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Analysis of Risk Factors for Recurrence of Giant Cell Tumor of the Sacrum and Mobile Spine Combined with Preoperative Embolization

Preoperatif Embolizasyonla Kombine Mobil Omurga ve Sakrum Dev Hücreli Tümörü Nüksü Risk Faktörleri Analizi

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ABSTRACT

AIM: To investigate the factors related to the local recurrence-free survival time (LRFS) after surgical treatment of GCT of the sacrum and mobile spine combined with preoperative embolization.

MATERIAL and METHODS: We retrospectively reviewed 28 consecutive patients with GCT of the sacrum and mobile spine who underwent initial surgical excision combined with preoperative embolization between 1995 and 2011. Data regarding age, gender, tumor location, tumor size, tumor extension, radiation therapy, and local recurrences were reviewed and analyzed statistically.

RESULTS: All patients underwent intralesional resection. The average duration of follow-up was 86.4 months (range, 15 - 193 months). 8 (28.6%) patients developed local recurrence. The average recurrence time was 35.6 months (range, 5 - 79 months), and the local recurrence-free survival rates at 3 and 5 years were 89.1% and 75.5%, respectively. LRFS was found statistically longer in intracompartmental (T1) tumors as compared with extracompartmental (T2) tumors ($P<0.05$), but not for age, gender, tumor location, tumor size, or radiation therapy.

CONCLUSION: Intralesional excision with preoperative embolization is a feasible choice for T1 tumors of the sacrum and mobile spine, but for T2 tumors, more aggressive treatment may be required. The choice of surgical treatment should be balanced between the complications and tumor recurrence.

KEYWORDS: Giant cell tumor, Spine, Local recurrence, Risk factor, Embolization

ÖZ

AMAÇ: Preoperatif embolizasyonla kombine mobil omurga ve sakrum dev hücreli tümör cerrahi tedavisinden sonra yerel nükssüz sağkalım süresi (LRFS) ile ilişkili faktörleri incelemek.

YÖNTEM ve GEREÇLER: 1995 ile 2011 yılları arasında preoperatif embolizasyonla kombine başlangıç cerrahi eksizyonu yapılan mobil omurga ve sakrum dev hücreli tümörü olan arka arkaya 28 hastayı retrospektif olarak değerlendirdik. Yaş, cinsiyet, tümör konumu, tümör büyüklüğü, tümör uzanması, radyasyon tedavisi ve yerel nükslerle ilişkili veriler değerlendirilip istatistiksel olarak analiz edildi.

BULGULAR: Tüm hastalara intralezyonel rezeksiyon yapıldı. Ortalama takip süresi 86,4 aydı (aralık, 15 - 193 ay). 8 (%28,6) hastada yerel nüks gelişti. Ortalama nüks süresi 35,6 aydı (aralık 5 - 79 ay) ve yerel nükssüz sağkalım oranı 3 ve 5 yılda sırasıyla %89,1 ve %75,5 bulundu. LRFS intrakompartmantal (T1) tümörlerde ekstrakompartmantal (T2) tümörlere göre istatistiksel olarak daha uzundu ($P<0,05$) ama yaş, cinsiyet, tümör konumu, tümör büyüklüğü veya radyasyon tedavisinin bir farkı yoktu.

SONUÇ: Preoperatif embolizasyonla intralezyonel eksizyon, mobil omurga ve sakrumun T1 tümörleri için iyi bir tercihtir ama daha agresif tedavinin gerekebileceği T2 tümörleri için iyi bir tercih değildir. Cerrahi tedavi tercihi komplikasyonlar ve tümör nüksü arasında dengelenmelidir.

ANAHTAR SÖZCÜKLER: Dev hücreli tümör, Omurga, Yerel nüks, Risk faktörü, Embolizasyon

INTRODUCTION

Giant cell tumor (GCT) of bone is a rare primary bone tumor that typically arises in the metaepiphyseal region of long bones (5). The sacrum is the third most common location, accounting for between 2%-8% of cases (5,29), and the incidence in the mobile spine ranges from 2% to 5% (24). Histologically, GCT has been described as a benign tumor consisting of three cell types: mononuclear histiocytic cells, multinucleated giant cells, and neoplastic stromal cells (32). The tissue is highly vascular and usually without stroma (4). Although it is a benign tumor, it can be aggressive locally and metastasize. GCTs can grow to a large size before patients

experience significant symptoms and they can involve the critical neurovascular structures. The main treatment is surgery, because of the anatomic characteristic of the region and hypervascularity of the tumor, surgical treatment is difficult and local recurrence is high (27). Until now, there are no single clinical, radiographic, histological or morphological aspects that allow surgeons to accurately predict the tumor to recur.

Although risk factors for local recurrence of giant cell tumor have been reported in many articles (1, 16, 22, 31) , there are few studies focusing on GCT of the sacrum and mobile spine (3), and the present authors have found no study on the risk of recurrence after surgery when combined with preoperative embolization by digital subtraction angiography (DSA) technique. The purpose of this study was to identify the risk factors for local recurrence of GCT of the sacrum and mobile spine after surgery, combined with preoperative embolization.

MATERIAL and METHODS

We retrospectively reviewed 28 consecutive patients (16 females and 12 males) with GCT of the sacrum and mobile spine who underwent initial surgical excision combined with preoperative embolization between 1995 and 2011. The average age was 29.6 years (range, 11-58 years). Data were collected from the medical records that included age at the time of diagnosis, gender, tumor location, tumor size (largest diameter), tumor extension, and radiotherapy. Tumor extension was graded T1 or T2 (intracompartmental or extracompartmental extension) according to the system of Enneking et al (7, 8) based on the clinical and operative findings (Figure 1A-C). All 28 patients were verified to be giant cell tumor by histology after operation.

The average follow-up time was 86.4 months (15 to 193 months). Patients were followed via clinical examination and imaging studies in the outpatient clinic every 3 months for 2 years, and then every 6 months thereafter.

Treatment

All patients underwent preoperative arterial embolization using the digital subtraction angiography (DSA) technique. We use gelfoam particles to embolize the small intratumoral arteries, and the stem of the tumor feeding arteries was embolized with a gelfoam strip. The surgery was performed 1 to 2 days after the embolization. The surgical approaches were decided case by case, based on the site and extent of the tumor. All tumor excisions were defined as intralesional. After exposure, the tumor perimeter was packed with gauzes to prevent spillage of tumor tissue during the curettage. The nerve roots were protected and preserved as more as possible. However, if the nerve roots or spinal dura mater were contaminated, the membrane was dissected carefully. The operation field was covered thoroughly with 95% degree alcohol gauze, and then cleaned with warm normal saline. Sterilized distilled water was used to lyse the residual microscopic tumor debris. If the mechanical stability of the spine was insufficient, instrumentations and reconstructions were required.

Statistical Analysis

Data were collected in an Excel spreadsheet. LRFS was defined as the time from primary surgery to tumor recurrence. Risk factors for recurrence after surgery, including age at the time of diagnosis, gender, tumor location, tumor size, tumor extension and radiotherapy, were compared by the log-rank test. The Kaplan-Meier estimator was used to create the LRFS curve. A p value of less than 0.05 was deemed significant.

RESULTS

Of the 28 patients, 12 were males and 16 were females. The average age at diagnosis was 29.6 years (range, 11 to 58 years). 13 were located in the mobile spine (8 thoracic, 5 lumbar) and 15 were located in the sacrum. Most patients (23/28) presented with pain. Neurologic deficit such as paresthesias, weakness and bowel and/or bladder dysfunction were observed in 17 patients. The average duration of symptoms before diagnosis was 4 months (range, 0.5 to 40 months). The mean tumor size was 6.9 cm (range, 3.0 to 20.0 cm) at the greatest diameter. 15 cases were identified as T2 tumors.

In the present study, all surgical procedures were intralesional, and reconstruction was performed in 14 patients. The average intraoperative blood loss was 1528.6 mL (range, 400 to 5800 mL) and the average operation time was 225.4 minutes (range, 120 to 470 minutes). 14 patients underwent reconstruction and 6 patients received adjuvant radiation therapy after surgery, with an average dose of 51 Gy (range, 40 to 60 Gy). No patients received chemotherapy.

Eight (28.6%) patients developed local recurrence (Figure 2A-D, 3A-C). The average recurrence time was 35.6 months (range: 5 - 79 months). The local recurrence-free survival rates at 3 and 5 years were 89.1% and 75.5%, respectively. 8 (28.6%) patients experienced complications perioperatively or during the follow-up. 6 (21.4%) patients had wound complications, 1 patient experienced cerebrospinal fluid leakage, and 1 thoracic patient developed kyphosis. At the final follow-up, 25 patients showed no evidence of disease, 1 patient was alive with disease and 2 patients died. No patients had metastases to the lungs. 24 (85.7%) patients retained normal neurologic function (13 patients in mobile spine and 11 patients in sacrum).

The results of the log-rank analysis indicated that tumor extension contributed to statistical significance in the LRFS ($p < 0.05$, Figure 4A-F). Other factors including age, gender, tumor location, tumor size and radiation therapy did not have a statistically significant impact on the LRFS ($p > 0.05$, Figure 4A-F). The details of the relevant factors of recurrence and the LRFS median are listed in Table I.

DISCUSSION

Giant cell tumor is a hypervascular lesion that rarely occurs in the spine. Because of the complicated location and highly

vascular of the tumor, massive blood loss often occurs during the operation (29,30). Several authors have reported that preoperative embolization of spinal tumors is a safe and effective technique in reducing the intraoperative blood loss (12, 28, 33). In the current study, the average intraoperative blood loss was 1528.6 mL (range, 400 to 5800 mL), which was significantly decreased compared with the cases (29,30) did not use preoperative embolization.

GCT is still one of the most controversial and discussed bone tumors. Although histologically benign, GCT can be locally aggressive and prone to recur. Surgery is the main treatment method, and surgical treatment includes intralesional excision and en bloc resection (13). En bloc resection with either a marginal or wide resection margin is well known to produce the lowest recurrence rate, but may increase the risk of perioperative complications and neurologic and functional deficits. Intralesional excision can spare nerve roots, pelvic support, and visceral structures depending on the location of the lesions, but may increase the risk of local recurrence. Most studies that aimed at identification of risk factors for local recurrence have included both intralesional excision and en bloc resection in analyses, which may results in a selection bias because of lower recurrence rates after en bloc resection. In the present study, we investigated the risk factors for local recurrence of GCT of the sacrum and mobile spine after intralesional excision combined with preoperative embolization.

In the study by Klenke et al (16), age was found to be an independent factor of postoperative recurrence and LRFS, and Boriani et al (3) also found that age less than 25 years was a risk factor for local recurrence. However, in the present study, LRFS was not found to be significantly different for patients with different age, and many authors found that the recurrence rate did not correlate with age. It may be partly explained by selection bias, younger patients may have been selected to have intralesional excision instead of en bloc resection, and most studies analyzing risk factors for local recurrence have included both intralesional excision and en bloc resection (3).

GCTs are slightly more common in women (19). However, gender was not thought to be a risk factor for local recurrence

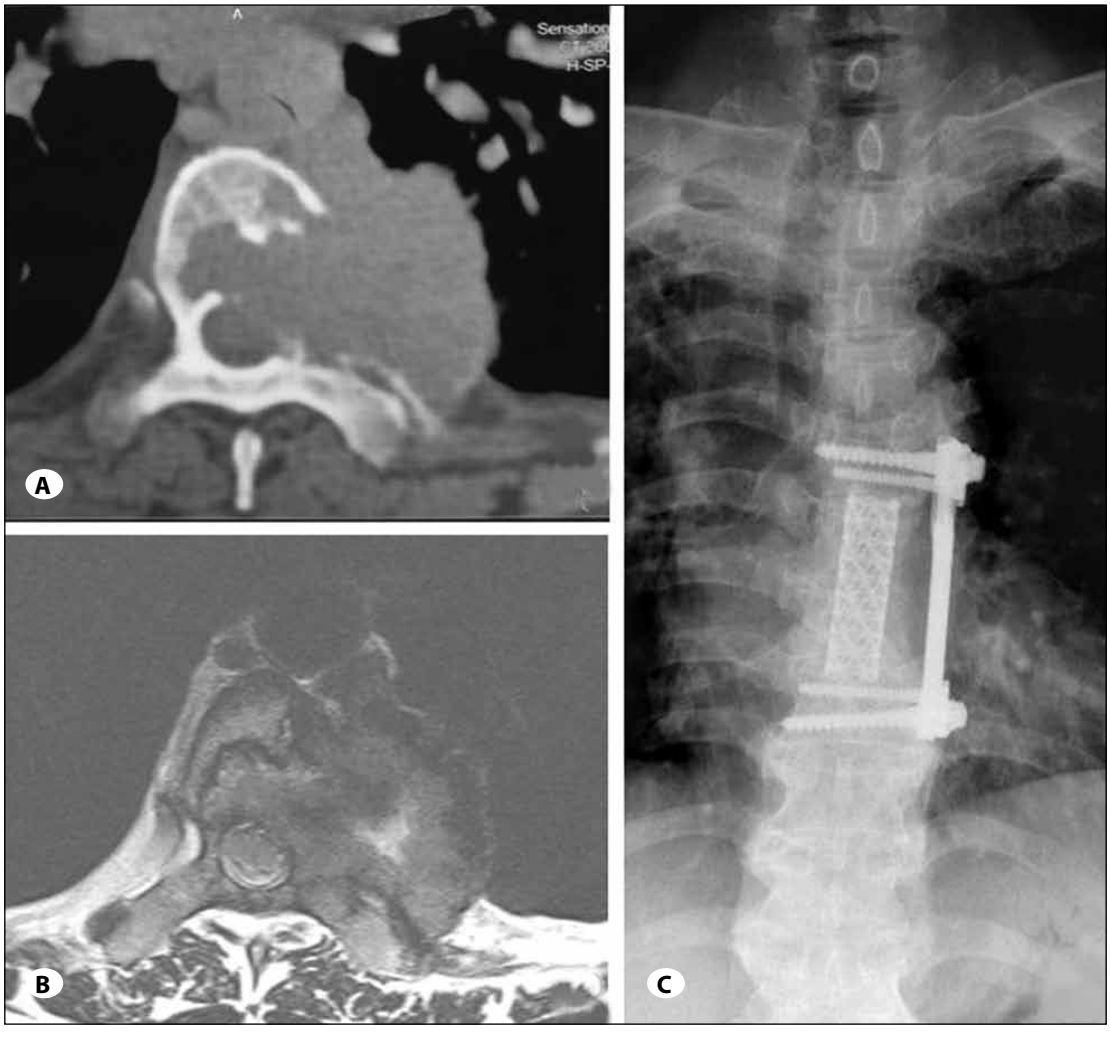

Figure 1:
A 53-year-old male who presented with back pain for about eight months.
A, B) Axial CT and T2-weighted MRI demonstrated a T2 (extracompartmental) giant cell tumor of the spine;
C) Anteroposterior radiograph after the operation.

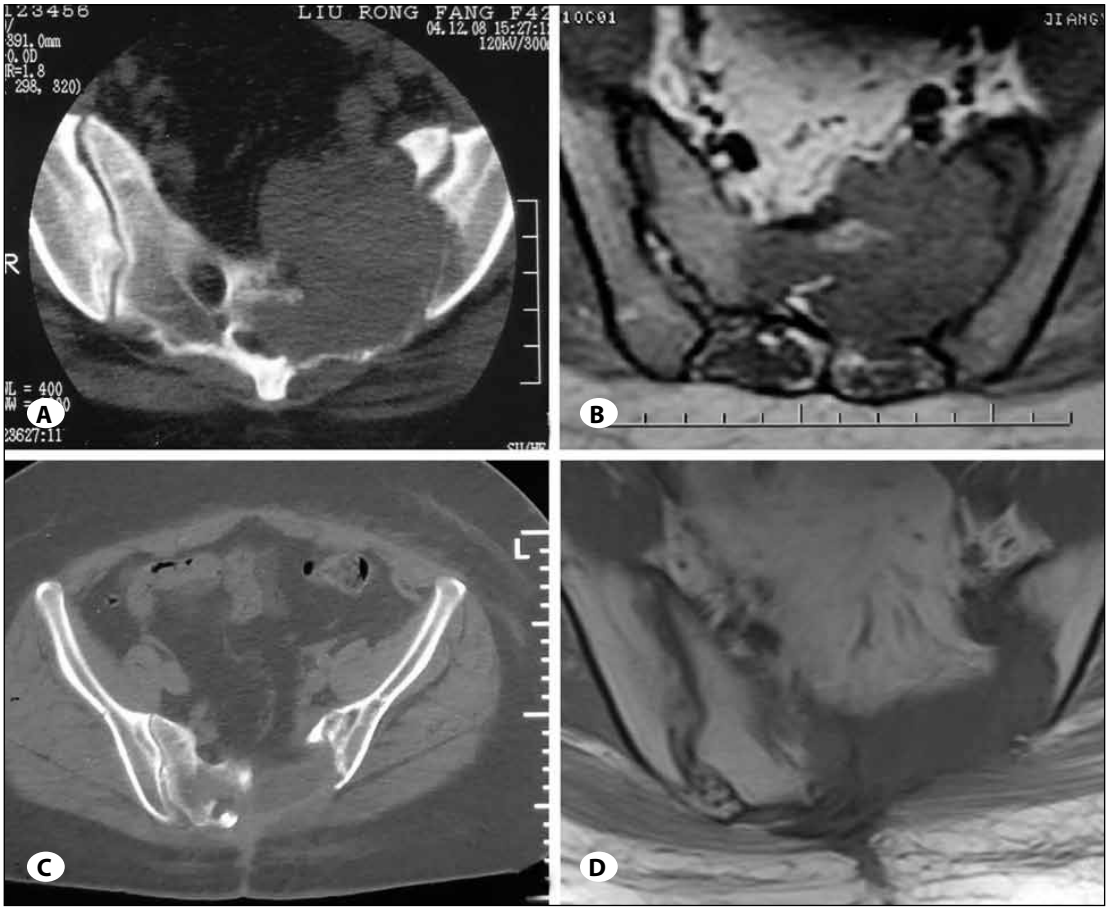

Figure 2:
A 41-year-old female who presented with sacral pain and bowel dysfunction. **A, B)** Axial CT and T1-weighted MRI demonstrated a large destructive mass at the left side of the sacrum; **C, D)** Axial CT and T1-weighted MRI after the primary operation, no tumor could be observed.

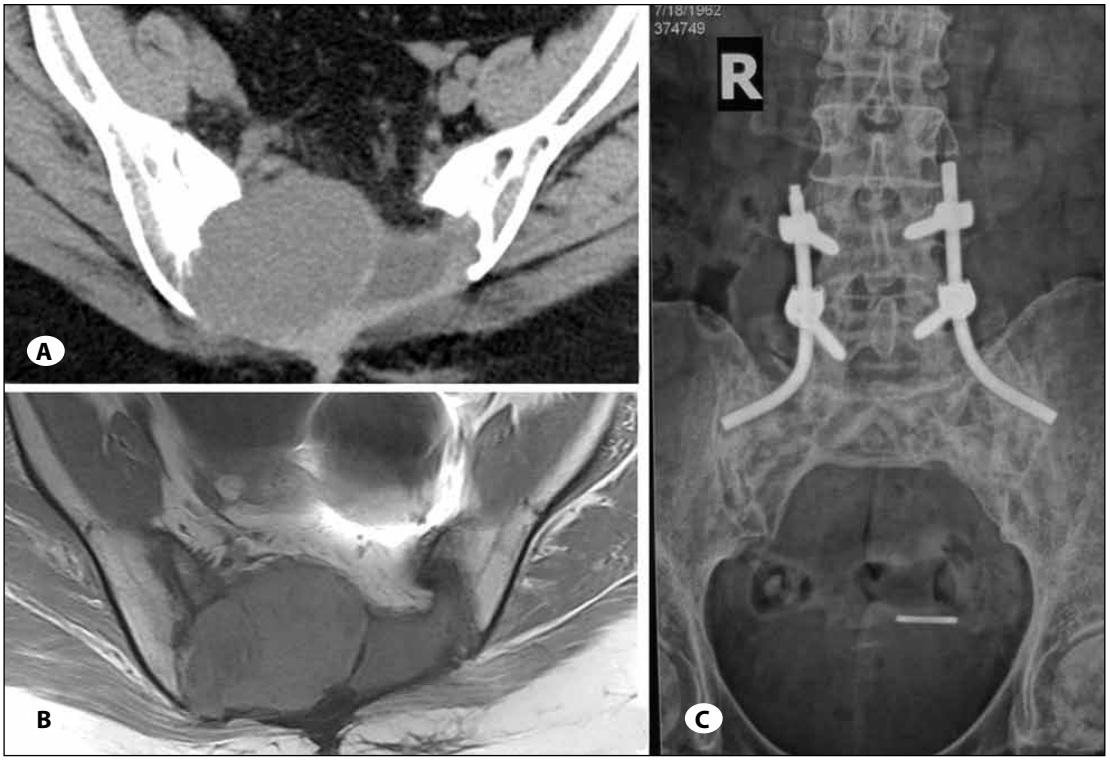

Figure 3:
A 41-year-old female who presented with sacral pain and bowel dysfunction. **A, B)** At 39-month follow-up after the primary operation, axial CT and T1-weighted MRI showed the tumor recurred at the right side of the sacrum.
C) Anteroposterior radiograph at 54-month follow-up after the second surgery, showed no recurrence.

in GCTs until recently (3). Of the 28 patients involved in the present study, 12 were male (LRFS median: 49 months) and 14 were female (LRFS median: 66 months). 4 of the male patients and 4 of the female patients experienced recurrence. There was no statistically difference between the LRFS medians for the men and the women.

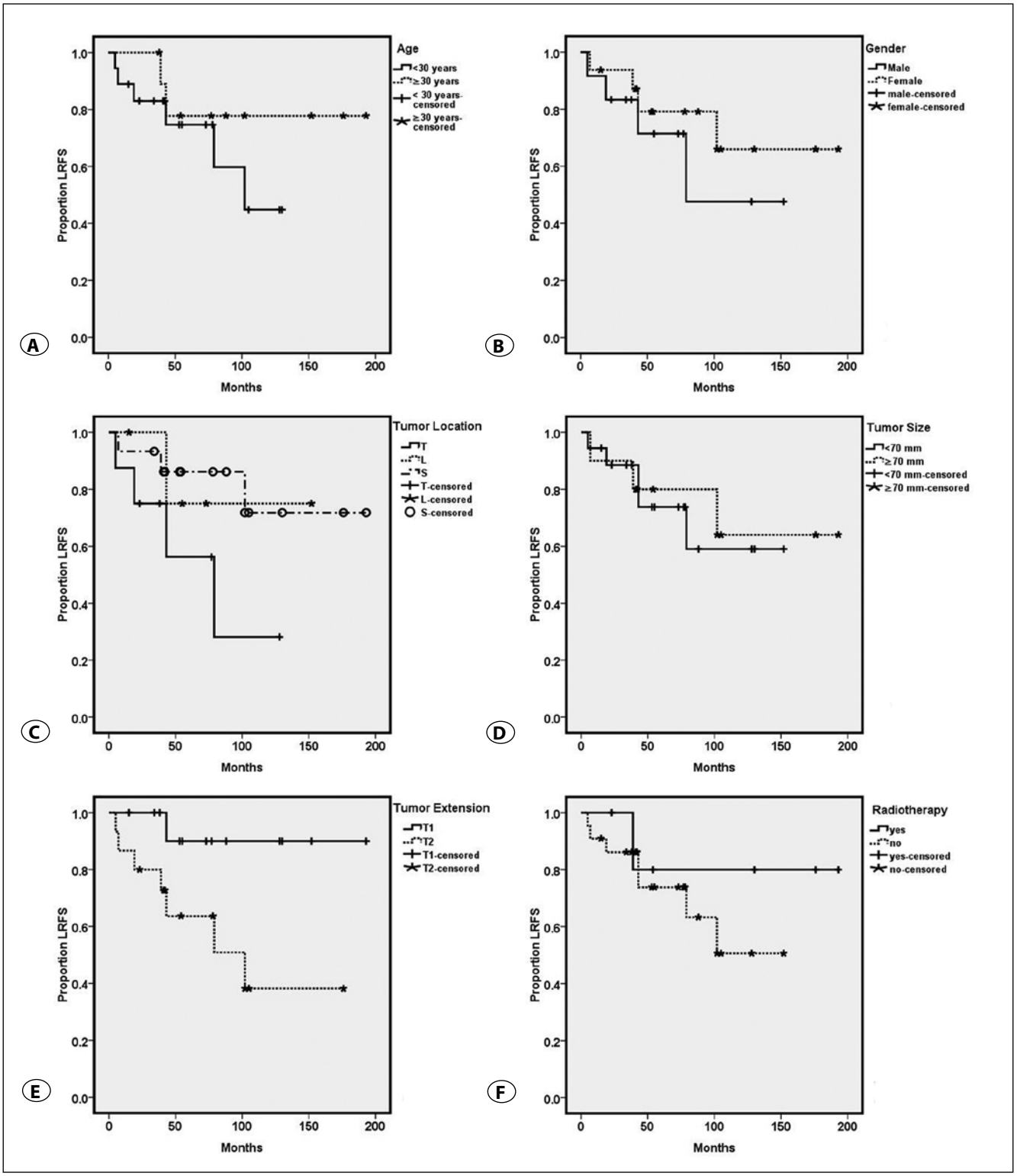

Figure 4: LRFS of patients grouped according to age **(A)**, gender **(B)**, tumor location **(C)**, tumor size **(D)**, tumor extension **(E)**, radiotherapy **(F)**, respectively.

Table I: Relevant Factors for Local Recurrence of Giant Cell Tumor of the Sacrum and Mobile Spine

Statistically factors	Local recurrence		Median LRFS (months)	χ^2	p-values
	Yes	No			
Sex					
Male	4	8	49	0.628	0.428
Female	4	12	66		
Age					
<30 yrs	6	12	48	1.092	0.296
≥30 yrs	2	8	88		
Tumor location					
T	4	4	40.5	3.658	0.161
L	1	4	64		
S	3	12	78		
Tumor size					
<70mm	5	13	54	0.051	0.821
≥70mm	3	7	78		
Tumor extension					
T1	1	12	82.5	4.627	0.031
T2	7	8	43		
Radiotherapy					
Yes	1	5	92	0.725	0.394
No	7	15	54		

Some authors (2, 9) found that the risk of recurrence was higher when the tumor is located in the distal radius than distal femur or proximal tibia, they believed that the complication rate and difficulty of the treatment in the distal radius are greater than in other site of extremities. However, there is limited data in literatures comparing local recurrence rates with different location through GCT lesions of the spine (3). In the present study, we found no significantly different LRFS for patients with different locations.

Tumor size often reflects the speed of tumor growth, correlating with the extension of the tumor and the outcome in malignant tumors, however, its effect on GCT recurrence has been contended (14, 15, 21). Miszczyk et al (21) found that tumor size significantly influenced local recurrence in patients treated with radiotherapy. The five year local control rate was 90% for tumors ≤ 4 cm, and decreased approximately 8% for each 1-cm increase in tumor diameter > 4 cm. The average diameter of the tumors among the 28 patients in the present study was 69.0 mm. 18 cases had tumors with diameters <70 mm, of which 5 had recurred (LRFS median: 54 months). 10 cases had tumors with diameters ≥70 mm, of which 3 had recurred (LRFS median: 78 months). There was no statistically difference between the LRFS medians of the two groups. This may be partly explained by the result of using preoperative embolization, which can significantly decrease intraoperative blood loss and increase the complete resection rate.

Tumor extension has been proven to be a prognostic marker concerning local recurrence in some studies (1, 2, 31). In the study of Arbeitsgemeinschaft Knochentumoren (1), T2 tumors were associated with a high hazard of recurrence (hazard ratio = 2.7, $p = 0.007$) compared with that for T1 tumors. Similarly, we found that tumor extension increase the risk of recurrence. In the present study, 13 cases were T1 tumors (LRFS median: 82.5 months) and 15 cases were T2 tumors (LRFS median: 43 months). 1 of the T1 tumors (7.69%) and 7 of the T2 tumors (46.67%) experienced recurrence. This may indicate that the T2 tumors are more active and aggressive, and technical difficulties may experience in the complete removal of tumor tissue when performing intralesional treatment and lack of adequate applicable local adjuvants. Therefore, intralesional excision can be a feasible treatment option for T1 tumors, but T2 tumors may require more aggressive treatment.

Although radiation therapy is a common adjuvant treatment for patients after the resection of their tumors, it is debatable as to whether it can reduce local recurrence or induce malignant transformation. Multiple studies have demonstrated low local control rates (42%-70%) for patients treated with radiation therapy (6, 11, 18, 20). However, some authors (23, 25) believed that these studies were performed in the 2-D era of radiation therapy and radiodiagnostics techniques were obsolete. Those patients were treated with orthovoltage radiation therapy, which was administered in low dose and multiple courses, resulting in high toxicity due to the unfa-

vorable dose distribution and probably increased the rates of secondary malignancies. With the improvement of the radiation therapy and imaging techniques in the last decades, some authors (10, 26) have shown a high rate of local control, and low malignant transformation. Kirz et al (17) reported 35 patients who received megavoltage radiotherapy in a median 65 months' follow-up, 16 cases were located in the spine, the actuarial 5-year overall and disease-free survival rates were 90% and 59%, respectively. No malignant transformations were observed. Roeder et al (25) found a local control rate of 80% in 5 patients treated with intensity modulated radiotherapy (IMRT), and they could not observe any severe acute or late toxicities. They believe that GCT is a radiosensitive lesion, and recommend modern radiation therapy as an effective alternative treatment for cases in which complete excision is not possible or morbidity is extreme. In the present study, only 6 patients were treated with radiation therapy, and we could not find a significant difference in LRFS between those cases who did and those who did not receive radiation. Given the limitation of the series, the value of adjuvant radiation therapy needs to be investigated in future prospective multi-institutional studies.

CONCLUSION

Tumor extension was the factor has significant influence on the LRFS. Patient's age at the time of diagnosis, gender, tumor location, tumor size, and radiation therapy were found to have no statistical significance on the LRFS. We recommend intralesional excision with preoperative embolization as a first choice treatment option for T1 GCT of the sacrum and mobile spine, with good oncological outcome and neurologic function, but for T2 tumors, more aggressive treatment may be required. The choice of surgical treatment should be balanced between the complications and tumor recurrence.

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