Pediatr Blood Cancer 2014;61:1472–1475

BRIEF REPORT
Outcome of Ewing Sarcoma in a Multidisciplinary Setting in Lebanon

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Treatment of Ewing sarcoma (ES) necessitates coordinated multidisciplinary care. We analyzed outcome for 39 patients treated at a single institution in Lebanon, a developing country with available multidisciplinary treatment modalities, where financial barriers to care are overcome by a fundraising system. Median follow-up was 58 months. Five-year overall and event-free survival were 76% and 58%, respectively, for localized disease, and 40% and 38%, respectively, for metastatic disease. We conclude that, in a country with emerging economy, by following international protocols and ensuring availability of needed resources, outcome of patients with ES is similar to that in developed countries. Pediatr Blood Cancer 2014;61:1472–1475. © 2014 Wiley Periodicals, Inc.

Key words: Ewing sarcoma; pediatric; prognostic factors

INTRODUCTION

With recent therapy intensification for Ewing sarcoma (ES), patients in developed countries with localized disease have overall and event-free survival (EFS) estimates of 70–75% and 60–70%, respectively, while those with metastatic disease have overall survival (OS) and EFS rates of 30–35% and 20–22%, respectively [1–4]. Prognostic factors shown to be important in localized disease include age [5–11], primary tumor site [9,12,13], histologic response to chemotherapy [5,7,14], and tumor size [7,10,11,14]. Treatment outcome in developing countries has not been adequately described to date. We conducted a retrospective review to analyze outcome of patients with ES at a single tertiary healthcare center in Lebanon, a developing country with available multidisciplinary treatment modalities.

PATIENTS AND METHODS

Forty-two patients with ES treated at the American University of Beirut Medical Center (AUBMC) from January 1999 till October 2012, were identified via retrospective review. The following information was collected: age, sex, tumor site, tumor size, stage, treatment, complications, and outcome. This study was approved by the AUBMC Institutional Review Board. ES was diagnosed based on standard immunohistochemical profile; all 39 tumors had histopathologic features of small round blue cell tumors. Positive staining for CD99 was seen in 38 tumors, while 1 tumor was diagnosed in 1999, prior to routine CD99 staining. Local tumor extent was assessed by computed tomography (CT) or magnetic resonance imaging, depending on site. Metastatic work-up included CT of the chest, bone scan, and bilateral bone marrow biopsies. All patients received uniform chemotherapy as per POG9354/CCG7942 Regimen A [2,3], and after 2009, as per the COG AEWS0031 Regimen B protocol, which is interval compressed [4]. Each cycle was followed by granulocyte colony-stimulating factor (G-CSF) support, and Mesna was used for uroprotection. Definitive local control was attempted at weeks 12–15 of treatment, with surgery, radiation therapy, or combination. Radiation therapy doses used were as per guidelines of the POG9354/CCG7942 study, ranging between 45 and 55.8 Gy, given as 1.8 Gy per fraction for 5 days/week, by three-dimensional conformal technique.

OS was defined as the time interval from diagnosis to either death from any cause or last follow-up. EFS was defined as time to disease progression, relapse, or death from any cause, whichever occurred first, or to date of last follow-up. Kaplan–Meier curves were constructed for the different groups. The prognostic significance of various characteristics and the associated relative risk, and respective confidence intervals, were assessed in proportional-hazards regression model.

RESULTS

Thirty-nine patients had complete information available. Patient characteristics are summarized in Table I. Median follow-up was 58 months (range 13–121). The 5-year overall and EFS rates were both at 69% (Fig. 1A). Tumor recurrence was local in seven, distant in six, and combined in three patients.

The chemotherapy regimen was well tolerated. There were 76 episodes of febrile neutropenia in 21 patients, and 4 episodes of septic shock. One patient had a postoperative bleed after rib resection. Grade 2–3 mucositis occurred in seven patients. There were no toxic deaths, nor any secondary malignancies.

Notably, 17 patients (44%) had a delay in local control by more than 3 weeks (beyond week 15). Of the 12 patients who underwent

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Conflict of interest: Nothing to declare.

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Received 4 November 2013; Accepted 12 December 2013

DOI 10.1002/pbc.24926
Published online 7 January 2014 in Wiley Online Library (wileyonlinelibrary.com).

TABLE I. Patient Characteristics and Cox-Regression Hazards Analyses of Prognostic Variables

Variable/patient characteristics	Five-year overall survival			Five-year event-free survival		
	Hazard ratio	95% CI	*P*-Value	Hazard ratio	95% CI	*P*-Value
Gender						
Male (n = 21, 54%); female (n = 18, 46%)	0.721	0.185–2.812	0.638	0.477	0.152–1.502	0.206
Age						
<10 years (n = 16, 41%); >10 years (n = 23, 59%)	1.300	0.335–5.056	0.704	1.354	0.462–3.972	0.581
Tumor size						
<8 cm (n = 17, 44%); >8 cm (n = 22, 56%)	1.003	0.268–3.757	0.996	0.820	0.287–2.342	0.711
Site (extremity)						
Extremity (n = 14, 36%); other (n = 25, 64%)	0.176	0.022–1.392	0.100	0.082	0.011–0.672	0.016
Tumor stage (metastasis)						
Metastatic (n = 8, 21%); localized (n = 31, 79%)	4.037	1.073–15.181	0.039	2.490	0.849–7.300	0.096
Local control (surgery)						
Surgery ± radiation (n = 27, 69%); radiation alone (n = 12, 31%)	0.225	0.058–0.874	0.031	0.214	0.074–0.622	0.005
Delay in local control						
Beyond week 15 (n = 17, 44%); no delay (n = 22, 56%)	16.123	1.996–130.231	0.009	5.002	1.653–15.135	0.004

radiation alone, 8 had a delay ranging 4–6 weeks (median = 5 weeks). Of the 27 patients who underwent surgery and radiation, 7 had a delay ranging 4–9 weeks (median = 5 weeks). Reasons for delays in local control included delays in procurement of prosthesis (n = 3), scheduling delays (n = 5), delays in multidisciplinary discussions (n = 3), attempts at better chemoreduction (n = 2), and no documented reasons (n = 4).

Using univariate cox-regression hazard model, we analyzed the prognostic importance of age, gender, metastatic disease, tumor site, tumor size, type of local control, and delays in local control, with regard to OS and EFS. Results are shown in Table I. By both cox-regression hazard model and Kaplan–Meier survival estimates, adverse prognostic factors included metastatic disease for OS (Fig. 1B), nonextremity site for EFS (Fig. 1C), and for both OS and EFS, lack of surgical resection (Fig. 1D), and delay in local control (Fig. 1E). Age, gender, and tumor size were not prognostically important in this analysis.

DISCUSSION

This retrospective review shows that children with ES treated at a multidisciplinary cancer center in Lebanon have OS rates comparable to those reported in developed countries. Patients with localized disease had an estimated 5-year OS of 76%, while estimated 5-year EFS was 58%. For patients with metastatic disease, OS and EFS were 40% and 38%, respectively. Of note, the barriers to clinical care typically associated with developing countries, such as availability of multidisciplinary care and financial barriers, are overcome at the Children's Cancer Center of Lebanon due to its association with a large academic hospital, and with a fundraising body for coverage of treatment expenses.

Our analysis showed that metastatic disease was significantly associated with worse OS, but not with EFS. Previous larger reports have shown a prognostic effect of metastatic disease on both OS and EFS [9,11]. Thus, while OS was significantly affected by metastatic disease in our patients, the lack of significant effect on EFS may be due to the small number of patients. Also, patients with extremity tumors did very well, with a 5-year OS rate of 90%, while those with pelvic tumors did extremely poorly, with only one survivor among 6. Patients who underwent surgical resection of the tumor had better survival and disease-free rates, as compared to patients who underwent radiation therapy alone, similar to other reports [7,9,15].

The effect of timing of local control on outcome has not been thoroughly investigated to date. In our study, there were 17 patients (44%) who had a delay in local control beyond week 15 of chemotherapy. Those patients fared worse, with 5-year OS rate of 36%, while patients who had timely local control achieved a 5-year OS rate of 93% (*P*-value < 0.001). The 5-year EFS rates were also significantly different, at 38% and 69%, respectively (*P*-value 0.002). However, the delays in local control occurred mostly in patients who underwent radiation therapy alone (8 of 12 patients, or 67% of those undergoing radiation were delayed), compared to those who underwent surgery (7 of 27 patients, or 26% were delayed). Also, patients with metastatic disease were more likely to have delays in local control, as 6 of 8 patients with metastases had delay in local control (75%), compared to 11 of 31 patients with localized disease (35%). These results suggest that tumors that are deemed nonresectable, especially in the setting of metastatic disease, are more likely to have delays in local control.

Our study is limited by the small number of patients. However, we can conclude that, in a country with emerging economy, by following international protocols and ensuring availability of needed resources, outcome of patients with ES is similar to that in developed countries. Metastatic disease and lack of surgical resection portends a poorer OS, and extremity tumors seem to do better. Finally, delays in local control were associated with worse outcome; but most delays occurred in the nonsurgery group and those with metastatic disease. Larger studies are needed to further evaluate this possible association.

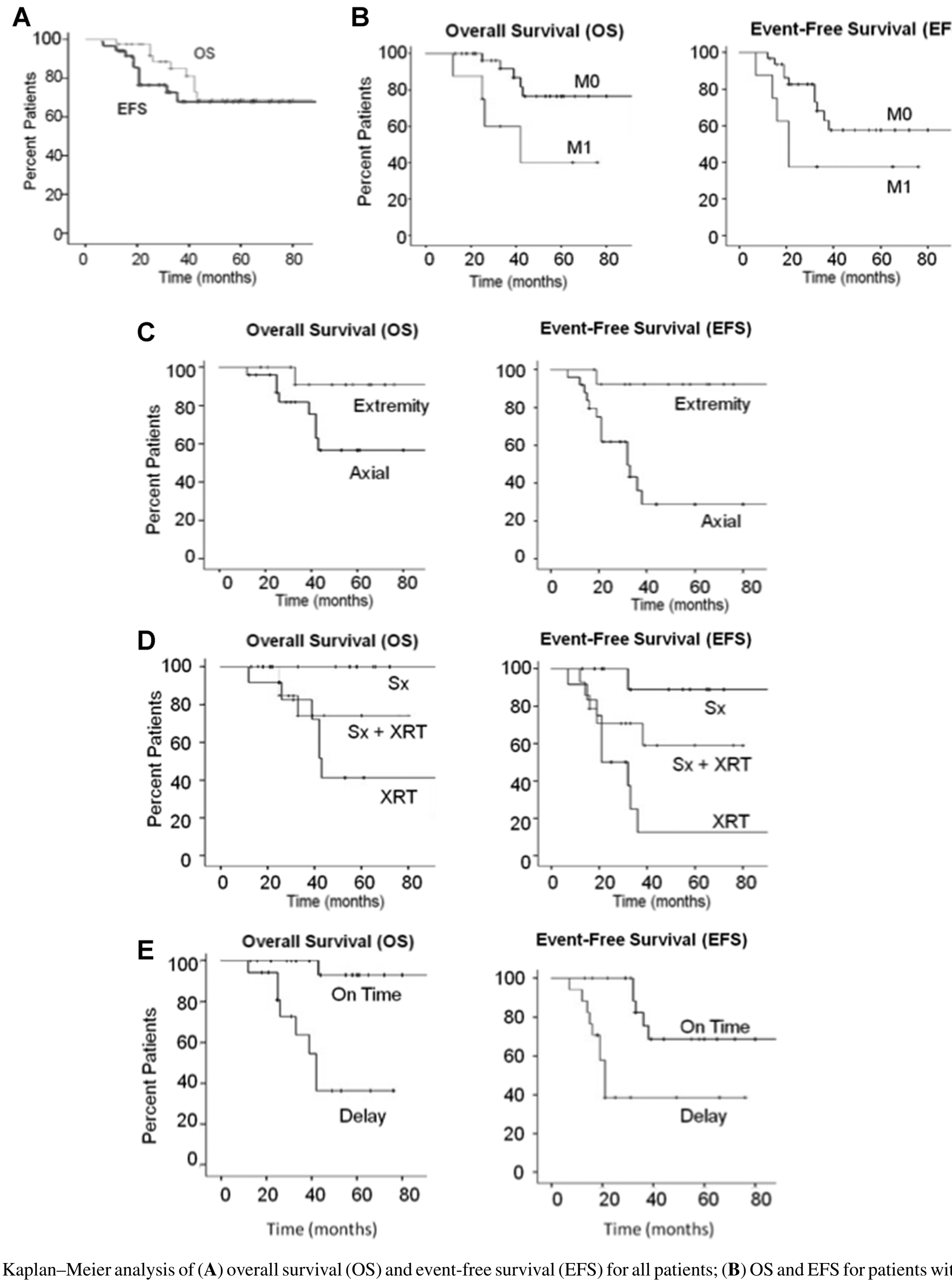

Fig. 1. Kaplan–Meier analysis of (**A**) overall survival (OS) and event-free survival (EFS) for all patients; (**B**) OS and EFS for patients with localized (M0) and metastatic (M1) disease, as indicated; P-value = 0.024 and 0.081, respectively; (**C**) OS and EFS for patients with extremity and axial tumor sites, as indicated; P-value = 0.061 and 0.002, respectively; (**D**) OS and EFS according to local control modality (surgery (Sx), radiation therapy (XRT), or both (Sx + XRT)) as indicated; P-value = 0.025 and 0.003, respectively; (**E**) OS and EFS by timing of local control (on time or delayed) as indicated; P-value < 0.001 and 0.002, respectively.

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