Analysis of Primary and Secondary Ewing Sarcoma Outcomes

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Introduction

Ewing Sarcoma (EWS) is a rare cancer of bone and soft tissue that predominately occurs in adolescents and young adults. Although potentially fatal, treatment protocols for Ewing Sarcoma have achieved a 5-year survival up to 75% for patients presenting with non-metastatic disease.

Unfortunately, long term survival is negatively impacted by the occurrence of secondary malignancies. Secondary malignancies are known to occur both before and after the onset of Ewing Sarcoma and can impact the quality and duration of life significantly. The occurrence of secondary EWS in which a patient is diagnosed with EWS after a different cancer diagnosis is far less common than primary EWS in which an EWS diagnosis occurs first followed by future cancer development.

Our purpose was to determine if there are cohorts of EWS patients who are at higher risk and have lower long-term survival. We hypothesized that patients with secondary EWS will have significantly lower average survival than patients with primary EWS.

Methods

A retrospective review was conducted of 46 patients who were treated for EWS at MD Anderson Cancer Center through the electronic health record EPIC. These patients either had a prior malignancy before developing Ewing's Sarcoma or developed a secondary malignancy after having a confirmed EWS diagnosis. EWS diagnoses were confirmed by the EWSR1-FLI1 fusion transcript in pathology reports at MD Anderson Cancer Center.

All statistical analyses were performed using IBM SPSS Statistics for Windows, Version 24.4. Overall survival rates were calculated using Kaplan-Meier methods and potential differences among groups was estimated using the log rank test. Differences in patient outcomes and characteristics between primary EWS and secondary EWS patients were evaluated with Fisher's test. Chi Square tests were used to determine the association of categorical variables. Comparisons of average survival time among treatment groups was determined by a two-sample t test.

Results

- Patients with secondary EWS were diagnosed with EWS at an older age than patients with primary EWS (p = 0.004).
- Secondary EWS patients had significantly worse survival after their EWS diagnosis than primary EWS patients (p = 0.001).
- Patients with secondary EWS had a longer time gap between malignancies than patients with primary EWS (p = 0.001)
- Secondary EWS patients who presented with metastasis at EWS diagnosis had significantly lower average survival than secondary EWS patients who did not present with metastasis at EWS diagnosis.
- Secondary EWS patients had a significantly worse response to radiation therapy than primary EWS patients.
- Patients with secondary EWS were more likely to be male.
- There were no significant differences in second malignancy type frequency. Additionally, there was no significant difference in EWS tumor size between primary and secondary EWS patients.

Table 1: Quantitative Characteristics of Pre and Post EWS Patients

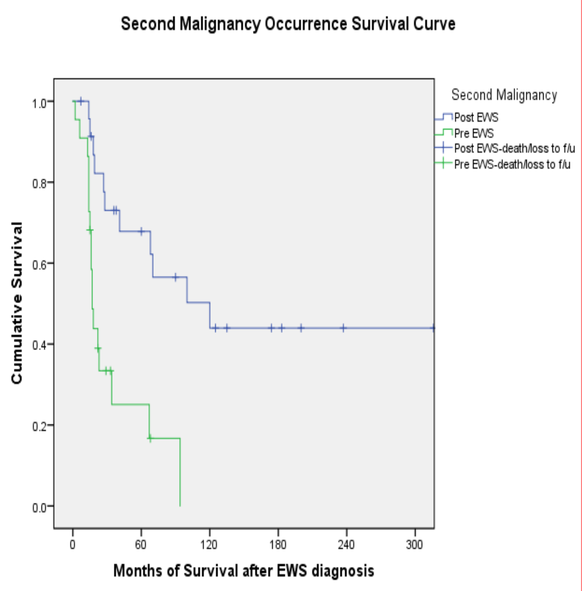
	Second Malignancy Occurrence				
	Post EWS		Pre EWS		
	Mean	Median	Mean	Median	P value
EWS Diagnosis Age	30.60		47.90		**0.004**
Months Survived after EWS Diagnosis	89	64	25.86	17.00	**0.001**
Months between Malignancy Diagnoses	39.49	20.67	109.65	88.52	**0.001**
Months survived with radiation therapy	113.50	105.00	22.58	16.50	**0.001**
Average EWS Tumor Size	5.45	4.90	7.20	5.00	0.318
Tumor Necrosis Percentage	16.33	10.50	46.30	42.50	0.101

Table 2: Categorical Characteristics of Pre and Post EWS Patients

		Second Malignancy Occurrence		
		Post EWS	Pre EWS	
		Count	Count	P Value
Sex	Female	15	7	**0.037**
	Male	9	15	
Second Malignancy	Carcinoma	10	10	0.314
	Germ Cell Tumor	0	2	
	Hematologic Malignancy	8	4	
	Melanoma	4	2	
	Neuroblastoma	0	2	
	Sarcoma	2	2	
Metastasis Present at EWS Diagnosis	no	14	11	0.605
	yes	10	11	
Radiation Therapy	no	10	10	0.796
	yes	14	12	
Tumor Resected	no	8	9	
	yes	16	13	
Cause of Death	EWS	5	11	0.315
	Non EWS	6	6	
Tertiary Malignancy Acquired	no	17	19	0.202
	yes	7	3	

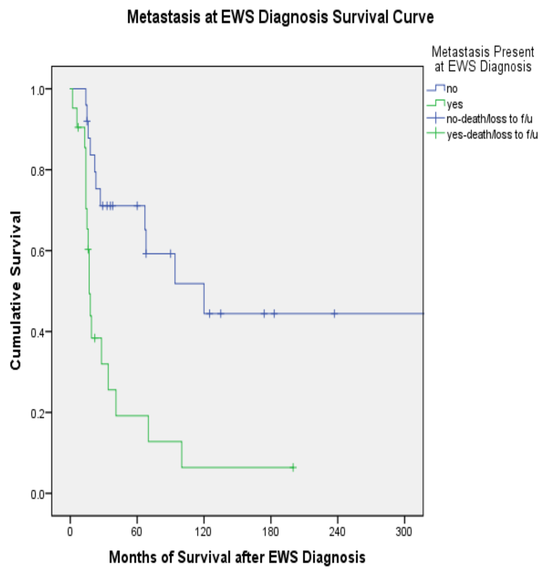
Figures

Figure 1: Kaplan-Meier Curve for Second Malignancy Occurrence



Patients with primary EWS had a better 5-year survival than secondary EWS patients (62.2% vs 16.7 %, p < 0.001). Patients with metastases present at the EWS diagnosis showed a lower five-year survival than those who did not present with metastases (12.8% vs 65.2%, p < 0.001).

Figure 2: Kaplan-Meier Curve for Metastasis at EWS Diagnosis



As expected, average survival was significantly longer in EWS patients without metastasis at EWS diagnosis than those with metastasis (82.9 months vs 32.5 months, p = 0.016). Additionally, average survival was significantly longer in secondary EWS patients without metastasis compared to secondary EWS patients with metastasis (36.4 months vs 15.4 months, p = 0.023).

Conclusions

Our findings show that patients who develop EWS after acquiring a prior malignancy have significantly worse survival outcomes and worse responses to treatment. Additionally, secondary EWS patients have a higher average tumor necrosis percentage, which is a poor prognostic indicator. Patients with secondary EWS and metastasis have the worst survival and are an extremely high-risk cohort.

The increase in prevalence and increased mortality in secondary EWS patients suggest they are a unique cohort and are at higher risk than primary EWS patients. Therefore, patients with secondary EWS should have special attention focused on prevention of developing future malignancies and comorbidities through sequencing and ensuring follow-ups.

We plan to continue studying our cohort of EWS patients by sequencing their genomes and comparing mutations in primary and secondary EWS patients.

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Acknowledgments

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