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Prognostic Factors for Patients with Ewing sarcoma (EWS) at First Recurrence Following Multimodality Therapy – A Report from the Children's Oncology Group

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Abstract

Background—The prognosis for patients with recurrent Ewing sarcoma is very poor with 5-year survival of 13%.

Methods—To evaluate prognostic factors for these patients we studied patients initially treated on the multi-institutional study INT0091.

Results—Two hundred and sixty-two patients experienced disease recurrence. The median time to first recurrence was 1.3 years (0 to 7.4 years), 1.4 years (0 to 7.4 years) for patients with initially localized disease and 1 year (0 to 6 years) for patients with initially metastatic disease. Time to first recurrence from date of initial diagnosis was a predictor of post-recurrence survival ($p<0.0001$). Twenty-one percent of patients, with recurrent or progressive disease ≥ 2 years from initial diagnosis, had an estimated 5 year survival of 30% (vs. 7% estimated 5 year survival with an earlier recurrence). No statistical difference was detected between patients whose disease recurred < 1 year and between 1–2 years from initial diagnosis. A stepwise relative risk model and backwards stepwise regression was used to explore factors significantly associated with risk for post-recurrence death. Significant risk factors for death after recurrence included recurrence at

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combined local and distant sites, elevated LDH at initial diagnosis and initial recurrence less than two years after diagnosis. Isolated pulmonary recurrence was not predictive of survival after recurrence.

Conclusion—Patients with a longer disease control interval represent the subset of patients most likely to survive following recurrence of Ewing sarcoma. All patients with recurrence would benefit from collaborative trials to investigate new therapeutic options.

Introduction

Ewing sarcoma (EWS), the second most common malignant bone tumor in children, accounts for 200 new cases of cancer per year in the US in patients < 20 years1. Multidisciplinary therapy, comprising local control with surgery, radiation or a combination of both, as well as the use of systemic chemotherapy, improved the event-free survival to 69%, with an overall survival of 72%, for patients with localized disease treated on the North American inter-group study INT 0091 2. Unfortunately the outcome for patients with initially metastatic disease remains poor, with event free survivals of only 28% in recent series 3. The outlook for patients with recurrent Ewing sarcoma is even worse. Thirty to 40% of patients with initially localized EWS develop recurrent disease 2;4–6 and patients with recurrence have a reported 5 year survival of 13% 7.

To evaluate prognostic factors in patients with recurrent disease, the Children's Oncology Group examined data from the phase III, multi-institutional study INT 0091, which accrued patients with Ewing sarcoma between 1988 and 1994. Diagnostic features of age, tumor stage, tumor site, tumor size, and serum LDH are all associated with risk of first recurrence for patients with EWS. These factors plus features at recurrence such as time to first recurrence, site of recurrence and whether patients were on therapy at the time of first recurrence were examined.

Methods

Patients

Between 1988 and 1992, 530 patients were enrolled onto the cooperative group study INT 0091, 518 of whom were eligible for analysis 2;8. Between 1992 and 1994, 60 further patients with initially metastatic Ewing sarcoma were non-randomly assigned to receive intensive therapy (Regimen C). Therefore 578 eligible patients were enrolled onto INT0091. Eligibility criteria included previously untreated Ewing sarcoma or PNET of bone, age <30 years of age. The protocol was approved by the institutional review boards at all participating centers and all patients or their guardians gave written informed consent to participate according to institutional and National Cancer Institute guidelines. The study design for INT0091 has been described in prior publications 2;3. At study entry all patients were assigned randomly to receive standard therapy (Regimen A) or experimental therapy (regimen B). Patients were stratified into groups based on the presence or absence of metastasis at diagnosis. After interim analysis it was determined that accrual would allow analysis of patients with localized disease alone. Enrollment was extended to provide sufficient power to address the study question in patients with initially localized disease. After completion of the revised enrollment requirements for patients with initially localized disease, the study was amended to allow piloting of intensive therapy only for patients with disease metastatic at diagnosis (Regimen C). Local control modality was left to the treating physician discretion although radiation was not recommended for patients with complete tumor resection.

Statistical analysis

Outcome current to 31st August, 2000 is represented in this analysis. Survival was taken to be the time from disease progression or recurrence ('recurrence') to death or last patient contact. Any patient, who died, regardless of cause, was considered to have experienced an event; in all other cases, the individual was censored at last contact. Comparisons of the risk for death across groups defined by treatment assignment or patient characteristic were accomplished using the log-rank test 9. Survival was estimated by the method of Kaplan and Meier 9. The standard errors of the Kaplan-Meier estimates were calculated according to the method of Greenwood 9. Factors identified as significantly prognostic for post-recurrence survival as single variables ($p \leq 0.05$) were considered in a backward stepwise relative risk regression model to explore the independent relationships between these factors and risk for post-recurrence death 9.

Patients whose disease was not metastatic at diagnosis were randomly assigned to receive regimen A or B as primary therapy. In contrast to this, a subset of patients with newly-diagnosed metastatic disease was assigned to receive regimen C. In order to avoid confounding the analysis of the prognostic association of initial treatment assignment on outcome subsequent to relapse with initial extent of disease, this analysis was restricted to patients with disease that was not metastatic at diagnosis. Similarly, the timing for local control was fully specified only for patients with disease that was not metastatic at initial diagnosis. The analysis of the prognostic association between local control measures employed and outcome was restricted to that patient group. Assigned regimen was not considered in the multivariate model because assignment to regimen C was restricted to patients with extensive metastatic disease

Results

Clinical features of patients with recurrent Ewing sarcoma

Two hundred and sixty-two patients initially enrolled onto INT 0091 for treatment of Ewing sarcoma and eligible for analysis experienced disease recurrence as their first analytic event. Clinical characteristics at the time of initial diagnosis for patients with recurrent disease are summarized in Table I. INT 0091 therapy assignments for patients with recurrent disease were regimen A (n=130, 49%), regimen B (n=99, 38%) and regimen C (n=33 patients, 13%). Among patients who experienced recurrence, 21% of patients experienced first recurrence 2 or more years from initial diagnosis while 79% were within 2 years of initial diagnosis. The median time to first recurrence for patients with localized disease at diagnosis was 1.4 years (range 0 to 7.4 years) and for patients with disease metastatic at diagnosis was 1 year (range 0 to 6 years). The median time to first recurrence for patients with localized disease by initial treatment regimen was 1.4 years and 2.1 years for Regimen A and B respectively, (p=0.006). Thirty percent of patients had disease that recurred in the lungs, but only 17% had isolated pulmonary recurrence. Initial local control was considered only for patients with initially localized disease, 28% of whom had surgery, 42% had radiation while 30% had both surgery and radiation. The median follow-up after recurrence for those patients who had not died by the date of last follow-up was 7.3 years. The median survival time from first recurrence was 9 months for all patients, with an estimated 12% 5 year survival from first recurrence (95% confidence interval: 8.0%–16%; Figure 1).

Predictive factors for survival after recurrence

Time to first recurrence was the most significant predictor of post-recurrence survival ($p<0.0001$) (Figure 2). Estimated 5 year survival was 30% (95% confidence interval: 17%–43%) for those whose disease recurred 2 or more years from initial diagnosis vs. 7% (95% confidence interval: 3.7%–11%) for those whose disease recurred earlier. Patients who

experienced recurrence 2 or more years from initial diagnosis had a median survival of 23 months, patients whose disease recurred between 1–2 years following diagnosis had a median survival of 10 months, while those with recurrent disease less than 12 months from diagnosis had a median survival of only 5 months. No significant difference was noted for survival between those whose disease recurred within the first year when compared with those whose disease recurred between 12 and 24 months from initial diagnosis. Patients with disease metastatic at initial diagnosis, females, and those with elevated LDH at diagnosis had a significantly worse post-recurrence survival, as did patients whose site of first recurrence included both local and distant sites of metastases (Table II). Age at diagnosis, age at recurrence (data not shown), tumor size at diagnosis and pulmonary recurrence were not predictive of post-recurrence survival. The median post recurrence survival for patients with isolated pulmonary recurrence was 17 months compared with 9 months for patients who had recurrences that had, as a component, some site other than the lung ($p = 0.08$). Of the factors significantly related to risk for post recurrence death, only time from diagnosis to first recurrence, extent of disease at first recurrence and LDH at diagnosis were independently prognostic of risk for death (Table III).

Discussion

The post-recurrence survival in patients with Ewing sarcoma is dismal. We demonstrated that certain clinical features identified at the time of diagnosis were significantly related to the risk for death after initial recurrence. We also confirmed the importance of time to recurrence as a prognostic factor for post-recurrence survival.

In agreement with previous reports, time to first recurrence was the most significant predictor for post-recurrence survival for patients treated with INT0091 [5–7;10;11]. However, certain differences exist between our data and other reported series. Time to first recurrence for patients with initially localized disease was significantly associated with the initial treatment regimen (2.1 vs. 1.4 years), consistent with the improved efficacy of the experimental regimen B as compared with regimen A [2;12]. The patient population described here included 46% patients with disease metastatic at initial diagnosis. The groups described by Rodriguez-Galindo et al. 10, Barker et al. 11 and McTiernan et al. 6 included patients with metastases at initial diagnosis (42%, 38% and 47% respectively) while other reports of survival in patients post-recurrence did not include patients with initially metastatic disease [5;7] .We report that only 21% of patients were 2 or more years from initial diagnosis, fewer than in prior reports (29% 11 and 44% 10). The patients reported here were all treated on a single prospective multi-institutional randomized study over a 6 year period. Although Shankar et al. 5 also reported data from a single multi-institutional trial (ET-2 UKCCSG), other reports describe outcome from single institutions for patients with recurrent Ewing sarcoma initially diagnosed over an 18 year period or treated with at least 3 protocols. Interestingly, although ET-2 was open only to patients with initially localized disease, the overall median post-recurrence survival is similar in patients treated on INT0091 and ET-2 UKCCSG (9 months and 14 months respectively). The 5 year overall survival for patients treated on INT0091 was 12%, quite different from the predicted survival reported by Barker et al. (23%) 11. No detailed data on post-recurrence therapy was collected on INT0091. Therefore, while previous reports suggest either a benefit for high-dose therapy [6;11] or pulmonary radiation 10 for patients at first recurrence, we cannot examine the components of post-recurrence therapy that could have impacted outcome and therefore can only provide information on prognostic factors but cannot comment on the role of post-recurrence therapy.

We have documented that several prognostic indicators at initial diagnosis continue to have prognostic significance in multivariate analysis with post-recurrence survival. In our study,

patient gender and stage at initial diagnosis were prognostic for post-recurrence survival as previously reported in studies by Shankar et al. 5 and Rodriguez-Galindo et al. 10. We have also demonstrated an inferior outcome for patients with elevated LDH at diagnosis.

We did not find a statistically significant post-recurrence survival advantage for patients with an isolated pulmonary recurrence. This is in contrast to the survival advantage reported by Bacci et al. 7 and McTiernan et al. 6 for patients who had lung only recurrence. However recurrence at both distant and local sites was associated with an inferior outcome, in agreement with prior reports. We conclude that all patients with recurrent Ewing sarcoma would benefit from collaborative trials to improve post-recurrence survival. A subset of patients with longer time to first recurrence, initially localized disease and a normal LDH at diagnosis, represent the patients most likely to survive.

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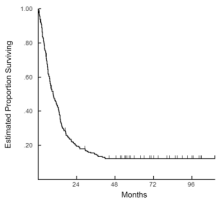

Figure 1.
Survival curve for all patients treated on INT0091 who developed recurrence as the first analytic event.

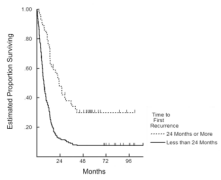

Figure 2.
Survival curve for all patients by time to first recurrence from initial diagnosis.

Table I

Clinical Characteristics for the 262 patients with Recurrent Ewing Sarcoma

Clinical criteria		No. of patients	% of Patients
Age at diagnosis (years)			
	<9	55	21
	10–17	155	59
	≥18	52	20
Gender			
	Female	103	39
	Male	159	61
Initial stage			
	Localized	142	54
	Metastatic	120	46
Primary site (non-metastatic only)			
	Extremity	56	21
	Pelvic	46	18
	Skeletal (not extremity, not pelvic)	40	15
LDH (IU/L) at initial diagnosis			
	≤ 250	86	35
	251+	161	65
Maximum dimension of primary tumor at diagnosis			
	≤ 7 cm	49	23
	8+ cm	167	77
INT0091 regimen			
	Regimen A	130	49
	Regimen B	99	38
	Regimen C	33	13
Time to recurrence (time from initial diagnosis)			
	< 1 year	103	39
	1–2 years	105	40
	> 2 years	54	21
Site of first recurrence (n=247)			
	Lung only	43	17
	Lung plus other sites	32	13
	Other sites	172	70
Extent of disease at recurrence (n=250)			
	Local Site Only	65	26
	Distant Site[1] Only	157	63
	Local Plus Distant Site[1]	28	11

Clinical criteria		**No. of patients**	**% of Patients**
Local control (n=122; patients with initially localized disease)			
	Surgery alone	34	28
	Radiation alone	51	42
	Surgery + Radiation	37	30

[1] Distant in this context is recurrence at a site not initially identified as involved by disease by patient staging at initial diagnosis.

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Table II

Probability of survival for Different Subsets of Patients with Recurrent Ewing Sarcoma

	Estimated Probability of Survival (Standard Error)			
	1 year	**2 year**	**3 year**	**P value**
Metastasis at diagnosis				
Yes (n=120)	34% (4.4%)	16% (3.5%)	12% (3.0%)	0.02
No (n=142)	49% (4.2%)	22% (3.5%)	16% (3.1%)	
Gender				
Male (n=159)	49% (4.0%)	21% (3.3%)	16% (2.9%)	0.05
Female (n=103)	32% (4.7%)	16% (3.7%)	12% (3.3%)	
LDH (IU/L)				
≤ 250 (n=86)	58% (5.3%)	28% (4.8%)	18% (4.2%)	0.0016
250+ (n=161)	34% (3.8%)	15% (2.9%)	12% (2.6%)	
Extent of Disease at Initial Relapse				
Local Site Only (n=65)	41% (6.1%)	19% (4.9%)	14% (4.4%)	<0.001
Distant[1] Site Only (n=157)	47% (4.0%)	22% (3.4%)	16% (3.0%)	
Local Plus Distant[1]	18%	-[2]	-[2]	

	Estimated Probability of Survival (Standard Error)			
	1 year	**2 year**	**3 year**	**P value**
Site (n=28)	(7.2%)			
Initial Randomized Treatment Assignment[3]				
Regimen A (n=84)	46%	19%	15%	0.42
Regimen B (n=58)	53%	25%	18%	
Local Control Modality[3]				
Surgery Only (n=34)	47%	18%	15%	0.86
Radiation Therapy Only (n=51)	55%	22%	17%	
Surgery plus Radiation Therapy (n=37)	54%	24%	13%	

[1] Distant in this context is recurrence at a site not initially identified as involved by disease by patient staging at initial diagnosis

[2] No patients in the category were at risk at this time point

[3] Analysis restricted to patients with non-metastatic disease at initial diagnosis.

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Table III

Prognostic factors significant in multivariate analysis for post recurrence outcome

Factor		Relative Risk	p-Value
Interval from Diagnosis to First Recurrence	0–23 Months	1.0	<0.001
	24+ Months	0.41	
Extent of Disease at First Recurrence	Local	1.0	0.021
	Distant	0.94	
	Local + Distant	1.8	
LDH at Initial Diagnosis	−250 IU/l	1.0	0.020
	251+ IU/l	1.4	