RESEARCH ARTICLE

Survival of Patients with Ewing's Sarcoma in Yazd-Iran

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Abstract

Background: The Ewing's sarcoma family is a group of small round cell tumors which accounts for 10-15% of all primary bone neoplasms. The aim of this study was to evaluate the survival of Ewing's sarcoma patients in our province and to determine of influencing factors. Materials and Methods: All patients with documented Ewing's sarcoma/ primitive neuroectodermal tumor(PNET) family pathology were enrolled in this study during a period of eight years. For all of them local and systemic therapy were carried out. Overall and event free survival and prognostic factors were evaluated. Results: Thirty two patients were enrolled in the study. The median age was 17.5 years. Twenty (65.2%) were male and 9 (28.1%) were aged 14 years or less. Mean disease free survival was 26.8 (95%CI; 13.8-39.9) months and five year disease free survival was 26%. Mean overall survival was 38.7 months (95%CI; 25.9-50.6) and median overall survival was 24 months. Five year overall survival was 25%. From the variables evaluated , only presence of metastatic disease at presentation (p value=0. 028) and complete response (p value =0. 006) had significant relations to overall survival. Conclusions: Survival of Ewing's sarcoma in our province is disappointing. It seems to be mostly due to less effective treatment. Administration of adequate chemotherapy dosage, resection of tumor with negative margins and precise assessment of irradiation volume may prove helpful.

Keywords: Ewing's sarcoma - radiation therapy - chemotherapy - survival.

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Introduction

Ewing's sarcoma family are a group of small round cells tumors and consisting of Ewing's sarcoma, peripheral primitive neuroectodermal tumor and Askin tumor (Lisa et al., 2013). Ewing's sarcoma after osteosarcoma is the second most common malignant bone tumor occurring in children and young adults, and accounts for 10-15% of all primary bone tumors (Burchill, 2003; Leavey et al., 2008; Lisa et al., 2013). During the last decades survival of patients with Ewing's sarcoma has been improved significantly (Cangir et al., 1990; Oberlin et al., 2001; Rosito et al., 1999; Ginsberg et al., 2010; Haeusler et al., 2010). Since there was no previous study on survival of Ewing's sarcoma family in Iran and of especially in Yazd, and that according to our daily observations it seemed that the survival rate of our patients was less than what was reported in the text books (Robert, 2008; Lisa et al., 2013) we decided to evaluate the survival of these patients.

Materials and Methods

All patients with documented pathology of Ewing sarcoma's/PNET referred to Shahid Ramazanzadeh Radiation Oncology Center between 2002 to 2010 enrolled in this study, however those referred in the relapse setting were excluded. For all of the patients chemotherapy had been started and continued after radiation therapy. In some of the patients surgery had been performed. Data contained in the patients' records were extracted and follow up was conducted through periodic visits and telephone contacts. Because chemotherapy of patients had been performed in other centers or in private offices, we contacted the patients' physicians to get information on their chemotherapy regimens, however for most of the patients we could not obtain the exact drug dose and dose intensity. Radiation therapy was performed by using Cobalt 60 machine or linear accelerator. Treatment volume was defined according to prechemotherapy and /or preoperative imaging. For all patients 3-5 cm longitudinal and 2cm lateral margin was considered. At least a 5000cGY radiation dose was used.

Statistical analysis

In this study survival rate was assessed using the Kaplan-Meier curves employing Log Rank model and SPSS 17 software. The relation between variable and survival rate was evaluated. We defined the overall survival from the day that pathological examination (biopsy or excision) had been performed until death or last visit (or telephone call) and disease free survival from the day of ending all treatments to the first pathological,

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radiological or clinical evidences of relapse.

Results

Between 2002 and 2010, 32 patients were enrolled in our study. Twenty (62.5%) were male and 12 (37.5%) were female. Mean age was 20.19 years and median age was 17.5 years. The patients were classified into two age groups: 9 (28.1%) were between 0-14 years and 23 (71.9%) above 14 years. Pain was the first symptom in 83.8% of patients and lower extremity was the commonest site of disease (43.2%) followed by pelvic girdle in 18.9% .Long bone involvement was seen in 45% of patients, diaphysial involvement was seen in 60% of them and metaphysical involvement in 40% of them. Elevated sedimentation rate and C-Reactive Protein, existed in 45% and 30% of patients respectively. Nine (28.1%) patients had metastases at presentation in seven of whom bone metastasis and in two others lung metastasis was evidenced. All patients received chemotherapy although through various regimens. However, almost all of them received a sort of combination of Adriamycin, Cyclophosphamide, Etoposide and Ifosfamide with or without other drugs. In metastatic setting the same drugs or other drugs such as Taxanes, Gemcitabine, Topotecan had been used. All patients had received local therapy. Surgery was performed in 13 patients, radiation therapy in 29 patients and combination of them in 12 patients. Documented negative surgical margins were confirmed in only 5 (38.4%) of the patients. During the follow up 19 (59.3%) patients became metastatic. The metastatic sites were, bones in 11 patients, lungs in 10 patients and brain in 4 patients respectively (some patients had more than one metastatic site). Among 18 patients achieving complete response, local recurrence occurred only in two cases in both of which cases distant metastases existed synchronously. Local treatment for both of them was radiation therapy.Mean disease free survival was 26.84 (95%CI; 13.75-39.92) months and five year disease free survival was 26% (Figure 1). By July 2012, 21 (65.6%) of patient deceased and 11 (34.4%) survived. Mean overall survival was 38.71 months (95%CI; 25.85-50.56) and median overall survival was 24 months. Five year overall survival was 25% (Figure 1). Overall survival in patients with metastases at presentation was 23.33 months (95%CI; 7.97-36.69) and 36.86 months (95%CI; 27.49-46.22) in the non-metastatic group.Five year overall survival was 28% and 12% in non metastatic and metastatic patients respectively.From the variables, only presence of metastatic disease at presentation (p=0.028)

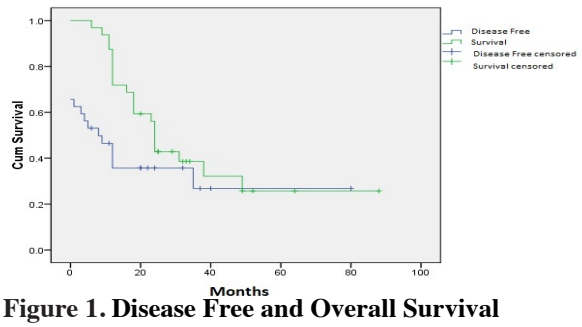

Figure 1. Disease Free and Overall Survival

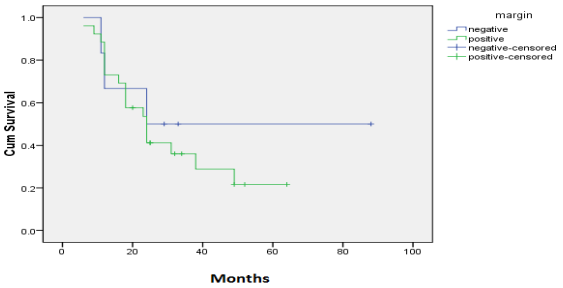

Figure 2. Overall Survival

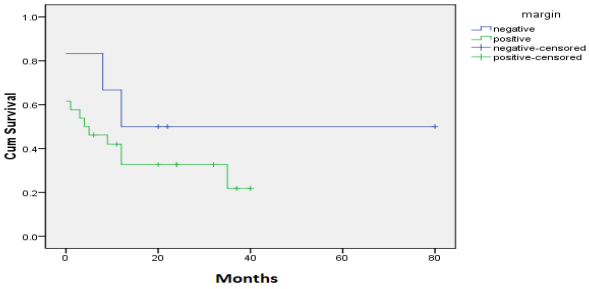

Figure 3. Disease Free Survival

and complete response, with no (clinical, radiological or pathological) evidence of disease post treatment (p=0.006) had significant relations to the overall survival. There was no significant relation between the survival and sex, age (≤14 years and >14 years), site of primary disease and positive surgical margin.

Discussion

Although Ewing's sarcoma is not a common cancer and only 225 new cases are diagnosed per year in North America (Lisa et al., 2013) it has some important characteristics. First, most of Ewing's sarcoma patients are between 10 to 20 years (Baldini et al., 1999). Second, the five year survival rate of disease increased in the past three decades from 42% to 58% and then to more than 60% worldwide (Oberlin et al., 2001; Haeusler et al., 2010). Increasing survival continued until some specialists suggested that 'cure' is possible for patients with Ewing's sarcoma (Weston et al., 2004). Third the five year survival rates in recurrent disease is only 13% (Leavey et al., 2008). Therefore appropriate therapy is critical.Our knowledge about Ewing's sarcoma in Iran turns back to only two epidemiologic studies. According to a retrospective study performed between 1997 to 2008 at Shiraz University in the south of Iran, among the 426 patients with musculoskeletal tumors 28 (15.9%) patients had Ewing's sarcoma (Solooki et al., 2011). In the second epidemiological study in Khozestan in the south west of Iran, clinicopathologic features of 47 children with Ewing's sarcoma between 1991 to 2007 was reviewed (Ghasemi et al., 2010). In none of these two studies survival of the patients was evaluated.

The median age of patients at diagnosis in our study was 17.5 years. Median age in an European study by Haeusler et al. (2010) and a Japanese study by Obata et al. (2007) was 16.2 years and 16 years respectively. In our study 62.5% of patient were male. Male predominance was also seen in other studies (Jurgens et al., 1988; Obata et al.,

2007; Haeusler et al., 2010). In our study lower extremity was the most common site of disease corresponding to what was mentioned in the textbooks (Robert, 2008; Lisa et al., 2013). In the Robert B M research, 24.7% of lesions were located in the pelvis, 16.4% in the femur,and 16.7% below the knee that means 33.1 of the tumors located in lower extremity (Robert et al., 2008). Extremities were the primary site of disease in 47%, 40.4% and 31.6% of patient in studies performed by Obata et al. (2007), Ghasemi et al. (2010) and Haeusler et al. (2010) respectively. There was no significant difference between age and sex distribution, and site of primary disease between our study and others.

Metastatic disease is present in approximately 25% of patients at initial diagnosis. The most frequent sites of metastases are the lungs, bones, and bone marrow (Lisa et al., 2013). Nine patients (28.1%) in this study were metastatic at presentation that bone and lung were the sites of metastases respectively. Although a bone marrow biopsy is one of the essential staging procedures, it was carried out only in two patients by their oncologists. It seems that at least clinical characteristics of Ewing's sarcoma patients at presentation in our province is similar to other parts of the world. Although genetic feature may have a role in clinical behavior of Ewing's sarcoma, it was not evaluated in this study.

Treatment of Ewing's sarcoma consists of local and systemic treatment. Although only 25% of patients have overt metastases at presentation, the relapse rate is very high in patients undergoing local therapy alone, therefore it is assumed that micrometastases exist in the majority of patients at presentation. Another reason for this matter is that prior to using combination chemotherapy regimens survival of Ewing's sarcoma patients was very poor due to early metastases (Jurgens et al., 1988). Local therapy consists of surgery and/or radiation therapy. By adding Adriamycin to a combination of Vincristine, Cyclophosphamide and Actiomycin D survival of non metastatic Ewing's sarcoma patients, five years relapse free and survival increased from 24% to 60% (Nesbit ME et al., 1990). Addition of alternative cycles of Ifosfamide and Etoposide to Vincristine, Cyclophosphamide and Adriamycin increased five year relapsed free survival in non metastatic Ewing's sarcoma from 54% to 69% (Grier et al., 2003). Administration of the same drugs every two weeks instead of every three weeks increased five years event-free survival from 65% to 73% in localized disease (Womer et al., 2008). The effect of dose dense chemotherapy on metastatic patients specially non pulmonary metastases is not clear. All of our patients had been receiving systemic chemotherapy in other centers or private offices.We know a combination of Adriamycin, Cyclophosphamide, Ifosfamide and Etoposide with or without Vincristine and Actinomycin had been used, however the exact regimen for each patient and their dosages is obscure, therefore we could not explain more about the chemotherapy regimens and compare it to other studies. However five year disease free survival in our study was 26% and it was similar to decade 1970. Seker et al. (2014) in our neighbourhood (Turkey) evaluated 26 Ewing's sarcoma patients. The median disease free survival was 72 months in patients with localized disease, and median progression free survival was 10 months with metastatic disease.Their patients had been received similar chemotherapy drugs. Surgery and /or radiation therapy had been used in localized disease. The patients had obviously better disease even those had been received only surgical resection. Extraskeletal Ewing's sarcoma considers as a poor prognostic factor(Tural et al., 2012; Somarouthu et al., 2014), however the outcome of the patients in our study that mainly were skeletal was worse than that Tao HT et al. (2013) reported in extraskeletal Ewing's sarcoma in China. In this study median event free survival and overall survival for entire group were 15.8 months and 30.2 months respectively. In a similar Japanese study was carried out by Obata et al. (2007), all patients received chemotherapy too, and for 183 (75.3%) patients surgery was performed as primary local therapy and 145 (79.2%) of them had negative margins, and 35 (19.1%) had marginal or positive margins. Of these 183 patients 96 received radiation therapy as well. Fifty three patients received radiation therapy alone. The five year overall survival and disease free survival were 48.7% and 40.7%, respectively. In non metastatic patients at presentation, the 5-year overall survival and disease free survival rates were 54.9% and 46.6%, and 13.2 and 6.8 in metastatic patients respectively. Five year overall survival in metastatic patients in our patients corresponds with the above said and in non metastatic patients, it is completely different. It may be due to the point that chemotherapy dose density is more effective in non metastatic patients and as a result we are concerned about the precise chemotherapy dose administration. On the other hand, it may be due to poor local treatment, because local control improves outcome even in disseminated disease (Haeusler et al., 2010). Since for 13 (40.6%) of our patients surgery was performed, only 5 (38.4%) of these patients had documented negative surgical margins in pathology reports. Twelve (37.5%) patients received a combination of surgery and radiation therapy. Although positive surgical margin did not show significant relation to overall survival and disease free survival (p=0.967 and 0.517), respectively) the curves (Figure 2, 3) indicate that both of them are better in margin negative patients. Radiation therapy was the only local treatment performed in 17 patients and in 7 of whom complete response happened. According to a study by H. Mameghan et al. on Ewing's sarcoma patients most of the patients received radiation therapy as the only local modality, the only factor predictive of local failure was an inadequate target volume irradiation (Mameghan et al., 1993). Local recurrence after complete response occurred in two patients, for both of whom radiation therapy was the only local treatment, however they had synchronous distant metastases. Although we did our best to determine target volume precisely and tried to deliver adequate radiation doses to the tumor, it is possible to have done make some mistakes.

The patients who achieved complete response had a significantly better overall survival (p=0.006) andeent free survival (p=0.006). This is similar to the results obtained in other studies (Cangir et al., 1990; Baldini et al., 1999; Oberlin et al., 2001; Lopez et al., 2012). Presence of metastases at presentation was a bad prognostic factor

(p=.028). It was similar to what was shown by some other investigators (Cangir et al., 1990; Mameghan et al., 1993; Baldini et al., 1999; Obata et al., 2007; López et al., 2012). Although older patients had a worse prognosis in some studies (Cangir et al., 1990; Baldini et al., 1999; Obata et al., 2007; Lopez et al., 2012) we could not authenticate this as O. Oberlin et al. (2001). Another possible reason for this disappointing results in our province maybe this fact that there is no a multidisciplinary clinic for treating these patients here. Abou Ali B et al. (2014) reported a 76% and 58% five year overall and event free survival in localized disease and 40% and 38% in metastatic disease respectively in Lebanon. Lee JA et al. (2011) reported a survival rate similar to Euro-American cases in South Korea when they only considerd the patients had been received the whole treatment (surgery, radiation therapy and chemotherapy) in a single institute.

In conclusion, Ewing's sarcoma's survival in our province is much lower compared with worldwide figures despite using new chemotherapeutic drugs, surgery and radiation therapy. Because presentation and clinical behavior of the disease did not show any significant difference with other parts of the world it can be concluded that when there is no multidisciplinary clinic ,the treatment will be inadequate and it might be the reason for such poor survival rates.

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