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Radiotherapy for Ewing sarcoma: A 5 year experience from Iran cancer institute

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► ***Short report***

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ABSTRACT

Background: Ewing Sarcoma Family of Tumors (ESFTs) is the second most common primary tumors of bone in childhood. The decision regarding the optimal modality for achieving local tumor control remains uncertain. The aim of this study was to report the clinical features and outcome as well as reviewing risk factors in patients. ***Materials and Methods***: This retrospective study included 75 ESFTs patients who were treated at cancer institute between 2004 and 2009. Files of all patients with ESFTs were reviewed retrospectively and we called them for follow up. Specific data were collected with regard to the age at diagnosis, gender, tumor site and size, clinical stage, surgical procedure, plan of radiotherapy and treatment outcome (5-year and median survival). ***Results:*** The mean age at diagnosis was 21 that ranged from 1 to 52 years (SD = 9.6). The mean tumor size at diagnosis was 4.8±4.48 cm. The percent of biopsy only, partial and complete resection was 54.7% (41 patients), 6.7% (5 patients) and 37.3% (28 patients) respectively. Radiotherapy was done as definitive treatment or postoperatively (adjuvant) in 46 (61.3%) and 16 (21.4%) patients respectively. Overall 5 year survival was 24% and median survival for patients with and without metastases was 21±17 and 75±10 months. ***Conclusion:*** Presence of metastases, age at diagnosis, positive surgical margin and tumor size were the prognostic factors that influenced outcome of patients. This study suggests that radiation therapy is an acceptable local treatment modality in patients with Ewing sarcoma family.

Keywords: *Ewing sarcoma, radiotherapy, multimodality treatment.*

INTRODUCTION

Ewing sarcoma family of tumors (ESFTs) is the second most common primary tumors of bone in childhood and also arises in soft tissue. ESFTs includes a spectrum of small round cell tumors that comprises osseous and extra-osseous Ewing's sarcoma, peripheral primitive neuroectodermal tumor (PNET) and Askins tumor of the chest wall. Cytogenetic studies have shown that ESFTs are the most undifferentiated tumors that contain neuroectodermal precursor cells that arrested at different stages of differentiation. Approximately 98% of ESFTs have a translocation between EWS gene on chromosome 22 and the FL11 gene on chromosome 11 (t [11; 22]) [1].

Results from large trial by the European Intergroup cooperative Ewing's sarcoma study (EICESS) group showed that median age of onset was l0 years. This study indicated that Ewing sarcoma is uncommon before 8 and after 25 years of age. In the EICESS study, pelvis, femur, leg, ribs and spine were the common sites of involvement in ESFTs [2].

Effective local and systemic therapy is necessary for the cure. The advent of combined modality treatment regimens incorporating multi-agents chemotherapy and radiotherapy

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(RT) and/or surgery as local therapy has markedly improved survival and local control [3]. The decision regarding the optimal modality for achieving local tumor control remains uncertain (RT, Surgery or both).

In the past, radical surgery has been associated with poor functional outcomes or even with amputation of organ and for this reason, patients received RT for local tumor control but the trend is now shifting toward conservative surgery (± neoadjuvant chemotherapy) and limb sparing procedures. RT is necessary for patients with inoperable disease, close or positive surgical margins, in which RT provides markedly improved functional outcomes, or in skeletally immature patients with limited surgical options [4, 5].

On the basis of data collected from patients treated with definitive or postoperative RT for ESFTs at cancer institute, we report the clinical features and outcome of patients. We also prove a concise comparison of the current study with other published literature.

MATERIALS AND METHODS

This retrospective study included 75 ESFTs patients who were treated at cancer institute between 2004 and 2009. Files of all patients with ESFTs were reviewed retrospectively and we called them for follow up. The study is approved by the Ethical Committee of the Cancer Institute, Tehran, Iran.

Based on pathologic report, all patients had a diagnosis of Ewing sarcoma, extra osseous Ewing sarcoma or primitive neuroectodermal tumor. All patients in this study had undergone routine systemic work up and disease evaluation including CT or MRI of the primary site, CT of thorax, bone scan and bone marrow aspiration and biopsy to evaluate any metastatic process. Biopsy had been taken for all with or without immunohistochemical (IHC) assessment. Specific data were collected with regard to the age at diagnosis, gender, tumor site and size, clinical stage, surgical procedure, plan of radiotherapy and treatment outcome. Progression free survival (PFS) was defined as the time of diagnosis until the date of disease progression or relapse. Overall survival (OS) was calculated from the time of diagnosis until the date of death or last follow-up.

SPSS statistical software version 18.0 was used for statistical analysis. PFS and OS were estimated using the Kaplan Meier method and cumulative survival rates were compared using log-rank test with $p<0.05$ considered significant.

RESULTS

During a 5 year period, 75 patients were treated at cancer institute. The mean age at diagnosis was 21 that ranged from 1 to 52 years (SD = 9.6). Only 8 patients were under 10 years old (10.6%) and majority of cases were older patients. Of patients, 43 were male and 32 were female (M/F: 1.34).

Table 1 shows the location and characteristics of the primary disease at diagnosis. The mean tumor size at diagnosis was 4.8±4.48 cm (ranged from 1 to 24 cm).

The percent of biopsy only, partial and complete resection was 54.7% (41 patients), 6.7% (5 patients) and 37.3% (28 patients) respectively. 1 patient underwent palliative surgery.

Radiotherapy was done as definitive treatment or postoperatively (adjuvant) in 46

Table 1. Tumor Characteristics:

Characteristic	N (%)
Extremities	34 (45.3 %)
Pelvis	19 (25.3%)
Head and neck	13 (17.4 %)
Mediastinum	3 (4 %)
Chest wall	4(5.3 %)
Spine	2 (2.7 %)
Tumor size	
< 10 cm	58 (81.7 %)
≥ 10 cm	13 (18/3 %)
Metastatic	
yes	22
No	53
Site of metastatic disease	
Lung	6
Vertebral	8
Pelvic Bone	2
Multiple	6

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(61.3%) and 16 (21.4%) patients respectively. 10 patients (13.3%) received radiotherapy as palliative treatment and 3 patients (4%) didn't received radiotherapy. The mean radiotherapy dose delivered was 5253±1088 cGy.

Overall 5 year survival was 24% and median survival for patients with and without metastases was 21±17 and 75±10 months.

DISCUSSION

Ewing sarcoma (ES) and peripheral primitive neuroectodermal tumor (PNET, previously called peripheral neuroepithelioma) were first described in the early 1900s as distinct clinicopathologic tumor. It has become evident that these entities are actually part of a spectrum, known as the Ewing Sarcoma Family of Tumors (ESFTs). Because of their similar histological and immunohistochemical character -istics and shared nonrandom chromosomal translocations, these tumors are considered to be derived from a common cell of origin; it means a mesenchymal progenitor cell origin for all ESFTs. In data reported by the Surveillance, Epidemiology and End Results (SEER) program of the National Cancer Institute, five year survival rates of localized disease for patients with Ewing sarcoma increased from 44% during 1973-1982, to 68 percent during 1993-2004 [6].

Several clinical and biologic characteristics can assist in defining prognosis and directing the intensity of therapy [7]. These includes the presence or absence of metastases, primary tumor location and size, age at diagnosis, response to therapy, and the presence of certain chromosomal translocations. Most ominous factor for prognosis, is synchronous or metachronous metastatic disease [8]. The five-year survival rates of patients with localized disease are 68 percent, whereas 5-year survival of metastatic disease is 39%.[6] In our study, overall 5 year survival rates was 24% (figure 1); for patients with metastatic disease, 5-year survival rate was 7.3%. Median survival for patients with and without metastases was 21±17 and 75±10 months. The main reason for this low 5-year survival rates, is probably due to large numbers of patients who had undergone thorough the biopsy only (41 patients) or partial resection of tumor (5 patients). As can be seen in figure 2, patients with positive margins have lower 5-year survival rate than patients with negative margins.

Older age has been linked to a poor prognosis in some reports [9], but not in others [10]. Younger children seems to have a better prognosis than older ones, As an example, in a report by Craft *et al.*, the five-year relapse-free survival was significantly better for children younger than 10 years compared to older children (86 versus 55

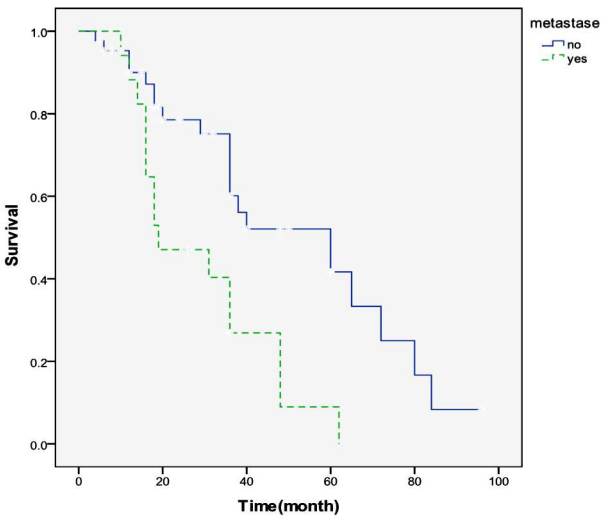

Figure 1. Effect of metastases on survival.

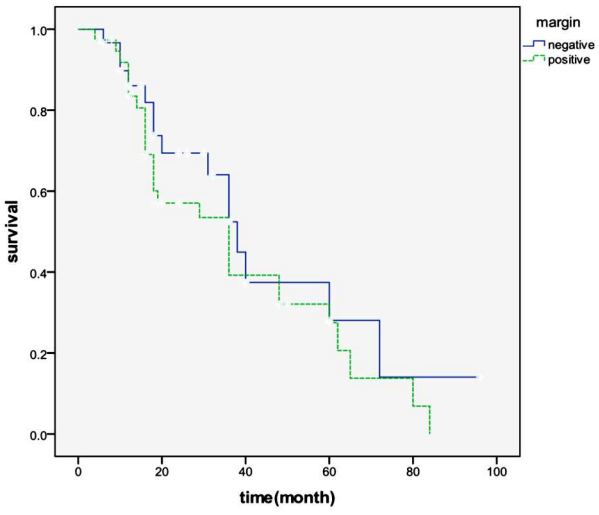

Figure 2. Effect of surgical margin on survival.

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percent, respectively) [11]. In our study, 89.4% of the cases belonged to older than 10 years age group. This selection bias and older age of patients could be another reason for low 5-year survival rate in our study.

For patients with localized ESFT, local and systemic therapies are applied in multimodality treatment. Either surgery or radiotherapy can provide effective local control. Most treatment guidelines, recommend surgical resection as the modality of choice if the tumor is respectable with negative margins and with anticipation of a reasonable functional result [12]. In this study, in the patients who had received radiotherapy as definitive treatment (61.3%), or adjuvant treatment (21.4%), local recurrence rate was 25.3%. despite the fact that 61.4% of surgeries were done as biopsy only or with positive margin(s), the cumulative incidence of local failure in our study is in agreement with results of CESS Group study (26.3% in 3 years) and lower than result of pediatric oncology group study (35% in 5 years) [13].

For patients who are not candidates for function-preserving surgery, because of location or extension of tumor, and for those who have clearly unresectable primary tumor, radiotherapy is recommended following induction chemotherapy. Adjuvant RT is used in the following situations: Bulky tumors in difficult sites; inadequate surgical margins or residual microscopic or gross disease after surgery;

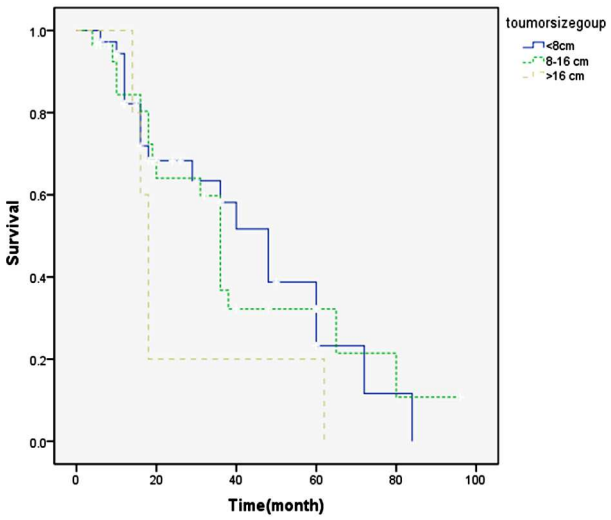

Figure 3. Effect of tumor size on survival.

Patients who are left with significant amounts of viable tumor in the resected specimen following neoadjuvant chemotherapy that have less than wide surgical margins [14-16]. In this study, positive surgical margin(s) and larger tumor size (>10 cm) was accompanied by significantly lower disease free and overall survival ($p<0.005$) (figure 2) which is consistent with other studies.

In this study, 46.5% of patients had primary tumor in unfavorable sites; however, this bias in selecting patients did not meet significantly impact on disease free survival. Factors such as gender and site of metastases did not influence survival and local control.

CONCLUSION

Presence of metastases, age at diagnosis, positive surgical margin and tumor size were the prognostic factors that influenced outcome of patients including local control and survival. This study suggests that radiation therapy is an acceptable local treatment modality in patients with Ewing sarcoma family.

Conflicts of interest: *none to declare.*

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