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ORIGINAL ARTICLE

Advantages in Prognosis of Adult Patients with Ewing Sarcoma: 11-years Experiences and Current Treatment Management

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Abstract Ewing sarcoma (ES) is an exceptionally rare tumor in adults. Data regarding outcomes of adult patients with ES and experiences with age-adapted therapeutic strategies are very limited. The aim of this study was to evaluate prognostic factors and clinical outcome in a cohort of adult patients treated according to pediatric protocols in the Czech Republic. The records of 58 adult ES patients diagnosed between 2002 and 2013 were reviewed and factors relevant to prognosis and survival were analyzed. The median age of study cohort was 29 years (range, 18–59). The most frequent location was axial (36.2%), followed by involvement of extraskeletal tissues (34.5%) and bones of the extremities (29.3%). Twenty-eight (48.3%) patients had metastatic disease. In cases with localized ES, the 5-year overall survival (OS) was 76.5%. Using the log-rank test, the presence of metastasis at diagnosis, local treatment without surgery and a failure to achieve complete remission were associated with significantly shorter survival. In a multivariate Cox proportional hazard analysis, the achievement of complete remission was an independent predictor of patients's survival time. Outcomes of adults with localized ES treated according to multimodal pediatric protocols are similar to children. The achievement of complete remission is an independent predictor of survival time in ES patients. Severe hematological toxicity is foreseeable and manageable. Prognosis of patients with metastases or progression remains dismal.

Keywords Ewing sarcoma · Adults · Multimodal treatment · Risk factors · Prognosis

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Introduction

The Ewing family of tumors originates from undifferentiated mesenchymal cells with a potential for neuroectodermal differentiation [14]. Based on the molecular genetic analysis, the Ewing family of tumors can be subdivided into two categories: classical Ewing sarcoma and Ewing sarcoma-like tumors. The former one is characterized by recurrent balanced translocations involving a member of the *FET* family of genes (*EWSR1* in almost all cases) and one of the *ETS* fusion partners (mostly *FLI1* or *ERG*). This entity also includes diagnoses previously known as peripheral neuroectodermal tumor and Askin's tumor. The Ewing sarcoma-like tumors are defined as small round-cell undifferentiated sarcomas caused by rearrangements of *EWSR1*, *CIC* or *BCOR* gene with some of the non-*ETS* fusion partners, e.g. *SMARCA5*, *DUX4* or *CCNB3* [14].

Ewing sarcoma (ES) is a highly malignant tumor arising from bone marrow and, to a lesser extent, extraskeletal soft tissue. After osteosarcoma, ES is the second most common primary bone cancer of children and adolescents, with the median age at diagnosis being 15 years and reported incidence

up to 3 cases per million Caucasians per year [12]. This incidence gradually decreases during the third decade of life and ES is exceptionally rare in patients older than 40 years of age. In childhood and young adults, ES has a tendency to involve the diaphyseal portion of the long tubular bones, the flat bones of pelvis, and chest wall, but practically every bone can be affected, including the acral skeleton and craniofacial bones. In adult patients, large pelvic primary tumors are more often seen and the prevalence of primarily extraskeletal localization is increased [8].

ES, as the extremely aggressive tumor, has a high propensity for local recurrences and distant metastases. At the time of diagnosis, the hematogenous spread is detectable in about 25% of patients. The most common metastatic sites are the lungs, bone/bone marrow, or combinations thereof. Regional lymph node involvement is rare and in most cases associated with disseminated disease [7]. Several clinical, pathological and laboratory factors, such as primary localization, tumor size and volume, the extent and the site of metastasis, histological response to chemotherapy and serum LDH levels, are considered to be predictive of prognosis [8, 12]. The most significant prognostic factor is the disease stage, thus the presence of metastases is the most unfavorable prognostic feature influencing the survival of patients with ES. On the other hand, the impact of age on the prognosis appear to be inconsistent among the published reports. Several studies have shown that older age is associated with an inferior clinical outcome [8, 11, 17, 25], whereas other reports did not found the relationship between older age and poorer prognosis [2, 5, 15, 21, 29].

ES is a systemic disease. Before the advent of chemotherapy in the 1970s, 5-year survival rate for patients with localized disease was less than 20%. With modern multimodal treatment strategy including intensified chemotherapeutic regimens, 5-year overall survival can be achieved in about 70% of patients with localized disease. However, the outcome for patients with early relapse or primary disseminated disease remains still dismal [7, 12, 22, 23]. In Europe, the approach to therapy for pediatric patients is standardized by clinical trial-based protocols, namely the EURO-E.W.I.N.G.99 and subsequent EWING 2008. According to these protocols, treatment begins with induction chemotherapy. All patients receive six cycles of VIDE, which is an abbreviation for vincristine (V), ifosfamide (I), doxorubicin (D), and etoposide (E). In the current EWING 2008 trial, the VIDE combination is enhanced with bisphosphonate treatment. After completion of initial chemotherapy, patients are stratified into 3 risk groups. In each of the risk arm, the emphasis is placed on local treatment of primary tumor. To ensure local control, the surgery is generally preferred over radiotherapy. In patients with disseminated disease, metastasectomy or radiation therapy to the affected organs are also recommended, if possible. Local treatment is followed by consolidation chemotherapy, which consist of a modified combination of agents used during an induction chemotherapy, VAC (C = cyclophosphamide) or VAI (A = actinomycin D) regimens are mostly applied. High-dose chemotherapy with hematopoietic stem cell transplantation represents a treatment option for patients with either metastatic disease and/or high tumor volume at diagnosis and/or poor histological response to neoadjuvant chemotherapy [13]. Chemotherapy intensity is positively associated with outcome [19]. Postoperative radiotherapy is indicated in cases of inadequate surgical margins or in the disease progression [8]. Because of lower tolerance to highly aggressive therapy and expected co-morbidities in elderly patients, both EURO-E.W.I.N.G.99 and EWING 2008 trials are intended for use in patients less than 50 years of age. Despite this, many adult oncology centers follow the pediatric protocols and modify them individually, according to tolerability of therapy for a given patient [1, 3]. However, the ideal treatment strategy for adults with ES is still undefined.

The aim of this retrospective study was to evaluate clinical outcome of adult patients with ES treated according to pediatric protocols in the Czech Republic and to compare these treatment results with the known survival rates of the ES in childhood and adolescence.

Patients and Methods

Patients and Treatment Modality

The retrospective analysis included the total number of 58 adult patients who were diagnosed with ES between August 2002 and November 2013, with follow-up data available until February 2016. These patients had received treatment according to the principles of EURO-E.W.I.N.G.99 or EWING 2008 protocols at one of the following Czech oncology centers: Masaryk Memorial Cancer Institute in Brno (34 patients) and Motol University Hospital in Prague (24 patients). All primary tumor tissue samples from untreated patients were examined by pathologists who had special expertise in sarcomas, and diagnosed according to the criteria specified in the WHO Classification of Tumours of Soft Tissue and Bone. Using immunohistochemistry, a distinct membranous CD99 expression was identified at least focally. All tumor samples were consistently positive for vimentin. Either initially or retrospectively, all biopsies were immunostained with Fli-1 antibody and unequivocal Fli-1 nuclear expression was detected in all cases. Droplets of diastase-sensitive periodic acid-Schiff material were demonstrated in sporadic tumor cells and the total destruction of the reticulin network was visualized using Gomori's silvering impregnation method. In all cases, the *EWSR1* gene rearrangement was confirmed by fluorescence in situ hybridization, using the ZytoLight SPEC EWSR1 Dual

Color Break Apart Probe (ZytoVision GmbH, Bremerhaven, Germany). Information regarding age, gender, tumor site, stage, chemotherapy drugs, timing of chemotherapy, modality and timing of local therapy (radiotherapy or surgery), and outcome was recorded. Data on tumor volume, LDH levels and histological response to chemotherapy were not uniformly available. The characteristics of the study cohort is listed in Table 1.

Patients were evaluated every 3 months for 2 years, every 4 months between 2 and 4 years, every 6 months between 4 and 6 years and annually thereafter. The diagnosis of recurrence was made on the basis of physical examination, imaging and biopsy, if required.

As local treatment, tumor resection was preferred whenever it was possible. Lower extremity amputation was necessary in one patient. Radiotherapy was administered in cases of inoperable lesions, incomplete surgical resection, in patients with poor histologic response to preoperative chemotherapy and during tumor progression. Depending on location, the total dose of radiation therapy was 45–54 Gy.

Table 1 Clinical characteristics of 58 patients

Variable	Number (Median)	% [Range]
Sex		
Male	32	55.2
Female	26	44.8
Age, years	(29)	[18–59]
< 40	39	74.1
≥ 40	19	25.9
Primary site		
Limbs	17	29.3
Axial bones	21	36.2
Extraskeletal	20	34.5
Metastases		
No	30	51.7
Yes	28	48.3
Site of metastases		
Lung	17	60.7
Others	11	39.3
Local treatment modality		
Surgery alone	12	20.7
Radiotherapy alone	10	17.2
Surgery and radiotherapy	28	48.3
None (progressive)	8	13.8
VIDE/VAC or VIDE/VAI	38	65.5
Complete remission	36	62.1
Relapse	33	56.9
Deceased	32	55.2
Disease-related death	29	50.0
Treatment-related death	3	05.2

For the purposes of the first-line chemotherapy, VIDE/VAC or VIDE/VAI protocols were used, consisted of vincristine 1.5 mg/m^2 on Day 1, and ifosfamide plus mesna 3000 mg/m^2, doxorubicin 20 mg/m^2, and etoposide 150 mg/m^2 daily for 3 days. Doxorubicin was replaced by actinomycin 0.75 mg/m^2 and ifosfamide by cyclophosphamide plus mesna 1500 mg/m^2 in VAI or VAC regimen, respectively. VIDE cycles were administered every 3 weeks for a total of 6 cycles, and after local therapy, patients received 8 cycles of VAC or VAI at 3-week intervals. Chemotherapy doses were reduced in 20 patients because of a significant hematological adverse events. Moreover, patients with high-risk or very-high-risk ES received high-dose chemotherapy with busulfan and melphalan followed by reinfusion of autologous haematopoietic stem cells. Patients with recurrent or progressive disease received the second-line chemotherapy, optionally combined with radiotherapy or surgery. Second-line chemotherapy consisted of combination of either temozolomide with irinotecan or cyclophosphamide with etoposide. Alternatively, topotecan was given instead of etoposide.

All procedures to obtain human tumor tissue samples and follow-up information were in accordance with legislation and ethical standards of the Czech Republic and with the 1964 Helsinki declaration (revised in 2013). All patients have given informed consent to a treatment. The individual patient cannot be identified from any material in a manuscript. The Ethics Committee of the Masaryk Memorial Cancer Institute (Brno, Czech Republic) confirmed that it was possible to evaluate the patient data in this retrospective study.

Statistical Methods

Standard measures of summary statistics were used to describe primary data: relative and absolute frequencies, arithmetic mean supplied with standard deviation of mean (SD).

Robust non-parametric tests were applied in comparative analyses among different groups of patients, i.e. standard Mann-Whitney for comparisons based on continuous variables and Fisher exact test for comparisons based on categorical variables. Follow-up time was summarized as median estimate, supplied with min/max values.

Standard Kaplan-Meier technique was applied to analyze principal time-to-event endpoints of the study, progression-free survival (PFS) and overall survival (OS). PFS was defined as the time from initiation of therapy until disease recurrence, progression or death from disease or from chemotherapy-related toxicity whichever occurred first. OS was defined as the time from initiation of therapy until death. Patients with neither disease progression nor death were censored at the last date of the last follow-up. Quantification of reached survival time as based on median estimates with corresponding 95% confidence intervals. Log-rank test was applied to compare statistically differences in PFS or OS profiled

among different groups of patients. Both univariate and multivariate Cox proportional hazard regression models were used to analyze association between various predictors and risk of progression or death in time. Hazard ratio (HR) estimates were supplied with 95% confidence limits.

A value $\alpha < 0.05$ was considered as a level of statistical significance in all analyses. Statistical analysis was computed using SPSS 22 (IBM Corporation 2013).

Results

Patient Characteristics

The study cohort consisted of 32 (55.2%) men and 26 (44.8%) women. The median age was 29 years (range 18–59) with 27 (46.6%) patients being older than 30 years and 19 (25.9%) patients were over 40 years of age. In this study, men were older (median age of 32 years, range 19–59) than women (median 28 years, range 18–56 years). The follow-up periods ranged from 4 to 157 months (median 36.5 months). Extraskeletal disease was identified in 20 (34.5%) patients. Among 38 (65.5%) primary osseous ES, twenty-one (36.2%) cases were localized in axial skeleton, while remaining 17 (29.3%) patients had affected limb bones. When compared tumor location according to gender, extraskeletal and limb bones involvement occurred more frequently in men (60.0% and 64.5%, respectively), while women were more likely to have affected axial bones (57.1%), however, these differences did not reach statistical significances ($p = 0.326$). Localized disease was noted in about 52% of patients ($n = 30$), and 48% of patients were metastatic at diagnosis, with pulmonary and extrapulmonary spread in 60.7% ($n = 17$) and 39.3% ($n = 11$), respectively. Metastatic disease occurred slightly more frequently in men than women (57.1% vs. 42.9%, respectively).

Total of 38 (65.5%) patients underwent surgery, either primarily ($n = 21$, 35.2%) or after neoadjuvant chemotherapy ($n = 17$, 29.3%). Radical resection was performed in 24 (41.4%) patients, while positive surgical margins were revealed in 14 patients. Among 20 patients who were not treated with surgery for their primary tumor, 12 were inoperable and 8 patients achieved complete remission after induction chemotherapy. The local therapy was surgery alone ($n = 12$), radiation alone ($n = 10$) or combination of surgery and radiotherapy ($n = 28$). Almost 14% of patients ($n = 8$) did not receive any form of local treatment due to rapid progression of primary metastatic disease.

VIDE/VAC or VIDE/VAI induction and consolidation chemotherapy was administered to the vast majority of patients ($n = 38$, 65.5%). The preoperative chemotherapy was managed in 17 patients, however, the histological response was available in only 11 patients who were treated in Masaryk Memorial Cancer Institute in Brno. Six of these patients (54.5%) had a poor histological response with <90% tumor necrosis rate in resected specimens. In high-risk and very-high-risk patients ($n = 18$, 31%), busulfan-melphalan myeloablative therapy followed by autologous stem cell transplantaion was applied. Twenty-four patients (41.4%) that had disease progression, received second-line chemotherapy. In these cases of refractory or recurrent disease, combination of two chemotherapeutic agents was mostly administered. Drugs used in second-line regimen included etoposide plus cyclophosphamide, temozolomide plus irinotecan, or topotecan plus cyclophosphamide. Side effects of treatment were observed and graded according to a modified National Cancer Institute Common Toxicity Criteria for Adverse Events scale. All patients developed grade IV hematologic toxicity. Renal and mucosal manifestations were only transient and did not exceed grade II toxicity. Treatment-related death occurred in three cases. In one patient, deep phlebothrombosis was complicated by fatal pulmonary embolism. The second patient died in complete remission due to graft failure after stem cell transplantation. The cause of death of the third patient was severe febrile neutropenia that was managed at local community hospital.

Median follow-up was 36.5 month (range 1–157 months). At the last censored time, 26 (44.8%) patients were alive. Of these 26 survivors, 21 remained with no evidence of disease, 4 went to the remission after receiving a treatment for relapse, and one patient was still alive with progressive disease. At least one complete remission (CR) was achieved in 36 (62.1%) patients. Total of 29 (50.0%) patients succumbed to disease progression with median PFS being 12 months (range, 3 to 56) and 3 patients died as a result of a treatment complication.

The 5-year OS for entire cohort was 52.5%. In the cases of localized disease, the median OS was 65.5 months and 5-year PFS and OS reached 66.3% and 76.5%, respectively. For metastatic patients, the median OS was 19 months, with 5-year of both PFS and OS being 18.5%. Metastatic spread was associated with significantly shorter survival ($p < 0.001$, Fig. 1a). Median OS was 64 months for patients who underwent radical tumor resection, 27 months for subtotal surgery and 19.5 months for patients without surgery. Univariate analysis showed that patients who underwent radical tumor resection had a significantly better OS compared with patients who were treated conservatively ($p = 0.001$, Fig. 1b). Similarly, achievement of CR was identified as another positive prognostic factor for longer survival ($p < 0.001$, Fig. 1c). Based on a multivariate Cox proportional hazard regression analysis, only the failure to achieve CR was identified as a significant prognostic factor for both OS and PFS, with Hazard Ratio 13.3 (95% CI, 3.1–57.9; $p < 0.001$) and 5.4 (95% CI, 1.9–14.8; $p = 0.001$), respectively. After adjusting a parameter of achievement of CR from the multivariate model, metastatic

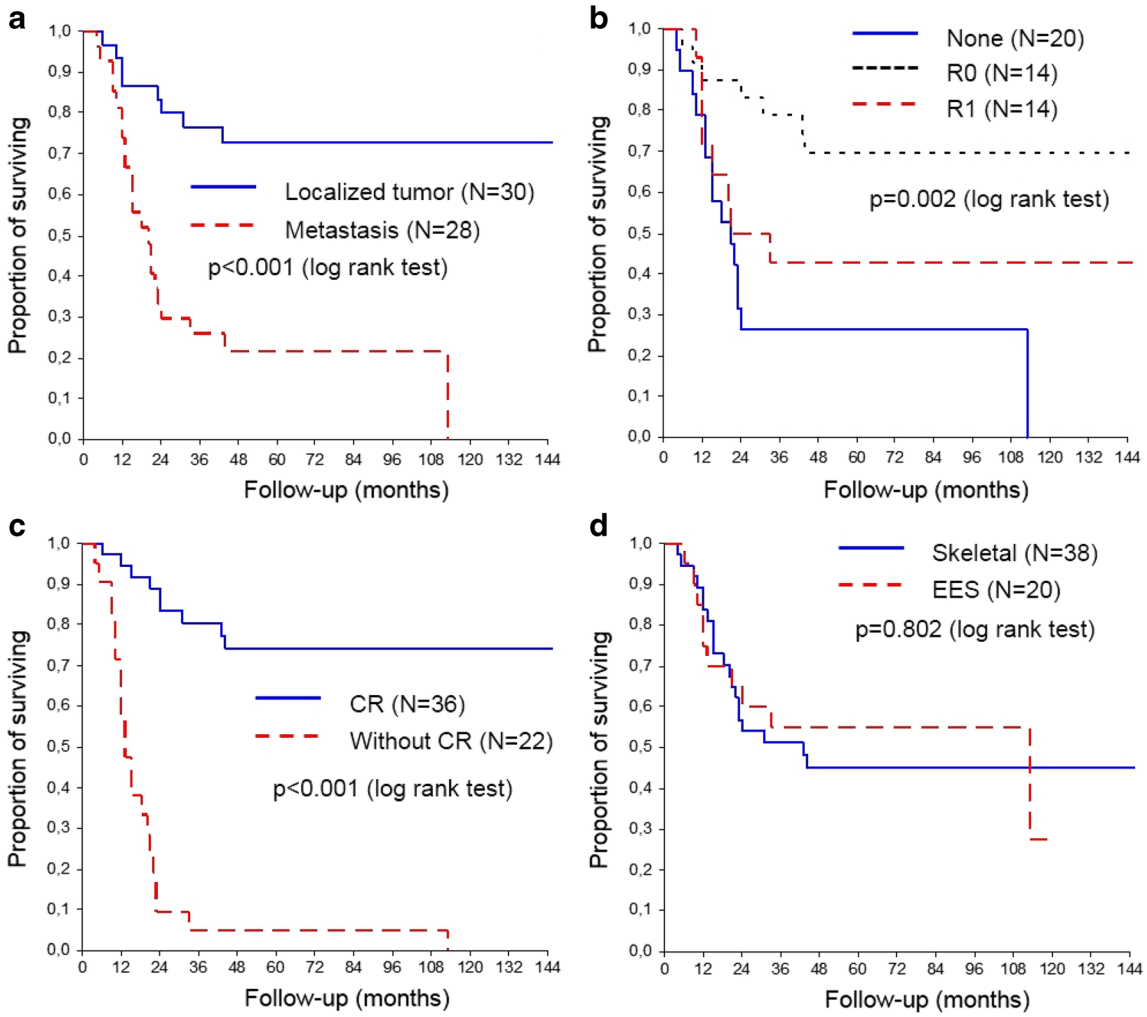

Fig. 1 Overall survival according to the extension of disease (**a**), type of resection (**b**), achievement of complete remission (**c**), and tumor localization (**d**)

disease and no surgery became the significant risk factors for decreased survival. On both univariate and multivariate analysis, no statistically significant relationship was found between tumor localization and prognosis (Fig. 1d). The results of univariate and multivariate analyses are summarized in Tables 2 and 3.

Discussion

ES is an uncommon, very aggressive malignancy that typically develops in young patients from childhood to early adulthood. Its occurrence in patients older than 40 year is exceptionally rare. Therefore, published data on treatment and clinical outcome of adult patients with ES are limited and specific age-adapted treatment regimens are yet not established.

The objective of this analysis was to estimate survival probabilities in adults with ES treated in the Czech Republic according to pediatric protocols. The study cohort consisted of 58 incident ES patient cases diagnosed between 2002 and 2013, with follow-up data available until February 2016. This study showed a markedly higher proportion of metastatic disease (48.3%), extraskeletal localization (34.5%) and involvement of axial/pelvic bones (36.2%) when comparing with data from the younger population in which metastatic spread, nonskeletal involvement and pelvic localization are reported in about 27%, 31% and 25% of patients, respectively [12, 20, 26]. All these are generally accepted to be negative prognostic factors [10, 17, 20]. In our study, the localized disease, radical tumor resection and achievement of CR were associated with significantly better survival ($p < 0.001$, $p = 0.001$, and $p < 0.001$, respectively). Furthermore, a multivariate adjusted model showed that the achievement of CR is an independent predictor of survival and the failure to achieve CR is a stronger adverse prognostic factor than metastatic disease at diagnosis or local treatment without surgery. Five-year OS for localized disease reached 76.5% of patients and this result is entirely comparable with survival of younger patients [10, 12].

Table 2 Univariate analysis for OS and PFS

	OS		PFS	
	p	HR (95% CI)	*p*	HR (95% CI)
Stage				
Localized		1		1
Metastatic	<0.001	5.1 (2.3–11.7)	<0.001	4.0 (2.0–8.1)
Primary site				
Limbs		1		1
Axial bones	NS	0.7 (0.3–1.7)	NS	1.0 (0.4–2.2)
Extraskeletal	NS	0.8 (0.3–1.8)	NS	1.0 (0.4–2.2)
Type of resection				
Radical resection		1		1
Incomplete resection	NS	2.6 (0.9–7.3)	0.015	2.9 (1.2–7.0)
None	0.001	4.4 (1.8–11.0)	<0.001	3.9 (1.8–8.7)
Complete remission				
Yes		1		1
No	< 0.001	11.8 (5.1–27.3)	<0.001	7.3 (3.6–14.7)

OS Overall survival, *PFS* Progression-free survival, *NS* Not significant

The impact of patient age on the prognosis has long been a subject of debate and remains unclear, with different studies reporting conflicting results. For example, Karski et al. [18] reported the largest review to date, analyzing outcome of 2780 patients, utilizing the Surveillance Epidemiology and End Results (SEER) database. According to their report, patients over the age of 40 years were more likely to have metastatic disease (35.5% vs. 30.0%), and extraskeletal (66.1% vs. 31.7%) or axial (64.0% vs. 57.2%) localization, and had significantly decreased OS (40.6% vs. 54.3%, $p < 0.0001$). They found that the main difference in survival between the two age groups occurs in the first 24 months, it means at the time of active treatment or shortly after completing therapy. Another study using SEER Program database [10] was focused on prognostic factors in 1163 patients with primary osseous ES, of which 32.8% were older than 20 years. They identified metastatic disease, tumor size >10 cm, patient age over 20 years, and axial tumor location as independent risk factors for decreased cause-specific survival. Few other studies have demonstrated increasing age as an independent unfavorable prognostic factor, however, the "critical" age limits vary from study to study. Thus, significantly shorter survival has been found in patients older than 10, 14, 15, 17, 18, 20, 26 and 40 years [6, 9, 10, 16, 18–20, 24]. A worse survival of elderly patients could be explained by coexistence of several other negative prognostic factors in adults, such as increased incidence of metastasis, more voluminous and inoperable tumors, and more frequent comorbidities that interfere with antitumor therapy. In addition, older patients, are more likely to have serious side effects of treatment, particularly hematologic toxicity. Therefore, it was assumed that older patients are unable to tolerate aggressive pediatric regimens, but results of some studies suggest otherwise [1, 4, 25]. It has been repeatedly confirmed that there is no association between older age and poorer prognosis when adult patients are treated according to pediatric protocols [1, 5, 25] and these findings are also consistent with our current results.

Several other studies have investigated clinical outcome in adults with ES. For example, in the cohort of 76 patients from Finnish National Cancer Registry, Serlo et al. [27] reported the 5-year disease-specific survival in cases of localized disease

Table 3 Multivariate analysis for OS and PFS

	OS		PFS	
	p	HR (95% CI)	*p*	HR (95% CI)
Stage				
Localized		1		1
Metastatic	NS	1.9 (0.7–5.4)	NS	1.9 (0.8–4.5)
Primary site				
Limbs		1		1
Axial bones	NS	1.0 (0.4–2.7)	NS	1.7 (0.7–4.0)
Extraskeletal	NS	0.6 (0.2–1.7)	NS	0.9 (0.4–2.2)
Type of resection				
Radical resection		1		1
Incomplete resection	NS	0.6 (0.1–2.8)	NS	1.4 (0.5–3.9)
None	NS	0.5 (0.1–2.5)	NS	1.1 (0.4–3.2)
Complete remission				
Yes		1		1
No	<0.001	13.3 (3.1–57.9)	0.001	5.4 (1.9–14.9)

OS Overall survival, *PFS* Progression-free survival, *NS* Not significant

being 70%. The survival probabilities in adult patients with ES are also evaluated in two following retrospective studies from Turkey: in 98 patients with localized disease [3] and 27 patients with non-metastatic extraskeletal ES [28] the 5-year OS was 65% and 64.5%, respectively. Gupta et al. [17] reported that 59% of 24 adult patients with localized ES survive for 3 years or more. In one series from the Mayo Clinic, 5-year OS of 52 non-metastatic adults with ES treated according to pediatric trails reached 73% [1]. Taken together, all these prior reported studies have shown that 3- or 5-year OS rates in adult patients with localized disease ranged from 59 to 73%. Our current results with 5-year OS being 76.5% are fully comparable and even slightly more favorable than the above mentioned reports.

In our study group, all patients developed grade IV hematologic toxicity and there was one death due to febrile neutropenia that was managed at a local community hospital. Treatment related toxicity in other cases was manageable with an intensive supportive care.

In conclusion, ES is exceptionally rare malignancy in patients older than 40 years, so the experiences with age-adapted therapeutic strategies are very limited. Our current study shows that outcomes of adults with localized ES treated according to multimodal pediatric protocols are similar to children. This improvement in survival is associated with intensification of chemotherapy and more consistent local control with giving preference to surgery when feasible. It is important to note that there is no need to restrict the use of the pediatric regimens for patients older than 50 years of age. Treatment-related toxicity is predictable and manageable and older patients can benefit from the aggressive pediatric treatment protocols leading to improved outcome, even though if necessary, chemotherapy doses should be adjusted. Of the anticipated prognostic factors, metastasis, local treatment without surgery and a failure to achieve CR were associated with significantly shorter survival ($p \leq 0.001$). In contrast, no statistically significant relationship was found between tumor localization and prognosis ($p = 0.878$).

Despite the survival improvement in patients with localized ES, the prognosis for patients with metastatic and/or recurrent disease remains poor and future investigations of regimens with new chemotherapeutic drugs as well as targeted agents appear to be necessary.

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Compliance with Ethical Standards

Conflict of Interest The authors declare no conflicts of interest.

Ethical Approval All procedure performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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