Chordomas: Is It Possible to Predict Recurrence?

Kordomalar: Rekürensi Öngörmek Mümkün Mü?

Banu SARSIK[1], Başak DOĞANAVŞARGİL[1], Gülçin BAŞDEMİR[1], Mehmet ZİLELİ[2], Dündar SABAH[3], Fikri ÖZTOP[1]

[1]Ege Üniversitesi, Tıp Fakültesi, Patoloji Anabilim Dalı, İZMİR, TÜRKİYE, [2]Ege Üniversitesi, Tıp Fakültesi, Nöroşirürji Anabilim Dalı, İZMİR, TÜRKİYE, [3]Ege Üniversitesi, Tıp Fakültesi, Ortopedi ve Travmatoloji Anabilim Dalı, İZMİR, TÜRKİYE

ABSTRACT

Objective: Chordoma is a rare tumor with an unpredictable behaviour, and can display malignant behavior because of its tendency to local invasion and recurrence. We searched the prognostic value of histologic features, growth pattern, localization and Ki-67 proliferation index to predict disease-free survival.

Material and Method: Twenty-nine cases diagnosed in a single center were included in the study and evaluated with their 81 surgical specimens, (29 primary tumors, 47 recurrent lesions and five metastatic foci) regarding their matrix formation (myxoid, chondroid), cellular features, (pleomorphism, necrosis, inflammatory infiltration), patterns of proliferation (solid, trabecular, mixed) and Ki-67 proliferation indices.

Results: Eleven of the cases were females (37.9%) while 18 of them were males (62.1%) with a mean age of 54.1±14.6 (ranged between age 23-78 years). Thirty-eight percent of tumors were located in sacrococcigeal region followed by skull base and vertebrae (31% for both). Skull base chordomas which occured in younger patients (p=0.048) showed more trabecular pattern (p=0.04), chondroid matrix (p=0.063), lower Ki-67 (p=0.146) and longer disease-free survival (p=0.021). In contrast, tumors located in vertebrae, showed more "atypical" morphology with solid pattern, nuclear pleomorphism and dedifferentiation, higher Ki-67 indices and shorter disease-free survivals (p=0.021). Sacral tumors were the "intermediate group" which occurred in older patients, and demonstrated average Ki-67 proliferation indices and disease-free survivals.

Conclusion: Vertebral localization, probably in relation with both histologic features and failure of surgery, appeared as a significant risk factor for recurrence and Ki-67 proliferation index retained its potential to predict disease-free survival.

Key Words: Chordoma, Recurrence, Ki-67 Antigen, Histology

ÖZ

Amaç: Kordoma, nadir görülen, sık lokal invazyon ve rekürrens yapması nedeniyle malign kabul edilen ve davranışı ön görülemeyen, bir tümördür. Çalışmamızda histolojik özelliklerin, büyüme paterninin, lokalizasyonun ve Ki-67 proliferasyon indeksinin hastalıksız sağkalımı öngörme değeri araştırılmıştır.

Gereç ve Yöntem: Tek bir merkezde tanı alan 29 olguya ait 81 cerrahi materyal (29 primer tümör, 21 olguya ait 47 reküren lezyon ve 5 metastazektomi) gözden geçirilmiş, tüm materyaller, matriks formasyonu (kondroid, miksoid), hücresel özellikler (nükleer pleomorfizm, nekroz, inflamatuvar infiltrasyon, solid, trabeküler veya mikst histolojik patern ve Ki-67 proliferasyon indeksine göre değerlendirilmiştir.

Bulgular: Olguların 11'i kadın (37.9%), 18'i erkek (62.1%), yaş ortalaması 54.1±14.6'dür (Dağılım: 23-78). Tümörlerin %38'i sakrokoksigeal yerleşimli olup, bunu eşit oranda (%31) kafa tabanı ve vertebra takip etmektedir. Kafa tabanı yerleşimli tümörler; genç hastalarda (p=0.048) izlenmekte olup trabeküler patern (p=0.040), kondroid matriks (p=0.063), düşük Ki-67 (p=0.146) ve uzun hastalıksız sağkalım süresi (p=0.021) ile karakterlidir. Buna karşılık vertebra lokalizasyonlu tümörler; solid patern, nükleer pleomorfizm ve dediferansiyasyon içeren atipik morfoloji göstermektedir ve yüksek Ki-67 proliferasyon indeksi ile kısa hastalıksız sağkalım süresine sahip bulunmuştur (p=0.021). Sakral tümörler ise, daha yaşlı hastalarda görülmekte olup Ki-67 proliferasyon indeksi ve hastalıksız sağkalım açısından ara gruptadır.

Sonuç: Vertebra yerleşimi, tümörlerin hem histolojik özellikleri, hem de cerrahi olarak tam çıkarılamamaları nedeniyle, rekürensi öngörmede önemli bir risk faktörüdür. Ki-67 proliferasyon indeksi hastalıksız sağkalımı belirlemede önemli role sahiptir.

Anahtar Sözcükler: Kordoma, Tekrarlama, Ki-67 Antijen, Histoloji

INTRODUCTION

Chordoma is a rare malignant bone tumor accounting for 1-4% all malignant bone tumors (1). It occurs in the axial skeleton and is most often localized in the sacrococcygeal region, followed by the skull base and vertebrae (1). Most patients are reported to be males who are over 30 years old, and its incidence increases after 50 years of age (1,2). Although chordomas are neoplasms with low malignant

Received : 25.11.2008
Accepted : 03.03.2009

Correspondence Address: Banu SARSIK
Ege Üniversitesi, Tıp Fakültesi, Patoloji Anabilim Dalı,
İZMİR, TÜRKİYE

potential (3), they usually display malignant behavior with a short disease-free survival (DFS) because of their tendency to invade adjacent tissues and recur (4). The main treatment of choice is surgery (1) and high recurrence rates are probably related to incomplete removal of tumor in surgically challenging regions (5). Metastases are recognized but are uncommon, and reported to be 5-30% in several series (6, 7). Histologically, the lesion is characterized by tumor cells arranged in sheets, cords or single cells floating within an abundant myxoid stroma. The hallmark "physaliphorous cells" have abundant pale vacuolated cytoplasm (8). There may be considerable variability in the appearance of the tumor from area to area in terms of matrix composition or cellular features. The matrix can be abundant or less prominent. The cells may present mild to prominent nuclear atypia with frequent mitotic figures (8). Chordoma has three histological subtypes as classical, chondroid and dedifferentiated variants (1). The chondroid variants contain areas that may mimic hyaline or myxoid cartilage (9) Chordoma associated with a high-grade sarcoma is called a "dedifferentiated" chordoma (10). The most common form is classical chordoma (11). These subtypes have some clinical importance. Dedifferentiated chordoma has a higher risk of metastasis and poor prognosis (12,13) while the chondroid variant has a better prognosis (14). However, apart from these histological subtypes, and localization associated with completeness of surgical excision, it is not easy to predict the outcome for these tumors. The prognostic importance of histological features such as nuclear pleomorphism, mitotic index or various histological patterns is controversial (7,15-17). We reviewed the clinicopathological features and proliferation indices of chordoma, with respect to their role in predicting disease-free survival.

MATERIALS AND METHODS

Cases were selected from a cohort of 43 cases diagnosed as chordoma in a single center between the years 1974-2004. Twenty-nine cases whose follow up information was available, including 11 females (37.9%) and 18 males (62.1%), were included in the study. The mean age of the patients was 54.1±14.6 (ranged between 23-78 years) and was higher in females (56.9±15.4 for women vs. 52.4±14.3 for men). A total of 81 surgical specimens including 29 primary tumors, 47 recurrent lesions belonging to 21 patients and five metastatectomy materials were reviewed retrospectively. There were 6 metastasizing cases confirmed radiologically but one of them was operated on. At the time of initial evaluation, the diagnosis was established using histological criteria and it confirmed immunohistochemically with cytokeratin, EMA and other immunomarkers such as S100, GFAP and vimentin, when needed. All specimens were retrospectively evaluated according to their cellular features and patterns of proliferation as well as matrix formation before enrollment in the study. Histological patterns were defined as "solid" when tumor cells showed diffuse proliferation; "trabecular", when they formed small clusters or cord-like structures in a relatively rich matrix; or "mixed" when almost equal proportions of both patterns were observed at the same time. Presence of nuclear pleomorphism, necrosis, extracellular myxoid or chondroid matrix and acute (polymorphonuclear leucocyte dominant)/chronic (lymphocytes and or plasma cells dominant) inflammatory infiltration were recorded. Dedifferentiated cases were also noted separately.

Ki-67 was used as a proliferation marker and it was searched immunohistochemically (clone: MIB-1, DAKO, DENMARK, 1/150 diluted) in selected blocks of the 29 cases. One thousand cells were counted and percent ratio of positive nuclear staining was recorded as the Ki-67 proliferation index (Ki-67 PI).

Clinical information and follow-up data were obtained from the Neurosurgery Department and complemented by recent telephone interviews of the patients or their family members. The mean follow-up period was 176-months (range: 6-288 months). Recent clinical information could not be obtained in 4 of the cases and they were not included in the analysis of follow-up results. The type of surgery was classified as described by Kawaguchi et al [18]. "Wide/curative excision" could be achieved only in 4 of the29 cases while 25 were treated by "intralesional surgery". Wide/curative-excised tumors (n=4) were all located in the sacrococcygeal region and treated with sacrectomy, while tumors located in the vertebra and skull base could only be treated with intralesional surgery (n=25). In two of these 25 cases, the intent of the surgical approach was initially "wide/curative excision" but "intralesional surgery" was decided upon on further examination as the surgical margins were found to be positive in microscopic examination. Of these 25 cases, a total of 22 cases received radiotherapy (RT) (11 after the initial operation, and 10 cases after the occurrence of recurrences while one case received RT both after the initial operation and the onset of recurrences). None of the cases received preoperative RT. Disease-free survival (DFS) was defined as the length of time after the initial surgery during which no disease is found until the first recurrence or metastasis.

Statistical Analysis

Statistical evaluation was carried on a PC-based analysis programme SPSS (15.0). Whenever appropriate, chi-square or Fisher's exact tests were used for the statistical analysis of the difference in incidence of clinical and histological findings such as gender, localization, recurrence, metastasis, microscopic presence of necrosis, inflammatory infiltration, nuclear pleomorphism, dedifferentiation, chondroid or myxoid matrix production and pattern of proliferation. Differences in Ki-67 PI were estimated by using the Mann-Whitney-U and Kruskall-Wallis tests. The t-test was applied when searching the relationship between age and DFS. The relationships among age, localization, gender and histological features were investigated by ANOVA analysis and the Duncan test. Kaplan-Meier survival curves with the log-rank test were used for survival analysis. A p value <.05 was accepted as significant.

RESULTS

Localization

The study group consisted of 11 females (37.9%) and 18 males (62.1%) with a mean age of 54.1±14.6 (range 23-78 years). The mean age of females was higher than males (56.9±15.4 for women vs. 52.4±14.3 for men). Thirty eight percent of the cases were localized in the sacrococcygeal region (n= 11) (Figure 1A) followed by the skull base and vertebrae (n=9, 31% for both). Skull base localization was more frequent in males (7 males vs. 2 females) and significantly observed in younger patients (the mean age was 44.78±16.3 for cases localized in the skull base vs. 55.67±15.6 and 60.55±8.2 for the vertebrae and sacrum respectively, p=0.048).

Histopathological Features

There was considerable variability in the appearance of the tumors from area to area in terms of matrix composition or cellular features (Figure 1B). Histopathological findings of the tumors and their relationship with recurrences were summarized in Table I.

Nuclear pleomorphism (Figure 1C), necrosis and inflammatory reaction were observed in more than half of the cases. Although statistically insignificant, necrosis and inflammatory reaction were slightly more frequent in males and in tumors located in the sacrum (Table I). All of the sixteen tumors showing inflammatory reaction demonstrated lymphocyte and plasma cell-predominant mixed inflammation. The type of inflammation was therefore not statistically correlated with the outcome.

Table I: Distribution of histologic features according to localization, gender, age and recurrences

				Localization			Gender		Age	Recurrence
Histologic features		**Cases (n)**	**Ratio (%)**	**Skull base (n, %)**	**Vertebrae (n, %)**	**Sacrum (n, %)**	**Male (n, %)**	**Female (n, %)**	**Mean age±SD (Range)**	**(n, %)**
Necrosis		17	58.6	3 (33.3)	6 (66.7)	8 (72.7)	10 (58.8%)	7 (41.2%)	54.29±13.54 (28-73)	13 (76.5)
Pleomorphism		15	51.7	3 (33.3)	6 (66.7)	6 (54.5)	9 (60)	6 (40)	58,73±15.37 (28-78)	10 (66.7)
Inflammatory infiltration		16	55.1	4 (44.4)	5 (55.6)	7 (63.6)	11 (68.8)	5 (31.3)	52.50±13.38 (28-73)	12 (75)
Dedifferentiation		1	0.34	0	1 (100)	0	1 (100)	0 (0)	28,00	1 (100)
Chondroid matrix		6	20.6	4 (44.4)	1 (11.1)	1 (9.1)	4 (66.7)	2 (33.3)	51.17±14.88 (37-78)	3 (50)
Myxoid matrix		23	79.3	9 (81.8)	5 (55.6)	9 (100)	13 (56.5)	10 (43.5)	54.39±15.38 (23-78)	15 (65.2)
Pattern of proliferation	Solid	5	17.2	0 (0)	3 (33.3)	2 (18.2)	5 (100)	0 (0)	51.40±14.76 (28-68)	5 (100)
	Trabecular	15	51.7	8 (89)*	4 (44.4)	3 (27.3)	8 (53.3)	7 (46.7)	50.67±15 (23-78)	11 (73.3)
	Mixed	9	31.0	1 (11.1)	2 (22.2)	6 (54.5)	5 (55.6)	4 (44.4)	61.44±12.87 (32.73)	5 (55.6)
Localization	Skull base	9	31.0	-	-	-	7 (77.8)	2 (22.2)	44.8±16.34 (23-78)**	4 (44.4)
	Vertebrae	9	31.0	-	-	-	5 (55.6)	4 (44.4)	55.67±15.68 (28-73)	9 (100)***
	Sacrum	11	37.9	-	-	-	6 (54.5)	5 (45.5)	60.55±8.23 (49-73)	8 (72.7)
Gender	Male	18	62.0	7 (77.8)	5 (55.6)	6 (54.5)	-	-	52.44±14.37 (23-78)	12 (66.7%)
	Female	11	37.9	2 (22.2)	4 (44.4)	5 (45.5)	-	-	56.90±15.40 (32-73)	9 (81.8%)
Recurrence	Present	21	72.4	4 (44.4)	9 (100)	8 (72.7)	12 (66.7)	9 (81.8)	52.43±14.17 (23-73)	-
	Absent	8	27.6	5 (55.6)	0 (0)	3 (27.3)	6 (33.3)	2 (18.2)	58.62±16.04 (37-78)	-

*n: Number of cases, %: Ratio of cases within the searched group *(p=0.04), **(p=0.048), ***(p=0,031)*

Figure 1A: Macroscopic view of chordoma located in sacrum (bisected). Tumor invades extraosseous tissue in both anterior and posterior aspects of sacrum.

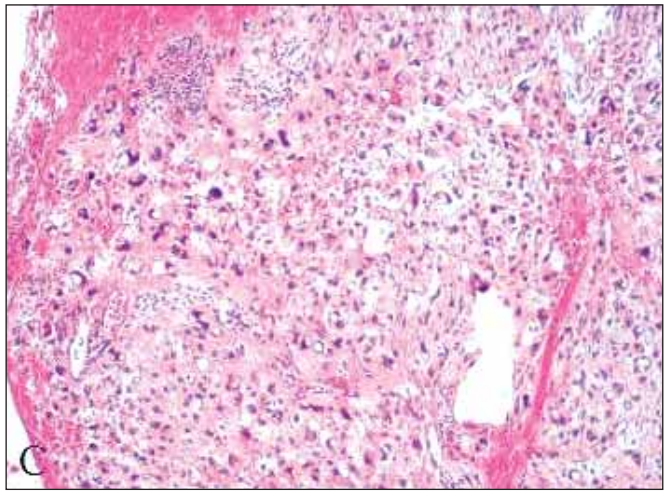

Figure 1C: Prominent nuclear pleomorphism. Those cases may require additional immunhistochemical examination to rule out a poorly differentiated carcinoma (H&E, x100).

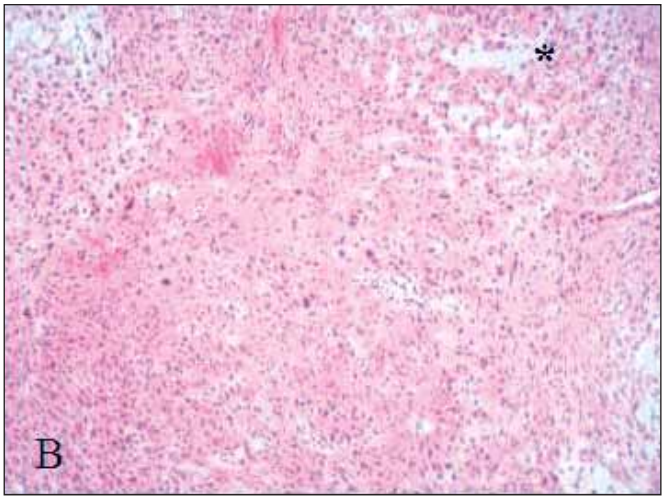

Figure 1B: Tumor with solid pattern of proliferation and less matrix production. Note the more typical appearing areas forming chords in the upper right corner of the area (asterisk) (H&E, x100)

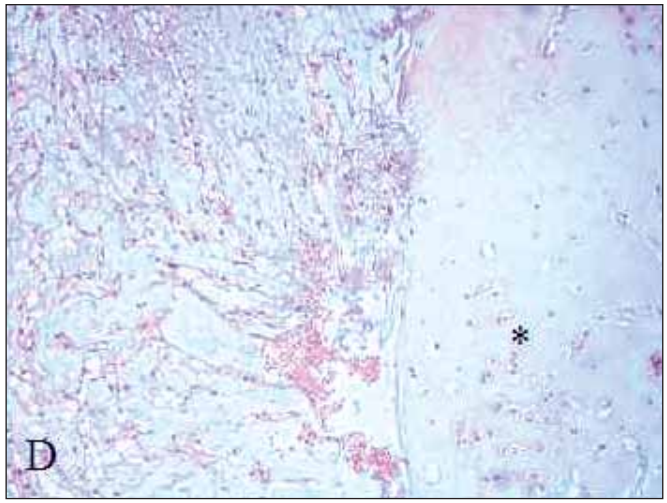

Figure 1D: Tumor with chondroid matrix. It can mimic hyaline matrix (asterisk) (H&E, x100).

Only one of the cases, located in the vertebrae, initially manifested a dedifferentiated form but two additional cases, also located in the vertebrae, showed dedifferentiation in their recurrences (data not shown). Chondroid appearance (Figure 1D) was observed in 6 cases, 4 of which were located in the skull base. Cases whose tumors were located in the skull base were also younger than those with vertebral and sacral tumors (p=0.048). The trabecular pattern was the most frequent pattern followed by mixed and solid patterns and was more frequent in cases located in skull base (p=0.04) (Table I). Cases with tumors showing nuclear pleomorphism, mixed pattern of proliferation or sacral localization were older than the rest of the patient population (Table I).

Although the cases with necrosis, inflammatory infiltration and solid pattern of proliferation recurred more frequently, no significant correlation was observed between the investigated histological features and the presence of recurrence (Table II).

Outcomes

21 (72.4%) of the 29 cases recurred and 6 (20.7%) showed metastases radiologically. In five of these six cases, metastatectomy materials were examined histologically while one of the cases could not be operated on and thus

Table II: Ki-67 proliferation indices, disease-free survival according to clinicopathologic parameters

	Ki 67 PI (%) Mean±SD (Range)	Cases (n)	p	DFS (months) Mean±SD (Range)	p
Gender			0.869		0.772
Female	6.09±9.02	11		29.90±8.53	
Male	5.11±7.26 (0-25)	18		31.73±6.46 (19.05-44.41)	
Localization			0.146		0.021
Sacrum	4.82 ± 5.45 (0-16)	11		30.85±6.92 (17.27-44.43)	
Vertebra	9.00 ± 10.55 (0-28)	9		15.88±4.84 (6.39-25.38)	
Skull base	2.78 ± 6.59 (0-20)	9		49.31±12.12 (25.55-73.07)	
Necrosis			0.626		0.617
Present	7.06±9.45 (0-28)	17		32.14±5.90 (20.57-43.71)	
Absent	3.25±4.11 (0-11)	12		30.27±10.06 (10.55-50)	
Nuclear pleomorphism			0.006		0.882
Present	8.73±8.98 (0-28)	15		31.41±6.46 (18.75-44.08)	
Absent	2.00±4.48 (0-16)	14		28.40±7.47 (13.76-43.05)	
Inflammatory infiltration			0.927		0.596
Present	7.25±9.91 (0-28)	16		27.25±6.02 (15.43-39.06)	
Absent	3.31±3.35 (0-11)	13		32.52±8.02 (16.79-48.25)	
Dedifferentiation	25	1		3±0	0.000
Myxoid matrix			0.028		0.296
Present	4.43±7.65 (0-28)	23		34.25±6.41 (21.68-46.82)	
Absent	9.50±7.86 (4-25)	6		21.66±6.51 (8.89-34.43)	
Chondroid matrix			0.865		0.816
Present	4.67±6.18 (0-16)	6		34.79±14.13 (7.09-62.48)	
Absent	5.70±8.32 (0-28)	23		31.15±5.47 (20.42-41.88)	
Pattern of proliferation			0.031		0.348
Solid	10.4±8.44 (4-25)	5		21.20±7.95 (5.60-36.8)	
Trabecular	2.20±4.32 (0-16)	15		28.05±7.69 (12.97-43.13)	
Mixed	8.22±10.13 0-28)	9		38.88±8.75 (21.72-56.04)	
Recurrence			0.428		0.08
Present	6.14±8.23 (0-28)	21		20.19±18.73 (3-72)	
Absent	3.75±6.86 (0-20)	8		35.25±24.93 (6-72)	

lacked histological confirmation. All metastasizing cases showed recurrences prior to occurrence of metastases apart from one case. Histopathological features of the primary tumors were also evaluated for their predictive value for foreseeing metastasis without any statistically significant correlation.

Number of recurrences ranged between 1 and 7 times. The mean DFS period was 24 months (range: 3-72 months with a 95% CI of 20-41 months). A 5-year DFS was found in 20% of the cases. Metastatic tumors originated from the vertebrae (n=4), and sacrum (n=2). Three of the tumors located in the vertebrae showed only lung metastases, while the fourth one showed additional costal and liver metastasis. One of the sacral tumors metastasized to rectum while the other one showed bone and lymph node metastasis in addition to lung metastasis. None of the tumors located in skull base showed metastasis. No further treatment was administered in one of these metastatic cases while metastatectomy was performed in 5. An "extramarginal" excision could be done in only one of these metastatectomy approaches while the procedure was regarded as "intralesional surgery" with compensatory RT in four. The overall survival rate of patients was 70%, and 17 patients remained alive while 8 died during the follow-up period. Four of 29 patients including one metastatic case did not attend follow-up visits after the first recurrence.

Relationships Between Ki-67 and Other Clinic and Morphological Parameters

The mean Ki-67 PI values of the tumors were 5.48±7.83% (range 0-28%). The mean Ki-67 PI scores and DFS period according to clinicopathological parameters were given in Table II. Tumors having pleomorphic nuclear changes and a solid pattern of proliferation had a significantly higher Ki-67 PI than tumors with classic nuclear features that were "non-solid" (trabecular/mixed patterns) (p=0.006 and p=0.031, respectively). In contrast, cases with myxoid matrix had lower Ki-67 PIs (p=0.028) (Table II). Vertebral tumors with necrosis, inflammatory infiltration and also tumors of female patients had higher Ki-67 PIs (Table II) without any statistical significance. Recurrent tumors had higher mean Ki-67 values relative to non-recurring ones (6.14±8.23 and (3.75±6.86, respectively) without any statistical significance. The mean Ki-67 in metastasizing and non-metastasizing cases was also similar (5.67±7.67 versus 3.75±6.01 respectively).

Factors Influencing DFS (Recurrence)

Cases with nuclear pleomorphism and chondroid/myxoid matrix had longer DFS while the cases with inflammatory

infiltration and solid pattern of proliferation had shorter DFS, although statistically insignificant. DFS was also shorter in females.

Recurring cases were younger than the non-recurring ones 52.43±14.17 (range: 23-73) vs. 58.62±16.04 (37-78). Tumors located in vertebrae recurred significantly more frequently than those located in sacrum and skull base (9 recurring tumors in vertebrae vs. 8 and 4 tumors located in the sacrum and skull base, respectively p=0.031). Mean DFS for cases with vertebral tumors was also shorter (15 months vs. 30 and 49 months for cases whose tumors were located in the sacrum and skull base, p=0.021). The type of surgical approach, "wide/curative excision" or "intralesional surgery", was the most important parameter predicting DFS. All recurring cases were previously treated by intralesional surgery so they had positive surgical margins. In contrast, none of the sacrectomy cases treated with "wide/curative excision" recurred, although one of them presented with metastases to bone, lymph nodes and lungs, 5 years (60 months) after initial surgery without showing any prior recurrence. Mean DFS time was 25 months for cases treated with "intralesional surgery". Postoperative radiotherapy did not prolong DFS. Eight of 11 cases that received RT after "intralesional surgery" recurred in a shorter mean period of 23 months (Figures 2, 3).

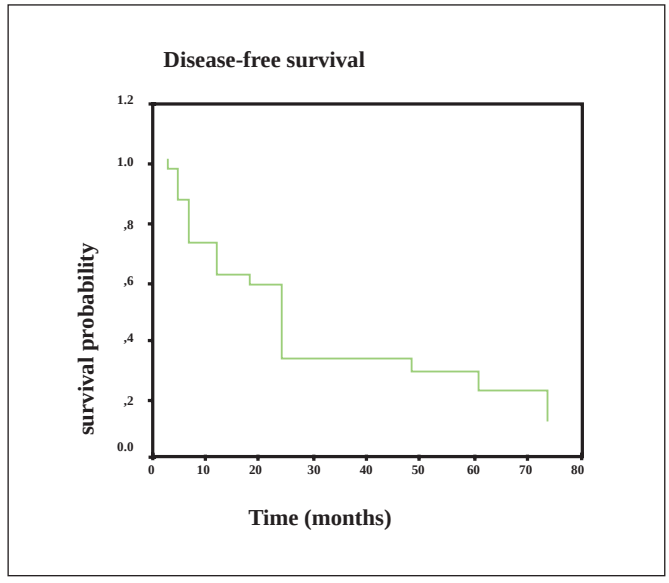

Figure 2: Kaplan-Meier disease-free survival curve. The Y-axis shows survival probability

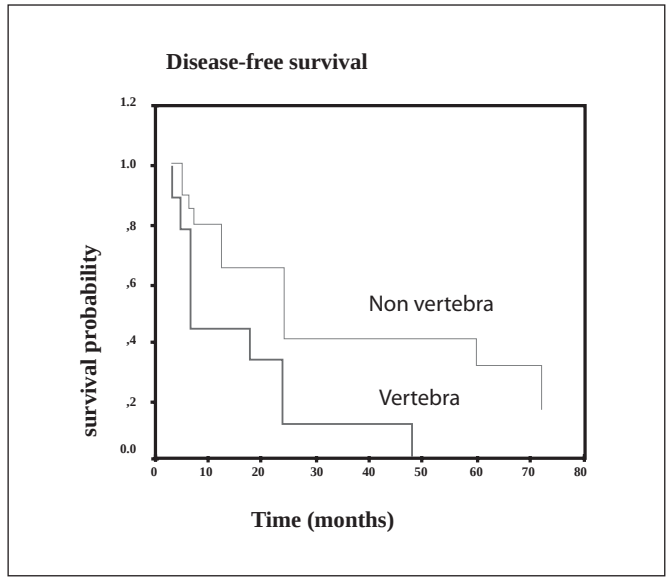

Figure 3: Kaplan-Meier survival curve for cases in vertebral (lower line) and non-vertebral localization (upper line). The Y-axis shows survival probability.

Factors Influencing Metastasis

Only six of the cases showed metastases and no correlation was found between the histopathological features and Ki-67 indices of primary tumors and presence of metastases. Besides, the histopathological features of metastatic tumors were not notably different.

DISCUSSION

The natural history is not well understood in chordomas because of their rare incidence and slow-growing nature. Completeness of initial surgery is a well-known prognostic parameter to predict DFS (5). However, association between histopathological features and disease outcome is controversial. In this study we evaluated clinicopathological features such as presence of pleomorphic nuclear features, necrosis, dedifferentiation, extracellular myxoid and chondroid matrix and acute/chronic inflammatory infiltration, histological pattern of proliferation (solid, trabecular or mixed) and Ki-67 proliferation index in respect to their potential to predict DFS. Chordoma is a tumor that can present with various histopathological compositions. We identified some common features observed in particular localizations. Tumors located in the skull base had chondroid matrix more frequently than those found in other localizations, in agreement with previous reports (11,15,17,19,20). A trabecular pattern of proliferation was also more frequent in this localization and they recurred less often. Ki-67 PI was lower than the rest of the cases. Most of them, occurred significantly in younger patients (p= 0.048). This difference in age may be due to the anatomic specificity in remnants of notochord (11).

In contrast, vertebral tumors harboured more atypical features with nuclear pleomorphism and a solid pattern of proliferation. The only initially dedifferentiated tumor was also seen in this localization. Ki-67 PI was higher than in other localizations and all cases recurred in the meantime. The surgical difficulties should also be considered in addition to these, more "atypical" features. Sacral tumors were characterized by necrosis, inflammatory infiltration and myxoid matrix. The Ki-67 PI and DFS were in an intermediate stage between tumors located in the skull base and vertebrae. They occurred in older patients, which led us to think that these histological features were late events in the course of the disease. We were unable to find an association between atypical histopathology, and disease outcome and most of the previous studies failed to show such an association (13,15,17,21) Chambers et al., found a relationship between nuclear pleomorphism and metastasis in classical chordoma (7). Naka et al., claimed that nuclear pleomorphism served as a prognostic marker only when applied to tumors located other than skull base (11).

We also searched Ki-67 PI of tumors and correlated them with DFSs. The relationship of histological features and Ki-67 PI is not well established because of the rarity of the studies on the issue. In one of the most detailed studies on proliferation indices, Naka et al., found a higher proliferation index in lesions with increased nuclear pleomorphism (5). Age, recurrence, and nuclear pleomorphism were the independent factors indicating higher Ki-67 PI in skull base chordomas (11,22) while no correlation was found for chordomas in other locations (11). Sell et al stated that Ki-67 PI was not an independent prognostic marker but had a potential to predict survival in cases with nuclear pleomorphism and atypical features (23). Regardless of its prognostic value, it must be kept in mind that proliferation markers have to be evaluated with caution since the divergent areas may present different proliferation indices (24). We found higher Ki-67 PI scores in tumors with solid areas, nuclear pleomorphism and chondroid areas although the associations did not reach statistical significance. Tumors having a solid pattern of proliferation had a higher Ki-67 PIs than those with trabecular and mixed patterns, probably related with the increased cellularity in the former pattern. Correlation of higher Ki-67 PIs with solid growth pattern of proliferation is controversial. This correlation was found to be indeed insignificant in a study, although a significant correlation was suggested previously by the same group (5,11). The only case with dedifferentiated areas had an apparently higher Ki-67 score than the rest of the cases (25% vs. 5.48%, respectively). Higher Ki-67 PI scores were also observed in cases with inflammatory tissue response, a feature, which to our knowledge was not defined in the literature before. Given the fact that most of this inflammatory infiltrate is comprised of lymphocytes, one may regard them as tumors harbouring reactive lymphocytes but still the presence of polimorphonuclear leucocytes in primary tumors needs further investigation. The present study revealed that Ki-67 PI was also higher in tumors located in vertebrae, but has an inclination to decline with age in contrast to previous reports suggesting that it increased with aging (11) DFS was also found to be longer in tumors located in the skull base, in agreement with reviews suggesting a favorable course for skull base chordomas (14). In the present study, recurrence was significantly more frequent in tumors located in vertebrae ($p=0.031$) and DFS was accordingly shorter ($p=0.021$). Given the fact that Ki-67 PI was also higher in tumors located in vertebrae, this association can be regarded as alarming for shorter DFS at least for tumors in this location. We find this observation important since it was not emphasized in previous reports. This finding may suggest growth of a residual tumor other than progressive tumoral proliferation in recurring cases. The most important parameter that affects survival seems to be the localization of tumor since it directly influences the effectiveness of surgery. Ki-67 PI is likely to predict DFS indirectly.

There are several reports suggesting radiotherapy following surgery as it prolongs DFS (25,26) or alters overall survival (2,27). We did not observe a significant difference between the radiotherapy applied group and the others. To our surprise, DFS was even shorter in this group. It is likely that this group of patients were more prone to local recurrence since the initial surgery was "more" ineffective.

In conclusion, we searched for possible histological prognostic factors to predict DFS in cases with recurring chordomas. Although no significant correlation was found between nuclear pleomorphism, dedifferentiation, presence of myxoid or chondroid matrix, acute and chronic inflammatory reaction and disease recurrence, we identified some discriminating features with respect to the localization of tumors. Skull base chordomas occur in younger patients and have more "indolent" morphology and course with trabecular pattern of proliferation, and chondroid matrix. Ki-67 PI is comparatively lower and DFS is longer than the others. In contrast, tumors located in vertebrae present with more "atypical" morphology with solid pattern of proliferation, nuclear pleomorphism and dedifferentiation having higher Ki-67 PI and shorter DFS. Sacral located tumors were the "intermediate group" occurring in older

patients showing necrosis, inflammatory infiltration and myxoid matrix with average Ki-67 PIs and DFS periods. Among the factors evaluated, vertebral localization appeared to be a significant risk factor for recurrence and Ki-67 PI retained its potential to predict DFS. The completeness of surgery is the single most important prognostic parameter that affects DFS. Among the evaluated clinicopathological findings including Ki-67 PI, none were found to be valuable in predicting metastasis. More clinicopathological studies are needed for better understanding of the relationship between histopathological features and disease outcome in chordoma.

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