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Primary metastatic Ewing's family tumors: results of the Italian Sarcoma Group and Scandinavian Sarcoma Group ISG/SSG IV Study including myeloablative chemotherapy and total-lung irradiation

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Background: The Italian Sarcoma Group and the Scandinavian Sarcoma Group designed a joint study to improve the prognosis for patients with Ewing's family tumors and synchronous metastatic disease limited to the lungs, or the pleura, or a single bone.
Patients and methods: The study was opened in 1999 and closed to the enrollment in 2008. The program consisted of intensive five-drug combination chemotherapy, surgery and/or radiotherapy as local treatment, and consolidation treatment with high-dose busulfan/melphalan plus autologous stem cell rescue and total-lung irradiation.
Results: During the study period, 102 consecutive patients were enrolled. The median follow-up was 62 months (range 24–124). The 5-year event-free survival probability was 0.43 [standard deviation (SD) = 0.05] and the 5-year

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overall survival probability was 0.52 (SD = 0.052). Unfavorable prognostic factors emerging on multivariate analysis were a poor histological/radiological response at the site of the primary tumor [relative risk (RR) = 3.4], and incomplete radiological remission of lung metastases after primary chemotherapy (RR = 2.6). One toxic death and one secondary leukemia were recorded.

Conclusions: This intensive approach is feasible and long-term survival is achievable in ~50% of patients. New treatment approaches are warranted for patients responding poorly to primary chemotherapy.

Key words: Ewing's sarcoma, high-dose chemotherapy, lung metastases, total-lung irradiation

introduction

Ewing's family tumors (EFTs) are undifferentiated sarcomas and include Ewing's sarcoma of bone, extraosseous Ewing's sarcoma, and peripheral primitive neuroectodermal tumor. EFT typically occurs in adolescents and young adults, and the disease is metastatic on presentation in 25% of cases [1]. For patients with overt synchronous metastatic disease, the prognosis is poor, but metastases to the lung alone carry a better prognosis than more extended metastatic disease [1–6].

Various studies have suggested a possible role for total-lung irradiation (TLI) and myeloablative therapy with autologous stem cell rescue in metastatic EFT [4, 6–12].

In 1999, the Italian Sarcoma Group (ISG) and the Scandinavian Sarcoma Group (SSG) started a joint prospective study, the 'ISG/SSG IV', for patients with metastatic EFT, including high-dose busulfan/melphalan and autologous stem cell rescue (HD-BuMel), and TLI. The study enlisted patients with lung-only metastases for the full treatment, while patients with isolated pleural involvement or single bone metastases were enrolled but not given TLI. The primary aim of the ISG/SSG IV was to assess the 5-year event-free (EFS) and overall survival (OS) probabilities using such an intensive treatment approach.

materials and methods

eligibility and pretreatment assessments

The eligibility criteria for inclusion in the ISG/SSG IV study were previously untreated histologically proven EFT; synchronous metastases to the lungs, or a single bone, or EFT of the chest wall with pleural involvement and/or massive effusion; age ≤40 years at the time of diagnosis; centralization of the histological material for review by a panel of ISG or SSG pathologists; local treatment with surgery and/or radiotherapy at one of the nine hospitals with specific experience of treating EFT in Italy or Scandinavia, as identified by the ISG/SSG IV protocol. Chemotherapy was delivered at eight ISG and eight SSG centers. The staging procedures consisted of computed tomography (CT) and magnetic resonance (MR) of the primary tumor site, chest CT, technetium bone scan, CT or MR of bone metastases, and bone marrow aspiration and biopsy.

The protocol was approved by the institutional review boards and ethical committees of the participating institutions. Informed consent was obtained from adult patients or from the legal guardians for children.

treatment

The treatment and the doses of chemotherapy are detailed in Figure 1.

Peripheral blood stem cell (PBSC) harvesting by apheresis was planned after the first course of cyclophosphamide + etoposide + granulocyte colony-stimulating factor 10 mg/kg/day (CE + G-CSF). The minimum number of PBSC for HD-BuMel was 2.5 × 10e6 CD34 + cells/kg of body weight. A second harvest was planned after the second CE + G-CSF if the stem cell yield was insufficient. G-CSF at the dose of 5 mg/kg/day until polymorphonucleates exceeded 0.5 × 10e9/l was mandatory after all the other courses of induction therapy too. Local therapy at the primary tumor site was planned after primary chemotherapy. Surgery aiming to obtain wide margins was the treatment of choice, where feasible. Radiotherapy was given whenever the tumor was judged inoperable, or when surgery was marginal or intralesional, according to Enneking's definitions [13]. Radiotherapy was planned with hyperfractionated and accelerated modalities, 1.5 Gy twice daily in 36 fractions for radiotherapy alone (total dose: 54 Gy), or 1.5 Gy twice daily in 28 fractions (total dose: 42 Gy) with a boost of 12 Gy in cases of intralesional surgery or marginal surgery, or limited chemotherapy-induced necrosis, as evaluated using a method described elsewhere [14]. When the tumor was located in the spine, the target volume included manifest tumor plus a margin of two vertebrae above and below. A 50% reduction in the dose of ifosfamide was allowed during the first course of maintenance chemotherapy for patients receiving contemporary radiotherapy. Surgery at the site of metastases was evaluated on an individual basis. Patients with lung metastases were eligible to receive TLI, 60–90 days after HD-BuMel. TLI was given in 10 daily fractions of 1.5 Gy (total dose 15 Gy); patients <14 years old received 10 daily fractions of 1.2 Gy (total dose 12 Gy).

The primary tumor's response to the induction chemotherapy was assessed histologically in resected cases and radiologically in inoperable cases. Histological response was based on chemotherapy-induced necrosis: a good histological response meant the absence of viable neoplastic cells or the detection of isolated microscopic nodules of neoplastic cells [14]. For radiological response, the complete disappearance of the soft tissue component was considered a good response, based on a previous retrospective ISG/SSG study revealing a strong correlation between a good

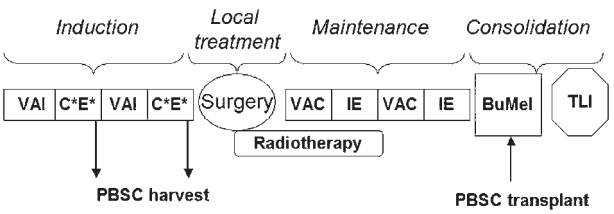

Figure 1. Italian Sarcoma Group and the Scandinavian Sarcoma Group (ISG/SSG) IV Protocol outline. A, doxorubicin 40 mg/m^2/day × 2 days; Bu, busulfan 1 mg/kg every 6 h × 4 days; C, cyclophosphamide 1200 mg/m^2; C*, cyclophosphamide 4 g/m^2; E, etoposide 150 mg/m^2/d x3 days; E*, etoposide 200 mg/m^2/day × 3 days; I, ifosfamide 3 g/m^2/day × 3 days; Mel, melphalan 140 mg/m^2; PBSC harvest = peripheral blood stem cell harvest by apheresis; PBSC transplant, peripheral blood stem cell reinfusion at 48 h after terminating BuMel; TLI, total-lung irradiation (12 Gy, <14 years of age; 15 Gy, ≥14years of age); V, vincristine 1.5 mg/m^2. Courses of chemotherapy at 3-week intervals.

histological response and the disappearance of the tumor's soft tissue component in patients with EFT [15, 16]. Response to the induction chemotherapy at metastatic level was assessed by CT scan. The complete disappearance of lung metastases, pleural metastases/effusion, or soft tissue involvement of bone metastasis was considered a good metastatic response.

statistical analysis

An intention-to-treat analysis was carried out, including all eligible patients. EFS was calculated from the start of chemotherapy to progression, recurrence, or death from treatment-related complications or secondary malignancy, or the latest follow-up. OS was calculated from the start of chemotherapy to death or to the latest follow-up. EFS and OS were calculated according to the Kaplan–Meier method. Variables influencing survival were compared by means of the log-rank test [17]. Given the limited number of patients with pleural involvement alone or isolated single bone metastases, the statistical significance of the prognostic factors was tested in the cohort of 88 patients with lung-only metastases. The variables considered for univariate analysis were sex, age at diagnosis, site of primary tumor, volume of primary tumor, serum alkaline phosphatase and serum lactate dehydrogenase (LDH) levels, interval between first symptoms and diagnosis, weight loss, fatigue, fever at diagnosis, response to induction chemotherapy of the primary tumor, and metastatic disease. A multivariate analysis was carried out using Cox's model on the prognostic factors found significant on univariate analysis. The statistical analyses were carried out using Statview software (SAS Institute Inc., Cary, NC).

results

The protocol was opened on 1 June 1999 and closed to patient enrollment on 31 December 2008; 102 consecutive patients were enrolled, whose clinical characteristics are shown in Table 1. Figure 2 is a flow chart summarizing the treatments they received.

induction and maintenance chemotherapy

In 5 of the 102 patients (5%), the disease progressed during induction therapy (at the site of the primary tumor in 2, with metastatic spread in 3). An adequate PBSC yield was obtained for all patients, with a median of 9.2×10^6 CD34 + cells/kg of body weight (range 2.6–54), and the minimum yield was obtained after one course of CE + G-CSF for 91% of the patients. The mean number of aphereses per patient was 1.2 (range 1–3). A good chemotherapy-induced necrosis was documented in 55% of resected tumors and a good radiological response was observed in 49% of unresectable cases. The response at metastatic level after completing the induction phase revealed a good response in 40 of 83 with lung metastases, 7 of 9 with pleural metastases, and 2 of 5 with single bone metastases.

Disease progression was recorded in 16 patients during the maintenance phase.

local treatment

The site of the primary tumor influenced the choice of local treatment. Primary tumors in the limbs were treated with surgery alone in 19 cases (54%), combined surgery and radiotherapy in 9 (26%), and radiotherapy alone in 7 (20%). For axial primary tumor sites, on the other hand, surgery alone was used in 17 cases (26%), surgery plus radiotherapy in 13 (22%), and radiotherapy alone in 34 (52%). Surgery was conservative in 53 cases (95%) and demolitive in 3 (1 metatarsus, 1 femur, 1 pelvis). Thoracic surgery on lung metastases was carried out in six patients with a partial remission after induction therapy (surgery was monolateral in two cases and bilateral in four).

Table 1. Patients' characteristics

Characteristic	No. of patients	Percentage
Age at diagnosis		
Median (years)	16	
Range (years)	2–40	
Sex		
Male	64	63
Female	38	27
Age groups (years)		
≤14	34	33
15–17s	25	24
≥18	43	43
Primary site		
Pelvis	35	34
Extremity	28	28
Ribs	19	18
Soft tissues	11	11
Spine	4	4
Other sites	5	5
Primary tumor volume ($n = 69$) (ml)		
<200	35	51
≥200	34	49
Metastatic sites		
Lung	88	86
Pleura/Pleural effusion	9	9
Single bone metastasis	5	5
Lactate dehydrogenase ($n = 92$)		
Normal	40	43
High	52	57
Serum alkaline phosphatase ($n = 93$)		
Normal	60	64
High	33	56
Fever ($n = 88$)		
Yes	23	26
No	65	74
First symptoms before diagnosis ($n = 92$) (months)		
>3	59	64
≤3	34	36
Fatigue ($n = 89$)		
Yes	35	39
No	53	61
Weight loss ($n = 90$)		
Yes	30	33
No	60	67

consolidation therapy

Seventy-nine of the 81 patients completing the maintenance therapy received HD-BuMel (parents refused this treatment in

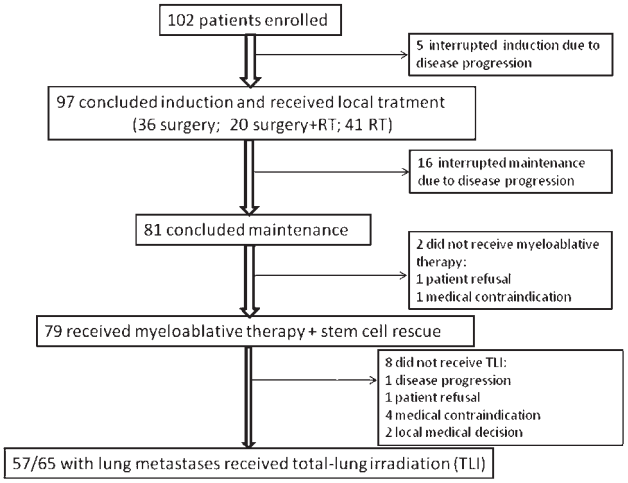

Figure 2. Flow chart of patients through reatment. RT, radiotherapy.

one case, and one had a significantly reduced cardiac ventricular function). After HD-BuMel, it took a median of 11 days (range 7–21) for polymorphonucleates to reach >0.5 × 10e9/l and 12 days (range 9–38) for thrombocytes to reach >20 × 10e9/l. The consolidation phase was completed with TLI as scheduled in 57 of 65 patients with lung metastases. The reasons for the other eight not receiving TLI were parents' refusal ($n = 1$); disease progression after HD-BuMel ($n = 1$); severe asthma ($n = 1$); poor general conditions ($n = 2$); pulmonary restrictive syndrome, exacerbated after HD-BuMel ($n = 1$); physicians' decision for two children who had no evident disease after metastasectomy.

In short, 71 patients (70%) received all the planned therapy, i.e. 57 with lung-only metastases, 9 with pleural involvement alone, and 5 with single bone metastases.

outcome

As at 31 December 2010, 53 (52%) patients were alive, 45 of them in first complete remission, and 8 with disease; 47 had died of their disease, 1 had died of treatment-related complications, and 1 of secondary leukemia. Recurrences were local in 4 cases, remote in 35, combined in 14, and unknown in 2. The median time to progression/relapse was 13 months (range 0–50).

The median follow-up for survivors was 62 months (range 24–124). The 5-year EFS probability was 0.43 [standard deviation (SD) = 0.05] and the 5-year OS probability was 0.52 (SD = 0.052) (Figure 3). For patients who had HD-BuMel ($n = 79$), the 5-year EFS probability was 0.54 (SD = 0.058) and 5-year OS probability was 0.65 (SD = 0.057). For patients with lung-only metastases ($n = 88$), the figures were 0.48 (SD = 0.057) and 0.49 (SD = 0.057), respectively, and for those given HD-BuMel and TLI ($n = 57$), they were 0.53 (SD = 0.70) and 0.66 (SD = 0.070).

toxicity and second malignancies

Induction and maintenance chemotherapy were complicated in 21% of the courses by febrile neutropenia. Radiotherapy at the primary tumor site caused dermatitis in five cases (grade 2 in

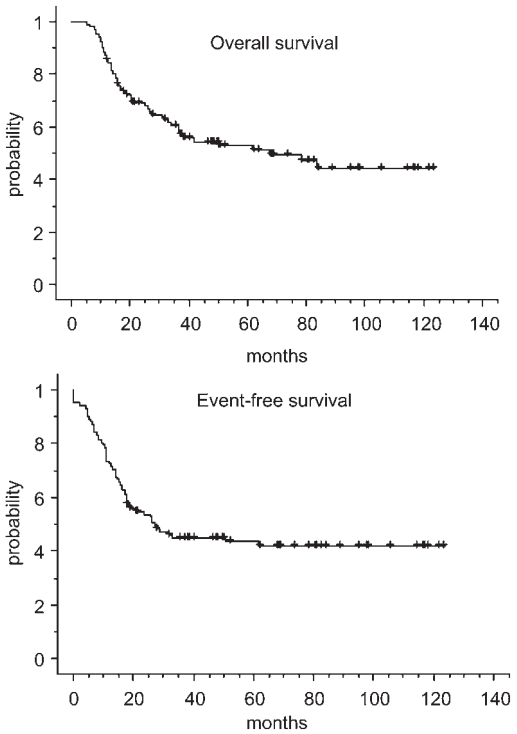

Figure 3. Kaplan–Meier estimates.

three cases and grade 3 in two), enterocolitis in six (grade 2 in five cases and grade 3 in one), vulvovaginitis in two (grade 3 in both), and transient grade 4 leucopenia in three patients.

One toxic death due to multiorgan failure after HD-BuMel was recorded in a 19-year-old boy with a single bone metastasis; HD-BuMel was complicated by hepatic veno-occlusive disease in another 12 patients (mild in 10 cases, moderate in 2), and by seizures in 1 case. Three months after TLI, a restrictive syndrome was recorded in three patients (severe in one, moderate in two), while a preexisting mild restrictive syndrome worsened after TLI in one patient. No therapy was required and no deterioration in pulmonary function was detected in these patients during the follow-up.

A second malignancy was recorded 60 months after the first diagnosis in a 10-year-old girl who developed a rapidly fatal secondary acute myeloid leukemia.

analysis of prognostic factors

Univariate analysis in patients with lung-only metastases revealed no significant differences in EFS and OS by sex, age, site of primary tumor or metastasis, serum alkaline phosphatase, fever, weight loss, fatigue, interval between onset of first symptoms and diagnosis, or local treatment modality at the site of the primary tumor. Significant prognostic factors for EFS and OS were tumor volume at diagnosis, LDH, histological/radiological response at the primary tumor site, and radiological response of lung metastases after induction therapy (Table 2).

Multivariate analysis identified the primary tumor's histological/radiological response and the response of lung

Table 2. Univariate analysis of OS and EFS for patients with lung-only metastases

Characteristic	Total	5-Year OS			5-Year EFS		
		No. of deaths	Probability (SD)	*P*	No. of events	Probability (SD)	*P*
Age groups							
≤14	29	14	0.57 (0.010)		17	0.42 (0.095)	
15–17	22	8	0.61 (0.10)		10	0.53 (0.10)	
≥18	37	22	0.37 (0.083)	0.19	25	0.31 (0.77)	0.22
Lactate dehydrogenase[a]							
Normal	33	12	0.64 (0.088)		16	0.53 (0.088)	
High	46	28	0.40 (0.074)	0.02	31	0.34 (0.070)	0.14
Primary tumor volume (ml)[b]							
<200	32	11	0.68 (0.089)		13	0.061 (0.089)	
≥200	26	18	0.32 (0.094)	0.001	21	0.19 (0.077)	0.001
Radiological/histological response of primary tumor after induction[c]							
Good	25	4	0.90 (0.066)		6	0.79 (0.081)	
Poor	35	25	0.23 (0.085)	<0.0001	28	0.17 (0.068)	<0.0001
Histological response of primary tumor after induction[d]							
Good	19	4	0.87 (0.084)		4	0.83 (0.085)	
Poor	21	11	0.33 (0.13)	0.003	14	0.30 (0.10)	0.002
Radiological response of lung metastases after induction[e]							
Complete	38	9	0.82 (0.066)		11	0.71 (0.076)	
Partial/no response	36	29	0.14 (0.65)	<0.0001	33	0.08 (0.046)	<0.0001

[a] Available in 79/88.
[b] Available in 58/88.
[c] Available in 60/83 patients who completed the induction phase.
[d] Available in 40/53 patients who completed the induction phase and received surgery at the primary tumor site.
[e] Available in 74/83 patients who completed the induction phase.
EFS, event-free survival; OS, overall survival; SD, standard deviation.

Table 3. Multivariate analysis of survival for patients with lung-only metastases

Prognostic factor	Relative risk (95% confidence interval)	*P*
Poor radiological/histological response of primary tumor after induction	3.4 (1.32 to 14.1)	0.004
Partial/no response of lung metastases after induction	2.6 (1.32 to 3.9)	0.01
Primary tumor volume ≥ 200 ml	1.46 (0.46 to 9.7)	0.19
High lactate dehydrogenase value	1.22 (0.47 to 7.58)	0.93

metastases after induction therapy as significant prognostic factors (Table 3).

discussion

The ISG/SSG IV trial was undertaken with a view to improving the prognosis for patients with EFT and metastatic disease at the onset limited to the lungs, or a single bone, or the pleura. Despite several cases of severe toxicity, including one treatment-related death and a secondary leukemia, our intensive approach proved feasible and achieved 5-year EFS and OS probabilities of 44% and 52%, respectively.

When patients with metastatic EFT receive the same standard chemotherapy as for patients without metastases, their chances of survival are poor. In a recent COG study exploring the addition of a combination of topotecan and cyclophosphamide to the standard five-drug chemotherapy with vincristine, doxorubicin, ifosfamide, etoposide, and cyclophosphamide, the reported 2-year EFS was 31% in patients with EFT and lung metastases alone [18]. In the last two decades, there have been contradictory reports on the benefits of consolidation with myeloablative therapy and autologous stem cell rescue for patients with EFT, but an increasing number of reports suggested its possible efficacy, and a recent study confirmed that even subsets of patients with disseminated metastatic EFT would benefit from HD-BuMel [4, 7–10, 15, 19–24].

Another strategy employed in the past two decades to improve the outcome of EFT metastasizing to the lung is TLI [3, 11, 12, 25]. In the St Jude's Children's Research Hospital studies, TLI was given to patients with persistent metastatic pulmonary disease after primary chemotherapy, while in the European Intergroup Cooperative Ewing Sarcomas Studies (EICESS), TLI was an option for patients with primary lung metastases who achieved a complete clinical remission after primary chemotherapy [3, 12]. In these studies, TLI was delivered depending on response to primary chemotherapy, and this could introduce a bias. The

role of TLI in EFT with lung metastases is consequently still debated [26].

The primary aim of the ISG/SSG IV was to test the efficacy of a very intensive regimen for patients with lung-only metastatic disease, including both HD-BuMel and TLI, which made it impossible to assess the role of each part of the treatment separately. The results nonetheless indicate a 5-year EFS probability of 0.48 and 0.53 for patients completing the consolidation phase. These findings support a role for such an intensive approach instead of conventional treatments, which led to 5-year EFS probabilities in the range of 0.23 and 0.36 [3, 4, 12, 27]. The small numbers of patients with isolated bone metastases or isolated pleural involvement or massive pleural effusion prevent us from conducting any subanalyses. In the present study, TLI was scheduled for all patients with lung-only metastases and no lung function impairment after HD-BuMel, thus avoiding any selection bias based on response to primary chemotherapy (as in previous studies) [4, 12]. The combined use of HD-BuMel and TLI as a consolidation treatment for patients with EFT is a novel strategy, used only in the present study, apart from a limited number of cases treated with myeloablative therapy and TLI in the EICESS experience [4]. A major concern regarding the use of HD-BuMel and TLI has been the additional pulmonary toxicity, and this has limited any more extensive use of this combination in other cooperative studies [7, 8, 12]. The results of the ISG/SSG IV trial demonstrate the feasibility of combining HD-BuMel and TLI, but it should be noted that these treatments were provided only at a few referral centers (as stated in the ISG/SSG IV protocol), and pulmonary function was carefully assessed to identify patients ineligible for the addition of TLI.

The use of maintenance chemotherapy did not prevent radiotherapy being administered to the primary tumor site with an acceptable toxicity (mainly ileitis or cystitis). We previously reported, based on the ISG/SSG III study, on severe toxicity after combining radiotherapy to axial tumors with HD-BuMel, including two cases of radiation-induced colitis requiring partial colectomy and one case of transverse myelitis [15]. Complications due to the combination of HD-BuMel with radiotherapy at axial sites have also been reported by the French group within the ongoing European Ewing Tumour Working Initiative of National Groups, Euro-EWING-99 trial (the largest international cooperative trial ever conducted on EFT), which also includes—among others—the option of radiotherapy to the primary tumor site and HD-BuMel. Some fatal bowel obstructions were observed, prompting the decision to amend the trial so as to avoid HD-BuMel being given to patients who were candidates for radiotherapy to the pelvis according to the treatment plan [28, 29]. We speculate that the acceptable toxicity recorded in our ISG/SSG IV relates either to the smaller tumor volumes involved or to the chronological order and timing of radiotherapy: in our study, at least 10 weeks elapsed between the end of the radiotherapy to the primary site and HD-BuMel. The one case of fatal post-transplant toxicity and one of secondary leukemia in our series confirm the other reports in the literature on the considerable risks of late effects in the treatment of EFT [1, 8, 10, 27, 30–32]. Long-term follow-up is mandatory, moreover, because previous studies on Ewing's sarcoma have shown that late sequelae (including pulmonary dysfunction) are more common 5 years after its diagnosis [31, 33, 34, 35].

In the present study, a poor histological or radiological response at the primary tumor site and an incomplete remission of lung metastases after primary chemotherapy were the most important factors pointing to a poor prognosis. The present study is the first to document these results prospectively in metastatic patients. The histologically assessed chemotherapy-induced response to induction therapy in localized Ewing's sarcoma is a well-known parameter for distinguishing between patients with a good or poor prognosis [13, 15, 32, 36]. The prognostic impact of radiological evidence of the remission of lung metastases after chemotherapy found in our study differs from the results of a previous EICESS report, which showed no difference in outcome in a series of 114 patients with EFT and lung-only metastases [3]; patients in partial remission were analyzed together with those in complete remission in said latter study, however, and three consecutive protocols were applied during the study period [3]. The results of the ISG/SSG IV study suggest that patients without a good response at the primary tumor site and at metastatic level after primary chemotherapy are not suitable for continuing therapy with our intensive approach, while those patients with a good response could benefit from consolidation with HD-BuMel and TLI. We are well aware that this evidence needs to be considered with caution until it has been confirmed in larger, controlled prospective trials. In fact, the subgroup of patients who received the consolidation treatment was event free, and for this reason was favorably selected for a better outcome. Hopefully, the ongoing randomized Euro-EWING-99 trial comparing HD-BuMel versus conventional chemotherapy will shed light on the therapeutic role of myeloablative therapy and contribute to a more accurate identification of the prognostic factors in EFT metastasizing to the lung.

In summary, the results of the present study demonstrate that our intensive approach resulted in 5-year probability to survive for about half of the patients. The prognosis remains dismal for those who do not respond well to primary chemotherapy, and innovative therapies are needed to improve their outcome. Since the prevalence of EFT is low, a good way forward is to further intensify cooperative efforts and international collaboration.

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disclosure

The authors have declared no conflicts of interest.

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