How to Treat the Ewing’s Family of Sarcomas in Adult Patients

MICHELLE SCURR, IAN JUDSON

Department of Cancer Therapeutics, Institute of Cancer Research, Sutton, Surrey, United Kingdom; Sarcoma Unit, Royal Marsden Hospital, London, United Kingdom

Key Words. Ewing’s sarcoma • Adult • Prognosis • Survival

Learning Objectives

After completing this course, the reader will be able to:

1. Describe how ESFT is not only a disease of children, but equally that of young adults.
2. Discuss the established prognostic variables in ESFT and the unresolved controversy surrounding the role of older age in patient outcome.
3. Explain that until large studies, such as the current EuroEwings study, can prospectively define the role of age as a prognostic variable, adult patients with ESFT need to be treated as intensively as younger patients.

Abstract

Ewing’s sarcoma, peripheral primitive neuroectodermal tumor, and Askin’s tumor comprise a single family of tumors, the Ewing’s family of tumors, which is characterized by chromosomal translocation. Ewing’s sarcoma is known as a malignancy of childhood, but with a median age of 15 years at diagnosis, it should equally be regarded as a malignancy of adolescence and young adulthood. There is much controversy regarding the role of age at diagnosis, with some studies showing older age to be associated with poorer outcome and others showing no association between age and survival. This has led to uncertainty in how best to manage nonpediatric patients with Ewing’s sarcoma. This article examines whether age does affect outcome and treatment in this group of tumors. The Oncologist 2006;11:65–72

Introduction

In 1921, James Ewing described the case of a 14-year-old girl with a highly malignant bone tumor composed of small round cells and named the condition diffuse endothelioma [1]. It is now known as Ewing’s sarcoma (ES). It is recognized that ES is part of a family called the Ewing’s sarcomat family of tumors (ESFT), which also includes peripheral primitive neuroectodermal tumor (PNET), extrasosseous Ewing’s sarcoma (EES), and Askin’s tumor (ES of the chest wall).

ES is regarded as a malignancy of childhood and adolescence. It is the second most common bone cancer of childhood [2, 3], accounting for 42% of cases [3]; in those patients who are 15 years or older, ES represents only 12% of cases of bone cancers, and it is a rare cancer in patients over 40 years [4]. The median age at diagnosis of ES according to the National Cancer Institute’s Surveillance Epidemiology and End Results (SEER) data for the period 1973 to 1987 was 15 years [2], and an analysis of a large cancer
registry in the United Kingdom for the period 1968 to 1995 found that 56% of the patients with ES were 15 years of age or older at diagnosis [5]. Thus, approximately one half of all patients diagnosed with an ESFT tumor will be over 15 years of age, and it is important to remember that it is equally a disease of young adults as much as it is a disease of children.

There is a widely held “truism” that older/adult patients fare worse than the younger patients, and this has led to uncertainty as to the appropriate management for what amounts to a significant proportion of the Ewing’s patient population. An important implication of this is the potential risk that young adults may not be receiving optimal treatment, either because they do in fact have a worse prognosis and should possibly be receiving more aggressive treatment or because they are not being treated as aggressively as younger patients and as a result have a poorer outcome.

If older patients do have a poorer outcome, is it a difference in the underlying biology? Or do these patients have an excess of other adverse factors? Or are these patients not receiving optimal treatment because of either inadequate dosing or differing pharmacokinetics compared with the pediatric population? This article reviews the evidence regarding the role of age as a prognostic variable for survival in ESFT patients, and from this, makes suggestions as to whether treatment of adult patients should differ from that of younger patients with ESFT tumors.

**Biology of Ewing’s Family of Tumors**

ESFT tumors are tumors of neural crest derivation that differentiate along a neuroendocrine lineage and are described as “small round cell tumors.” Although there are light microscopy variations between ES and PNETs, the finding that all ESFT tumors are characterized by a balanced chromosomal translocation between the 5′ half of the EWS gene (22q12) and the 3′ half of members of the ETS family of transcription factors has led to the understanding that the ESFT represents a single neoplastic entity. The resulting fusion gene transcribes an oncogenic transcription factor that has been demonstrated to play a critical role in maintaining the malignant phenotype in Ewing’s tumor cells [6, 7] and may also act by modulating gene expression at the RNA level [8]. In 85% of cases, the gene fusion is a result of a translocation between EWS and FLI1 (11q24) [9], and in 5%–10% of cases it is a result of a translocation between EWS and ERG (21q22) [10]. It has been found that, within the gene fusions, there is marked heterogeneity resulting from translocation of different exons. For EWS-FLI1, there are two common fusions: type 1, in which EWS exon 7 in-frame is fused with exon 6 of FLI1, and type 2, in which EWS exon 7 in-frame is fused with exon 5 of FLI1. Some studies have suggested that the type of fusion may have prognostic significance, with some studies, although not all [11], showing a positive association between type 1 EWS-FLI1 fusions and longer survival [12, 13]. There does not appear to be any significant association between age at diagnosis and fusion type.

Secondary nonrandom chromosomal changes also occur commonly in ESFT, the most common being trisomies of chromosomes 8 or 12, seen in up to 50% of cases, and gains or losses in chromosome 1, which are also common [14–16]. Small retrospective studies have shown an association between these chromosomal changes and poorer outcome, although the data are conflicting [14–17]. There is limited information regarding any relationship between age at diagnosis and secondary chromosomal abnormalities. Hattinger et al. [17] performed cytogenetic studies on tumor samples from 134 patients and compared results of these studies with the patients’ clinical data. Trisomy of chromosome 8 was found in 52% of patients but was not predictive of outcome, whereas gain of 1q or loss of 16q were both associated with poorer outcome. Both 1q gain and 16q loss correlated with age >15 years at diagnosis (34% vs. 13%, p = .005; and 31% vs. 15%, p = .035). Prospective studies are needed that compare these chromosomal changes (both primary and secondary) with factors including age, as well as more accurately define their role as prognostic variables. Until that time, the data are too limited to determine whether there is any evidence for age-associated differences in the biology of ESFT.

**Age as a Prognostic Factor**

The presence of primary metastases, that is, metastases present at diagnosis, is the single most important factor in determining survival in ESFT patients, with patients with metastatic disease having a dismal 5-year survival rate, varyingly reported from 0%–25%, compared with 40%–79% for those with localized disease. In patients with localized disease, established predictors of poorer survival include large (>100 ml) primary tumor volume and central/pelvic site of primary disease. The significance of patient age at the time of diagnosis as a prognostic variable is less certain; many studies have shown increasing age at diagnosis to be a significant and adverse variable for survival, and yet others have shown age to have no significant influence on outcome.

Several studies have specifically evaluated adult patients with ESFT (Table 1) [18–26]. All of these are retrospective and, most often, are from tertiary cancer centers, thus introducing a potential for selection bias in favor of patients with more adverse factors. Sinkovics et al. [18] reviewed 50 adult patients treated at the M.D. Anderson...
Cancer Center from 1970 to 1980. The average age in that cohort was 21.5 years, ranging from 17 to 34 years, and 34 patients had localized disease. At the time of reporting, 50% of those with localized disease had died, at an average follow-up of 27 months, and the authors concluded that “the prognosis of adult patients with Ewing sarcoma is worse than that of children.” However, those patients with localized disease of an extremity had a markedly better outcome, with 63% of patients disease free and 52.6% relapse free at a mean follow-up of 29 months. The Dana Farber Cancer Institute has published two case reviews of adult patients with ESFT tumors [19, 20]. The first study reviewed 16 patients treated from 1975 to 1985 and found the outcome for adults to be poor; however, half of the patients included in the study had recurrent or refractory or metastatic disease and thus had a highly significant adverse prognostic factor independent of their age [19]. The second study reported on 37 newly diagnosed adult patients, with a median age of 26 years (range, 16–55). All but two patients (99%) were treated with chemotherapy, most with an anthracycline-based regimen, and most were treated within a prospective trial. The 5-year OS rate was 41% and the 5-year PFS rate was 32%. If the 29% of patients with metastatic disease at diagnosis are excluded, then the 5-year OS rate for localized disease is 54% and the 5-year PFS rate is 43%. Age was not found to affect prognosis, whether an age cut-off of 20 years, 30 years, or 40 years was used. Martin et al. [22] reviewed the data from 81 adult patients with a median age of 27 years (range, 16–72) treated at the Memorial Sloan-Kettering Cancer Center within a prospective clinical trial. The 5-year OS rate was 60% and the 5-year PFS rate was 60%. Age ≥ 16 yrs not significant (p = .05).

Other reviews found no association between older age and poorer prognosis. Fizazi et al. [26] reported the largest review to date, analyzing outcomes of 182 patients (median age, 21.5 years; range, 16–55). All but two patients (99%) were treated with chemotherapy, most with an anthracycline-based regimen, and most were treated within a prospective trial. The 5-year OS rate was 41% and the 5-year progression-free survival (PFS) rate was 32%. If the 29% of patients with metastatic disease at diagnosis are excluded, then the 5-year OS rate for localized disease is 54% and the 5-year PFS rate is 43%. Age was not found to affect prognosis, whether an age cut-off of 20 years, 30 years, or 40 years was used. Martin et al. [22] reviewed the data from 81 adult patients with a median age of 27 years (range, 16–72) treated at the Memorial Sloan-Kettering Cancer Center.

Table 1. Studies of “adult” patients with Ewing’s sarcoma family of tumors

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of patients (localized)</th>
<th>Median age, years (range)</th>
<th>Survival Overall</th>
<th>Localized disease</th>
<th>Adverse prognostic significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sckovics et al. [18]</td>
<td>34 (19)</td>
<td>21 (16–36)</td>
<td>DFS (27 mos), 50%</td>
<td>DFS (29 mos), 58.3%</td>
<td>Authors state adverse, no statistical analysis</td>
</tr>
<tr>
<td>Siegel et al. [19]</td>
<td>16 (8)</td>
<td>22 (17–50)</td>
<td>Median OS, 34 mos; median DFS, 10 mos</td>
<td>Not given</td>
<td>Authors state adverse, no statistical analysis</td>
</tr>
<tr>
<td>Baldini et al. [20]</td>
<td>37 (26)</td>
<td>26</td>
<td>5-yr OS, 37%</td>
<td>5-yr OS, 49%</td>
<td>Age ≥ 26 yrs significant (p = .05)</td>
</tr>
<tr>
<td>Klaassen et al. [21]</td>
<td>30 (25)</td>
<td>21.8 (16–38)</td>
<td>3-yr OS, 23%</td>
<td>3-yr OS, 40%</td>
<td>Authors state adverse, no statistical analysis</td>
</tr>
<tr>
<td>Fizazi et al. [26]</td>
<td>182 (129)</td>
<td>21.5 (16–55)</td>
<td>5-yr OS, 41%; 5-yr PFS, 32%</td>
<td>5-yr OS, 54%; 5-yr PFS, 43%</td>
<td>No age group significant adverse factor</td>
</tr>
<tr>
<td>Martin et al. [22]</td>
<td>59 (46)</td>
<td>27 (16–72)</td>
<td>5-yr OS, 60%</td>
<td>5-yr OS, 60%</td>
<td>Age ≥ 26 yrs not significant</td>
</tr>
<tr>
<td>Verrill et al. [23]</td>
<td>59 (42)</td>
<td>24 (14–51)</td>
<td>5-yr OS, 38%; 5-yr PFS, 27%</td>
<td>5-yr OS, 52%; 5-yr PFS, 34%</td>
<td>Age ≥ 20 yrs not significant (p = .12)</td>
</tr>
<tr>
<td>Bacci et al. [24]</td>
<td>23 (23)</td>
<td>&gt;39</td>
<td>All localized disease</td>
<td>5-yr OS, 59%; 5-yr PFS, 53%</td>
<td>Not significant (compared with historical controls &lt;39 yrs)</td>
</tr>
<tr>
<td>Argon et al. [25]</td>
<td>25 (20)*</td>
<td>19 (15–40)</td>
<td>2-yr OS, 32.7%; 2-yr PFS, 19%</td>
<td>Not given</td>
<td>Age ≥ 20 not significant (p = .4)</td>
</tr>
</tbody>
</table>

*The authors gave the average age.

*bThis study evaluated only patients with Ewing’s sarcoma of the axial bones.

Abbreviations: DFS, disease-free survival; OS, overall survival; PFS, progression-free survival.

Cancer from 1970 to 1980. The average age in that cohort was 21.5 years, ranging from 17 to 34 years, and 34 patients had localized disease. At the time of reporting, 50% of those with localized disease had died, at an average follow-up of 27 months, and the authors concluded that “the prognosis of adult patients with Ewing sarcoma is worse than that of children.” However, those patients with localized disease of an extremity had a markedly better outcome, with 63% of patients disease free and 52.6% relapse free at a mean follow-up of 29 months. The Dana Farber Cancer Institute has published two case reviews of adult patients with ESFT tumors [19, 20]. The first study reviewed 16 patients treated from 1975 to 1985 and found the outcome for adults to be poor; however, half of the patients included in the study had recurrent or refractory or metastatic disease and thus had a highly significant adverse prognostic factor independent of their age [19]. The second study reported on 37 newly diagnosed adult patients, with a median age of 26 years (range, 18–46) treated at the same institution over the time period 1979 to 1996 [20]. All but two patients were treated with chemotherapy (both of those patients had localized distal disease, and both relapsed and died). The outcome for the patients (n = 11) with metastatic disease was very poor, but for those with localized disease, the actuarial 5-year overall survival (OS) rate was 49% ± 11% standard deviation (SD). The 5-year OS rate for those younger than 26 years was 48%, compared with 25% for older patients, but this was not significant (p = .3). On multivariate analysis, however, age ≥ 26 years was found to independently influence survival adversely regardless of stage (hazard ratio [HR], 3.7; p = .02), including for those with localized disease (HR, 5.0; p = .07). Klaassen et al. [21] also concluded that adult patients have a poor outcome in a review of 30 adult patients treated at the Institut Curie, with an overall 3-year survival rate of 23%, and a survival rate of only 40% for those with localized disease of the extremity.

Other reviews found no association between older age and poorer prognosis. Fizazi et al. [26] reported the largest review to date, analyzing outcomes of 182 patients (median age, 21.5 years; range, 16–55). All but two patients (99%) were treated with chemotherapy, most with an anthracycline-based regimen, and most were treated within a prospective trial. The 5-year OS rate was 41% and the 5-year progression-free survival (PFS) rate was 32%. If the 29% of patients with metastatic disease at diagnosis are excluded, then the 5-year OS rate for localized disease is 54% and the 5-year PFS rate is 43%. Age was not found to affect prognosis, whether an age cut-off of 20 years, 30 years, or 40 years was used. Martin et al. [22] reviewed the data from 81 adult patients with a median age of 27 years (range, 16–72) treated at the Memorial Sloan-Kettering Cancer Center.
from 1982 to 2000 and found that the outcome for patients was not dissimilar to results seen in pediatric populations, with a 5-year OS rate of 60%. Verrill et al. [23] analyzed 59 adult patients with a median age of 24 years (range, 14–51) and determined that the estimated 5-year OS rate for the cohort was 38%, and it was 52% for those with localized disease. There was no association found between age at diagnosis and survival, whether the cut-off point chosen was 20 years or 24 years, although a nonsignificant trend toward poorer survival was seen in patients <20 years old. Metastases at presentation and the size of the tumor were found to be significant variables for 5-year OS and 5-year PFS. The 5-year OS rate for those patients with tumor volume <100 ml was 84%; for those with larger tumors it was 38%, and for those with metastatic disease it was only 8% (p = .002). Bacci et al. [24] published a study specifically focusing on the outcomes of 23 patients older than 39 years who had localized ES of bone and compared this group with 327 younger patients treated using the same study regimens from the same institution. The older and younger groups were similar for risk factors such as tumor size, primary site, and histological response to chemotherapy, as well as for the type of local and systemic treatment used. Age greater than 39 years was not found to adversely affect survival, with 5-year PFS rates of 53% and 58% and 5-year OS rates of 58% and 62% for those older than 39 years and younger patients, respectively. Finally, there has been a small review published reporting on 25 adult patients with axial primaries [25]. The outcome for this cohort was poor, with a 2-year OS rate of 32.7% (SD, ±9.8%). Patients with pelvic primaries were found to fare worse than those with vertebral primaries, but age (cut-off, 20 years) was not found to affect outcome in this group of patients with high-risk features.

There have been many studies evaluating treatment regimens that have also included prospective analyses of prognostic variables. Most of these studies are by children’s cancer groups, and the population pool in these studies reflects this. This does lead to a potential “selection” bias because the “older” patients enrolled into these studies may not be representative of adult ESFT patients in general. Several studies have found age to be an adverse predictive variable of survival and even of risk for local recurrence, whereas other studies have found no association at all. The first Intergroup Study (IESS-I) which compared VAC (vincristine [Oncovin®; Eli Lilly and Company, Indianapolis, http://www.lilly.com], actinomycin [Cosmegen®; Merck & Co., Inc., Whitehouse Station, NJ, http://www.merck.com], and cyclophosphamide) with VACA (VAC and doxorubicin [Adriamycin®; Bed ford Laboratories, Bedford, OH, http://www.bedfordlabs.com]) and VAC with bilateral pulmonary radiotherapy in 342 patients with localized ES of bone found increasing age to adversely influence relapse-free survival (RFS) (p < .01) and OS (p < .001) [27]. In a second study by the same group, randomizing 214 patients to different VACA regimens, age did not influence RFS, OS, or the local recurrence rate [28]. Grier et al. [29] recently published the results of a large study of 398 patients comparing VACA with VACA plus ifosfamide (Ifex®; Bristol-Myers Squibb, Princeton, NJ, http://www.bms.com) and etoposide (Etopophos®, VePesid®; Bristol-Myers Squibb). The 5-year event-free survival (EFS) rate for patients under 10 years of age was 70%; for those aged 10–17 years, it was 60%, and it was only 44% for older patients (p < .001). Although the addition of ifosfamide improved EFS overall, the benefit was not seen for those aged over 17 years. No other study evaluating ifosfamide in ESFT has shown an age-related response to ifosfamide. Two studies of the French Society of Pediatric Oncology Group (FSOP) that explicitly evaluated the potential role of age as a prognostic variable found no significant associations [30, 31]. The Scandinavian Sarcoma Group performed two neoadjuvant studies, SSGIV and SSGIX, and in neither study was age found to be a significant prognostic variable for either metastasis-free survival or OS [32, 33].

Two large clinical trial groups, the Cooperative Ewing Sarcoma Study (CESS) group and the Medical Research Council/United Kingdom Children’s Cancer Study Group (MRC/UKCCSG), formed a larger collaborative group, the European Intergroup Cooperative Ewing’s Sarcoma Study (EICESS) and in doing so have combined their respective databases of patients registered into study protocols from 1977 to 1993 (1981 in the case of CESS). Using this database, EICESS has published the largest analysis to date of prognostic factors in 975 patients with ES of the bone [34]. The majority of patients had been entered into one of the studies performed by these groups [35–38], but, in addition, ineligible patients who received treatment as per the respective study protocol were also included in the analysis to enable the results to be more generalized. The median age for the overall cohort was 14 years, ranging from <1 year to 47 years old. As expected, those with metastatic disease had a significantly poorer 5-year RFS (p < .001), and both central site and larger tumor volume were independent predictive factors in patients with localized disease. The two studies from CESS [35, 36] found no association between age at diagnosis and outcome, whereas the two studies from the UK group [37, 38] both found increasing age to negatively affect survival. When the two databases were combined and nonprotocol patients included, age was found to independently confer a poorer 5-year RFS (p < .001) for those patients 15 years and older at diagnosis compared with younger patients [34]. That study also found a signif-
icant association between an age of 15 years or older and both pelvic primary ($p = .015$) and larger tumor volume ($p < .001$). The former may be a true association, but the latter could equally be interpreted as a result of a greater likelihood that older patients with adverse prognostic factors are referred to pediatric units in which there is centralization of expertise in ES management, or simply a greater likelihood of delayed diagnosis in older patients. Investigators at the Rizzoli Institute in Bologna have performed five nonrandomized studies using differing multimodality regimens over the last three decades [39–41]. The earliest two studies involved adjuvant chemotherapy in 144 patients and found no association between age and disease-free survival (DFS) [39]. They then performed two further studies using induction chemotherapy (one including ifosfamide in maintenance therapy), and again age was not found to significantly influence DFS for either of the treatment cohorts [40]. The latest study of 157 patients evaluated the role of the addition of ifosfamide to induction chemotherapy [41]. In that study, those patients older than 15 years had a poorer 5-year EFS rate, 66%, compared with 81% for younger patients ($p < .045$); however, the significance disappeared on multivariate analysis. The follow-up data for the 402 patients enrolled into these five studies were recently updated and the results were combined to evaluate long-term survival and prognostic variables [42]. The mean follow-up was 10 years (range, 10–30) and the 10-year EFS and 10-year OS rates were 45.5% and 48.9%, respectively. With the combined cohort, age older than 14 years was found to predict both a poorer 10-year EFS (38.2%, vs. 51.6% for younger patients; $p = .01$) and a poorer 10-year OS (44.7%, vs. 55.6%; $p < .02$). In multivariate analysis, the significance was maintained, although not as strongly ($p < .04$), suggesting that other factors influence the effect of age on outcome.

The use of large epidemiological studies decreases the risk for “selection” bias. SEER in the U.S. and EURO-CARE in Europe are large databases pooling information from many cancer registries across many states/countries, and both provide some information about age differences in survival for ESFT patients. SEER has published data for the time period 1975 to 1995 regarding survival in ESFT for age groups 0–19 years [43]. The overall 5-year OS rate for the time period 1975 to 1984 was 42%, which improved to 58% for the time period 1985 to 1994; this improvement was seen across the different age groups. Comparing age groups demonstrated a difference in 5-year survival rates favoring those patients aged 4–9 years (71%) over patients aged 10–19 years (56%), although with the 10–19 years age group there was no difference seen between those aged 10–14 and those aged 15–19 years. The EURO-CARE Working Group evaluated survival data for children aged 14 years or younger from 16 countries registered from 1978 to 1989 and found survival to be poorer in those patients aged 10–14 years [3]. The risk ratio for these older children compared with those aged 5–9 was 0.76 (95% confidence interval [CI], 0.60–0.96), and compared with those aged 4 years or younger, the risk ratio was 0.75 (95% CI, 0.5–1.11). EURO-CARE also performed an analysis for the time period 1990 to 1994, evaluating survival data for patients aged 15–24 years [44]. The 5-year survival rate for patients with ES was 41.8%. For all cancers combined, adolescents (15–19 years old) were found to have a poorer outcome than young adults (20–24 years old); however, in those patients with ES, no age-related difference in survival was seen.

These data show the lack of clarity as to the significance of patient age on outcome. The small patient numbers, the issues surrounding trial design (in particular, retrospective reviews), and the real possibility of selection bias means that at this point in time, it is not possible to accurately define the role of age, if any, on outcome.

**ASSOCIATION BETWEEN AGE AND OTHER PROGNOSTIC FACTORS**

Whether age is truly an independent adverse variable in ESFT is very uncertain. If older patients do have a poorer outcome, and this is also very uncertain, then it may be that older patients are high risk because they have an excess of other high-risk features. One adverse prognostic variable that, not unreasonably, may be more likely to occur in older patients is that of greater tumor volume. Hense et al. [45] analyzed data from 945 German patients enrolled into (E)CESS studies from 1980 to 1997 to determine what factors were associated with tumor volume and primary metastases. A significant association between age and primary tumor volume $≥100$ ml was found, and the likelihood of having a tumor volume $≥100$ ml increased by 50% with every 10-year increase in age ($p = .004$). A significant association was also seen between greater tumor volume and primary metastatic disease, but the occurrence of primary metastatic disease was independent of age. Using the EICESS database (see above), Cotterill et al. [34] demonstrated a significant relationship between older age at diagnosis and established adverse prognostic factors. Patients aged 15 years or older had a significantly greater tumor volume ($p = .005$) than younger patients. Pelvic primary site is another well-established predictor of poorer outcome, and that study also found a significant correlation between age of 15 years or older and pelvic primary site ($p = 0.015$). In contrast, Evans et al. [46] reported a review of 59 eligible patients with localized ES of the pelvis or presacrum who had participated in IESS-I [27] or IESS-II [28]. The median age and range of patients with pelvic/presacral primaries...
were not different from the median age and range seen for the overall populations of both studies, suggesting no association between age and pelvic primary location, at least in that cohort. A good histological response to preoperative chemotherapy has been shown to be a strong predictor of longer survival [36, 47, 48]. One retrospective review of 243 patients treated at the Rizzoli Institute found that age (cut-off, 14 years) was a significant predictor of histological response ($p = .04$); however, the influence of other factors was not evaluated by multivariate analysis [49]. There are few solid conclusions that can be drawn based on the limited data that are available. It may be that older patients do tend to have larger tumor volumes at time of diagnosis, or even other high-risk features, but for this to be resolved, older patients need to be entered into studies. In addition, studies must not include only those with high-risk features, and these end points need to be evaluated prospectively.

**Tolerance of Adult ESFT Patients to Chemotherapy**

One hypothesis that has been formed regarding why adult patients may not have as good an outcome as younger patients is that they are unable to tolerate pediatric chemotherapy regimens, but the evidence suggests otherwise. In a study from the Rizzoli Institute [41], evaluating an intense six-drug regimen in 157 patients of any age with localized ES of bone, it was found that older patients were able to tolerate treatment as well as younger patients. The mean dose intensity for patients aged 15 years or younger was 95.8%; for the age group 16–30 years, it was 90.1%, and for those older than 30 years, it was 96.2%. The rates of grade IV hematological toxicities were 10% in patients 15 years or younger, 14% in those aged 16–30 years, and only 4% in those older than 30 years. The second Intergroup study (IESS-II) compared a high-dose intermittent VACA regimen with a moderate continuous method of delivery of the same combination [28]. An analysis comparing toxicity between age groups was performed, and older patients had significantly lower rates of “severe or worse” leukopenia. A comparison of overall toxicity between age groups found a nonsignificant trend toward better tolerability of treatment by older patients ($p = .09$). Verrill et al. [50] reported on 30 evaluable patients treated at an adult institution using the same regimen used in the ET-2 trial [38]. The preoperative chemotherapy consisted of four cycles of IVAD3 (ifosfamide, 9 g/m²; doxorubicin, 60 mg/m²; and vincristine, 1.4 mg/m² [maximum 2 mg]) followed by local treatment and then two cycles of IVAD2 (ifosfamide decreased to 6 g/m²). The median age in that study was 23 years (range, 16–48), with 10 patients over the age of 30 years. Hematological toxicities were significant, with 83% of patients experiencing an episode of grade IV neutropenia; however, only 12% of treatment cycles were delayed as a result of myelosuppression. Despite the toxicity, the overall received dose intensity was 92% when compared with six cycles of standard IVAD, and the authors concluded that dosing adults at a “pediatric” intensity is feasible. In a study reviewing patients older than 39 years, the tolerance of the 23 older patients was compared with that of 327 younger patients treated with the same chemotherapy regimens [24]. Older patients were more likely to have significant hematological adverse events, with grade IV hematological toxicity seen in 36% of cycles in the older cohort, compared with 15% in younger patients, and hospitalization for hematological toxicity was seen in 2.4% versus 0.4% of cycles, respectively. Despite this, no difference was seen between those aged over 39 years and the younger patients in the frequency of dose delays of more than 1 week (6% vs. 4%, respectively). The mean dose intensities were similar in these two age groups (93.8% vs. 95.1%), and 83% of the older patients received at least 90% of the predicted dose.

Pau1ussen et al. [51] analyzed data from 1426 patients treated in three consecutive (E1)CESS treatment protocols and compared the 10-year EFS rates for patients treated in pediatric oncology units and those treated in other institutions (Table 2). In that study, both age older than 15 years and not being treated in a pediatric oncology unit were found to confer a poorer EFS in both univariate and multivariate analyses. Interestingly, in patients older than 15 years, those that were treated in a pediatric oncology unit had a significantly better survival than those treated at other institutions ($p = .0003$). Although the review is retrospective, these results do suggest that differences in adult outcomes compared with those of younger patients may, in part, be related to a difference in the ethos between pediatric and adult oncology units with regard to the importance of adhering to dose-intensive protocols for a potentially curable malignancy.

**Table 2.** Relationship of type of treating institution and survival in pediatric and adult patients treated with standardized multimodal treatment according to CESS 81, CESS 86, and EICESS 92.

<table>
<thead>
<tr>
<th>Type of treating institution</th>
<th>≤15 yrs</th>
<th>&gt;15 yrs</th>
<th>$p$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>0.5</td>
<td>0.35</td>
<td>.0001</td>
</tr>
<tr>
<td>Pediatric Institution</td>
<td>0.51</td>
<td>0.43</td>
<td>.916</td>
</tr>
<tr>
<td>Other Institution</td>
<td>0.29</td>
<td>0.29</td>
<td>.0003</td>
</tr>
</tbody>
</table>

Abbreviations: CESS, Cooperative Ewing Sarcoma Study; EICESS, European Intergroup Cooperative Ewing’s Sarcoma Study.

From [51].
CONCLUSIONS
As can be seen from the above sections, the answer to the question of whether adult patients have poorer outcomes than younger patients is by no means certain. Although there is some evidence that does suggest a poorer outlook, there are significant flaws in these data that preclude any definite answer. What can be said is that, if there is an age effect, then it is not as significant as other adverse prognostic factors, such as the presence of primary metastatic disease, larger tumor volume, pelvic/central primary site, and poor histological response to preoperative chemotherapy. These factors are clearly far more important and could potentially be influencing the effect of age. It is also probable that older patients can tolerate “pediatric”-style protocols and even benefit from strict adherence to these protocols, as happens in pediatric oncology units. Thus, it would seem appropriate that older patients are treated as aggressively as pediatric patients and, even more importantly, that there be no age limit in study protocols depending on response to these treatments.

It will be several years, however, before any meaningful data are reported and, until then, the most appropriate way to treat adult patients is as if they were children.

DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST
The authors indicate no potential conflicts of interest.

REFERENCES


