Published in final edited form as:
Pediatr Blood Cancer. 2013 April ; 60(4): 611–615. doi:10.1002/pbc.24251.

Clinical features and outcomes in patients with secondary Ewing sarcoma

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Abstract

Background—Ewing sarcoma (EWS) is rarely diagnosed as a second malignancy. We sought to describe a cohort of patients with secondary EWS and investigate if patient characteristics and survival differ between patients with secondary and primary EWS.

Procedure—Patients with EWS or peripheral primitive neuroectodermal tumor (PNET) reported to the SEER database from 1973 to 2008 were evaluated based on primary or secondary tumor sequence. Overall survival was estimated by Kaplan-Meier methods and evaluated using the log-rank test. Competing risk analysis was used to describe risk of death due to malignancy rather than other causes.

Results—58 cases of secondary EWS were reported, accounting for 2.1% of all EWS cases. The median latency from primary malignancy to secondary EWS was 64 months (range 1–282 months). 12.1% of patients with secondary EWS received radiation to the site of secondary tumor during therapy for their primary malignancy. Patients with secondary EWS were more likely to have axial tumors (77.4% vs. 62.5%; $p = 0.03$) and smaller tumors (75.0% vs. 48.2% < 8 cm; $p = 0.001$). Five-year overall survival from diagnosis was inferior for patients with secondary compared to primary EWS (34.3% vs. 52.2%; $p = 0.002$). However, patients with secondary tumors were less likely than those with primary EWS to die from their malignancy (hazard ratio 0.44; 95% CI 0.23–0.85).

Conclusions—Secondary EWS accounts for a minority of cases of EWS. Tumor size and site and patient survival differ among patients with primary and secondary EWS.

Introduction

Ewing sarcoma (EWS) is an aggressive malignancy of bone and soft tissues with a peak incidence in adolescence. Due to more intensive treatment protocols used, patients with EWS are at higher cumulative risk of developing secondary malignancies compared to most other cancers of children and young adults [1–4]. Rarely, EWS itself is diagnosed as a secondary malignancy [5–7]. To date, there has been only one study attempting to characterize these tumors using a cohort of six patients from a single institution [8].

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Disclaimers/Disclosures: None

Given this scarcity of previous data, it is uncertain if the clinical characteristics and survival differ for patients with secondary EWS compared to those with primary EWS. We hypothesized that patients with secondary EWS might have different baseline tumor characteristics at time of diagnosis and different outcomes compared to patients with primary EWS. Using data from the Surveillance, Epidemiology and End Results Program (SEER), we examined this hypothesis in a cohort of patients diagnosed with Ewing sarcoma as a secondary malignancy.

Methods

Patients and Variables

We gathered patient information from the US National Cancer Institute's SEER 17 database, which included data from 1973–2008. The SEER system is used in regions that represent ~26% of the US population. The SEER program provides data on cancer incidence, patient demographics, primary tumor site, tumor morphology, stage at diagnosis, limited treatment data, and survival data.

All patients with histologically confirmed Ewing sarcoma, Askin tumor, or peripheral primitive neuroectodermal tumor (PNET) arising outside the brain were eligible for the study. While the peak incidence of EWS is in adolescence, we chose to evaluate all ages in order to obtain as many cases of secondary EWS as possible. From 1973–2008, the SEER database included 2,814 cases of Ewing sarcoma or PNET.

Classification as primary or secondary EWS was determined using the sequence number field in SEER. Tumor sequence was verified for all secondary tumors using the record number and sequence number recode fields. Five patients were diagnosed with EWS concurrent with another tumor. Of these, three patients were categorized in SEER as primary EWS and two patients were categorized as secondary EWS in SEER based on severity of disease being less than the other concurrent tumor. As all five cases were noted concurrently with another malignancy, they were analyzed in the primary EWS group for the purposes of this analysis. Cause of death was determined using the SEER cause-specific death classification and SEER other cause of death classification fields, which denote if a patient died from their malignancy or from another, unspecified cause. These are based on ICD-8, ICD-9, and ICD-10 codes entered into the SEER database.

Patient characteristics and clinical presentation were evaluated according to diagnosis of primary or secondary EWS. Predictor variables of interest included: sex; stage (metastatic vs. localized); age (analyzed as a continuous variable); year of diagnosis (in sequential 5-year blocks); race (white vs. non-white); histology (PNET vs. Ewing sarcoma); tissue origin (skeletal vs. extraskeletal); primary tumor site (axial vs. appendicular and also pelvic vs. non-pelvic); and tumor size (< 8 vs. ≥ 8 cm in maximal dimension). Anatomic site codes were classified according to the ICD-O coding scheme. Patients were classified as extraskeletal or skeletal Ewing sarcoma based on ICD-10-CM coding used by the SEER database as previously reported [9].

Data on treatment received were also collected. Data regarding the use of surgery were dichotomized as performed or not performed (including biopsy, curative and palliative procedures). For analysis related to use of surgery, patients were excluded if they had missing data for surgery (n=94). Radiation therapy (including radioactive implants and radioisotopes) was dichotomized as given or not given if delivered to any tumor site (primary and/or metastatic) at any time point during treatment for either previous cancer or for EWS. For analysis related to use of radiation, patients were excluded if they had missing data for radiation (n=82). A patient was determined to have secondary EWS at the site of

prior radiation if it arose from the same location as their primary tumor and the patient had received radiation for that tumor. Other treatment details, including the use of chemotherapy, were not available.

Statistical Methods

Patient and tumor categorical characteristics were evaluated for differences between patients with primary vs. secondary EWS using the Fisher exact test. A two-sample t-test was used to compare patient age between groups.

Overall survival from the time of diagnosis was estimated by Kaplan-Meier methods and potential differences between patients with primary and secondary EWS were evaluated using the log-rank test. Overall survival was expressed as Kaplan-Meier estimates with 95% confidence interval (CI). The median follow-up time for the analyzed cohort was 73 months. A univariate competing risk regression was used to determine the hazard ratio (with 95% CI) for death due to cancer, rather than other causes, in patients with secondary EWS relative to patients with primary EWS [10]. Multivariate competing risk regression was then used to assess these findings while controlling for other known prognostic factors.

The SEER database was accessed using SEER*Stat version 7.0.5. All statistical analyses were performed using SAS, version 9 and STATA, version 11.

Results

Patient Characteristics

Of the 2,814 patients in the analytic cohort, 58 (2.1%) had secondary EWS and 2,756 (97.9%) had primary EWS. The clinical characteristics of patients with secondary EWS are shown in Table I. Secondary EWS occurred following a heterogeneous group of primary malignancies, though the majority of cases occurred after a primary carcinoma or hematologic malignancy. Only 7 patients (12.1%) with secondary EWS had received radiation to the site of recurrence for their primary malignancy. The median latency from diagnosis of primary malignancy to diagnosis with secondary EWS was 64 months (range 1–282 months). Only four patients with secondary EWS were diagnosed prior to 1994.

Significant differences in clinical presentation were noted between patients with primary and secondary EWS (Table II). As expected, patients with secondary EWS were older than patients with primary EWS (median age 47.8 years vs. 22.5 years; $p < 0.001$). Patients with secondary EWS were more likely to have extraskeletal tumors (56.4% vs. 36.5%; $p = 0.004$) and axial primary tumor locations (77.4% vs. 62.5%; $p = 0.03$) compared to patients with primary EWS. Other key differences were that patients with secondary EWS were more likely to be female (60.3% vs. 40.1%; $p = 0.003$) and have smaller tumors (75.0% vs. 48.2% less than 8 cm in maximal diameter; $p = 0.001$) compared to patients with primary EWS. There were no statistically significant differences in race, stage or proportion with pelvic primary tumors between patients with primary and secondary EWS.

Use of Radiotherapy and Surgery

Radiation therapy was used for treatment of EWS in 49.9% of all patients. Radiation use did not differ between patients with secondary EWS compared to those with primary EWS (38.1% vs. 50.1%, respectively; $p = 0.10$). Similarly, there was no difference in patients who had any form of surgery in patients with secondary EWS compared to those with primary EWS (65.5% vs. 59.6%, respectively; $p = 0.41$).

Patient Outcomes

Overall survival was inferior for patients with secondary EWS compared to patients with primary EWS (Figure 1). In patients with secondary EWS, the 5-year estimates of overall survival were 34.3% (95% CI 20.4–48.7%) compared to 52.2% (95% CI 50.1–54.2%) for patients with primary EWS ($p = 0.002$). Five-year estimated overall survival for patients diagnosed prior to 1993 with secondary EWS was 0% compared to 46.1% (95% CI 42.5–49.7%) for patients with primary EWS ($p < 0.001$). For those diagnosed after 1993, five-year estimated overall survival was 37.6% (95% CI 22.5–52.6%) for patients with secondary EWS compared to 55.3% (95% CI 52.8–57.8%) for patients with primary EWS ($p = 0.008$).

The negative impact of secondary EWS on overall survival was also seen in the subset of patients with localized disease. Five-year estimates of overall survival for patients without metastasis with secondary EWS were 43.5% (95% CI 24.9–60.7%) compared to 64.2% (95% CI 61.6–66.6%) for patients with primary EWS ($p = 0.003$). In the cohort of patients with distant metastasis at initial diagnosis, outcomes did not differ between patients with primary and secondary EWS.

Our finding that patients with secondary EWS are significantly older than patients with primary EWS is not surprising. These older patients are therefore at higher risk for competing causes of mortality due to other co-morbidities, including late effects of treatment for their primary malignancy. As such, we sought to determine if the increased mortality seen in patients with secondary EWS was cancer-related mortality or from other causes. The cumulative incidence of death due to cancer for patients with secondary EWS and for patients with primary EWS is shown in Figure 2. We utilized competing risk regression to evaluate the risk of death specifically due to malignancy. A univariate analysis controlling only for primary vs. secondary EWS showed that patients with secondary EWS were less likely than those with primary EWS to die from causes related to their malignancy (hazard ratio 0.44; 95% CI 0.23–0.85).

We then constructed a multivariate competing risk regression model to evaluate this finding while also controlling for clinical characteristics that differed between patients with primary vs. secondary EWS from Table II. Initial covariates in the model included sex, age at diagnosis, year of diagnosis (evaluated as before or after 1993), histology, tumor origin (skeletal vs. soft tissue), and tumor location. Tumor origin and histology did not reach statistical significance at the $p < 0.05$ level and were removed from the model. Our final regression model again demonstrated that patients with secondary EWS were less likely than those with primary EWS to die from causes related to their malignancy (hazard ratio 0.31; 95% CI 0.16–0.60). A sensitivity analysis was then performed in the 53.3% of patients with known tumor size data and yielded similar results when tumor size was added to the model.

Discussion

In this study, we observed that secondary EWS accounts for a small minority of cases of EWS. We also found significant differences in patient and tumor characteristics between patients with primary and secondary EWS. We observed that patients with secondary EWS had inferior overall survival compared to patients with primary EWS but are less likely to die from their cancer.

We described the largest cohort of secondary EWS published to date. Not surprisingly, patients with secondary EWS were older than those with primary tumors. Despite this, 31% of secondary tumors were seen in patients 30 years and younger. The median latency of 64 months emphasizes the need for close monitoring in the first five years after diagnosis of a primary malignancy [11,12]. While only four patients were diagnosed with secondary EWS

prior to 1994, we feel this is likely due to an increase in reporting to the tumor registry in recent years rather than a true change in incidence. In addition, only a minority of secondary EWS arose from a site that had received radiation for a primary malignancy, a finding consistent with prior results [8]. Unfortunately, our data do not provide direct information regarding etiology of secondary EWS. It remains unclear to what extent previous treatment or genetic predisposition contributed to the development of these cases, or whether these cases of secondary EWS are chance occurrences [2,13]. The heterogeneous histologies of the primary malignancies that preceded these cases of secondary EWS suggest that a specific genetic predisposition may not account for development of secondary EWS.

There are important differences demonstrated between patients with primary and secondary EWS. Those with secondary malignancies were more likely to be female, have extraskeletal and axial locations, and have histological classification as PNET. The findings of increased rates of axial tumors and PNET histology in patients with secondary EWS are consistent with previous results showing that extraskeletal tumors are more likely to be coded with these characteristics in the SEER database [9]. Not surprisingly, secondary EWS was also more likely to be diagnosed more recently. Patients with secondary EWS also had smaller tumors. We suspect this difference in size may be due to more frequent medical screening and increased vigilance by patients with a previous malignancy resulting in earlier diagnosis of secondary EWS compared to primary EWS.

The current study provides evidence that patients with secondary EWS have inferior outcomes. Interestingly, while patients with secondary EWS are more likely to die, they are less likely to do so because of their malignancy. While we can not account for other factors not recorded in the SEER registry, there are several explanations that may account for this observation. Patients with secondary EWS were older and therefore may have other life-threatening co-morbidities that result in increased mortality during treatment for their secondary malignancy [14,15]. If patients with secondary EWS are being diagnosed earlier in the disease process, as our size data suggest, it may be that treatment is more likely to be curative for these smaller tumors and thus decrease tumor related mortality. Finally, patients with secondary EWS needed to survive treatment for their primary malignancy. Having survived this previous treatment may result in a “healthy survivor” selection bias, in which only patients less likely to succumb to cancer-related causes of death, including toxic death, survive to develop a second malignancy. There may also be other biologic or treatment differences that account for this set of observations. Unfortunately, additional biological and treatment data, including chemotherapeutic regimen used, are not available from the SEER database and these possibilities cannot be further elucidated by the current study.

We have confirmed that secondary Ewing sarcoma is rare. In order to study this subset of patients, we utilized the SEER database to evaluate the largest group of secondary EWS patients to date. However, there are several limitations to analyzing data from a tumor registry, all of which necessitate further evaluation to verify our results. We were limited to the available data in the registry. As such, we were unable to report on important variables, such as amount and exact location of previous radiation used, extent of surgery, or chemotherapy regimen utilized for treatment of the primary or secondary malignancy. We could not confirm the exact location of radiation given for a primary tumor for those patients with secondary EWS. Thus, we could not verify that the secondary EWS did or did not reoccur at the site of radiation. We were also unable to confirm that the reported cases of EWS met current diagnostic standards for this disease, nor were we able to evaluate *EWSR1* translocation status for these tumors. In addition, due to our small sample size, we were unable to assess the independent prognostic impact of secondary vs. primary EWS by controlling for important known prognostic factors such as metastatic status, size, site and age [16–18]. We note that the incidence of metastatic disease was similar in both groups and

our stratified analysis showed differential survival for patients with secondary EWS compared to primary EWS among patients with localized disease.

Based on our findings, we conclude that there are significant differences in clinical presentation and outcomes for patients with primary and secondary Ewing sarcoma. Our findings suggest that patients with secondary EWS represent a unique subset of this disease and special attention should be placed on minimizing co-morbidities from both tumor and its treatment. Additional efforts should be directed at verifying our findings and subsequently determining the etiology of these cases of secondary Ewing sarcoma.

Acknowledgments

Support: Supported by the Campini Foundation and NIH/NCI 1K23CA154530-01. The contents are solely the responsibility of the authors and do not necessarily represent the

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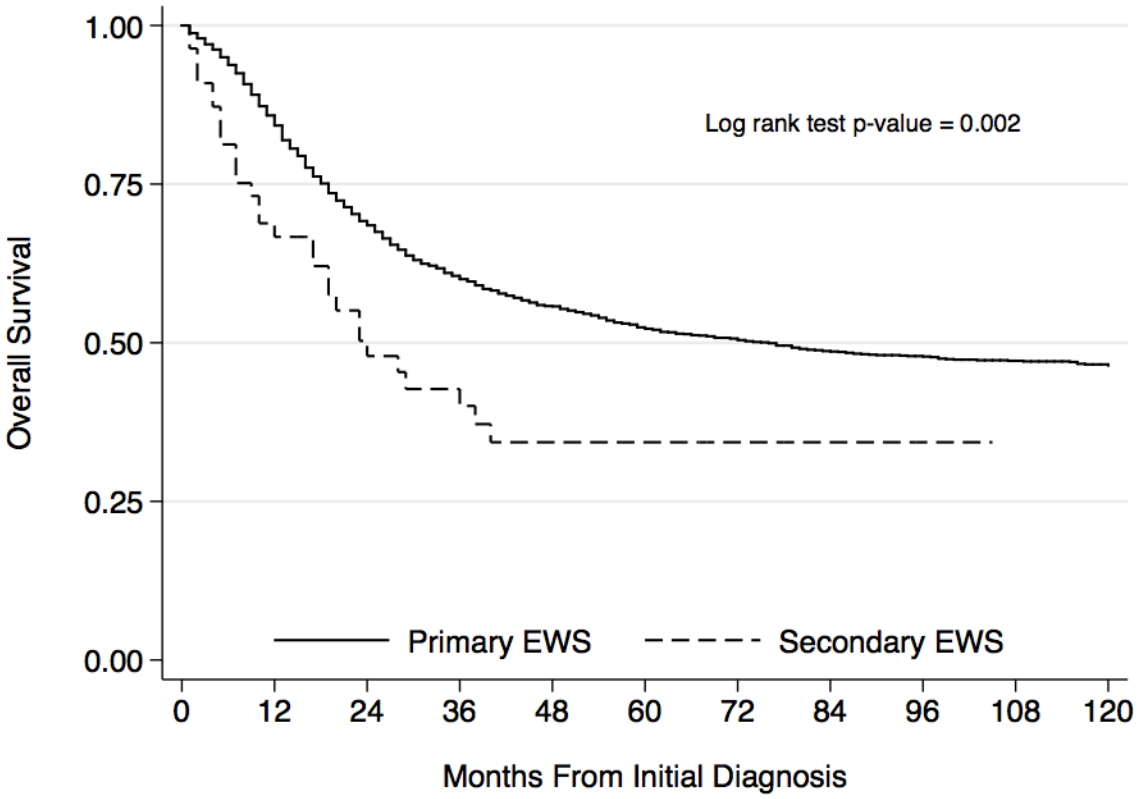

Figure 1.
Kaplan-Meier estimates of overall survival from time of diagnosis according to primary or secondary Ewing sarcoma.

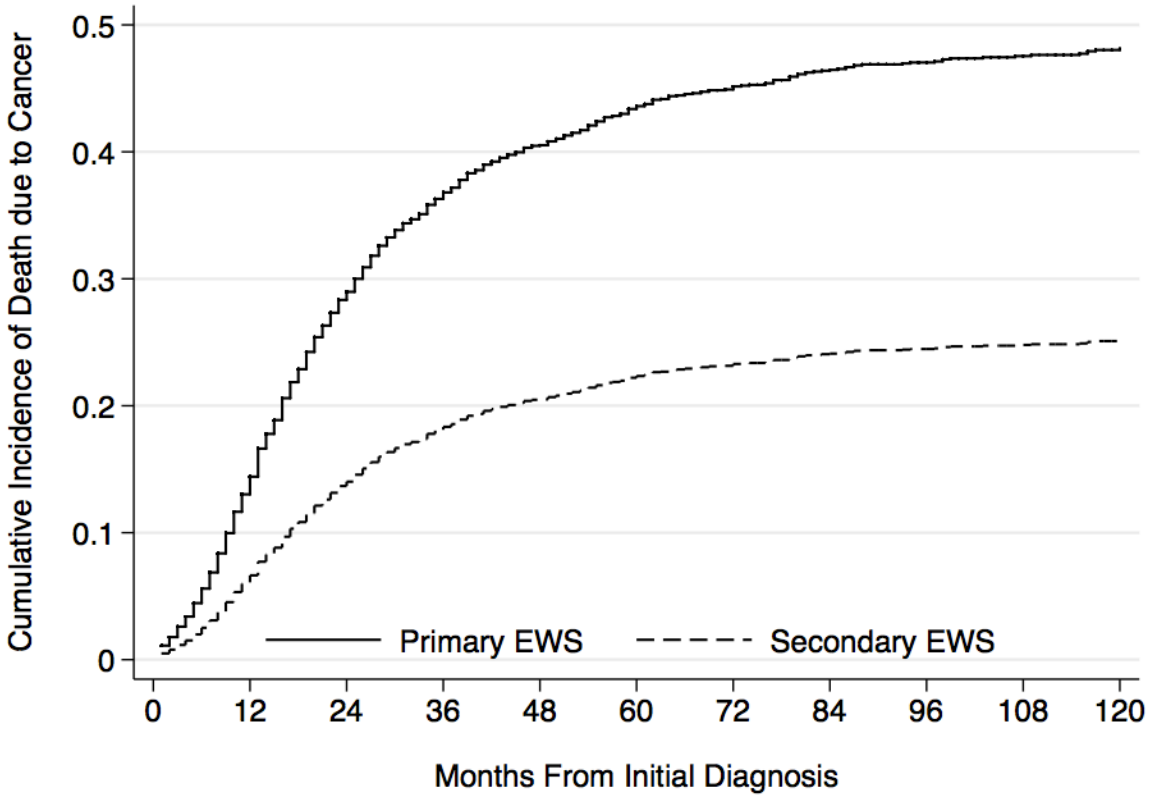

Figure 2.
Cumulative incidence of death due to cancer from time of diagnosis according to primary or secondary Ewing sarcoma.

Table I

Characteristics of 58 patients with Ewing sarcoma reported as a second malignancy.

Characteristic	n = 58
Median Age at Ewing Sarcoma Diagnosis (Range)	48 years (4–85 years)
Median Latency from Primary Cancer (Range)	64 months (1–282 months)
Stage of Primary Cancer	
Distant Metastasis	14 (24.1%)
No Distant Metastasis	34 (58.6%)
Unknown	10 (17.3%)
Histology of Primary Cancer	
Carcinoma	24 (41.4%)
Hematologic Malignancy	14 (24.1%)
Sarcoma	5 (8.6%)
Melanoma	4 (6.9%)
Skin Cancer, Non-melanoma	2 (3.5%)
Brain Tumor	2 (3.5%)
Other / Unknown	7 (12.1%)
Radiation for Primary Cancer	
Not Received	34 (58.6%)
Received	22 (37.9%)
Unknown	2 (3.5%)
Prior Radiation at Site of Secondary Ewing Sarcoma	
No Radiation	34 (58.6%)
Radiation to Site of Secondary Ewing Sarcoma	7 (12.1%)
Radiation to Other Site	10 (17.2%)
Unknown	7 (12.1%)
Previous Surgery for Primary Cancer	
Performed	36 (62.1%)
Not Performed	21 (36.2%)
Unknown	1 (1.7%)

Table II

Characteristics of 58 patients with secondary Ewing sarcoma compared with 2756 patients with primary Ewing sarcoma.

Characteristic	Secondary Ewing Sarcoma n = 58 (2.1%)	Primary Ewing Sarcoma n = 2756 (97.9%)	p-value
Median age	47.8 years	22.5 years	<0.001
Range	4–85 years	0–92 yeas	
Male	39.7%	59.9%	0.003
Race			
White	87.9%	89.5%	
Non-White	12.1%	10.5%	0.80
Stage[a]			
Distant Metastasis	24.0%	32.0%	
No Distant Metastasis	76.0%	68.0%	0.28
Histology			
PNET	51.7%	27.7%	
Ewing sarcoma	48.3%	72.3%	0.001
Tissue Origin			
Skeletal	43.6%	63.5%	
Extraskeletal	56.4%	36.5%	0.004
Primary Site			
Axial	77.4%	62.5%	
Non-axial	22.6%	37.5%	0.03
Pelvic	20.8%	23.7%	
Non-pelvic	79.2%	76.3%	0.74
Size[b]			
≥8cm	25.0%	51.8%	0.001
Year of Diagnosis			
1973–1978	1.7%	5.7%	0.014
1979–1983	0.0%	6.1%	
1984–1988	1.7%	6.2%	
1989–1993	3.5%	9.5%	
1994–1998	20.7%	14.3%	
1999–2003	25.9%	28.0%	
2004–2008	46.6%	30.3%	

[a] Based on stage data available for 86.2% of secondary tumors and 90.6% of primary tumors.

[b] Based on size data available for 68.9% of secondary tumors and 52.9% of primary