Access to clinical trials for adolescents with soft tissue sarcomas: Enrollment in European pediatric Soft tissue sarcoma Study Group (EpSSG) protocols


Correspondence to: Andrea Ferrari  andrea.ferrari@istitutotumori.mi.it
Pediatric Oncology Unit, Fondazione IRCCS Istituto Nazionale Tumori, Via G. Venezian, 1 20133 Milano, Italy.

Abbreviations
AIEOP Italian Pediatric Oncology Association—Associazione Italiana Ematologia Oncologia Pediatrica
AYA adolescents and young adults
CI confidence interval
EpSSG European pediatric Soft tissue sarcoma Study Group
ICG Italian Cooperative Group
NRSTS non-rhabdomyosarcoma soft tissue sarcomas
O/E observed-to-expected
RMS rhabdomyosarcoma
SEER Surveillance, Epidemiology, and End Results
SIOP-MMT International Society of Pediatric Oncology—Malignant Mesenchymal Tumor Committee
STS soft tissue sarcomas
UK United Kingdom
Abstract

Background

Adolescents with cancer are enrolled in clinical trials at far lower rates than children. This report compares the number of adolescents (15–19-year-olds) and children (0–14-year-olds) enrolled in the protocols of the European pediatric Soft tissue sarcoma Study Group (EpSSG) with the number of cases expected to occur.

Methods

The observed-to-expected (O/E) ratio was detected in the EpSSG countries contributing most of the cases, that is, Italy, France, Spain, the Netherlands, United Kingdom, and Ireland. The observed cases included patients enrolled in any of the EpSSG protocols from October 2008 to October 2015, when all EpSSG protocols were open in these countries. The number of expected cases was calculated from the incidence rates estimated throughout the RARECAREnet database in the countries’ population-based cancer registries.

Results

In the countries considered, 2,118 cases aged 0–19 years were enrolled in the EpSSG trials from 2008 to 2015: 82.8% were children and 17.2% were adolescents. The O/E ratio was 0.30 among patients 15–19 years old, as opposed to 0.64 for those 0–14 years old. The O/E ratio differed for the different subtypes: in adolescents, it was 0.64 and 0.18 for rhabdomyosarcoma (RMS) and non-rhabdomyosarcoma soft tissue sarcomas (NRSTS), respectively; in children, it was 0.77 and 0.50, respectively. The O/E ratios differed across the countries considered.

Conclusions

Adolescents were less well represented than children on the EpSSG protocols, with better enrolment for RMS than for NRSTS for all age groups.
INTRODUCTION

Adolescents with cancer form a subgroup of patients whose optimal clinical management and best possible access to care remain a challenge. It has been frequently reported that adolescents with cancer are enrolled in clinical trials at far lower rates than children,[1] and it has been suggested that this is one of the reasons why adolescents with certain tumor types have worse survival rates than children with the same disease.[2, 3] Such age-related differences in survival have been described for soft tissue sarcomas (STS).[4-8] a group of tumors occurring in children and adolescents, as well as adults. The recent EUROCARE-5 study reported 5-year survival rates of 66.6% among patients 0–14 years of age with rhabdomyosarcoma (RMS) diagnosed between 2000 and 2007, as opposed to 39.6% for patients 15–19 years of age.[9] This finding is likely multifactorial; clinical trial participation, as well as biological factors, may have an impact.

The European pediatric Soft tissue sarcoma Study Group (EpSSG) is an international cooperative dedicated to conducting clinical studies and promoting research on STS in children and adolescents. It was jointly established in 2005 by the International Society of Pediatric Oncology—Malignant Mesenchymal Tumor Committee (SIOP-MMT) and the Italian Pediatric Oncology Association (Associazione Italiana Ematologia Oncologia Pediatrica [AIEOP]—Soft Tissue Sarcoma Committee, originally called the Italian Cooperative Group [ICG]). The EpSSG activated four clinical trials for newly diagnosed patients up to 21 years of age with STS (RMS and non-rhabdomyosarcoma soft tissue sarcomas [NRSTS]) over a 10-year period ending in 2015.

The present report compares the number of adolescents (defined as patients 15 to 19 years old) and children (0–14 years old) enrolled in the EpSSG's protocols with the number of adolescent cases expected to occur, estimated from the incidence rates in population-based cancer registries.

METHODS

The analysis of observed-to-expected ratios (O/E) for newly diagnosed cases of RMS and NRSTS in children and adolescents was done for patients 0–19 years of age. The EpSSG studies cover 15 different countries and 131 centers, but our analysis focused on the five datasets contributing most of the cases (more than 85%), that is, Italy, France, the dataset from United Kingdom (UK) and Ireland (considered together for the purposes of this analysis), Spain, and the Netherlands.

The observed cases included patients enrolled in any of the four EpSSG protocols from October 1, 2008 to October 1, 2015 (Table 1), a time period chosen because all four EpSSG studies were open in the countries noted above.
The number of expected cases was estimated from the STS incidence rates in the countries’ population-based cancer registries. Age-specific incidence rates (for the age groups: 0–4, 5–9, 10–14, and 15–19 years) were calculated in each country for the years 2000–2007 and then multiplied by the corresponding population figures. The RARECAREnet (www.rarecarenet.eu) database was used to estimate the incidence rates. The population coverage of the registries varied across age groups and countries. For children, it was 40% in Italy, 37% in Spain, and 100% in France, UK plus Ireland, and the Netherlands. For adolescents, it was 30% in Italy, 15% in Spain, 12% in France, and 100% in UK plus Ireland, and the Netherlands. The population considered when estimating the number of expected cases was drawn from the EUROSTAT database,[10] and the period considered was 2009–2015, that is, much the same as for the observed cases. The population figures for 2015 were still unavailable in the EUROSTAT database at the time of the study, so the 2014 figures were used instead.

Ninety-five percent confidence intervals (CIs) were calculated for the O/E ratio, assuming a Poisson distribution of the observed cases with the mean and variance equating to those of the expected cases.

**RESULTS**

In the countries considered, there were 2,118 cases of STS in patients aged 0–19 years enrolled in the EpSSG trials from October 2008 to October 2015: 1,754 (82.8%) were 0–14 years old and 364 (17.2%) were aged 15–19. The number of 15–19-year-olds remained stable throughout the study period (with 46–54 cases/year, median 48). By histotype, 1,340 enrolled cases were RMS (63.3%) and 778 were NRSTS (36.7%), with more cases of RMS than of NRSTS being observed in both children (RMS accounted for 65% of the cases) and adolescents (RMS cases were 55%). Regarding the expected cases, the epidemiologic data suggested that NRSTS should account for 54.2% of all STS (45.3% in children and 74.1% in adolescents).

The O/E ratio for all STS among patients 15–19 years of age was 0.30 (95% CI 0.27–0.33), as opposed to 0.64 (95% CI 0.61–0.68) for children up to 14 years of age. As shown in Table 2, the O/E ratio differed for the different STS subtypes. In adolescents, it was 0.64 (95% CI 0.55–0.73) and 0.18 (95% CI 0.15–0.21) for RMS and NRSTS, respectively; in children, it was 0.77 (95% CI 0.72–0.81) and 0.50 (95% CI 0.46–0.54), respectively. In the group with NRSTS, synovial sarcoma was the most common histotype (with 134 cases observed: 98 in children and 36 in adolescents). The O/E ratio for synovial sarcoma was 0.66 for children and 0.31 for adolescents.
The results differed across the countries considered. The percentages of adolescent cases recruited by the EpSSG protocols were 23.1 in Italy, 15.1 in France, 14.9 in UK and Ireland, 8.7 in Spain, and 21.0 in the Netherlands. Table 3 shows the O/E ratios for the different countries: the O/E ratio was always lower for adolescents than for children, especially for NRSTS.

**DISCUSSION**

This report analyzed the accrual rate of patients with STS by age in European pediatric trials from October 2008 to October 2015. While the study showed a satisfactory enrollment rate for children, especially those with RMS, it demonstrated that adolescents were less represented in EpSSG protocols, even though they were open to patients up to 21 years of age.

While there is no question that clinical trials are a fundamental part of cancer research, benefiting subsequent generations of patients and furthering our scientific knowledge, it remains unclear whether participating in clinical trials improves survival on an individual level. However, there is some indirect evidence to suggest a positive effect of such trials on participants’ outcomes, however (e.g., a better quality of care thanks to the involvement of a broader group of highly specialized professionals and/or to the stricter process control demanded by clinical protocols).[1, 11, 12]

It has often been said that adolescents with cancer are a medically underserved population and their limited participation in clinical protocols is widely acknowledged. Various studies reported that the proportion of adolescent patients entering clinical protocols ranged from 5 to 34%.[13-19]

Our results confirm the discrepancy in the rates of access to clinical protocols for STS between adolescents and children, albeit with some important differences depending on the STS subtypes involved. The O/E ratio for adolescents with RMS was much higher than for NRSTS and superior to that reported in previous studies (0.27 in the Italian AIEOP analysis in the 1988–2005 period).[4] RMS is a pediatric-type tumor generally managed by pediatric oncologists,[5, 6] likely prompting preferential referral to pediatric centers and facilitating inclusion in clinical trials. In fact, the pattern of initial referral may have a marked influence on whether or not young patients access clinical trials. Because NRSTS are mainly adult-type tumors, adolescents with this type of cancer are more likely to be referred to adult (or orthopedic) wards, even when they are very young. It is beyond the scope of this study to discuss the adequacy of this approach, balancing the advantages of the care providers’ expertise against the particular psychosocial needs of adolescent patients, and the value of age-appropriate inpatient facilities.[20, 21]
Adolescent STS patients might not be included in EpSSG trials either because they are referred to adult oncology centers (as mentioned above), or because, even when they are admitted to pediatric oncology units, the centers involved do not enroll them in the EpSSG protocol. In other words, a part of the difference in the EpSSG O/E ratios for children and adolescents with NRSTS vis-à-vis RMS may be attributable to pediatric oncologists taking a different attitude to the inclusion of the former in their clinical protocols. Judging from their incidence, NRSTS should account for more than one in two cases of STS occurring in 0–19-year-olds, but the proportion in the EpSSG registry was 36.7%. It is worth noting that the O/E ratio was higher for synovial sarcoma than for other NRSTS, possibly because pediatric oncologists have always tended to consider it as an RMS-like tumor and have gained considerable experience caring for it.[22] Another reason for the low accrual rate to the EpSSG trial for NRSTS may be that for some patient subgroups the treatment protocol required surgery alone (or surgery plus radiotherapy) and some clinicians might see no advantage to register patients treated with surgery only. In any case, EpSSG centers should improve their capability for treating NRSTS patients, also because the countries concerned have no other protocols competing with the EpSSG that might enroll patients under 18 years of age.

Another part of our analysis concerns the differences identified in the countries considered. These differences relate to national policies and how cancer treatment for adolescents and young adults (AYAs) is organized in each country, but also to differences in the way a given country's pediatric centers cooperate on STS. While in many countries the EpSSG protocols involve the majority of the pediatric oncology centers, in Spain, for example (where a discrepancy in the O/E ratios emerged for children as well as adolescents), many pediatric oncology centers have not become involved in the EpSSG.

National programs dedicated to AYAs have been developed across Europe in recent years.[23] The UK pioneered these projects, developing several age-specific units and healthcare policy directives. It has particularly focused on a strategy to increase AYA enrollment in clinical protocols.[19] Our present findings suggest, however, that further efforts are needed in this direction (only one in four British adolescents with STS were included in the EpSSG protocols, for instance). National/international AYA programs should increase the exchanges with the disease-specific cooperative groups running clinical trials. For example, changing the eligibility criteria concerning age (raising the cutoff for pediatric protocols, or admission to pediatric wards,[24] or opening adult protocols to pediatric patients[25]) may prove useless without closer links between the parties developing the trials. In fact, the EpSSG only considered pediatric oncology groups and institutions—no adult centers or adult groups dealing with STS—despite raising the age limit for participation in their trials to 21 years. Much the same could be said about the policies to set up dedicated units with age-appropriate facilities: providing dedicated spaces or recreational events and age-specific psychosocial support becomes pointless if such units are not closely linked
with the groups running clinical protocols and patients are unable to enter age-appropriate clinical trials.

The findings reported here (especially regarding individual countries) may suffer from several limitations. First, the RARECAREnet database did not cover all countries equally well due to variation in the implementation of cancer registration across Europe. The extent to which a population sampled by a regional registry is representative of a country as a whole depends on the differences and similarities in the national population’s socioeconomic status. Rather than comparing different countries, our data should be considered for all five countries together (pooled data are less likely to be biased). Another limitation of our study lies in the fact that the incidence rates estimated for adolescents are based on a limited number of cases, and this could lead to fluctuations in the figures that would have an impact on the O/E ratios. The 95% CIs give an indication of the likely range of values for the O/E ratios and should be taken into account in order to interpret the figures properly. It is worth noting that the incidence rates for children and adolescents (for RMS and NRSTS) did not differ across the considered countries and were comparable with those previously described in Europe and in international studies.[26-28] Similarly, no major differences in the incidence rate were seen for RMS between the EpSSG countries and the United States (as reported for by the Surveillance, Epidemiology, and End Results [SEER] Program), while the incidences of NRSTS in Europe were lower than that reported by the SEER.[29]

In conclusion, our study represents just the pediatric view of the access to care of adolescents with STS. No data are available on where and how the adolescents not admitted to the EpSSG centers were treated, or on the survival of the patients treated in the EpSSG trials compared with those treated elsewhere. However, the main message of the study is that adolescents’ access to clinical trials is still a challenge, despite the implementation of various AYA-dedicated programs and institutional policies.
# Tables

Table 1. EpSSG clinical protocols for newly diagnosed patients

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Activation date</th>
<th>Status as on October 2015</th>
<th>Total number of cases registered as on October 2015&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Cases 0–19 years old registered from 2008 to 2015 by the five datasets enrolling most of the cases&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>EpSSG RMS 2005 prospective randomized trial on localized RMS</td>
<td>March 31, 2005</td>
<td>Ongoing</td>
<td>1,655</td>
<td>1,041</td>
</tr>
<tr>
<td>EpSSG NRSTS 2005 prospective observational study on localized NRSTS</td>
<td>March 31, 2005</td>
<td>Ongoing</td>
<td>1,010&lt;sup&gt;c&lt;/sup&gt;</td>
<td>684</td>
</tr>
<tr>
<td>EpSSG MTS 2008 prospective observational study on metastatic RMS and NRSTS</td>
<td>September 22, 2008</td>
<td>Ongoing</td>
<td>396</td>
<td>264</td>
</tr>
<tr>
<td>EpSSG/ITCC/Roche Bernlie RO209244 protocol prospective randomized trial on metastatic RMS and NRSTS</td>
<td>July 1, 2008</td>
<td>Patients recruitment closed at October 31, 2013; analysis ongoing</td>
<td>154</td>
<td>129</td>
</tr>
</tbody>
</table>

ITCC, Innovative Therapies for Children with Cancer; MTS, metastatic.

<sup>a</sup> From 15 countries: France, Italy, UK and Ireland, Spain, the Netherlands, Belgium, Israel, Czech Republic, Brazil, Argentina, Norway, Slovakia, Switzerland, Slovenia, and Denmark.

<sup>b</sup> France, Italy, UK and Ireland, Spain, and the Netherlands.

<sup>c</sup> Lesions of intermediate malignancy not included (101 cases overall and 64 in the five countries discussed).
Table 2. Observed and expected cases with O/E ratio and 95% CI

<table>
<thead>
<tr>
<th></th>
<th>Observed</th>
<th>Expected</th>
<th>O/E ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>0-14 years old</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RMS</td>
<td>1,139</td>
<td>1,488</td>
<td>0.77</td>
<td>0.72</td>
</tr>
<tr>
<td>NRST5</td>
<td>615</td>
<td>1,234</td>
<td>0.50</td>
<td>0.46</td>
</tr>
<tr>
<td>All STS</td>
<td>1,754</td>
<td>2,722</td>
<td>0.64</td>
<td>0.61</td>
</tr>
<tr>
<td><strong>15-19 years old</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RMS</td>
<td>201</td>
<td>315</td>
<td>0.64</td>
<td>0.55</td>
</tr>
<tr>
<td>NRST5</td>
<td>163</td>
<td>902</td>
<td>0.18</td>
<td>0.15</td>
</tr>
<tr>
<td>All STS</td>
<td>364</td>
<td>1,217</td>
<td>0.30</td>
<td>0.27</td>
</tr>
</tbody>
</table>
Table 3. Crude incidence rate (IR) per 1,000,000, observed cases, expected cases, and O/E ratio with 95% CI by country

<table>
<thead>
<tr>
<th>Country</th>
<th>RMS 0-16 years old</th>
<th></th>
<th></th>
<th></th>
<th>RMS 15-19 years old</th>
<th></th>
<th></th>
<th></th>
<th>NRS 0-16 years old</th>
<th></th>
<th></th>
<th></th>
<th>NRS 15-19 years old</th>
<th></th>
<th></th>
<th></th>
<th>All STS 0-16 years old</th>
<th></th>
<th></th>
<th></th>
<th>All STS 15-19 years old</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IR</td>
<td>Observed</td>
<td>Expected</td>
<td>O/E ratio</td>
<td>95% CI</td>
<td>IR</td>
<td>Observed</td>
<td>Expected</td>
<td>O/E ratio</td>
<td>95% CI</td>
<td>IR</td>
<td>Observed</td>
<td>Expected</td>
<td>O/E ratio</td>
<td>95% CI</td>
<td>IR</td>
<td>Observed</td>
<td>Expected</td>
<td>O/E ratio</td>
<td>95% CI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Italy</td>
<td>4.5</td>
<td>254</td>
<td>264</td>
<td>0.96</td>
<td>0.85-1.08</td>
<td>4.9</td>
<td>254</td>
<td>288</td>
<td>0.71</td>
<td>0.61-0.81</td>
<td>9.5</td>
<td>496</td>
<td>552</td>
<td>0.83</td>
<td>0.76-0.91</td>
<td>9.3</td>
<td>544</td>
<td>753</td>
<td>0.72</td>
<td>0.66-0.79</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>France</td>
<td>5.3</td>
<td>307</td>
<td>435</td>
<td>0.77</td>
<td>0.64-0.86</td>
<td>3.9</td>
<td>267</td>
<td>318</td>
<td>0.65</td>
<td>0.57-0.75</td>
<td>9.3</td>
<td>544</td>
<td>753</td>
<td>0.72</td>
<td>0.66-0.79</td>
<td>9.3</td>
<td>166</td>
<td>450</td>
<td>0.86</td>
<td>0.81-0.92</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UK and Ireland</td>
<td>4.2</td>
<td>254</td>
<td>423</td>
<td>0.64</td>
<td>0.75-0.93</td>
<td>4.0</td>
<td>123</td>
<td>226</td>
<td>0.27</td>
<td>0.19-0.34</td>
<td>8.8</td>
<td>477</td>
<td>759</td>
<td>0.63</td>
<td>0.57-0.69</td>
<td>9.3</td>
<td>166</td>
<td>450</td>
<td>0.86</td>
<td>0.81-0.92</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spain</td>
<td>5.1</td>
<td>123</td>
<td>296</td>
<td>0.48</td>
<td>0.43-0.54</td>
<td>4.2</td>
<td>43</td>
<td>260</td>
<td>0.21</td>
<td>0.15-0.27</td>
<td>9.3</td>
<td>166</td>
<td>450</td>
<td>0.86</td>
<td>0.81-0.92</td>
<td>9.3</td>
<td>166</td>
<td>450</td>
<td>0.86</td>
<td>0.81-0.92</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>The Netherlands</td>
<td>5.3</td>
<td>71</td>
<td>110</td>
<td>0.85</td>
<td>0.76-0.91</td>
<td>4.4</td>
<td>38</td>
<td>89</td>
<td>0.43</td>
<td>0.35-0.53</td>
<td>9.3</td>
<td>109</td>
<td>199</td>
<td>0.71</td>
<td>0.63-0.80</td>
<td>9.3</td>
<td>109</td>
<td>199</td>
<td>0.71</td>
<td>0.63-0.80</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
REFERENCES


