

## An evidence-based medicine model for rare and often neglected neoplastic conditions

### Clinical article

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**Object.** The National Institutes of Health recommends strategies to obtain evidence for the treatment of rare conditions such as primary tumors of the spine (PTSs). These tumors have a low incidence and are pathologically heterogeneous, and treatment approaches are diverse. Appropriate evidence-based care is imperative. Failure to follow validated oncological principles may lead to unnecessary mortality and profound morbidity. This paper outlines a scientific model that provides significant evidence guiding the treatment of PTSs.

**Methods.** A four-stage approach was used: 1) planning: data from large-volume centers were reviewed to provide insight; 2) recruitment: centers were enrolled and provided the necessary infrastructure; 3) retrospective stage: existing medical records were reviewed and completed with survival data; and 4) prospective stage: prospective data collection has been implemented. The AOSpine Knowledge Forum Tumor designed six modules: demographic, clinical, diagnostic, therapeutic, local recurrence, survival, and perioperative morbidity data fields and provided funding.

**Results.** It took 18 months to implement Stages 1–3, while Stage 4 is ongoing. A total of 1495 tumor cases were captured and diagnosed as one of 18 PTS histotypes. In addition, a PTS biobank network has been created to link clinical data with tumor pathology and molecular analysis.

**Conclusions.** This scientific model has not only aggregated a large amount of PTS data, but has also established an international collaborative network of spine oncology centers. Access to large volumes of data will generate further research to guide and enhance PTS clinical management. This model could be applied to other rare neoplastic conditions. Clinical trial registration no.: NCT01643174 (ClinicalTrials.gov). (<http://thejns.org/doi/abs/10.3171/2014.7.SPINE13954>)

**KEY WORDS** • spine • primary tumor • scientific model • rare disease • surgery • network • oncology

Abbreviations used in this paper: AOSKFT = AOSpine International Knowledge Forum Tumor; FFPE = formalin-fixed paraffin-embedded; NIH = National Institutes of Health; PTS = primary tumor of the spine; WBB = Weinstein-Boriani-Biagini.

THE National Institutes of Health (NIH) Office of Rare Diseases recently made key recommendations regarding strategies for conducting research in spinal cord tumors.<sup>13</sup> These research strategies are equally relevant for improving research and subsequent treatment

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of other rare neoplastic conditions. Among these recommendations are the establishment of a population-based public registry and a central pathological review of tumor collections. In addition, the NIH recommended instituting a collaborative clinical trials network and mechanisms for improved preclinical research.<sup>9,13</sup> Until these types of recommendations are implemented, patients with rare neoplastic conditions are at risk of receiving suboptimal treatment given a lack of familiarity by clinicians and a paucity of high-level evidence to guide treatment. In tumor types for which such evidence exists, that evidence is central to surgical decision making, evaluating treatment efficacy, assisting in prognostication, and generating treatment algorithms, as well as forming the basis of discussions between the patient and the treating clinician.

Primary tumors of the spine (PTSS), which are often aggressive and fatal neoplasms,<sup>26</sup> represent one such class of rare, poorly understood tumors. In the last decade or so, based on extremity oncological principles and low-quality evidence, these tumors are being treated with more aggressive surgical modalities, such as en bloc resection, a method of removing the tumor in one piece without violating the tumor itself, minimizing the risk of local recurrence, and providing the greatest potential for cure. This technique often requires the sacrifice of neural elements such as nerve roots and complex reconstruction of the spine and surgical cavity. En bloc resections are complex, time- and resource-intensive procedures involving multidisciplinary teams and may be associated with significant patient morbidity, adverse events, and long-term disability;<sup>14,16,27</sup> these realities dictate the need for the highest possible level of evidence on treatment outcomes.

Answering the question of whether this aggressive surgical approach improves patient survival with satisfactory quality of life requires critical evaluation using the principles of evidence-based medicine.<sup>15</sup> Most of the research to date has stemmed from case reports or case series. When larger cohort studies have been performed, the cohorts are heterogeneous, representing an array of tumor histotypes, each with distinct biological and clinical characteristics, and thus limiting conclusions. Conducting the necessary studies is arduous, as PTSS are rare, treatment is varied and multidisciplinary, and the staging, classifications, and definitions are inconsistently used and ambiguous.<sup>29</sup> Furthermore, correlating clinical parameters and outcomes with histology and genetic profiling is becoming the new standard in achieving targeted therapies;<sup>8,22</sup> establishing tumor banks is therefore essential.<sup>19</sup> The aforementioned recommendations of the NIH can be used to assist in overcoming these challenges; however, this requires collaboration at an international, multicenter level using a standardized approach with sufficient funding.

With the aim of offering patients the most appropriate treatment based on the best available evidence, a scientific model was developed and used for the first time in PTSS. The purpose of this paper is to delineate the model and present the unprecedented global data on the rare condition of PTSS. We believe the model is readily transferrable to other similarly rare conditions.

## Methods

Centers throughout the world with experience in the treatment of PTSS, along with a research track record, were identified. A feasibility questionnaire was sent to provide insight into infrastructure, epidemiology, tumor pathology, treatment modalities, and outcomes. Centers with sufficient patient volumes (10 patients per year), multidisciplinary oncology care, and prospectively collected data were identified.

### *Ethics Approval*

This study was registered with the ClinicalTrials.gov database (<http://clinicaltrials.gov>), and its registration no. is NCT01643174. All centers obtained institutional review board or ethics committee approval prior to initiating the study.

### *Infrastructure and Funding*

This study was developed and funded under the umbrella of the AOSpine International Knowledge Forum Tumor (AOSKFT). AOSpine is a not-for-profit international organization of spine care professionals dedicated to delivering knowledge, experience, and evidence to improve patient care and outcomes (<https://aospine.aofoundation.org>).

### *Model Design*

A PTS database consisting of a secure, web-based application to support data capture (REDCap) was created. The AOSKFT Steering Committee, made up of spine oncology surgeons, oncologists, musculoskeletal pathologists, and epidemiologists, developed six modules: demographic, clinical, diagnostic, therapeutic, cross-sectional survival, local recurrence, and perioperative morbidity. Captured data included patient demographic and diagnosis details, preoperative neurological status, tumor location and size, surgical details, pathology margin results, peri- and postoperative complications, adjuvant therapy details, local recurrence details, last clinical follow-up details, and current vital status. Two staging classifications were used to characterize tumors. Data accrual was by an ambispective, cross-sectional design. A study coordinator was employed to assist with data collection, data entry, and capture of cross-sectional survival data. Data fields deemed as mandatory and quantifiable (that is, dates, estimated blood loss, and so forth) were screened for inconsistencies and incompleteness. Outstanding or unclear issues were reported to the centers and discussed to ensure accuracy.

### *Definitions and Staging*

Two staging systems are used to classify spine tumors: 1) Enneking classification, which was initially developed for primary bone tumors of the extremities, and 2) the Weinstein-Boriani-Biagini (WBB) classification, which determines the feasibility of tumor resection in the spine.<sup>7,27</sup> The essence of the Enneking classification is that the type of tumor resection is dictated by the grade and extent of the tumor. The central tenet is that in malignant and

aggressive benign tumors, the lesion should not be entered during resection. The WBB classification recognizes the unique anatomical complexity of the spine. The fundamental concept of this system is to ensure sparing of the spinal cord without compromising tumor margins.<sup>6,7,16</sup>

#### *Inclusion and Exclusion Criteria*

Patients were included only if they were admitted to one of the participating spine centers with a diagnosis of PTS and received treatment and clinical follow-up appropriate to the tumor histotype. Data at each center were prospectively collected in the majority of cases (> 75%). When necessary, governmental vital statistics databases were accessed for mortality information, including cause of death. For retrospectively captured patients, prospectively collected databases were used along with clinical charts.

#### *Collaboration and Development*

The nature of treatment of PTSs necessitates a multidisciplinary approach from spine surgeons, surgeons of other subspecialties, oncologists, pathologists, radiologists, epidemiologists, and allied health professionals. Development of the featured model has fostered both intrahospital and interhospital collaboration. The AOSKFT had frequent international meetings with co-investigators to establish a framework for studying PTSs. Further discussions were held to formulate initial and future research questions designed to evaluate outcomes from the model and facilitate changes in treatment.<sup>15</sup>

#### *Statistical Analysis*

Descriptive statistics were summarized using the mean  $\pm$  standard deviation or frequency or percentage. Data on mortality and time to tumor recurrence were displayed using Kaplan-Meier curves.

In all survival analyses, the most recent querying time of the governmental vital statistics database was used as the “end of study.” All statistical analyses were performed using Stata (version 12.0, StataCorp).

## **Results**

#### *Overall Data*

Thirteen spine centers from around the world participated and contributed cases to the data set (Table 1). Within 18 months, the retrospective phase was completed. A total of 1495 cases were captured and diagnosed as one of 18 histotypes (Fig. 1). There were 674 females and 821 males. The mean age at the time of surgery was  $43 \pm 19$  years. The most common diagnosis was chordoma (344). The specific survival of the entire cohort was 71.9% at 5 years postsurgery and 53.3% at 10 years postsurgery, with a median survival of 13 years postsurgery (Fig. 2).

A detailed analysis of the model's data is beyond the scope of this paper, but the survival and local recurrence Kaplan-Meier curves for the entire cohort (Fig. 3) and specifically for chordoma (Fig. 4) demonstrate the potential for the generation of high-impact evidence on both PTS as a large cohort and distinct homogeneous histotypes.

#### *Subsequent Initiatives*

With completion of the model and overall data analysis, structured multidisciplinary meetings were held to refine the model and establish the analysis for individual histotypes. The focus of the data will be the evaluation of large homogeneous cohorts of specific tumor types. In addition, the clinical data of one distinct histotype cohort (chordoma) is being linked to their molecular profiles using archival formalin-fixed paraffin-embedded (FFPE) tissue. Sixty-four percent of the cases in our model had accessible archived paraffin samples. These FFPE samples are currently being analyzed to link biological characteristics of the tumor to clinical outcomes.

Another result was the formulation of future research questions designed to evaluate outcomes and improve treatment. Hence, the model is adaptive, iterative, and perpetually evolving, with the database now prospectively collecting. The evidence is appraised and clinically applied, and the data are revisited, all to establish evidence-based care and improve patient outcomes.

## **Discussion**

With this model, it has been possible to attain the largest collection of PTSs and their histotypes to date. The international nature of the model is critical to obtain adequate numbers of this rare condition and achieve optimal generalizability. This model overcomes the potential problems of most registries that are national or population specific. National registries may fail to identify regional differences in the epidemiology of or survival in neoplastic diseases, as is the case for colorectal,<sup>18</sup> lung, breast, and ovarian cancers.<sup>10</sup> Another common problem with these registries is that they are administrative, not research focused, and thus are prone to missing, incomplete, or inaccurate data. This is much less an issue when data are obtained directly from hospitals,<sup>24</sup> as is done in our model. The approach is in keeping with the recommendations of the NIH Office of Rare Diseases.<sup>9</sup>

Most malignancies are best treated through a multimodal approach. Cancer registries and clinical trials are often used to evaluate new chemotherapeutics; however, designing and implementing trials that evaluate surgery are difficult<sup>1</sup> given the complexities in standardizing techniques, having control arms, and blinding.<sup>23</sup> There has been a call for surgeons to become more involved in evaluating their results using evidence-based medicine.<sup>20</sup> A prerequisite to this is the utilization of a psychometrically sound classification system (Enneking and WBB classifications),<sup>7</sup> which is critical in standardizing diagnosis and terminology to allow for valid comparisons.<sup>16</sup> Moreover, the design of our model allows for the evaluation of patient outcomes after both surgery and multimodal treatment. The collaborative nature of our model has facilitated review and discussion of techniques, complications, and approaches to PTSs, as well as the implementation of new technology. Such an approach has been shown to improve health care outcomes<sup>17</sup> and is more than a method of mere data collection.

Although previous studies have demonstrated that

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**TABLE 1: Centers participating in a study of PTS treatment\***

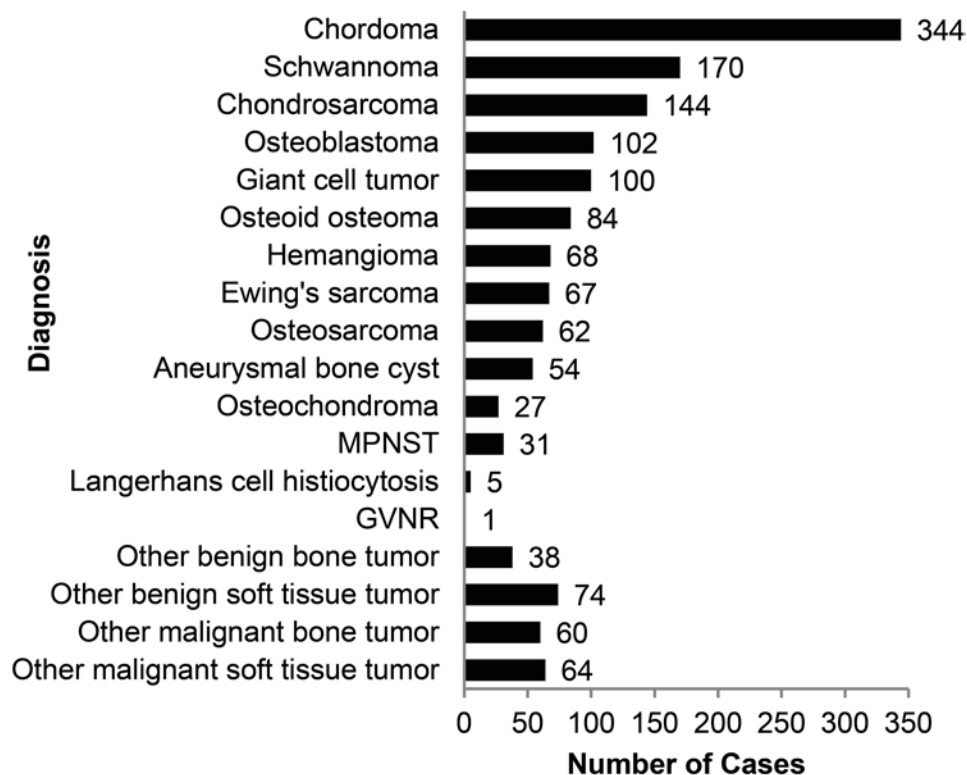
| No. of Cases | Center   | Country        | Region |
|--------------|--|----------------|--------|
| 286          | Istituto Ortopedico Rizzoli  | Italy          | EU     |
| 280          | Buda Health Center and National Center for Spinal Disorders          | Hungary        | EU     |
| 165          | Johns Hopkins University School of Medicine                          | United States  | NA     |
| 147          | The University of Texas MD Anderson Cancer Center                    | United States  | NA     |
| 135          | University Health Network, University of Toronto                     | Canada         | NA     |
| 121          | Istituto Ortopedico Galeazzi   | Italy          | EU     |
| 100          | Vancouver General Hospital, University of British Columbia           | Canada         | NA     |
| 99           | Memorial Sloan-Kettering Cancer Center                               | United States  | NA     |
| 73           | Mayo Clinic  | United States  | NA     |
| 26           | Oxford University Hospitals NHS Trust                                | United Kingdom | EU     |
| 25           | University of California, San Francisco                              | United States  | NA     |
| 25           | Queensland University of Technology, Brisbane Spine Reference Centre | Australia      | AP     |
| 13           | Queens Medical Centre, Nottingham University Hospitals NHS Trust     | United Kingdom | EU     |

\* AP = Asia Pacific; EU = Europe; NA = North America.

Enneking-appropriate resection reduces local recurrence, which has a high concordance with mortality,<sup>2-5,16,25</sup> this has not been proved in a multicenter international cohort. Heterogeneity of tumor cohorts, a limitation of previous studies, has been overcome with the large number of PTSs accrued with our model. Each histotype represents a different pathological, biological, and clinical entity, ranging from benign to aggressive. For example, osteosarcoma is best treated with neoadjuvant chemotherapy, whereas chordomas are resected primarily.<sup>26,29</sup> An analysis of these re-

sults is beyond the scope of the present paper but will be the first analysis of this model's data. Specific studies on each tumor histotype are in progress. We hope these studies will demonstrate the utility of our approach to studying rare, orphan tumors arising in the spine.

One of our initiatives has been to link our chordoma clinical data directly to biological and pathological data through the analysis of archived paraffin samples. This initiative evolved from a technology coined "SNapShot" that determines the mutational status of several of the



**Fig. 1.** The diagnosis of 1495 PTS cases captured within the AOSKFT data set. GVNR = giant vertebral notochordal rest; MPNST = malignant peripheral nerve sheath tumor.



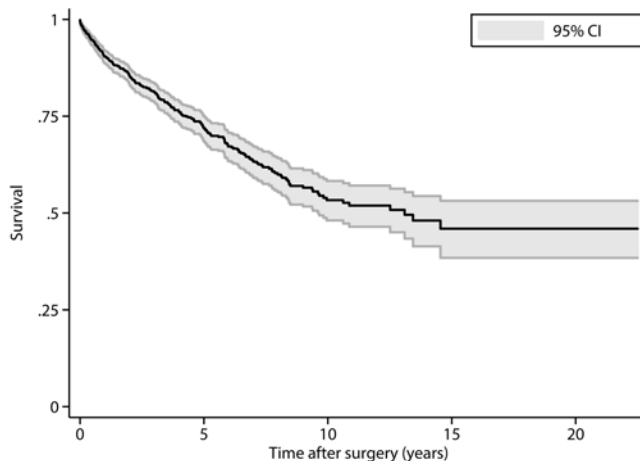


Fig. 2. Kaplan-Meier curve for entire cohort survival following surgery.

most common cancer genes. Investigators at the Massachusetts General Hospital have been able to demonstrate a high frequency of mutations in *BRAF* in archival specimens of rare brain tumors.<sup>12</sup> Such an approach immediately empowers clinicians to use clinically approved therapies targeting mutant *BRAF* in the management of these tumors. Rationally designed treatment strategies are desperately needed for PTSs, especially chordomas for which there exist limited therapeutic options.

Our model, with or without minimal alterations, is readily transferable to other rare neoplastic diseases. For example, acromegaly caused by a pituitary gland tumor. It has an incidence of 3–4 cases per million persons, and patients, if untreated, have twice the mortality rate as the normal population.<sup>11</sup> Dilemmas and controversies exist in managing patients and are currently based largely on Class III evidence.<sup>21</sup> We believe applying our model could

help to improve evidence and guide clinicians' management of patients with acromegaly.

Producing and implementing a model such as the one described is not possible without several critical elements. Adequate funding is essential, and we acknowledge that industry-based funding in oncological research has the potential to influence reporting of results.<sup>28</sup> In the present case, funding was obtained through a not-for-profit organization. We advocate having a transparent funding body that has no vested interests in outcome. Leadership and collaboration are essential. Fortunately, for rare conditions clinicians and researchers are often a close-knit group, which facilitates collaboration, but also creates the potential for bias. The use of independent study coordinators and prospective data collection reduces this potential. Another advantage of the small incidence of PTSs is the reduced demand on research staff for enrollment and follow-up, but this is challenged by consistency of collection and dropouts as many patients travel great distances to subspecialized centers. Although most of our data were prospectively collected, each center followed its own collection protocols, and these were not identical across centers, as would be required in a prospective study. This limitation must be considered in the analysis of results.

Going forward, this model has provided the basis for the implementation of a prospective adaptive study on the clinical outcome and treatment of patients with PTSs that will allow for ongoing adjustment to treatment guidelines. A number of data fields have been removed because of ambiguity or their noncontributory status. Others have been added or enhanced as a result of the lessons learned from the retrospective analyses. It is only by doing the retrospective analyses that one can learn which data are and are not important and amendable to analysis. Furthermore, we have embraced a long-standing challenge in oncology to identify biological determinants of clinical outcome that

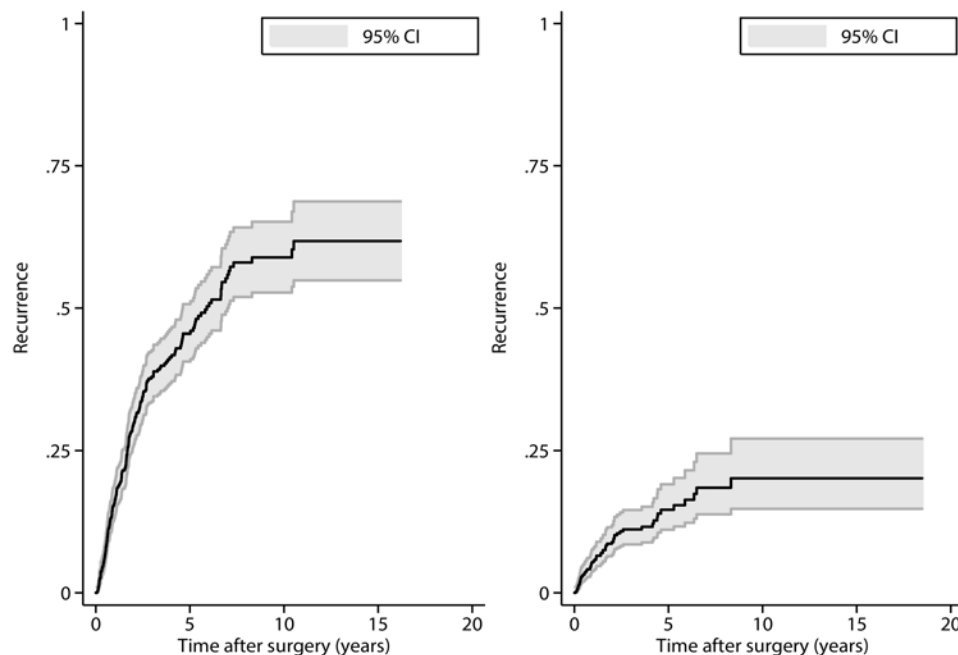


Fig. 3. Left: Time to first local recurrence of malignant tumors. Right: Time to first local recurrence of benign tumors.

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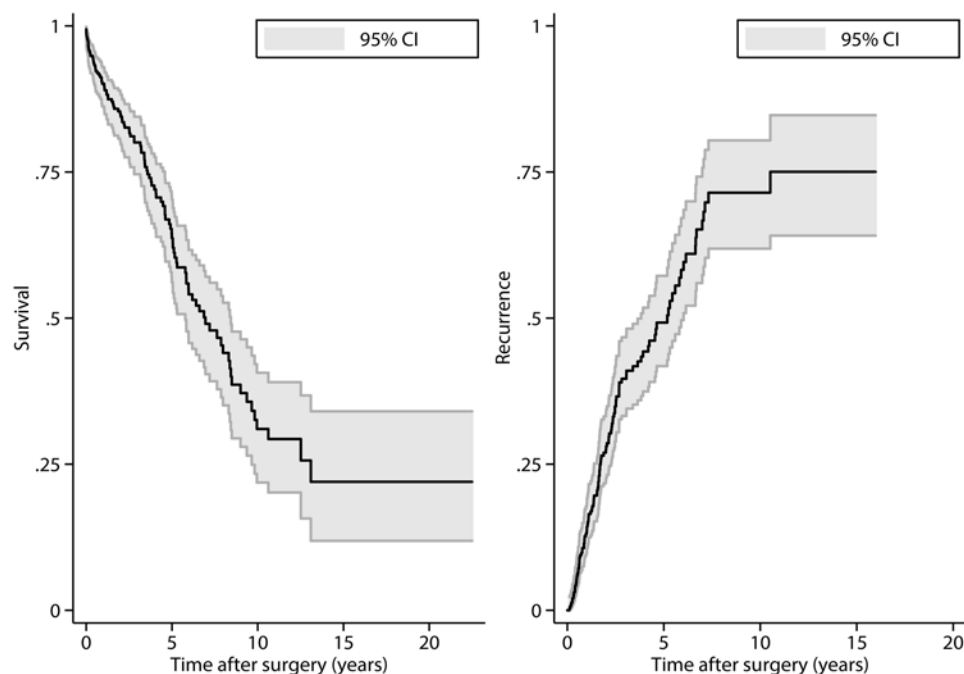


Fig. 4. **Left:** Chordoma-specific survival following surgery. **Right:** Chordoma-specific time to first local recurrence.

enable health care providers and patients to make more informed decisions. With our prospective clinical database linked to biological specimens, we can begin to make important clinical observations and study the biological basis of PTSs. By having a standardized biobanking protocol, we hope to maximize the knowledge gained by building a robust repository of specimens that is tightly linked to high-quality clinical data. Only through rigorous investigation of the histotypes of the biological samples and links to clinical outcomes can we develop novel diagnostic, prognostic, and therapeutic avenues.

### Conclusions

The world's leading medical research agency has stressed the importance of strategies for conducting research of rare disorders. Primary tumors of the spine are rare and lethal and involve complex, resource-intensive surgical and medical treatments. For patients with PTSs and clinicians, management decisions are agonizing because of the morbidity and mortality associated with treatments validated only by low-quality evidence. Our model has led to the largest collection of generalizable, standardized, high-quality data on PTSs to date, which will allow for generic PTS analysis as well as analysis of previously chronically underpowered PTS histotypes. Finally, the model has initiated and set the stage for adaptive prospective clinical outcome studies, including the incorporation of a biobanking protocol that for the first time will link the robust clinical data of PTSs to their molecular profiles.

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mentation for their support in maintaining the database and providing statistical support.

### Disclosure

This study was funded and managed by AOSpine International through the AOSpine Knowledge Forum Tumor, which is a pathology-focused working group acting on behalf of AOSpine International. The forum consists of a steering committee of up to ten international spine experts who meet biannually to discuss research, assess the best evidence for current practices, and formulate clinical trials to advance the field of spine oncology. All steering committee coauthors disclose that they were provided with only necessary travel funds from the study sponsor (AOSpine International) to participate in 1–2 research meetings per year, which were integral to the study. Study support was provided directly through AOSpine's Research Department and AO's Clinical Investigation and Documentation Unit. There are no other institutional subsidies, corporate affiliations, or funding sources supporting this work unless documented and disclosed.

AOSpine is a clinical division of the AO Foundation—an independent medically guided not-for-profit organization. The AO has strong financial independence thanks to the foundation's endowment. The annual operating activities are financed through three pillars: collaboration and support agreements with DePuy Synthes and other industrial partners, return on its own financial assets, and other third party income (for example, participant fees, research and development projects, memberships).

Author contributions to the study and manuscript preparation include the following. Conception and design: Fisher, Goldschlager, Boriani, Varga, Rhines, Fehlings, Bettgowda, Gokaslan. Acquisition of data: Fisher, Boriani, Varga, Rhines, Fehlings, Luzzati, Dekutoski, Reynolds, Chou, Berven, Williams, Quraishi, Gokaslan. Analysis and interpretation of data: Fisher, Goldschlager, Boriani, Varga, Rhines, Fehlings, Bettgowda, Gokaslan. Drafting the article: Fisher, Goldschlager, Bettgowda. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Fisher.

## References

- Bandopadhyay P, Goldschlager T, Rosenfeld JV: The role of evidence-based medicine in neurosurgery. **J Clin Neurosci** **15**:373–378, 2008
- Boriani S, Amendola L, Bandiera S, Simoes CE, Alberghini M, Di Fiore M, et al: Staging and treatment of osteoblastoma in the mobile spine: a review of 51 cases. **Eur Spine J** **21**:2003–2010, 2012
- Boriani S, Bandiera S, Biagini R, Bacchini P, Boriani L, Cappuccio M, et al: Chordoma of the mobile spine: fifty years of experience. **Spine (Phila Pa 1976)** **31**:493–503, 2006
- Boriani S, Bandiera S, Casadei R, Boriani L, Donthineni R, Gasbarrini A, et al: Giant cell tumor of the mobile spine: a review of 49 cases. **Spine (Phila Pa 1976)** **37**:E37–E45, 2012
- Boriani S, Bandiera S, Donthineni R, Amendola L, Cappuccio M, De Iure F, et al: Morbidity of en bloc resections in the spine. **Eur Spine J** **19**:231–241, 2010
- Boriani S, Weinstein JN, Biagini R: Primary bone tumors of the spine. Terminology and surgical staging. **Spine (Phila Pa 1976)** **22**:1036–1044, 1997
- Chan P, Boriani S, Fourny DR, Biagini R, Dekutoski MB, Fehlings MG, 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 (Phila Pa 1976)** **34**:384–391, 2009
- Chapman PB, Hauschild A, Robert C, Haanen JB, Ascierto P, Larkin J, et al: Improved survival with vemurafenib in melanoma with BRAF V600E mutation. **N Engl J Med** **364**:2507–2516, 2011
- Claus EB, Abdel-Wahab M, Burger PC, Engelhard HH, Ellison DW, Gaiano N, et al: Defining future directions in spinal cord tumor research. Proceedings from the National Institutes of Health workshop. **J Neurosurg Spine** **12**:117–121, 2010
- Coleman MP, Forman D, Bryant H, Butler J, Rachet B, Maringe C, et al: Cancer survival in Australia, Canada, Denmark, Norway, Sweden, and the UK, 1995–2007 (the International Cancer Benchmarking Partnership): an analysis of population-based cancer registry data. **Lancet** **377**:127–138, 2011
- Del Porto LA, Liubinas SV, Kaye AH: Treatment of persistent and recurrent acromegaly. **J Clin Neurosci** **18**:181–190, 2011
- Dias-Santagata D, Lam Q, Vernovsky K, Vena N, Lennerz JK, Borger DR, et al: BRAF V600E mutations are common in pleomorphic xanthoastrocytoma: diagnostic and therapeutic implications. **PLoS ONE** **6**:e17948, 2011
- Fehlings MG, Chua SY: Editorial. Spinal cord tumor research. **J Neurosurg Spine** **12**:115–116, 2010
- Fisher CG, Keynan O, Boyd MC, Dvorak MF: The surgical management of primary tumors of the spine: initial results of an ongoing prospective cohort study. **Spine (Phila Pa 1976)** **30**:1899–1908, 2005
- Fisher CG, Keynan O, Ondra S, Gokaslan Z: Introduction to focus issue in spine oncology: the synthesis of evidence and expert opinion for best practice recommendation. **Spine (Phila Pa 1976)** **34** (22 Suppl):S21–S25, 2009
- Fisher CG, Saravanja DD, Dvorak MF, Rampersaud YR, Clarkson PW, Hurlbert J, et al: Surgical management of primary bone tumors of the spine: validation of an approach to enhance cure and reduce local recurrence. **Spine (Phila Pa 1976)** **36**:830–836, 2011
- Forsetlund L, Bjørndal A, Rashidian A, Jamtvedt G, O'Brien MA, Wolf F, et al: Continuing education meetings and workshops: effects on professional practice and health care outcomes. **Cochrane Database Syst Rev** **2**:CD003030, 2009
- Gingras D, Béliveau R: Colorectal cancer prevention through dietary and lifestyle modifications. **Cancer Microenviron** **4**:133–139, 2011
- Hewitt RE: Biobanking: the foundation of personalized medicine. **Curr Opin Oncol** **23**:112–119, 2011
- Horton R: Surgical research or comic opera: questions, but few answers. **Lancet** **347**:984–985, 1996
- Katznelson L, Atkinson JLD, Cook DM, Ezzat SZ, Hamrahian AH, Miller KK: American Association of Clinical Endocrinologists medical guidelines for clinical practice for the diagnosis and treatment of acromegaly—2011 update. **Endocr Pract** **17** (Suppl 4):1–44, 2011
- O'Hare T, Zabriskie MS, Eiring AM, Deininger MW: Pushing the limits of targeted therapy in chronic myeloid leukaemia. **Nat Rev Cancer** **12**:513–526, 2012
- Posther KE, Wells SA Jr: The future of surgical research: the role of the American College of Surgeons Oncology Group. **Eur J Surg Oncol** **31**:695–701, 2005
- Sanders CM, Saltzstein SL, Schultzel MM, Nguyen DH, Stafford HS, Sadler GR: Understanding the limits of large datasets. **J Cancer Educ** **27**:664–669, 2012
- Schwab J, Gasbarrini A, Bandiera S, Boriani L, Amendola L, Picci P, et al: Osteosarcoma of the mobile spine. **Spine (Phila Pa 1976)** **37**:E381–E386, 2012
- Sciubba DM, Okuno SH, Dekutoski MB, Gokaslan ZL: Ewing and osteogenic sarcoma: evidence for multidisciplinary management. **Spine (Phila Pa 1976)** **34** (22 Suppl):S58–S68, 2009
- Sundaresan N, Boriani S, Okuno S: State of the art management in spine oncology: a worldwide perspective on its evolution, current state, and future. **Spine (Phila Pa 1976)** **34** (22 Suppl):S7–S20, 2009
- Valachis A, Polyzos NP, Nearchou A, Lind P, Mauri D: Financial relationships in economic analyses of targeted therapies in oncology. **J Clin Oncol** **30**:1316–1320, 2012
- Yamazaki T, McLoughlin GS, Patel S, Rhines LD, Fourny DR: Feasibility and safety of en bloc resection for primary spine tumors: a systematic review by the Spine Oncology Study Group. **Spine (Phila Pa 1976)** **34** (22 Suppl):S31–S38, 2009

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