ-at-risk volume margin of 3 to 6 mm. In areas in which the spinal cord was challenging to
delineate, the entire spinal canal was contoured. Maximum doses to 0.1 cm³ and the cord surface of the spinal canal were 20.97 and 24.02 CGE, respectively. Mean doses to the oral cavity, esophagus, and larynx were at 0.12, 9.94, and 12.09 CGE, respectively. The patient did not receive prophylactic steroids and experienced no acute toxicities, with the exception of one episode of transient, grade 1 nausea. There were no exacerbations of his baseline weakness or pain.

A PET/CT scan performed 1 week after delivery of the final 10 CGE dose showed a significant decrease in avidity (range, 6.2 to 3.4) when compared with the PET/CT performed 1 month before the start of radiation therapy.

The patient is now approximately 1 year out from proton therapy and has had a significant improvement in symptoms. He has not experienced any late toxicities. The CT imaging performed at his last follow-up showed stable disease (Figure 4).

Discussion

Osteosarcomas of the head and neck are rare, accounting for <10% of all osteosarcomas and <1% of all head and neck cancers [2, 14]. Most head and neck osteosarcomas are diagnosed in the patient's third and fourth decade—about a decade later than appendicular osteosarcomas—with a slight male predominance. Most head and neck osteosarcomas occur in the mandible and maxilla [2]. Other head and neck sites, such as the vertebrae and cervical soft tissues, as in our patient, can also give rise to osteosarcoma, although this is relatively rare. For example, in a relatively large series of patients with osteosarcoma of the head and neck from MD Anderson, only 1 of 119 tumors arose from the cervical soft tissues [15].

Prognosis is relatively poor with head and neck osteosarcoma, and even worse outcomes have been associated with head and neck osteosarcomas arising outside of the mandible or maxilla [1, 2]. Furthermore, patterns of failure for head and neck osteosarcoma are unique compared with osteosarcomas arising in other regions. For example, even with adequate surgical resection, high rates of local failure have been observed in head and neck osteosarcomas, which greatly exceed those of osteosarcomas arising from other bones [2]. Conversely, distant metastases have been reported to occur in 10% to 20% of head and neck osteosarcomas, compared with 50% to 75% of osteosarcomas outside of that region [2, 3]. Thus, it is unclear whether treatment paradigms for other osteosarcomas are applicable to those occurring in the head and neck region.

Clinical presentation depends on the location of the tumor. In a study of 44 patients with head and neck osteosarcoma from our institution [5], a clinically detectable mass was the most common presenting symptom, occurring in 84% of patients. Other common symptoms are pain or dental complaints.

Once a thorough history and physical are obtained, imaging studies are essential for staging, diagnosis, and therapeutic recommendations in head and neck osteosarcoma. Although no study is diagnostic, a combination of plain radiographs, CT scans, magnetic resonance imaging, and fludeoxyglucose-PET imaging are useful, both for defining the local extent of disease and for staging. Although conventional osteosarcoma is readily identified on plain films as an intramedullary mass with an
immature, clouddlike bone formation in the metaphyses of the long bones, the imaging features of less-common subtypes (eg, telangiectatic, small cell, periosteal, among others) are variable and often overlap with those of other entities.

After imaging workup, a pathologic diagnosis must be obtained [4]. In many cases, needle biopsy fails to yield sufficient tissue for accurate classification of benign or malignant bone tumors [16], and studies have shown that fine-needle aspiration can be nondiagnostic in up to 25% bone sarcomas [4, 17]. By contrast, core needle biopsies performed by orthopedic surgeons have a success rate of 98% [18]. Open surgical biopsy is considered the diagnostic gold standard. In addition to establishing the diagnosis of osteosarcoma, biopsy is also important to establish the grade of the tumor [19].

Adequate surgical resection is the mainstay of treatment for osteosarcoma, and gross total resection with negative margins has been shown to be a crucial factor affecting both cause-specific and overall survival in numerous studies [1, 5–7]. However, obtaining widely negative margins in the head and neck can be challenging because of the region’s complex anatomy and its control of critical functions, including speech, swallowing, and breathing. Patients with borderline resectable or unresectable disease, such as our patient, often undergo neoadjuvant chemotherapy in attempt to sufficiently downsize the tumor so that gross total resection is feasible.

The most efficacious systemic agents in osteosarcoma are methotrexate, doxorubicin, cisplatin, and ifosfamide [8]. One combination (doxorubicin and cisplatin) achieves an overall histopathologic response rate of approximately 30% and, in combination with surgery, a 5-year overall survival and progression-free survival of 55% and 44%, respectively [20]. However, most patients do not have durable responses to conventional cytotoxic therapies, highlighting the need for new approaches. Molecularly targeted agents have also shown activity in osteosarcoma. For example, the multitargeted tyrosine kinase inhibitor sorafenib has shown progression-free survival of 46% at 4 months in patients who failed standard multimodal therapy with 8% partial responses, 6% minor responses, and 34% stable disease. However, improving on these modest results by combining sorafenib with other molecularly targeted agents has been a challenge. For instance, a recent study combining sorafenib and everolimus was unable to attain a prespecified target of 6-month progression-free survival of ≥50% and resulted in significant grade 3 and 4 toxicities [21, 22]. Our patient did demonstrate a minor radiographic and symptomatic response to sorafenib, but the drug was discontinued because of fatigue.

Unfortunately, given that our patient’s osteosarcoma did not achieve a sufficient response with any systemic agent to be deemed surgically resectable, curative therapy was not possible. Given his increasing symptomatology and continued progression of the tumor in an anatomically vital area adjacent to critical neurovascular structures, radiation therapy was recommended. Osteosarcoma has traditionally been considered a radiation-resistant disease [9], and photon therapy has been used primarily in the setting of unresectable or incompletely resected disease. Several series have demonstrated a trend toward improved local control with doses >55 Gy [23, 24]; one representative study of this treatment group demonstrated 5-year local control of 71% ± 9% (mean ± SD). Nonetheless, local outcomes remain suboptimal.

Given the radioresistance of this disease and the critical normal structures in the head and neck, proton therapy was recommended for our patient to allow delivery of relatively high biologically equivalent doses of radiation while protecting the spinal cord, oral cavity, esophagus, and larynx from an excess dose. Proton therapy is capable of delivering highly conformal radiation dose distributions with essentially no exit dose, thereby markedly reducing the dose to critical structures in specific scenarios [25]. The available data for particle therapy in osteosarcoma has been promising but limited. In the largest series to date, Matsunobu and colleagues [26] demonstrated 5-year local control and overall survival rates of 62% and 33%, respectively, in 78 patients with medically inoperable osteosarcoma of the trunk treated with carbon ion therapy. Another study from the Massachusetts General Hospital [27] reported that 5-year disease-free survival for all cases was 65%, and the 5-year overall survival was 67% when delivering 68.40 CGE with either protons or mixed protons and photons to 55 unresected or partially resected osteosarcomas, although only 5 cases involved head and neck osteosarcomas. More recently, Jingu and colleagues [28] demonstrated a 91.8%, 3-year local-control rate and a 74.1%, 3-year overall survival in 27 unresectable bone and soft tissue sarcomas of the head and neck treated with carbon ions.

We chose to use hypofractionated proton radiation therapy to take advantage of the biology of high dose per fraction radiation and to maximize patient convenience. Hypofractionated radiation therapy has been demonstrated to be safe in head and neck squamous cell carcinomas in several prospective studies [10–12]. Using this approach, we were able to deliver a biologically equivalent dose of 116 CGE to the target volume while meeting normal tissue constraints. Interestingly, when we created a 3-fraction, hypofractionated photon intensity–modulated radiation therapy plan posttreatment for dosimetric comparison (Figure 5) using 8 beams (2/8 noncoplanar) of 6 MV x-rays, we noted equivalence (maximum 0.1 cm³ spinal canal, 20.97 CGE versus 2170 centigray (cGy); mean oral cavity, 12 CGE versus 439 cGy; mean esophagus, 9.94 CGE versus 451 cGy; mean larynx, 12.09 CGE versus 900 cGy).
Conclusion
Proton therapy was a safe and effective modality for the treatment of this cervical osteosarcoma. However, retrospective dose comparison between our proton plan and a photon intensity–modulated radiation therapy plan demonstrated equivalence; therefore, at a minimum, we would recommend judicious use of this expensive modality and, at a maximum, for complex, off-protocol cases in which there is no high-quality evidence supporting particle therapy, it may be worth considering a priori photon/proton treatment planning comparisons before embarking on a course of proton therapy. To our knowledge, no study investigating the effects, economic and otherwise, of such an approach has been undertaken. Regardless, the role of proton beam therapy in this setting warrants further investigation.

ADDITIONAL INFORMATION AND DECLARATIONS

Conflicts of Interest: The authors have no conflicts to disclose.

References
1. Smith RB, Apostolakis LW, Karnell LH, Koch BB, Robinson RA, Zhen W, Menck HR, Hoffman HT. National Cancer Data Base report on osteosarcoma of the head and neck. Cancer. 2003;98:1670–80.
2. Kassir RR, Rassekh CH, Kinsella JB, Segas J, Carrau RL, Hokanson JA. Osteosarcoma of the head and neck: meta-analysis of nonrandomized studies. Laryngoscope. 1997;107:56–61.
3. Giuliano AE, Feig S, Eilber FR. Changing metastatic patterns of osteosarcoma. Cancer. 1984;54:2160–4.
4. Ward WG, Savage P, Boles CA, Kilpatrick SE. Fine-needle aspiration biopsy of sarcomas and related tumors. *Cancer Control*. 2001;8:232–8.

5. Patel SG, Meyers P, Huvos AG, Wolden S, Singh B, Shaha AR, Boyle JO, Pfister D, Shah JP, Kraus DH. Improved outcomes in patients with osteogenic sarcoma of the head and neck. *Cancer*. 2002;95:1495–503.

6. Canadian Society of Otalaryngology-Head and Neck Surgery Oncology Study Group. Osteogenic sarcoma of the mandible and maxilla: a Canadian review (1980–2000). J *Otolaryngol*. 2004;33:139–44.

7. O’Neill JP, Bilsky MH, Kraus D. Head and neck sarcomas: epidemiology, pathology, and management. *Neurosurg Clin N Am*. 2013;24:67–78.

8. Yamamoto N, Tsuchiya H. Chemotherapy for osteosarcoma—where does it come from? what is it? where is it going? *Expert Opin Pharmacother*. 2013;14:2183–93.

9. Ogawa Y, Takahashi T, Kobayashi T, Kariya S, Nishioka A, Mizobuchi H, Noguchi M, Hamasato S, Tani T, Seguchi H, Yoshida S, Sonobe H. Mechanism of apoptotic resistance of human osteosarcoma cell line, HS-Os-1, against irradiation. *Int J Mol Med*. 2003;12:453–8.

10. Vargo JA, Ferris RL, Ohr J, Clump DA, Davis KS, Duvvuri U, Kim S, Johnson JT, Bauman JE, Gibson MK, Branstetter BF, Heron DE. A prospective phase 2 trial of reirradiation with stereotactic body radiation therapy plus cetuximab in patients with previously irradiated recurrent squamous cell carcinoma of the head and neck. *Int J Radiat Oncol Biol Phys*. 2015;91:480–8.

11. Vargo JA, Heron DE, Ferris RL, Rwigema JC, Wegner RE, Kalash R, Ohr J, Kubicek GJ, Burton S. Prospective evaluation of patient-reported quality-of-life outcomes following SBRT ± cetuximab for locally-recurrent, previously-irradiated head and neck cancer. *Radiother Oncol*. 2012;104:91–5.

12. Heron DE, Ferris RL, Karamouzis M, Andrada RS, Deeb EL, Burton S, Gooding WE, Branstetter BF, Mountz JM, Johnson JT, Argiris A, Grandis JR, Lai SY. Stereotactic body radiotherapy for recurrent squamous cell carcinoma of the head and neck: results of a phase I dose-escalation trial. *Int J Radiat Oncol Biol Phys*. 2009;75:1493–500.

13. Fitzpatrick CL, Farese JP, Milner RJ, Salute ME, Rajon DA, Morris CG, Bova FJ, Lurie DM, Siemann DW. Intrinsic radiosensitivity and repair of sublethal radiation-induced damage in canine osteosarcoma cell lines. *Am J Vet Res*. 2008;69:1197–202.

14. Mendenhall WM, Fernandes R, Werning JW, Vaysberg M, Malyapa RS, Mendenhall NP. Head and neck osteosarcoma. *Am J Otolaryngol*. 2011;32:597–600.

15. Guadagnolo BA, Zagars GK, Raymond AK, Benjamin RS, Sturgis EM. Osteosarcoma of the jaw/craniofacial region: outcomes after multimodality treatment. *Cancer*. 2009;115:3262–70.

16. Gumay S. Pathological diagnosis of bone sarcoma. *Gan To Kagaku Ryoho*. 2000;27(suppl 2):420–6.

17. Kilpatrick SE, Cappellari JO, Bos GD, Gold SH, Ward WG. Is fine-needle aspiration biopsy a practical alternative to open biopsy for the primary diagnosis of sarcoma? experience with 140 patients. *Am J Clin Pathol*. 2001;115:59–68.

18. Yuan J, Zhang H, Jiang Z, Zhou J, Yang Q, Zhang Z. Accuracy of different preoperative biopsy techniques in diagnosis of osteosarcomas and their value in prognostic evaluation [in Chinese]. *Zhonghua Bing Li Xue Za Zhi*. 2015;44:315–9.

19. Guillou L, Coindre JM, Bonichon F, Nguyen BB, Terrier P, Collin F, Vilain MO, Mandam AM, Le Doussal V, Leroux A, Jacquemier J, Duplay H, Sastre-Garau X, Costa J. Comparative study of the National Cancer Institute and French Federation of Cancer Centers Sarcoma Group grading systems in a population of 410 adult patients with soft tissue sarcoma. *J Clin Oncol*. 1997;15:350–62.

20. Souhami RL, Craft AW, Van der Eijken JW, Nooij M, Spooner D, Bramwell VH, Wierzbicki R, Malcolm AJ, Kirkpatrick A, Uscinska BM, Van Glabbeke M, Machin D. Randomised trial of two regimens of chemotherapy in operable osteosarcoma: a study of the European Osteosarcoma Intergroup. *Lancet*. 1997;350:911–7.

21. Grignani G, Palmerini E, Dileo P, Asaftei SD, D'Ambrosio L, Picci P, Fagioli F, Casali PG, Ferrari S, Aglietta M. A phase II trial of sorafenib in relapsed and unresectable high-grade osteosarcoma after failure of standard multimodal therapy: an Italian Sarcoma Group study. *Ann Oncol*. 2012;23:508–16.

22. Grignani G, Palmerini E, Ferreira E, D'Ambrosio L, Bertulli R, Asaftei SD, Tamburini A, Pignocino Y, Sangiolo D, Marchesi E, Capozzi F, Biagini R, Gambarotti M, Fagioli F, Casali PG, Picci P, Ferrari S, Aglietta M, Italian Sarcoma G. Sorafenib and everolimus for patients with unresectable high-grade osteosarcoma progressing after standard treatment: a non-randomised phase 2 clinical trial. *Lancet Oncol*. 2015;16:98–107.

*Gutiontov et al. (2017), Int J Particle Ther*
Proton therapy for a neck osteosarcoma

23. Machak GN, Tkachev SI, Solovyev YN, Sinyukov PA, Ivanov SM, Kochergina NV, Ryjkov AD, Tepliakov VV, Bokhian BY, Glebovskaya VV. Neoadjuvant chemotherapy and local radiotherapy for high-grade osteosarcoma of the extremities. *Mayo Clin Proc*. 2003;78:147–55.

24. DeLaney TF, Park L, Goldberg SI, Hug EB, Liebsch NJ, Munzenrider JE, Suit HD. Radiotherapy for local control of osteosarcoma. *Int J Radiat Oncol Biol Phys*. 2005;61:492–8.

25. Holliday EB, Frank SJ. Proton radiation therapy for head and neck cancer: a review of the clinical experience to date. *Int J Radiat Oncol Biol Phys*. 2014;89:292–302.

26. Matsunobu A, Imai R, Kamada T, Imaizumi T, Tsuji H, Tsuji H, Shiyama Y, Honda H, Tatezaki S, Working Group for B, Soft Tissue S. Impact of carbon ion radiotherapy for unresectable osteosarcoma of the trunk. *Cancer*. 2012;118:4555–63.

27. Ciernik IF, Niemierko A, Harmon DC, Kobayashi W, Chen YL, Yock TI, Ebb DH, Choy E, Raskin KA, Liebsch N, Hornick FJ, Delaney TF. Proton-based radiotherapy for unresectable or incompletely resected osteosarcoma. *Cancer*. 2011;117:4522–30.

28. Jingu K, Tsuji H, Mizoe JE, Hasegawa A, Bessho H, Takagi R, Morikawa T, Tonogi M, Tsuji H, Kamada T, Yamada S; Organizing Committee for the Working Group for Head-and-Neck C. Carbon ion radiation therapy improves the prognosis of unresectable adult bone and soft-tissue sarcoma of the head and neck. *Int J Radiat Oncol Biol Phys*. 2012;82:2125–31.