Future Advances in Spine Surgery

Spine Oncology – Primary Spinal Tumors

Nicolas Dea, MD, MSc, FRCSC[1], Ziya Gokaslan, MD[2], Mark Bilsky MD[3], David Choi MD[4] and Charles Fisher, MD, MHSc, FRCSC[5]

[1] Division of Neurosurgery, Department of Surgery, Université de Sherbrooke, Sherbrooke, Quebec, Canada

[2] Department of Neurosurgery, The Warren Alpert Medical School of Brown University, Providence, Rhode Island, USA

[3] Department of Neurosurgery, Memorial Sloan-Kettering Cancer Center, New York, NY, USA

[4] Department of Neurosurgery, The National Hospital for Neurology and Neurosurgery, University College London, London, UK

[5] Department of Orthopaedics, Division of Spine, University of British Columbia and Vancouver General Hospital, Vancouver, BC, Canada

Corresponding author

Nicolas Dea

Division of Neurosurgery

3001 12th Avenue North, Local 5110

Sherbrooke, Quebec, Canada, J1H 5N4

Tel: 819-346-1110 ext 73324

Fax: 819-820-6452

Email: nicolas.dea@usherbrooke.ca

Sources of support: AOSpine North America

Abstract

Primary tumors originating from the spine are very complex and challenging entities to treat. Because of their rarity, a multicenter collaborative network is essential to shepherd the best research and contribute to the dissemination of the best evidence possible. Over the last few years, several advances have occurred in many different fields. Surgery is still the cornerstone of treatment in most cases. The occasional suboptimal outcomes and high morbidity of surgical treatment have however encouraged professionals caring for these patients to explore safer treatment options and alternatives or adjuncts to surgical treatment. A number of novel treatment strategies have emerged from the medical, interventional radiology, radiation oncology and molecular worlds. This has truly positioned primary spine tumors at the forefront of multidisciplinary care. This article discusses these recent advances in detail to equip the oncologic spine surgeon and their team to better counsel and treat these patients. Most of these advances allow for a more tailored, efficient and, most importantly less morbid management of primary spine tumors. Some of these advances are still under investigation however and evidence-based oncological principles should still be strongly encouraged.

Running title: Primary Spinal Tumors

Keywords: en bloc resection, interventional radiology, medical treatment, molecular sequencing, primary spine tumors, radiation oncology, surgery

Introduction

Advances in primary spinal tumor management have been numerous in many different fields, reflective of the multidisciplinary approach that its treatment requires. Once considered incurable, primary spinal tumors are now the research focus of many subspecialties, both surgical and medical, all sharing one common goal: cure. Advances in imaging and surgical techniques allow a broader application of evidence-based oncologic surgical principles for tumors originating from the spine. Surgery plays a central role in the management of these tumors, but many non-surgical modalities are also becoming available to the oncologic spine surgeon and their team to better deal with these highly complex patients. Medical treatment, percutaneous techniques, radiation therapy and molecular sequencing should now all be part of the decision making process when treating a patient harbouring a primary spinal tumor. The low prevalence of this type of tumor forces us to rely on international collaborative network of spine oncology centers[1]. Over the last few years, this shared and collaborative model has allowed access to large volumes of patients, which not only generated, but also contributed to the dissemination of the best evidence to date to guide management of primary spinal tumors. This article will first highlight the basic principles of management of primary tumor of the spine and then present the most recent advances in the different domains discussed above.

Primary spinal tumors should be managed in experienced quaternary centers with appropriate multidisciplinary support teams[2]. Performance of invasive

morphologic diagnostic procedures outside of such a tumor center has been demonstrated to independently impact prognosis[3]. Consequently, even prior to having their diagnosis, these patients should be referred to centers where definitive care will occur. The initial management will then include local and systemic staging that will culminate in a well-planned, CT-guided trocar biopsy. Open biopsy is correlated with increased risk of local recurrence and should therefore be avoided[2]. The surgeon should ideally perform the biopsy procedure since, depending on the final histology, the biopsy tract may have to be excised. Once the local and systemic staging are complete, and histological diagnosis made, the tumor can be classified using the Enneking classification[4]. Originally described in the 1980s for primary tumor of the appendicular skeleton, this classification remains the foundation for approaching tumors originating from the spine. Based on the Enneking stages, a specific surgical margin for tumor control is recommended[5]. Terminology is of utmost importance when studying primary spinal tumors. Inconsistencies in previous reports were in part due to variations in the terminology describing the resection margins. En bloc resection means an attempt at resecting the whole tumor in one piece, as opposed to curettage or piecemeal resection, which refers to a deliberate intralesional resection. However, on its own and without appropriate description of margins by an experienced musculoskeletal pathologist, “en bloc resection” has very little value. En bloc resection can have intralesional, marginal, wide or radical margins. Intralesional resection refers to a plane of dissection that has transgressed into the lesion. A marginal margin denotes that the dissection has been within the reactive zone or

the pseudocapsule surrounding the tumor, as opposed to wide margins where the plane of dissection is within normal tissue, beyond the reactive zone. Finally, radical resection refers to extracompartmental resection, which is not usually practical in the spine. Once the appropriate margin for control has been identified, the Weinstein-Boriani-Biagini (WBB) classification assists surgical planning by establishing feasibility criteria and strategies for achieving oncologic resection[6].

Surgical advances

Despite considerable advancements in non-surgical care, surgery still is the common denominator in most cases. Respecting the Enneking principles (Enneking appropriate, EA) is correlated with lower recurrence rates and improved survival for primary bone tumors[7-9]. Due to its rarity, very few studies however examined tumors arising from the spine specifically[3,10-14]. Moreover, most are single center retrospective studies of multiple different histological diagnoses. Using the collaborative effort outlined above, the AO Spine Knowledge Forum Tumor has conducted the largest multicenter analyses of diagnosis-specific primary bone tumors of the spine, providing the best available evidence to date on the surgical management of these tumors. They showed that respecting Enneking principles results in lower local recurrence (LR) rates and increased median survival (MS) for both osteosarcomas (LR 10 vs 44%; MS: 6.8 vs 3.7 years)[15] and chordomas of the mobile spine (LR 16 vs 46%; MS 8.4 vs 6.4years)[16]. Enneking appropriateness has furthermore been correlated with lower recurrence rates for chondrosarcomas (21 vs 48%, HR: 2.09)[17] and sacral chordomas (HR: 2.43)[18].

Interestingly however, despite local recurrence being strongly associated with mortality, these 2 last studies failed to show a relationship between respecting Enneking principles and survival. Short median follow-up (3 years in both studies) and the retrospective design of these reports might be an explanation for this lack of relationship. For aneurysmal bone cysts, no local recurrences were observed after EA resection compared to 12% for intralesionally resected benign aggressive tumors[19]. More analyses are currently underway for other benign aggressive tumors.

The unique anatomy of the spine and its relationship with the surrounding neural structures makes treatment of primary bone tumors a risky undertaking. The cost of achieving appropriate margins from a patient risk and impairment perspective is high. The importance of thorough surgical planning and multidisciplinary support cannot be overemphasized. Many adjuncts have also proven to be useful to reduce the morbidity of surgery. Surgical navigation can decrease injury to vital structures and allow for tumor free osteotomy cuts, which may further improve the rate of EA surgery[20]. Wound problems are among the most prevalent adverse events after these morbid interventions. Vancomycin powder[21], negative pressure wound therapy[22] and assistance from the plastic surgery team[23] are all key principles to decrease adverse events in this patient population.

Medical and percutaneous advances

Of the most meaningful recent advances in primary spinal oncology, non-surgical treatment of primary benign spine tumors is worth a mention. Despite their benign

histology, some benign tumors may have an aggressive behaviour and be associated with undesirable outcomes even with appropriate oncologic resections. Moreover, considering the benign nature of some of these tumors, it might be unacceptable to inflict irreversible neurological deficit that an Enneking appropriate resection would command. Until recently, there were however no other suitable options and surgical resection was the mainstay of treatment. Alternative therapies are now emerging that offer promising outcomes, with potentially less morbidity.

In 2009, the Spine Oncology Study Group recommended en bloc resection for sacral and mobile spine giant cell tumors (GCT) when deemed feasible based on staging [24]. Since then however a new medical option has arisen. Multinucleated giant cells found in GCT have been found to express high levels of an essential mediator in bone resorption: RANKL. The use of Denosumab, a monoclonal antibody that specifically inhibits RANKL, has been correlated with good disease control and allows for less morbid surgery and may even allow the avoidance of surgery in some cases[25-27]. Goldschlager et al. reported on our initial experience with Denosumab for GCT originating from the spine[28]. Results were encouraging: all tumors showed radiologic response, and surgical resection was facilitated by a firmer tumor and easier dissection. This new data support the use of Denosumab as a neo adjuvant therapy to shrink tumors and facilitate surgical resection as well as in the case of inoperable GCT. Although very promising, our experience with this treatment modality is still limited and further studies are needed. Specifically, long-term effect of treatment, optimal duration of treatment and its adjuvant role is still uncertain (ref spine focus issue paper).

Aneurysmal bone cyst (ABC), another benign tumor, has traditionally been treated with pre-operative selective arterial embolization (SAE) followed by intralesional gross total resection[19,24]. This is however associated with a high recurrence rate[29]. Although en bloc resection is associated with an extremely low risk of recurrence, potential morbidity associated with this type of surgical treatment has once again led to the search for alternative treatment options. Among them, SAE as a stand-alone treatment has emerged[30,31] showing initial regression and recurrence rates similar to surgical excision, but without surgical complications. However, multiple embolizations might be required (35% involved 6 SAE procedures or more) to achieve tumoral response, which raises the issue of radiation exposure, especially in the paediatric population in whom this type of tumor is prevalent. While pre-operative SAE is well accepted for this vascular tumor, stand-alone treatment is another treatment option to consider in selected cases of ABC without extensive neural element involvement or high risk of pathological fracture.

Osteoid osteomas (OO) are small latent or active benign tumors that will characteristically present with nocturnal pain and deformity in the paediatric population. Until recently, the gold standard treatment was surgical curettage. Percutaneous thermal ablation has changed the treatment paradigm for OO of the appendicular skeleton with failure rates as low as 5% being reported[32,33]. This minimally invasive treatment is now gaining popularity for spinal tumors showing very good results, similar to OO of the appendicular skeleton[34]. The main concern using this technique for tumors originating from the spine is their close vicinity to neural structures and the associated risk of thermal

injury. In cases where there is no cortex surrounding the tumor or for tumors in close proximity to neural elements, thermal protection strategies such as epidural irrigation have been described with successful outcomes[34-36].

Radiation therapy advances

Appropriate oncologic resection remains the gold standard when treating chordomas of the spine. However, even in experienced hands, en bloc resection with marginal or wide margins is possible in only a few cases (21%)[37]. Consequently, neo-adjuvant or adjuvant treatment is often necessary to increase local control. Primary malignant tumors of the spine are known to be radioresistant. As such, radiation doses of at least 60 to 65 Gy equivalents has been recommended as adjuvant treatment for chordomas and chondrosarcomas of the spine when there has been incomplete resection or an intralesional margin[38]. While the best radiation therapy regimen is still unknown, many new radiation therapy modalities and schedules of treatment are becoming available and are changing the treatment paradigm for these tumors.

Photon-based intensity modulated radiation therapy (IMRT) is a technique that allows 3 dimensional conformal delivery of radiation. This permits the required high dose to be delivered to the tumor without exceeding the safety limits that can be transmitted to the surrounding tissues. With advances in image guidance and radiation delivery methods, radiation doses that were only possible with proton beam radiotherapy can now be delivered with photon-based treatment, which is more widely available[39-41].

Another promising advance using photons is high-dose single fraction stereotactic radiosurgery. Higher doses per fraction result in more irreparable and lethal DNA damage, which may confer a significant biological advantage for this radioresistant tumor. Favourable 2-year local control rate of 95% has been reported with low morbidity in a heterogeneous chordoma population[42]. This however constitutes preliminary data and long-term local control from high-dose single-fraction treatment is still unknown.

Proton beam radiation therapy (RT), because of its ability to deliver targeted very high doses of radiation while limiting dosage to surrounding tissues, has traditionally been the preferred option for radioresistant tumors in proximity to critical structures such as chordomas. Using a combination of photons and protons (median dosage 70.2 Gy Relative Biological Effectiveness-RBE), 5-year local control rate as high as 94% has been published for primary spine sarcomas[43]. Recurrent disease was associated with worse outcomes than primary or de novo treatment. To reduce the risk of tumor seeding at surgery, a combination of pre and post-operative radiation treatment has moreover been advocated[43-45]. In one study, the combination of preoperative RT, en bloc resection, and post-operative RT boost resulted in the highest rate of local tumor control when compared to post-operative RT alone[44]. The main concern of administering pre-operative RT is its potential negative effect on wound healing, especially for sacral tumors. By limiting the accuracy of treatment, the presence of hardware is moreover correlated with lower local control rates, which can also be an advantage of pre-operative RT[43,45,46]. As such, multidisciplinary cooperation and discussion between surgeons and radiation oncologists is imperative.

Lastly, carbon ion therapy constitutes another promising treatment strategy. This heavy charged particle seems to have a biologic advantage compared with photons or protons, due to its increased RBE[47]. Excellent local control rates for chordomas have been reported in retrospective single center studies using this technology [48,49]. One Japanese study reported a 5-year local control rate of 89% for unresectable sacral chordomas[50]. Even more impressive, Nishida et al. and reported better outcomes and less morbidity with carbon ion RT alone compared to surgery[51]. Although these are small series, it seems that carbon ion radiotherapy may be a promising alternative to surgery and that sacral chordomas may have the potential to be treated with radiation only.

In summary, the most recent literature reveals similar LC and MS regardless of the radiation therapy modality used (photon, proton, carbon ion) as long as doses are escalated to higher levels (>70GyRBE). Studies with long-term LC rates and well defined toxicity profiles are underway[52] and will hopefully help to answer which RT modality and schedule of treatment is more effective for these tumors (ref spine focus issue paper).

Molecular sequencing

Molecular targeted therapy is changing the way we treat cancer. Knowing the molecular signature of a specific tumor can lead to targeted therapy and improved outcomes. Liang et al. evaluated the expression of Aurora Kinase A and B in chondrosarcomas[53]. The ratio of positive expression of both the Aurora Kinase A and B was correlated with higher

degree of invasiveness and recurrence rates. Moreover, expression of Aurora Kinase A was found to be an independent factor predicting poorer survival. Another group found that the loss of RUNX3 expression, a tumor suppressor gene, was significantly associated with more aggressive chondrosarcoma types and decreased survival[54].

The T gene is central in chordoma pathogenesis [55-57]. Brachyury, the protein encoded by the T gene, is a transcription factor that plays a key role in the development of the notochord. It has been suggested that a single nucleotide polymorphism in the T gene is strongly linked to chordoma formation[55]. Although these molecular advances are still in their infancy, they may become important prognostic markers in the future and may form the basis of targeted medical therapy. It is thus crucial to prospectively analyse these markers and to create a collective bio bank to achieve this goal.

Health related Quality of life (HRQOL)

Quality of life studies are mandatory to investigate if the invasive treatment often required to treat primary spinal tumors is associated with acceptable quality of life for patients. Many articles have explored this important topic in recent years and have contributed to advancement in our understanding of the matter [58-62]. Interestingly, studies with long follow-up reveal that quality of life scores improve to close to normal values with time. Moreover, tumor recurrence seems to be correlated with worst HRQOL than the invasive treatment itself[59,61]. Evidence-based oncologic principles should thus be

strongly encouraged to reduce local recurrence and improve HRQOL. (ref spine focus issue paper)

Conclusion

Primary spinal tumor oncology is a very exciting field, benefitting from numerous important advancements over the past few years. While some of these may still be at an early stage, they seem very promising nonetheless. Prospective, collaborative data collection will hopefully shed more light on the topic and help confirm or refute novel treatment strategies. Until further studies are completed, we must however rely on the best available evidence to date and to adhere to evidence-based oncologic principles. Active research will hopefully lead to cure for more of these patients while reducing the complications of the multidisciplinary management of these patients.

Reference

1. Fisher CG, Goldschlager T, Boriani S, et al. An evidence-based medicine model for rare and often neglected neoplastic conditions. *Journal of Neurosurgery: Spine*. 2014;21(5):704–710. doi:10.3171/2014.7.SPINE13954.

2. Yamazaki T, McLoughlin GS, Patel S, Rhines LD, Fourney DR. Feasibility and safety of en bloc resection for primary spine tumors: a systematic review by the Spine Oncology Study Group. *Spine*. 2009;34(22 Suppl):S31–S38. doi:10.1097/BRS.0b013e3181b8b796.

3. Bergh P, Kindblom LG, Gunterberg B, Remotti F, Ryd W, Meis-Kindblom JM. Prognostic factors in chordoma of the sacrum and mobile spine: a study of 39 patients. *Cancer*. 2000;88(9):2122–2134.

4. Enneking WF. A system of staging musculoskeletal neoplasms. *Clin Orthop Relat Res*. 1986;(204):9–24.

5. Chan P, Boriani S, Fourney DR, et al. An assessment of the reliability of the Enneking and Weinstein-Boriani-Biagini classifications for staging of primary spinal tumors by the Spine Oncology Study Group. *Spine*. 2009;34(4):384–391. doi:10.1097/BRS.0b013e3181971283.

6. Boriani S, Weinstein JN, Biagini R. Primary bone tumors of the spine: terminology and surgical staging. *Spine*. 1997;22(9):1036–1044.

7. Weinstein JN, McLain RF. Primary tumors of the spine. *Spine*. 1987;12(9):843–

851.

8. Lee FY, Mankin HJ, Fondren G, et al. Chondrosarcoma of bone: an assessment of outcome. *J Bone Joint Surg Am*. 1999;81(3):326–338.

9. Spanier SS, Shuster JJ, Vander Griend RA. The effect of local extent of the tumor on prognosis in osteosarcoma. *J Bone Joint Surg Am*. 1990;72(5):643–653.

10. Sciubba DM, la Garza-Ramos De R, Rory Goodwin C, et al. Clinical, surgical, and molecular prognostic factors for survival after spinal sarcoma resection. *Neurosurgical FOCUS*. 2016;41(2):E9. doi:10.3171/2016.5.FOCUS16118.

11. Amendola L, Cappuccio M, De Iure F, Bandiera S, Gasbarrini A, Boriani S. En bloc resections for primary spinal tumors in 20 years of experience: effectiveness and safety. *Spine J*. 2014;14(11):2608–2617. doi:10.1016/j.spinee.2014.02.030.

12. Fisher CG, Saravanja DD, Dvorak MF, et al. Surgical Management of Primary Bone Tumors of the Spine. *Spine*. 2011;36(10):830–836. doi:10.1097/BRS.0b013e3181e502e5.

13. Boriani S, Chevalley F, Weinstein JN, et al. Chordoma of the spine above the sacrum. Treatment and outcome in 21 cases. *Spine*. 1996;21(13):1569–1577.

14. Sciubba DM, Okuno SH, Dekutoski MB, Gokaslan ZL. Ewing and osteogenic sarcoma: evidence for multidisciplinary management. *Spine*. 2009;34(22 Suppl):S58–S68. doi:10.1097/BRS.0b013e3181ba6436.

15. Dekutoski MB, Clarke MJ, Rose P, et al. Osteosarcoma of the spine: prognostic

variables for local recurrence and overall survival, a multicenter ambispective study. *Journal of Neurosurgery: Spine*. March 2016:1–10. doi:10.3171/2015.11.SPINE15870.

16. Gokaslan ZL, Zadnik PL, Sciubba DM, et al. Mobile spine chordoma: results of 166 patients from the AOSpine Knowledge Forum Tumor database. *Journal of Neurosurgery: Spine*. December 2015:1–8. doi:10.3171/2015.7.SPINE15201.

17. Fisher CG, Versteeg AL, Dea N, et al. Surgical Management of Spinal Chondrosarcomas. *Spine*. February 2016:1. doi:10.1097/BRS.0000000000001485.

18. Varga PP, Szövérfi Z, Fisher CG, et al. Surgical treatment of sacral chordoma: prognostic variables for local recurrence and overall survival. *Eur Spine J*. 2014;24(5):1092–1101. doi:10.1007/s00586-014-3728-6.

19. Boriani S, Lo S-FL, Puvanesarajah V, et al. Aneurysmal bone cysts of the spine: treatment options and considerations. *J Neurooncol*. 2014;120(1):171–178. doi:10.1007/s11060-014-1540-0.

20. Dasenbrock HH, Clarke MJ, Bydon A, et al. En Bloc Resection of Sacral Chordomas Aided by Frameless Stereotactic Image Guidance. *Neurosurgery*. 2012;70:ons82–ons88. doi:10.1227/NEU.0b013e31822dd958.

21. Ghobrial GM, Cadotte DW, Williams K Jr., Fehlings MG, Harrop JS. Complications from the use of intrawound vancomycin in lumbar spinal surgery: a systematic review. *Neurosurgical FOCUS*. 2015;39(4):E11. doi:10.3171/2015.7.FOCUS15258.

22. Adogwa O, Fatemi P, Perez E, et al. Negative pressure wound therapy reduces incidence of postoperative wound infection and dehiscence after long-segment thoracolumbar spinal fusion: a single institutional experience. *Spine J*. 2014;14(12):2911–2917. doi:10.1016/j.spinee.2014.04.011.

23. Garvey PB, Rhines LD, Dong W, Chang DW. Immediate soft-tissue reconstruction for complex defects of the spine following surgery for spinal neoplasms. *Plast Reconstr Surg*. 2010;125(5):1460–1466. doi:10.1097/PRS.0b013e3181d5125e.

24. Harrop JS, Schmidt MH, Boriani S, Shaffrey CI. Aggressive "benign" primary spine neoplasms: osteoblastoma, aneurysmal bone cyst, and giant cell tumor. *Spine*. 2009;34(22 Suppl):S39–S47. doi:10.1097/BRS.0b013e3181ba0024.

25. Thomas D, Henshaw R, Skubitz K, et al. Denosumab in patients with giant-cell tumour of bone:an open-label, phase 2 study. *Lancet Oncology*. 2010;11(3):275–280. doi:10.1016/S1470-2045(10)70010-3.

26. Chawla S, Henshaw R, Seeger L, et al. Safety and efficacy of denosumab for adults and skeletally mature adolescents with giant cell tumour of bone: interim analysis of an open-label, parallel-group, phase 2 study. *Lancet Oncol*. 2013;14(9):901–908. doi:10.1016/S1470-2045(13)70277-8.

27. Rutkowski P, Ferrari S, Grimer RJ, et al. Surgical downstaging in an open-label phase II trial of denosumab in patients with giant cell tumor of bone. *Ann Surg Oncol*. 2015;22(9):2860–2868. doi:10.1245/s10434-015-4634-9.

28. Goldschlager T, Dea N, Boyd M, et al. Giant cell tumors of the spine: has

denosumab changed the treatment paradigm. *Journal of Neurosurgery: Spine*. February 2015:1–8. doi:10.3171/2014.10.SPINE13937.

29. Vergel De Dios AM, Bond JR, Shives TC, McLeod RA, Unni KK. Aneurysmal bone cyst. A clinicopathologic study of 238 cases. *Cancer*. 1992;69(12):2921–2931.

30. Amendola L, Simonetti L, Simoes CE, Bandiera S, De Iure F, Boriani S. Aneurysmal bone cyst of the mobile spine: the therapeutic role of embolization. *Eur Spine J*. 2012;22(3):533–541. doi:10.1007/s00586-012-2566-7.

31. Boriani S, De Iure F, Campanacci L, et al. Aneurysmal bone cyst of the mobile spine: report on 41 cases. *Spine*. 2001;26(1):27–35.

32. Lanza E, Thouvenin Y, Viala P, et al. Osteoid Osteoma Treated by Percutaneous Thermal Ablation: When Do We Fail? A Systematic Review and Guidelines for Future Reporting. *Cardiovasc Intervent Radiol*. 2013;37(6):1530–1539. doi:10.1007/s00270-013-0815-8.

33. Rehnitz C, Sprengel SD, Lehner B, et al. CT-guided radiofrequency ablation of osteoid osteoma: correlation of clinical outcome and imaging features. *Diagn Interv Radiol*. 2013;19(4):330–339. doi:10.5152/dir.2013.096.

34. Tsoumakidou G, Thénint M-A, Garnon J, Buy X, Steib J-P, Gangi A. Percutaneous Image-guided Laser Photocoagulation of Spinal Osteoid Osteoma: A Single-Institution Series. *Radiology*. 2016;278(3):936–943. doi:10.1148/radiol.2015150491.

35. Weber M-A, Sprengel SD, Omlor GW, et al. Clinical long-term outcome, technical success, and cost analysis of radiofrequency ablation for the treatment of osteoblastomas and spinal osteoid osteomas in comparison to open surgical resection. *Skeletal Radiol*. 2015;44(7):981–993. doi:10.1007/s00256-015-2139-z.

36. Rybak LD, Gangi A, Buy X, La Rocca Vieira R, Wittig J. Thermal ablation of spinal osteoid osteomas close to neural elements: technical considerations. *American Journal of Roentgenology*. 2010;195(4):W293–W298. doi:10.2214/AJR.10.4192.

37. Boriani S, Bandiera S, Biagini R, et al. Chordoma of the mobile spine: fifty years of experience. *Spine*. 2006;31(4):493–503. doi:10.1097/01.brs.0000200038.30869.27.

38. Boriani S, Saravanja D, Yamada Y, Varga PP, Biagini R, Fisher CG. Challenges of local recurrence and cure in low grade malignant tumors of the spine. *Spine*. 2009;34(22 Suppl):S48–S57. doi:10.1097/BRS.0b013e3181b969ac.

39. Zabel-du Bois A, Nikoghosyan A, Schwahofer A, et al. Intensity modulated radiotherapy in the management of sacral chordoma in primary versus recurrent disease. *Radiother Oncol*. 2010;97(3):408–412. doi:10.1016/j.radonc.2010.10.008.

40. Sahgal A, Chan MW, Atenafu EG, et al. Image-guided, intensity-modulated radiation therapy (IG-IMRT) for skull base chordoma and chondrosarcoma: preliminary outcomes. *Neuro-Oncology*. 2015;17(6):889–894. doi:10.1093/neuonc/nou347.

41. Hug EB, Fitzek MM, Liebsch NJ, Munzenrider JE. Locally challenging osteo- and chondrogenic tumors of the axial skeleton: results of combined proton and photon radiation therapy using three-dimensional treatment planning. *Radiation Oncology Biology*. 1995;31(3):467–476. doi:10.1016/0360-3016(94)00390-7.

42. Yamada Y, Laufer I, Cox BW, et al. Preliminary Results of High-Dose Single-Fraction Radiotherapy for the Management of Chordomas of the Spine and Sacrum. *Neurosurgery*. 2013;73(4):673–680. doi:10.1227/NEU.0000000000000083.

43. DeLaney TF, Liebsch NJ, Pedlow FX, et al. Long-term results of Phase II study of high dose photon/proton radiotherapy in the management of spine chordomas, chondrosarcomas, and other sarcomas. *J Surg Oncol*. 2014;110(2):115–122. doi:10.1002/jso.23617.

44. Rotondo RL, Folkert W, Liebsch NJ, et al. High-dose proton-based radiation therapy in the management of spine chordomas: outcomes and clinicopathological prognostic factors. *Journal of Neurosurgery: Spine*. September 2015:1–10. doi:10.3171/2015.3.SPINE14716.

45. Indelicato DJ, Rotondo RL, Begosh-Mayne D, et al. A Prospective Outcomes Study of Proton Therapy for Chordomas and Chondrosarcomas of the Spine. *Int J Radiat Oncol Biol Phys*. 2016;95(1):297–303. doi:10.1016/j.ijrobp.2016.01.057.

46. Staab A, Rutz HP, Ares C, et al. Spot-scanning-based proton therapy for extracranial chordoma. *Int J Radiat Oncol Biol Phys*. 2011;81(4):e489–e496.

doi:10.1016/j.ijrobp.2011.02.018.

47. Krämer M, Weyrather WK, Scholz M. The increased biological effectiveness of heavy charged particles: from radiobiology to treatment planning. *Technol Cancer Res Treat*. 2003;2(5):427–436.

48. Uhl M, Welzel T, Jensen A, et al. Carbon ion beam treatment in patients with primary and recurrent sacrococcygeal chordoma. *Strahlenther Onkol*. 2015;191(7):597–603. doi:10.1007/s00066-015-0825-3.

49. Schulz-Ertner D, Nikoghosyan A, Thilmann C, et al. Results of carbon ion radiotherapy in 152 patients. *International Journal of Radiation Oncology*Biology*Physics*. 2004;58(2):631–640. doi:10.1016/j.ijrobp.2003.09.041.

50. Imai R, Kamada T, Tsuji H, et al. Effect of carbon ion radiotherapy for sacral chordoma: results of Phase I-II and Phase II clinical trials. *Int J Radiat Oncol Biol Phys*. 2010;77(5):1470–1476. doi:10.1016/j.ijrobp.2009.06.048.

51. Nishida Y, Kamada T, Imai R, et al. Clinical outcome of sacral chordoma with carbon ion radiotherapy compared with surgery. *Int J Radiat Oncol Biol Phys*. 2011;79(1):110–116. doi:10.1016/j.ijrobp.2009.10.051.

52. Uhl M, Edler L, Jensen AD, et al. Randomized phase II trial of hypofractionated proton versus carbon ion radiation therapy in patients with sacrococcygeal chordoma-the ISAC trial protocol. *Radiation Oncology*. 2014;9(1):100. doi:10.2106/JBJS.D.02533.

53. Liang X, Wang D, Wang Y, Zhou Z, Zhang J, Li J. Expression of Aurora Kinase A and B in chondrosarcoma and its relationship with the prognosis. *Diagnostic Pathology*. 2012;7(1):1–1. doi:10.1186/1746-1596-7-84.

54. Jin Z, Han Y-X, Han X-R. Loss of RUNX3 expression may contribute to poor prognosis in patients with chondrosarcoma. *J Mol Hist*. 2013;44(6):645–652. doi:10.1007/s10735-013-9511-x.

55. Pillay N, Plagnol V, Tarpey PS, et al. A common single-nucleotide variant in T is strongly associated with chordoma. *Nat Genet*. 2012;44(11):1185–1187. doi:10.1038/ng.2419.

56. Yang XR, Ng D, Alcorta DA, et al. T (brachyury) gene duplication confers major susceptibility to familial chordoma. *Nat Genet*. 2009;41(11):1176–1178. doi:10.1038/ng.454.

57. Wang K, Hu Q, Wang L, et al. T gene isoform expression pattern is significantly different between chordomas and notochords. *Biochem Biophys Res Commun*. 2015;467(2):261–267. doi:10.1016/j.bbrc.2015.09.178.

58. Mazel C, Owona P, Cogan A, Balabaud L, Grunenwald D. Long-term quality of life after en-bloc vertebrectomy: 25 patients followed up for 9 years. *Orthopaedics & Traumatology: Surgery & Research*. 2014;100(1):119–126. doi:10.1016/j.otsr.2013.09.008.

59. Liljenqvist U, Lerner T, Halm H, Buerger H, Gosheger G, Winkelmann W. En bloc spondylectomy in malignant tumors of the spine. *Eur Spine J*.

2008;17(4):600–609. doi:10.1007/s00586-008-0599-8.

60. Kato S, Murakami H, Demura S, et al. Patient-reported outcome and quality of life after total en bloc spondylectomy for a primary spinal tumour. *Bone Joint J*. 2014;96-B(12):1693–1698. doi:10.1302/0301-620X.96B12.33832.

61. Colman MW, Karim SM, Lozano-Calderon SA, et al. Quality of life after en bloc resection of tumors in the mobile spine. *Spine J*. 2015;15(8):1728–1737. doi:10.1016/j.spinee.2015.03.042.

62. Charest-Morin R, Dea N, Fisher CG. Health-Related Quality of Life After Spine Surgery for Primary Bone Tumour. *Curr Treat Options Oncol*. 2016;17(2):9. doi:10.1007/s11864-015-0383-z.