Neurosurgical Forum

LETTERS TO THE EDITOR

Influence of age on survival outcomes in patients with spinal chordoma

TO THE EDITOR: We read with great interest the recent article by Gokaslan et al.³ (Gokaslan ZL, Zadnik PL, Sciubba DM, et al: Mobile spine chordoma: results of 166 patients from the AOSpine Knowledge Forum Tumor database. *J Neurosurg Spine* 24:644–651, April 2016). The authors performed a retrospective multicenter cohort analysis of prognostic factors in mobile spine chordoma after resection in 166 patients. They found on multivariate analysis that Enneking-inappropriate resection was significantly associated with an increased risk of local recurrence in the patients.

We commend the authors for performing this interesting study as their helpful results will be useful in making balanced treatment decisions to prolong patient survival. However, we noted that the authors did not find patient age to be an independent predictor, which contradicts the results from previous studies.^{7,8,10} Furthermore, although an increasing number of studies have investigated the influence of age on spinal chordoma prognosis, the results are still inconclusive or controversial. Therefore, we aimed to further examine the prognostic role of age in spinal chordoma by performing a systematic review and to grade the evidence according to the quality of included studies. We also attempted to establish pooled estimates of the effect of age on the survival of spinal chordoma patients by performing a meta-analysis.

We searched the MEDLINE and Embase databases to identify eligible English-language studies from database

inception to September 9, 2016. We included only those studies that specifically evaluated age as a factor predicting survival in spinal chordoma patients. Methodological quality for study inclusion was assessed according to the criteria previously described.^{1,5,11} Studies without sufficient detailed data for statistical pooling were excluded. Level of evidence was determined according to the criteria proposed by Harbour and Miller.⁴

A total of 11 papers met the initial methodological criteria and were thus included.^{2,3,6–10,12–15} Characteristics of the included studies are shown in Table 1. All studies were retrospective, and most (9/11) provided Level 2++ evidence. Sample size ranged from 36 to 167 patients with spinal chordoma. Most studies (10/11) only evaluated the prognostic role of age on survivorship to local recurrence or death.^{2,6–10,12–15} Although most studies (8/11) found that patient age had no significant predictive value,^{2,3,6,9,10,12,13,15} 3 studies showed significant prognostic implications for age on the overall survival (OS) of patients.^{7,8,10} Five studies evaluated age as a factor of OS in multivariate analyses by regarding it as a continuous variable,^{3,7–10} and pooled analysis showed that increasing age was associated with an increased risk of death (HR 1.03, 95% CI 1.02–1.05, $p < 0.0001$, $I^2 = 52\%$, p for heterogeneity = 0.08; Fig. 1). Although 5 studies evaluated age as a factor of local relapse-free survival with the same cutoff point,^{2,12–15} 4 of them shared exactly the overlapped patient data.^{12–15} Therefore, we did not pool the results in order to allow the credibility and accuracy of the outcomes.

According to the evidence available, we cannot derive valid conclusions regarding the prognostic role of patient age in spinal chordoma. The difference in categorization

FIG. 1. Pooled RR of death for increasing age. Figure is available in color online only.

TABLE 1. Characteristics of studies that evaluated age as a prognostic factor

Authors & Year	Study Design	No. of Patients	End Point	Median		Disease Recurrence	Disease Metastases	OS	Variable Type for Age (cutoff point)	Age as Factor of LRFs w/ Adjusted RR (p value)		Level of Evidence
				LRFS (yrs)	OS (yrs)							
Li et al., 2013	RCS	36	LRFS	2–14.3*	NA	52.8%	NA	NA	Categorical (45 yrs)	0.730 (0.280)	NT	2+
Zou et al., 2014	RCS	42	RFS	2.3†	2.3	76.2%	NA	NA	Categorical (50 yrs)	0.965 (0.139)	NT	2++
Stacchiotti et al., 2010	RCS	130	LRFS, OS	10.9†	5.25	59%	22%	57%	Continuous	NT	1.450 (0.062)	2++
Varga et al., 2015 ²	RCS	167	LRFS, OS	3.2‡	4	35%	NA	70%	Continuous	NT	1.020 (0.039)	2++
Zou et al., 2015 ²	RCS	42	RFS	2.3†	2.3	76.2%	NA	NA	Categorical (50 yrs)	0.949 (0.059)	NT	2++
Schoenfeld et al., 2016	RCS	86	OS	6.5‡	NA	NA	23%	34%	Continuous	NT	1.040 (0.001)	2++
McGirt et al., 2011	RCS	114	OS	NA	8.3	NA	NA	NA	Continuous	NT	1.050 (0.001)	2++
Chen et al., 2015	RCS	37	PFS	3.5†	3.5	48.6%	NA	13.5%	Categorical (50 yrs)	1.755 (0.386)	NT	2++
Gokaslan et al., 2016	RCS	166	LRFS, OS	2.6†	5.3	35%	NA	34%	Continuous	1.010 (0.375)	1.020 (0.157)	2++
Zou et al., 2016 ⁵	RCS	54	LRFS, OS	3.5‡	1.75	75.9%	NA	55.6%	Categorical (50 yrs)	1.950 (0.100)	NT	2++
Zou et al., 2016 ⁴	RCS	54	LRFS, OS	3.5‡	1.75	75.9%	NA	55.6%	Categorical (50 yrs)	1.693 (0.250)	NT	2++

LU = follow-up; LRFS = local relapse-free survival; NA = not available; NT = not tested; PFS = progression-free survival; RCS = retrospective cohort study; RFS = recurrence-free survival; RR = relative risk.

* Range.

† Median.

‡ Average.

for age between papers and the heterogeneity of the included studies render the pooled results less reliable. Subsequent methodologically high-quality studies with more uniform study design and data reporting are needed to further define the role of age in spinal chordoma prognosis.

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infiltrating lymphocytes is associated with favorable spinal chordoma prognosis. **Am J Transl Res** 8:3274–3287, 2016

Disclosures

The authors report no conflict of interest.

Response

We appreciate the letter from Zou et al., who should be commended for their effort and rigor in actually conducting a review of the literature in their response. Specifically, they first noted that our study did not find a predictive association between increasing patient age and worse survival following resection of mobile spine chordomas. They then conducted a literature review to provide evidence for or against such an association.

Interestingly, although they found that some prior studies show that increasing age is associated with worse survival following mobile spine chordoma resection, they also found multiple studies that show no association, similar to our study. As a result, they concluded that the body of current literature does not support an association between age and survival, and thus that more research should be done on the subject.

With regard to our original study, we sought to retrospectively evaluate prospectively acquired data on patients undergoing surgery for mobile spine chordomas from multiple centers in multiple nations. Given the rarity of these tumors in general and the limited long-term data following such surgeries, a multicenter study was performed to generate larger numbers. Not surprisingly, we found that local control following surgery is associated with the extent of oncological resection in the original surgery. However, we did not find an association between age and survival. Although Varga et al., in using a very similar methodology employed through the participating centers of the AOSpine Knowledge Forum Tumor network, did find an association between age and worsening prognosis following resection of sacral chordomas, it is unclear why such an association does not exist for mobile spine chordomas in our study.¹

It is important to note that the clinical behavior of clival,

mobile spine, and sacral chordomas are indeed different, suggesting an underlying difference in pathophysiology among tumors in these distinct locations. As more work is done to elucidate the mechanisms by which chordomas appear, grow, recur, and metastasize, it is likely that molecular factors will soon be identified as the most accurate predictors of survival following the diagnosis of spinal chordoma. Such molecular studies,^{2–6} which have been provided in many forms by Zou and colleagues, will undoubtedly improve our clinical management of patients with these very challenging lesions.

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