Aim of the study was to investigate the demographics of Ewing sarcoma family of tumours (ESTF) patients, treatment alternatives, clinical outcomes, and prognostic factors for survival.

Material and methods: We retrospectively reviewed 39 patients with ESFT who were admitted to our institute between September 2008 and September 2012.

Results: The patients included 32 (82.1%) males and seven (17.9%) females of median age 24 (range, 18–66) years. Among the 27 patients with a primary osseous localization, 17 (43.5%) had a central axis localization. Fifteen patients (38.5%) had metastases at the time of diagnosis. Patients were followed up for a median period of 18 (range, 2–134) months. The median event-free survival (EFS) was 23 (range, 1–64) months, and the 1- and 4-year EFS were 60% and 48%, respectively. The median overall survival (OS) was 91 (range, 1–188) months, and the 1- and 4-year OS were 78% and 54%, respectively. Gender, age, primary tumor site, and local treatment modalities, either alone or in combination, did not have a significant effect on OS ($p = 0.210$, $p = 0.617$, $p = 0.644$, and $p = 0.417$, respectively). In contrast, osseous site of peripheral localization, limited stage, and metastasis to the bone significantly affected OS ($p = 0.015$, $p < 0.001$, and $p = 0.042$, respectively).

Conclusions: ESFTs are aggressive tumors with a high rate of relapse and metastatic potential. Patients with peripheral bone involvement and limited stage had a good prognosis. Appropriate surgical resection, radiotherapy, and aggressive chemotherapy regimens are recommended.

Key words: Ewing’s sarcoma family of tumors, adult, treatment.
ucation and Research Hospital between September 2008 and September 2012. Age, gender, primary tumor location, stage, site of metastasis, the presence of surgical operation, radiotherapy, chemotherapy, and the treatments administered were recorded. The tumor was considered to be central or peripheral when its primary localization was confined to the trunk and pelvis or to the limbs, respectively. Event-free survival (EFS) was defined as the time from diagnosis to disease recurrence, progression, disease-related death, or toxicity-related chemotherapy. Overall survival (OS) was defined as the time from the date of diagnosis to death or last contact.

**Statistical analyses**

Data were analyzed using SPSS software (ver. 16 for Windows; SPSS Inc., Chicago, IL, USA). Continuous variables are presented as medians (ranges) and categorical variables as numbers (percentages). A p-value ≤ 0.05 was considered to indicate statistical significance. Kaplan-Meier survival analyses followed by log-rank tests were used to identify significant relationships among EFS, categorical variables, and OS. The median EFS and OS values, 95% confidence intervals (95% CI), and standard deviations were calculated for all variables. The significance of the effects of categorical variables on survival was assessed using multivariate Cox’s proportional hazard regression analysis. The relative risk and 95% CI were calculated for all variables.

**Results**

A total of 39 patients with ESFT were followed up and treated at our clinic. The median age of the patients was 24 (range, 18–66) years. Thirty-two patients (82.1%) were male, and seven (17.9%) were female. Nine patients (23%) were < 19 years of age, whereas 30 (77%) were ≥ 20 years. Tumors arose from an osseous site in 27 patients (69.2%) and an extraosseous site in 12 (30.8%). In patients with a primary osseous tumor, 10 (25.7%) were located in the extremities and 17 (43.5%) in the axial skeleton. The extraosseous primary tumor location sites included the lymph node (five cases, 12.8%), lungs (three cases, 7.7%), brain (three cases, 7.7%), and uterus (one case, 2.6%). Twenty-four patients (61.5%) who did not have any metastasis at the time of diagnosis were considered to be in the “limited stage”. Fifteen patients (38.5%) had metastases at the time of diagnosis were considered to be in the “limited stage”. Fifteen patients (38.5%) had metastases at the time of diagnosis. The most common sites of metastasis were bone in nine cases (23.1%) and bone plus lung in three (7.7%). Regarding treatment, two (5.2%) patients did not agree to undergo chemotherapy: one underwent surgery only and the other radiotherapy only. Eight patients (20.5%) received chemotherapy alone, one died of febrile neutropenia due to the toxic effects of chemotherapy, and one developed recurrence while on chemotherapy prior to local treatment. In addition, six patients who were at the metastatic stage at the time of diagnosis received chemotherapy alone, rather than alternating chemotherapy with local treatment of surgery and/or radiotherapy. For local treatment in addition to chemotherapy, 14 (35.9%) patients underwent surgery, eight (20.5%) radiotherapy, and seven (17.9%) both radiotherapy and surgery (Table 1).

Apart from the two patients who chose not to receive chemotherapy, 31 (79.5%), including nine of the 15 patients with metastasis at the time of diagnosis, were administered an alternating chemotherapy regimen every 3 weeks for a total of 17 cycles, consisting of cyclophosphamide (1,200 mg/m²/day on day 1) / adriamycin (75 mg/m²/day on day 1) / vincristine (maximum 2 mg/day on day 1) (CAV) or ifosfamide (1.8 g/m²/day, days 1–5) / etoposide (100 mg/m²/day, days 1–5) (IE) as the first-line chemotherapy. Local treatment, which was planned for week 12, included radiation therapy, surgery, or both [12]. Of the six remaining patients who had metastasis at the time of diagnosis, three (7.7%) underwent CAV chemotherapy, one (2.6%) IE chemotherapy (2.5 g/m²/day ifosfamide, days 1–3; 120 mg/m²/day etoposide, days 1–3), one (2.6%) VCE chemotherapy, and one (2.6%) cisplatin (60 mg/m²/day on day 1) plus adriamycin (60 mg/m²/day on day 1) chemotherapy.

| Parameter                        | n  | %  |
|----------------------------------|----|----|
| **Gender**                       |    |    |
| male                             | 32 | 82.1|
| female                           | 7  | 17.9|
| **Age of diagnosis**             |    |    |
| ≤ 19                             | 9  | 23  |
| ≥ 20                             | 30 | 77  |
| **Primary tumor site**           |    |    |
| osseous                          | 27 | 69.2|
| extraosseous                     | 12 | 30.8|
| **Extraosseous site**            |    |    |
| lymph node                       | 5  | 12.8|
| lung                             | 3  | 7.7 |
| brain                            | 3  | 7.7 |
| uterus                           | 1  | 2.6 |
| **Osseous site**                 |    |    |
| extremity                        | 10 | 25.7|
| axial skeleton                   | 17 | 43.5|
| **Stage**                        |    |    |
| limited                          | 24 | 61.5|
| metastatic                      | 15 | 38.5|
| **Site of metastasis**           |    |    |
| osseous                          | 10 | 66.7|
| extraosseous                     | 5  | 33.3|
| **Treatment modalities**         |    |    |
| surgery alone                    | 1  | 2.6 |
| radiotherapy alone               | 1  | 2.6 |
| chemotherapy alone               | 8  | 20.5|
| surgery/chemotherapy             | 14 | 35.9|
| radiotherapy/chemotherapy        | 8  | 20.5|
| radiotherapy/surgery/chemotherapy| 7  | 17.9|
The median follow-up period of the patients was 18 (range, 2–134) months. At the end of this period, 16 patients (41%) had died, one due to the toxic effects of chemotherapy and 15 due to disease progression. The median EFS was 23 months (95% CI: 1–64), the 1-year general EFS was 60%, and the 4-year general EFS was 48%. Gender, age, site of the primary tumor, surgery, radiotherapy, or local treatment with chemotherapy (surgery and radiotherapy, alone or in combination) did not have a significant effect on EFS ($p = 0.547$, $p = 0.922$, $p = 0.708$, $p = 0.673$, and $p = 0.534$, respectively). However, an osseous site of peripheral localization, limited stage, or bone metastasis correlated significantly with EFS ($p = 0.005$, $p < 0.001$, and $p = 0.07$, respectively) (Table 2; Figs. 1–3).

Univariate analysis revealed that central axis osseous localization had a greater effect on EFS than did a peripheral osseous localization ($p < 0.025$). The most important prognostic factors for OS were central axis localization and surgical treatment in primary osseous tumors ($p = 0.041$ and $p = 0.058$, respectively; Tables 3 and 4).
Discussion

The ESFT generally involves the bones, particularly the long bones of the lower limbs, followed by the pelvis and thoracic bones. The lower extremities are the most common primary sites for ES, accounting for 40–45% of newly diagnosed patients, with ~50% of these occurring in the femur [9]. In a study performed in 98 ESFT patients aged ≤ 18 years, 52 presented with a primary lesion confined to the limbs [14]. In another study in adults, the primary tumors were localized to the trunk in 53.8% of cases or to peripheral sites in 41.7% of cases [15]. Consistent with this, in the current study, the number of patients with centrally localized tumors was higher than those with peripheral tumors.

ESFT has a strong potential to metastasize. Metastases occur most commonly in the lungs and bone [16]. More than 10% of patients present with multiple bone metastases at initial diagnosis. Although metastases to the lungs, bone, bone marrow, or a combination thereof are detectable in ~25% of patients, metastases to the lymph nodes are rare [11]. A study by Grier et al. in ESFT patients reported that 23.1% of patients had metastasis, and that the most common metastatic sites were the lungs, bones, and bone marrow [12]. Kutluk et al. reported that the rate of metastasis was 34% at the time of diagnosis [17]. An additional study in adult extraskeletal ES patients showed that 31% of the patients were metastatic at the time of diagnosis [18]. Another study in adult and adolescent extraskeletal ES patients demonstrated that 43% of patients admitted to

Table 3. Analysis of combined effects of all risk factors believed to predict event free survival

| Parameter                  | RR     | 95% CI (lower limit–upper limit) | p   |
|----------------------------|--------|----------------------------------|-----|
| Gender (male)              | 1.457  | 0.41–5.06                        | 0.554|
| Age (≤ 19)                 | 1.052  | 0.37–2.92                        | 0.923|
| Localization (osseous)     | 2.04   | 0.45–3.21                        | 0.711|
| Osseous site (peripheral)  | 0.093  | 0.01–0.74                        | 0.025|
| Surgery (positive)         | 0.489  | 0.19–1.21                        | 0.123|
| Radiotherapy (positive)    | 1.200  | 0.49–2.91                        | 0.677|

RR – relative risk; CI – confidence interval

Table 4. Analysis of combined effects of all risk factors believed to predict overall

| Parameter                  | RR     | 95% CI (lower limit–upper limit) | p   |
|----------------------------|--------|----------------------------------|-----|
| Gender (male)              | 3.363  | 0.44–5.64                        | 0.242|
| Age (≤ 19)                 | 1.059  | 0.36–3.05                        | 0.916|
| Localization (osseous)     | 1.285  | 0.43–3.79                        | 0.649|
| Osseous site (peripheral)  | 0.111  | 0.01–0.91                        | 0.041|
| Surgery (positive)         | 0.366  | 0.13–1.03                        | 0.058|
| Radiotherapy (positive)    | 1.149  | 0.42–8.64                        | 0.783|

RR – relative risk; CI – confidence interval
the hospital were in the metastatic stage [8]. Smorenburg et al. demonstrated the most common sites of metastasis to be the lungs and bone [19]. In the current study, a higher percentage of patients had metastasis at the time of diagnosis. The most common metastatic sites were the lungs and bones, consistent with previous studies.

Modern day ESFT treatment consists of 3–6 cycles of initial combination chemotherapy after diagnosis by biopsy, followed by surgery and/or local therapy and then 6–10 cycles of chemotherapy [20, 21]. The 5-year survival rate among patients with ESFT, particularly those with localized disease, has increased from 10 to 60% with the use of combination chemotherapies. The most commonly used chemotherapeutic drugs are adriamycin, vincristine, ifosfamide, etoposide, dactinomycin, and cyclophosphamide [6, 7, 9, 12, 13, 22–24].

As part of the local control method, preoperative radiotherapy can be combined with surgery to avoid intraleisional resection and to obtain negative surgical margins. If surgery is impossible, then radiotherapy can be performed alone. Postoperative radiotherapy should be administered in patients with inadequate surgical margins and considered if there is a poor histological response of the surgical specimen to chemotherapy [8, 25, 26]. When surgery is considered, effort should be made to perform limb-sparing surgery [9]. In another study, the authors found that better local control was achieved in patients who underwent surgery [27]. In addition, Haukesler et al. reported that local treatment was a poor prognostic factor for survival [28].

Systemic chemotherapy is effective for microscopic and macroscopic metastases due to its tumor volume-depleting effects. In an INT-0091 study performed by the Pediatric Oncology Group Children’s Cancer Group, non-metastatic ESTF patients received cyclophosphamide–adriamycin–vincristine-dactinomycin (CAVD) chemotherapy, or alternating CAVD and IE chemotherapies. In the metastatic group, the 5-year disease-free survival (DFS) and OS were not altered by the chemotherapy. However, in the non-metastatic group, intensive chemotherapy extended the rates of both DFS and OS [29]. The ESMO guidelines state that chemotherapy should be used in patients with metastatic disease, such as those with localized disease. In patients with lung metastasis, the combination of total lung irradiation with thoracotomy is essential for achieving complete remission and controlling localized residual microscopic disease. For patients with bone metastasis, palliative radiotherapy should be performed in addition to chemotherapy [6].

Extraskeletal ES is an aggressive type of tumor with a high incidence of local recurrence and distant metastasis. El Weshi et al. demonstrated that the outcome of adult extraskeletal ES is similar to that of skeletal ES in terms of the response to multi-modality treatment and the prognostic factors that influence treatment outcomes. Adequate surgical resection, aggressive chemotherapy, and adjuvant local radiation therapy, when indicated, comprise the optimal treatment for best results with this rare disease [30]. In the Euro-EWING 99 R3 study, treatment consisted of six cycles of vincristine, ifosfamide, doxorubicin, and etoposide (VIDE), one cycle of vincristine, dactinomycin, and ifosfamide (VAD), local treatment (surgery and/or radiotherapy), and high-dose busulfan-melphalan followed by autologous stem-cell transplantation. Age, tumor volume, and the extent of metastatic spread are relevant risk factors [31]. In advanced stage ES, the combination of temozolomide and irinotecan was a well-tolerated and reliable palliative treatment regimen [32, 33]. Raciborka et al. demonstrated that the combination of temozolomide, irinotecan, and vincristine was effective and well tolerated in patients with relapsed or refractory ES [34]. In the current study, we used a chemotherapy protocol in which local control methods were administered to most patients, despite their metastatic status at the time of diagnosis. Metastatic disease status at the time of diagnosis, tumors arising from extra-osseous rather than osseous tissue, and age ≥26 years at the time of diagnosis were reported to be poor prognostic factors for survival [13, 35]. The current study also revealed unfavorable effects on survival caused by centrally localized tumors in osseous primary sites, metastasis at the time of diagnosis, and non-bone metastasis.

We were unable to demonstrate that surgery and/or radiotherapy performed for local control yielded a significant improvement in survival. The results suggested that palliative but less toxic treatments might be preferable over more aggressive treatments, particularly in patients with metastatic disease.

The authors declare no conflict of interest.

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