ASSESSMENT FOR RISK FACTORS ASSOCIATED WITH LOCAL RECURRENCE IN CHORDOMA

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BACKGROUND

Chordoma is a rare but locally aggressive malignant neoplasm showing notochordal differentiation. The clinical differential diagnoses can be extensive, and definitive diagnosis often relies on histopathologic evaluation. Histologically, chordoma shows dual epithelial and mesenchymal differentiation, with various morphologies. Despite surgical resection and use of adjuvant radiation therapy, the local recurrence rate of chordoma remains high. We aim to establish factors associated with the increased risk of recurrence and help guide treatment decisions.

DESIGN

We performed a retrospective study of patients diagnosed with chordoma between 1990 and 2014 who underwent surgical treatment at our institution. The study was approved by the Institutional Review Board at TJUH. Pathologic database was searched, and 60 patients were identified, with a total of 107 pathology cases. Medical charts were reviewed, and all available pathology cases (n=94) were reviewed by two pathologists (W.J. and S.M). Clinical and pathologic variables were recorded (see Tables 1 and 2). Overall survival (OS) was defined as [date of death/last follow-up - date of diagnosis of primary tumor], and disease free survival (DFS) was defined as [date of recurrence/metastasis - date of diagnosis of primary tumor]. Log-rank tests were used to assess whether each potential predictor affected the DFS. Analyses were performed using R 3.1.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Table 1. Clinical variables

Age (yrs)		56.4 (19-83)
Sex (M:F)		1.3:1
Race (n=56)		W = 89%, B = 7%, A = 4%
Anatomic Site	Clivus/skull base	40%
	Vertebral body	40%
	Sacrococcygeal bone	20%
Tumor size (cm) (n=42)		5.1 (1.6-15.0)
Radiation therapy		47.4%
Local recurrence (n=52)		42.3 %
Metastasis (n=52)		13.4%
Overall Survival (months) (n=56)		76 (2-257)
Disease free survival (months) (n=55)		61 (1-263)
Follow up time (months)		97 (1-232)

Table 2. Pathologic variables (n=94)

Histologic type	Classic	86%
	Chondroid	12%
	De-differentiated	2%
Tumor heterogeneity		19%
Nuclear atypia		14%
Giant cells		49%
Mitotic activity		56%
Necrosis		26%

Figure 1. Histologic features of chordoma.

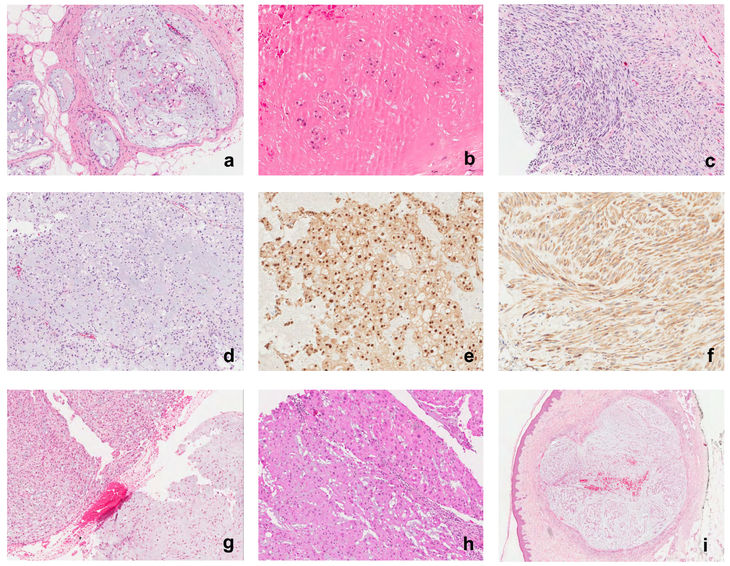


Figure 1. Classic (a), chondroid (b), and de-differentiated chordoma (c). In de-differentiated chordoma, the brachyury staining is lost (f), whereas the well-differentiated component (d) maintains the staining (e). Heterogeneity defined as significant difference in histologic type, cellularity (g), and/or cytologic atypia (h). Metastatic chordoma to skin dermis (i).

Statistical analyses

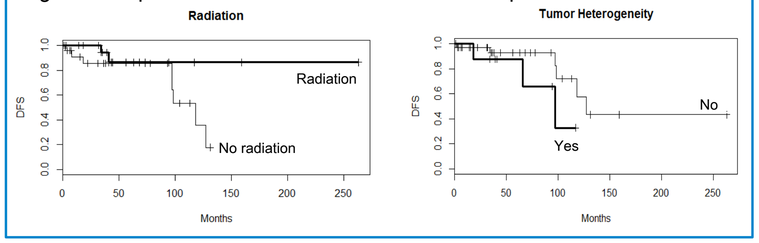
Using the log rank model, the only two variables that were near statistical significance were radiation therapy (p=0.12) and tumor heterogeneity (p=0.11) (see Table 3). When both radiation and tumor heterogeneity were included in a Cox regression model, they were more significant but still had p-values > 0.05. Radiation had a hazard ratio of 0.13 (95% CI 0.02-1.18, p = 0.070), and tumor heterogeneity, 4.78 (0.78-29.45, p = 0.09).

Table 3. Statistical analyses

	Bivariate log rank	Full Cox
Gender	0.103	0.219
Age	0.742	0.325
Race (non-white)	0.497	0.228
Tumor size	0.149	0.485
Anatomic site	0.680	0.758
Radiation	0.117	0.227
Tumor type	0.440	0.958
Tumor heterogeneity	0.109	0.660
Cellularity	0.921	0.561
Nuclear atypia	0.455	0.214
Mitotic activity	0.173	0.985
Necrosis	0.211	0.938

For age and size, bivariate done with Cox regression

Figure 2. Kaplan-Meier curves for the bivariate comparisons.



DISCUSSION

Our cohort is one of the largest clinicopathologic series of chordoma from a single institution with long-term follow up data. A diagnosis of chordoma may be challenging on both clinical and histological grounds. In our study, CT and/or MRI were the main diagnostic imaging modalities, and the radiologic differential diagnoses included chondrosarcoma, pituitary adenoma (sellar region), nerve sheath tumor (cervical spine), meningioma, lymphoma, and metastasis; chordoma was suspected in only 43% of cases prior to surgery. In a few cases (n=6), the "physaliphorous" cells were not prominent, and pathologic differential diagnosis included metastatic renal cell carcinoma and chondrosarcoma. IHC for brachyury showed diffuse positivity in all of these cases, with the exception of the de-differentiated component in one case. Therefore, brachyury is helpful in confirming the diagnosis of chordoma when the histology is not classic, especially in the context of other commonly expressed antigens (S100, CK19, EMA and AE1/AE3).

Tumor heterogeneity, defined as significant difference in tumor type, cellularity, and/or cytologic atypia within the same tumor (Figure 1), and radiation therapy, appear to have an effect on disease free survival, which are interesting findings. Although they are not statistically significant, this could be due to the underpower of the study.

FUTURE DIRECTIONS

The high rate of local recurrence seems to dictate the clinical outcome, and our finding of histologic heterogeneity associated with local recurrence is quite interesting. Larger multicenter studies are needed to validate the result, which may influence the clinical management of these lesions.

Currently, the therapy for chordoma is largely limited to surgery and radiation therapy. Adjuvant radiation therapy is considered standard of care despite conflicting data regarding its effect on clinical outcome. Understanding the molecular basis of the tumorigenesis is key to the endeavor in finding new therapeutic regimen for these patients. We are currently working on exploring the molecular pathways, by using IHC analyses on tissue microarrays generated from this cohort. Whole-exome sequencing will also help identify new genes and pathways important for tumor development.

ACKNOWLEDGEMENT

The study was partially supported by the American Cancer Society Institutional Research Grant (IRG) #08-060-04 awarded to JA.
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