RESEARCH COMMUNICATION

Sarcoma in Iran

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Abstract

Purpose: **To review the clinical characteristics of 1470 sarcoma cases and to define the factors in patients that predict out come, relapse and survival .**

Methods: **Retrospective analysis of the database for the period 1991-2002, focusing on demographic, tumor related and treatment related variables, relapse free survival (RFS) and overall survival (OS) using the Kaplan- Meier method. Statistical significance was evaluated using the chi square and t- tests for univariate influence and a Cox regression model for multivariate influence.**

*Results***: Mean age was 30 years. The male to female ratio was 3/2 and 23%of the cases were under 16 years of age. Median tumor diameter was 10.5 centimeters. The bone to soft tissue sarcoma ratio was 3/1 in children and 1/3 in adults. Osteosarcoma, Ewing's tumours and rhabdomyosarcomas accounted for 83% of childhood tumors. In adults osteosarcomas, synovial sarcomas and malignant fibrous histocytomas (MFHs) were the most common subtypes. Mean follow up time was 56 months. Of the total, 25% had initial metastasis, 86% received chemotherapy and 41 % underwent radiotherapy. The main prognostic factors for survival were tumor size, margin of surgery, neurovascular involvement in the pathological report, initial metastasis and no complete response to first therapy. Adjuvant radiotherapy, small tumor size, curative surgery with chemotherapy and free surgical margins were significantly associated with reduced recurrence.**

Conclusion: **Our patients are characterised by diagnosis with a large tumor size, advanced stage of disease and short survival. A complete response to primary therapy is the main independent variable for overall survival. Earlier diagnosis and an experienced team including surgical, medical and radiotherapy oncologists are needed for a better response and longer survival of patients.**

Key Words: Sarcoma - clinicopathological parameters - survival - Iran

Introduction

Sarcomas are rare (less than 1 % of all malignancies) mesenchymal neoplasms that arise in bone and soft tissues. The tumors are usually of mesodermal origin, although a few are derived from neuroectoderm, and they are biologically distinct from the more common epithelial malignances. Sarcomas affect all age groups, 15% being found in children younger than age 15 and 40% occurring after age 55. Soft tissue include muscle, tendons, fat, fibrous tissue, synovial tissue, vessels and nerves. Malignant transformation of a benign soft tissue tumor is extremely rare. With the exception of malignant peripheral nerve sheet tumors can arise from neurofibromas in patients with neuro fibromatosis. The overall annual age adjusted incidence of sarcoma is 2 per 100000 population but the incidence varies with age.

The aim of this study was to make an extensive and broad review of sarcomas in Iranian patients to establish the natural history and to determine factors affecting disease outcome .

Materials and Methods

In this study, we retrospectively examined our experience with sarcoma in patients treated and followed up in central hospital from 1991 to 2002. Information was from review of the original histopathology reports from the referring hospitals when the patient presented having already had excisional biopsy, local recurrence or metastatic disease. In nearly all cases, original histopathology had been reviewed at the time of refferal by one anatomic pathologist with a specialized interest in sarcoma. Detailed information was recorded on tumor charactristics, including immuno-histochemistry findings. Follow up information was obtained from regular visits in the majority of cases.

Definitions

The following definitions was used in this study: Lower extremity was defined as the thigh, knee and below; Upper extremity as the arm, elbow and below; Trunk as the shoulder, chest wall & abdominal wall, hip as buttock, hip

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bone & joint and groin area. Childhood was defined as 1 to 15 year old and adulthood as more than 15 years. Complete surgery was defined as wide local excision, amputation and limb salvage surgery with no macroscopic residue. Chemotherapy was coded separately.

Complete surgery with adjuvant disease was defined as local, regional or metastatic at time zero. Response to first treatment in central hospital was defined as complete if all clinical and radiologic evidence of disease disappeared after therapy, partial if more than 50% recovery was seen, stable if less than 50% recovery or less than 25% progression. Progressive disease was defined as more than 25 % increase in tumor dimension or discovery of new lesions. Survival figures (OS) were calculated from the time of the earliest histologic verification of the diagnosis of sarcoma to the death or last recorded medical contact. Disease free survival (DFS) were calculated, only for responders to therapy, from diagnosis to first relapse of disease.

Statistical Analysis

SPSS/ Windows version 10 was used for data analysis. Prognostic factors for relapse and death were tested by the chi -square and t-test for univariate analysis, whereas a logistic regression model was applied to search for independent prognostic factors. Overall survival (OS) and relapse free survival (RFS) were compared between different groups using the log-rank test. Life table curves were calculated using the Kaplan-Meier method. Analysis of the effect of prognostic factors on survival was undertaken using Cox proportional hazard regression. Confidence intervals (CI) were added to life table curves.

Results

Ninety five percent Sarcoma's cases were 11% of admitted patients to central hospital in this period. There were 1492 patients identified, 25 were excluded from analysis because of giant cell tumor (3 cases), Karposi's sarcoma after kidney transplantation (6), lymphosarcoma (6), metastatic carcinoma (4), germ cell tumor (3) and Hodgkin's disease (3), diagnosed after review. We found the underlying cause for sarcoma in 1 % of patients: 11 with previous radiation to site of sarcoma, 9 with neuro fibromatosis, 2 with xeroderma pigmentosa, 1 with basal cell nevoid syndrome, 1 with history of colon & breast cancer and 1 with Li-Fraumeni syndrome. A total of 25 patients had benign histology for 1 to 4 times (fibroma, myositis, osteomyelitis, lymphangioma, hemangioma, periostitis, reactive tissue, nodular facitis, benign fibrohistiocytoma) before malignancy was diagnosed at central hospital. The mean / median age at diagnosis was 30/25 years (range 1 to 103). The ratio of male to female patients was 1.6:1 and the ratio of children to adults was 1:4 .The distribution of tumor location is provided in Figure 1 .The most common site of disease was the lower limbs. The site distribution of the 791 cases of upper and lower extemity sarcomas are further assessed in Figure 2. Duration of symptoms ranged from I

month to 7 years with mean / medion 7 n /5 month. ratio of soft tissue to bone sarcoma was 1:3 in children and 3:1 in adults.

Histologic subtypes of sarcoma are provided in Table 1. Some 25% of patients had metastatic disease at the diagnosis (10.5% lung, 5% lymph node, 3% bone, 2.5% 0.5% brain & 1.5% other). The method of first histologic diagnosis was with surgical material for all the patients (758 incisional and 702 excisional biopsy). In 49% of patients with tumors more than 5 cmin diameter, excisional biopsy was performed. 79.9% of involved margins and 52% of free margins in pathologic reports were from this group. (P<0001). Complete surgery had down for 50% of patients. (732 patients) but only 23% of patients (350 cases) received adjuvant or neoadjvrant chemotherapy in addition to complete surgery. In the course of disease 86.2% of patients received chemotherapy (295 palliative and 967 adjuvant or neo adjuvant) but only 350 cases had complete surgery in addition to chemotherapy. Number of drugs range were 1 to 8 (mean 3 SD 1) and number of cycles were 1-36 (mean=5). 41% of patients received radiation therap. Adriamycin was used in almost all single or combination drug therapy. Ifosfamide was used in 180 and cisplatin in 457 cases, Response to chemotherapy with or without surgery was defined in 1423 patients. Complete response occurred in 651 (45.7%), partial response in 205 (14.5%), stable disease in 114 (8%) and progressive disease in 345 (31.8%).
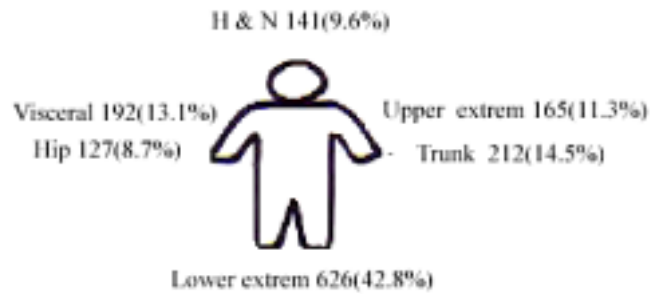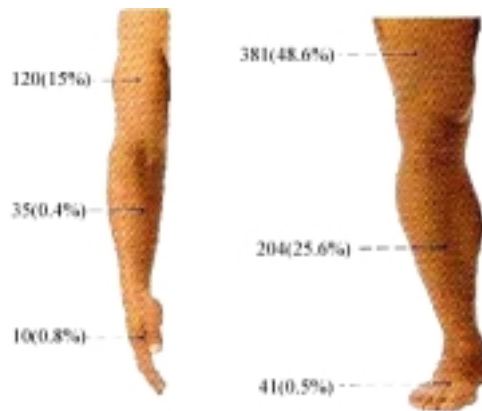

Figure 1. Overall Distribution of Sarcomas

Figure 2. Distribution of Sarcomas on the Upper and Lower Extremities.

Outcome

The mean / median follow up period was 838 / 804 days. Over all 5 year survival rate was 22.5% (Fig 3). At final analysis, 31% of the patients were alive (986 deaths, 444 alive, 40 missing). Site of disease recurrence (see Fig 4) was noted with tumor size, diagnosis with excisional biopsy, soft tissue versus bone sarcoma, neurovascular and margin involvement in the pathologic report. With the rhabdomyosarcoma subtype, the adriamycin cisplatin combination chemotherapy predicted a lower relapse rate although there was no significant relationships between patient's sex, age, tumor localisation and pathologic grade and relapse. Multivariate analysis showed involved surgical margins (P=0.001), no radiation therapy (P=0.021), no complete response to primary therapy (p=0.003), no complete surgery with chemotherapy (P=0.03) and excisional biopsy (P=0.016) as significant and independent variables associated with a higher risk of relapse. Fig 5 shows relapse free survival with incisional in comparison to excisional biopsy. On multivariate analysis, failure to obtain complete remission in the central hospital (P < 0.001), large tumor size (P=0.05), neurovascular (P=0.044) and margin involvement (P = 0.034), fewer cycles of chemotherapy (P

= 0.002), incomplete surgery (P=0.035) and metastatic recurrence versus local recurrence P=0.036), remained significantly and independently associated with a higher risk of death. Fig 6 shows the relation between tumor size and survival, and Fig 7 the relation to adjuvant chemotherapy. Fig 8 illustrates the influence of response to chemotherapy on overall survival of patients.

Discussion

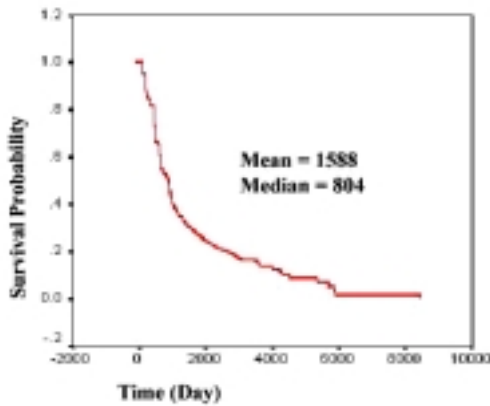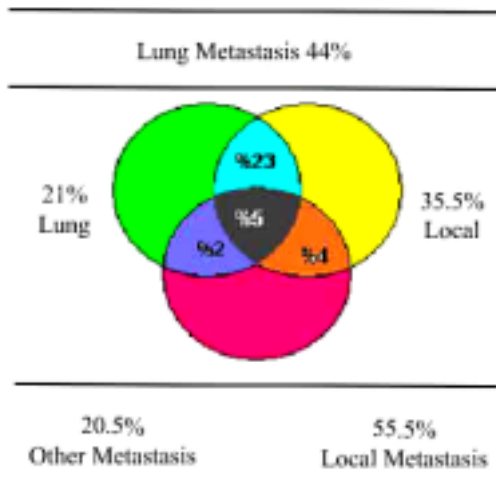The first coherent and effective prognostic classification

Figure 5. Relapse-free Survival According to Biopsy Type

Figure 3. Overall Survival
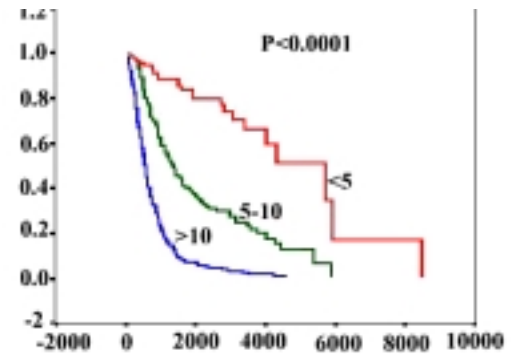
Figure 6. Overall Survival According to Tumor Size

Figure 4. Sites of Sarcoma Metastasis
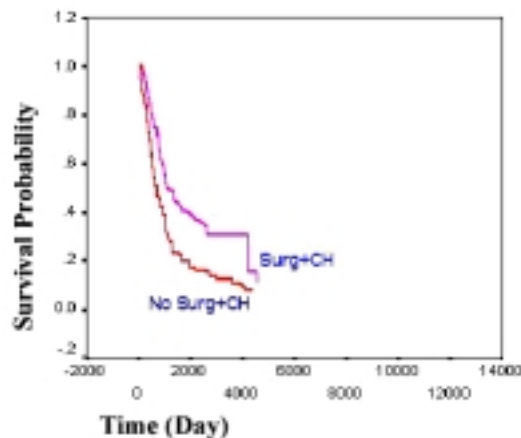
Figure 7. Overall Survival after Surgery According to Adjuvant Chemotherapy
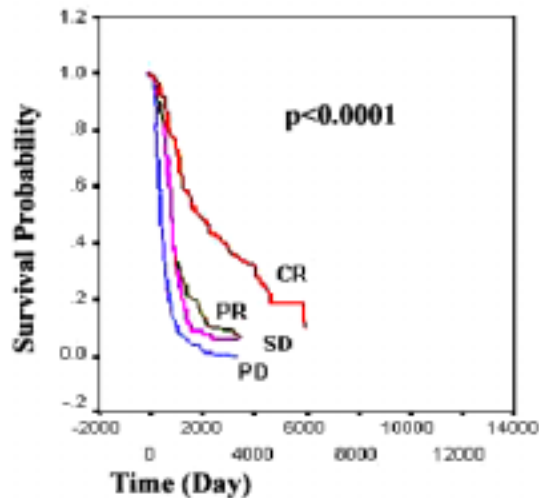
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Figure 8.Overall Survival According to the First Treatment Response

of sarcoma was proposed by Russell in 1977. Prognosis of sarcoma is dominated by local recurrence and distant metastasis. Overall survival and metastasis are related to histological grade. Local recurrence is related to quality of surgical margins. The present analysis of prospectively collected data provides reliable evidence that complete response to surgery with chemotherapy is the most factor for predicting overall survival of sarcoma patients in Iran.

Should we adopt this treatment as a new standard of care? Can we establish a standard of care regarding adjuvant chemotherapy for sarcoma? As for breast cancer, we need to define high risk groups most likely to benefit from chemotherapy. Most sarcoma specialists would agree that patients with small <5 cm) and low grade sarcomas or with retroperitoneal soft tissue sarcomas should not receive chemotherapy outside a trial setting. In our study especially young patients who have large high grade extremity sarcomas are good candidate for adjuvant chemotherapy.

Large case series of this nature are published most often by specialist referral centers and tend to be biased by the number of cases with recurrent and metastatic disease at presentation to the institution This can bias the clinical impression of the disease, with the worst cases self -selecting for referral to centers with higher levels of expertise. We had 25% metastasis at first presentation and 59% tumors more than l0cm in size. Our patients had more than 5 months of symptoms before diagnosis and 50% died in less than 3 years and we had 22% 5 year survival. Our health services need to teach general physicians about sarcomas.

Because of the rarity of sarcomas, many surgeons are unfamiliar with these tumors, often leading to unforeseen findings during or after an surgery for a soft tissue mass. Inadequate treatment, specially inadequate skin incision, post operative bleeding or hematoma, can seriously hamper definitive surgery. Many of our patients were referred from general surgeons around the country These patients had excisional biopsy of large tumors and excisional vs incisional biopsy had significant effects on the outcome of the disease,

especially regarding relapse-free survival.

We had not statistically significant relation between patient's survival and grade of tumor .Mter stablishing the diagnosis of sarcoma, the most critical piece of informatin the patholigist can provide to the clinician is histologic grade, unfortunately, the criteria for grading are neither specific nor standardized. Further more, several grading scales are used, a four grade system (Broders), a three grade system (AJCC: and a binary system (Memorial hospital). Even when there is agreement about the number of grades to be used, expert pathologist disagree about specific criteria for defining

Conclusion

Sarcomas are rare and heterogeneous group of tumors. There should be collaboration of surgical, medical and radiotherapy oncologists in specialised centers to achieve the best results. Clearly early diagnosis is of prime importance.

Acknowledgements

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