Cohort Study

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The risk of developing acute myeloid leukemia in patients with Ewing sarcoma and trend analysis: a SEER-based study

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Background: Ewing sarcoma (ES) is a neoplasm of neuroectodermal origin arising from bone or soft tissue. The annual incidence of ES is 2.93 per 1, 000, 000. Acute myeloid leukemia (AML) is one of the most described second malignancies as a complication of primary cancer therapy. There is a lack of recent studies elaborating on the incidence rates of such complications. So, the aim was to quantify the risk of developing AML as a second primary malignancy (SPM) in ES patients and to provide an updated evidence to the literature.

Methods: We extracted the data from the Surveillance, Epidemiology and End Results (SEER) program statistical analysis software package (SEER*Stat, version 8.4.1.2). We used an MP-SIR session to identify patients diagnosed with AML as an SPM after ES as a first primary malignancy between 2000 and 2020. We assessed the SIR as Observed/Expected(O/E) and Excess Absolute Risk (EAR) per 10, 000 with a 95% confidence interval (CI) and statistical significance at 0.05.

Results: A total of 2631 patients with ES were recorded in the SEER database, with a median follow-up of 120 + months. Patients with ES had an increased risk of developing AML with an O/E of 145.98 ($P < 0.05$, EAR = 21.79). Gender played a role in AL development; both males (O/E = 52.94, $P < 0.05$, 95% CI: 31.87–82.670) and females (O/E = 105.62, $P < 0.05$) had a high risk of AL SPM. About 35 patients developed acute non-lymphocytic leukemia with an O/E 130.92 ($P < 0.05$, 95% CI: 91.19–182.08, EAR 21.77). There was a significantly increased risk of developing SPMs in different sites among ES patients (O/E = 5.85, $P < 0.05$)

Conclusion: Patients treated for a primary ES have a significant risk of developing AML, among other second primary malignancies. Thus, we recommend screening for AML from 2 to 11 months after the diagnosis of ES for early detection and better management outcomes.

Keywords: acute myeloid leukemia, Ewing sarcoma, radiotherapy, SEER

Introduction

Ewing sarcoma (ES) is a rare bone malignancy among pediatrics and young adults[1,2]. It arises from a primitive mesenchymal origin and is associated with the EWSR1-F.LI1 fusion due to t (11;22) gene translocation[3]. The diagnosis of ES depends on a multimodal approach, using imaging techniques such as CT and MRI for detection and staging, biopsy for diagnosis, and further characterization using immunohistochemistry and molecular methods[4].

In ES, the possible treatment modalities include surgery, radiotherapy, and a course of polychemotherapy[1]. Although combined treatment modalities help to improve the ES survival outcome, ES survivors face considerable risk and unpleasant consequences, including acute myeloid leukemia (AML)

HIGHLIGHTS

- Ewing sarcoma (ES) is a rare bone malignancy among pediatrics and young adults.
- The development of acute myeloid leukemia as a second primary malignancy (SPM) after ES diagnosis alters the management outcome and requires an aggressive chemotherapy protocol.
- Hematological SPMs are more common among the white race, pediatrics, and young adults. This disparity underscores the need for further research into potential contributing socioeconomic and environmental factors.
- Age, race, treatment modality, and tumor stage at diagnosis should be considered when designing individualized survivorship care plans to enhance long-term outcomes.

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development[4,5]. Therapy-related AML is attributed to the use of genotoxic substances such as alkylating agents and topoisomerase II inhibitors[6]. Cumulative damage has also been shown to lead healthy cells to acquire mutations that promote viral oncolytic activity, increasing the risk of second primary malignancies (SPMs)[7].

The ES survivors are also susceptible to other SPMs, such as osteosarcoma and soft tissue sarcomas, which emphasizes the necessity of prolonged evaluation and follow-up measures to detect and control these challenges in a timely manner[1,8,9]. In response to the burden of SPMs, further studies have been initiated to minimize the risk of SPMs in patients with ES. These studies include finding alternatives to radiotherapy or more targeted radiotherapy[10], or investigating new chemotherapeutic agents with better therapeutic ratios[11]. Moreover, two new approaches, gene editing and gene silencing, have emerged, which aim at the selective destruction of ES cells, leaving the surrounding normal tissue intact. These therapies seek to use specific biological abnormalities characteristic for ES to eliminate tumor proteins or processes needed for its growth and target the biological alterations[12]. These strategies would be similar to "gene therapy," which aims to correct chromosomal translocations or mitotic spindles in cancer cells or tissues, or "gene therapy," which aims to decrease the activity of oncogenes[7].

The development of AML as an SPM after ES diagnosis considerably alters the management outcome and requires an aggressive chemotherapy protocol, which is considered an additional burden for SPM patients due to the poor general condition following ES management[8]. Thus, our aim was to assess the risk of SPMs, especially AML in ES patients. Additionally, we sought to identify the associated risk factors contributing to the development of these malignancies, thereby providing insights that could inform long-term surveillance strategies and improve patients' long-term quality of life.

Methods

Data source and extraction

This retrospective cohort study was conducted using the Surveillance, Epidemiology, and End Results (SEER) program, a population-based cancer registry sponsored by the U.S. National Cancer Institute. The SEER program is one of the most extensive and detailed resources for cancer-related data in the U.S., covering approximately 48% of the population and providing detailed cancer incidence, clinical characteristics, and outcomes linked with demographic and socioeconomic data at the county level[13]. Data extraction and analysis were performed using SEER*Stat beta software (Version 9.0.32.0). Frequency analyses used the "Incidence—SEER Research Data, 17 Registries, Nov 2023 Sub (2000-2021)" dataset. The Multiple Primary-Standardized Incidence Ratio (MP-SIR) analysis used the "Incidence—SEER Research Data, 17 Registries (excl AK), Nov 2022 Sub (2000-2020)" dataset. The study was reported in line with STROCSS criteria[14] and registered at ClinicalTrials.gov.

Patient and variable selection

We identified patients diagnosed with first primary ES (ICD-O-3 histology code 9260/3) between 1 January 2000, and 31 December 2020. Only cases with known age were included. Records based solely on autopsy or death certificates were excluded. Patient characteristics included age [pediatric/young adult (0–24 years), middle-aged (25–64 years), and elderly (65 + years)], sex, race (White, Black, Other races: American Indian/AK Native and Asian/Pacific Islander), marital status (married, unmarried, unknown), and year of diagnosis. Tumor-related variables were also extracted using SEER-defined fields: SEER grade (grade I: well differentiated, grade II: moderately differentiated, grade III: poorly differentiated, grade IV: undifferentiated or anaplastic, and unknown grade) and SEER stage at diagnosis (localized, regional spread, distant spread, or Unknown). Treatment-related data included surgical intervention, radiotherapy, and chemotherapy.

To evaluate hematologic SPMs, we identified patients diagnosed with acute leukemia (AL) or other hematologic cancers after a prior diagnosis of ES. Hematologic neoplasms were classified using the rare tumor site recode: AL including acute lymphocytic leukemia, AML, acute monocytic leukemia, and chronic leukemia, chronic lymphocytic leukemia and chronic myeloid leukemia, lymphoid malignancies including Hodgkin and non-Hodgkin lymphoma, myelodysplastic syndromes (MDS), and myeloproliferative neoplasms. Patients were required to have an index hematologic malignancy diagnosis preceded by ES.

Statistical analysis

Descriptive statistics for the patients' baseline characteristics were generated using the SEER*Stat frequency session. The risk of subsequent AML and other hematologic SPMs following ES was quantified using the MP-SIR session. The SIR was calculated as Observed/Expected (O/E) by dividing the observed case count (O) by the number expected (E) based on age, sex, race, and calendar year-specific incidence rates from the SEER 17 registries. The event was defined as the occurrence of hematological SPM after ES diagnosis.

The risk was evaluated across defined latency periods following the initial diagnosis: < 1 year, 1–5 years, 5–10 years, and 10 + years. Stratification by attained age was applied. A 95% Confidence interval (CI) for the SIRs was calculated using the exact method. Excess risk (ER), representing the excess number of AML cases per 10,000 person-years at risk, was calculated as (Observed – Expected)/Person-Years * 10, 000.

Ethical considerations

The study used de-identified, publicly available SEER data with no direct interaction with human participants. Therefore, institutional review board approval was not required, and informed consent was not needed for this study. All data handling complied with SEER's usage policies and guidelines.

Results

We identified 2,875 patients with ES: 1,709 (59.4%) were males, and 1,166 (40.6%) were females, as shown in Table 1. The majority were white, 2493 (86.7%), while the black patients accounted for only 113 (3.9%). Regarding age distribution, adolescents and young adults were the majority (68.5%), middle-aged patients accounted for 28.6%, while elderly patients only accounted for 2.9%, which reflected ES scarcity

Table 1

Baseline characteristics of patients diagnosed with Ewing sarcoma

Variables	N	Percent (%)
Race		
White	2493	86.7
Black	113	3.9
Others	248	8.7
Unknown	21	0.7
Marital status		
Single	2267	79.1
Married	537	18.7
Unknown	63	2.2
Year of diagnosis		
2000–2009	1237	43.0
2010–2019	1467	51.0
2020 +	171	5.9
Gender		
Male	1709	59.4
Female	1166	40.6
Age		
<25	1970	68.5
25–64	821	28.6
>65	84	2.9
Chemotherapy		
No/unknown	236	8.2
Yes	2639	91.8
Surgery		
No	1110	38.8
Yes	1734	60.6
Unknown	17.0	0.6
Radiotherapy		
No	1472	52.2
Yes	1349	47.8
Stage		
In situ	0.00	0.00
Localized	754	31.4
Regional	729	30.3
Distal	792	32.9
Unknown	130	5.4
SEER grade		
Grade I (well differentiated)	7.0	0.2
Grade II (moderately differentiated)	13	0.5
Grade III (poorly differentiated)	161	5.6
Grade IV (undifferentiated)	458	15.9
Unknown	2236	77.8

among the elderly. Regarding tumor grade, grade IV represented 15%, while localized ES was diagnosed in 754 (31.4%) patients. ES diagnosed when regionally spread was 30.3%, and distant spread accounted for 32.9%. Regarding treatment modality, 1,734 (60.6%) had surgical intervention, 2,639 (91.8%) received chemotherapy, and 1,349 (47.8%) received radiotherapy. In a nutshell, ES is more prevalent among young age, white, and single patients.

Out of 53 patients with hematological SPMs after ES diagnosis, 40 had AL as the most common SPM (57.5%), followed by 10 cases diagnosed with lymphoma SPM (18.9%), and only three cases of MDS, as shown in Table 2. The majority were adolescents and young adults, with 80% in AL, 60% in lymphoma and 100% in MDS. Regarding race, the white race accounted for 92.5% in AL and 66.7% in MDS.

Gender played a role in AL development; both males (O/E = 52.94, $P < 0.05$, 95% CI: 31.87–82.670) and females (O/E = 105.62, $P < 0.05$, 95% CI: 64.52–163.12) had a high risk of AL SPM as shown in Table 3. Diagnosis occurred at a relatively young age with the mean age at diagnosis being 19.27 years for males and 24.93 for females. Pediatrics and young adults demonstrated a significant risk of hematologic SPMs (O/E = 92.61, $P < 0.05$, 95% CI: 62.48–132.21). White patients exhibited a notably higher incidence of AL post-ES, with an O/E of 71.11 ($P < 0.05$, 95% CI: 49.81–98.45), while no cases were reported among the Black race. Furthermore, the average mean age at diagnosis for white patients was significantly older (22.83 years) compared to non-White patients (14.39 years).

Chemotherapy was a significant risk factor with an increased risk of AL SPMs (95% CI: 52.42–101.67, $P < 0.05$). Both surgical (O/E = 51.37, $P < 0.05$, 95% CI: 31.38–79.33) and non-surgical treatment modalities (O/E = 125.73, $P < 0.05$, 95% CI: 75.70–196.35) had an increased risk of AL SPMs after ES diagnosis. ES patients with localized stage had an O/E of 67.13 ($P < 0.05$, 95% CI: 32.19–123.46), while those with regional spread had an O/E of 51.34 ($P < 0.05$, 95% CI: 20.64–105.78) compared to distant spread (O/E = 165.39, $P < 0.05$, 95% CI: 90.42–227.50) had an increased AL SPM risk. However, findings regarding tumor grade were inconclusive, as many AL cases had an unknown grade while grade III was associated with an increased risk (O/E = 56.13, $P < 0.05$, 95% CI: 20.60–122.16).

There was a significantly increased risk of AL SPMs overs 10 years of follow-up with an O/E of 71.13 ($P < 0.05$, 95% CI: 50.58–97.24, ER = 23.45) as shown in Table 4, and the risk peaked within 1–5 years of follow-up post-ES diagnosis with an O/E of 146.3 ($P < 0.05$, 95% CI: 99.45–207.76, ER = 49.21). The risk for lymphoma development after ES was also apparent among all time intervals (O/E = 4.83, $P < 0.05$, 95% CI: 1.94–9.95, ER = 3.39), and the risk was noted to peak within the first year after ES diagnosis (O/E = 9.98, $P < 0.05$, 95% CI: 1.21–36.07, ER = 7.25). However, no cases of chronic leukemia, myeloma, Aleukaemic, or subleukaemic leukemia were detected across all time intervals (O/E = 0.00).

ES patients demonstrated a significantly increased overall risk of developing SPMs in different sites (O/E = 5.85, $P < 0.05$, 95% CI: 4.80–7.05) as shown in Figure 1, with notably elevated risks for bone and joint SPMs (O/E = 88.71, $P < 0.05$), soft tissue and heart SPMs (O/E = 18.68; $P < 0.05$), endocrine SPMs (O/E = 1.47, $P < 0.05$), and skin SPMs (O/E = 3.67; $P < 0.05$). Exceptionally high risks were observed for pleural SPMs (O/E = 1328.77, $P < 0.05$, 95% CI: 33.64–7403.44) and liver SPMs (O/E = 14.49, $P < 0.05$, 95% CI: 2.99–42.33). In contrast, significantly decreased risk was observed for breast SPMs (O/E = 0.93, $P < 0.05$) and urinary system SPMs (O/E = 0.79, $P < 0.05$).

Discussion

The results provided important insights into the risk of SPM development among ES survivors. The findings confirm the increased risk and highlight specific concerns, including

Table 2

Baseline characteristics of patients' acute leukemia SPMs after previous diagnosis with Ewing sarcoma compared to other hematologic cancers

	Number (*N*%)					
	Acute leukemia	Lymphoma	Myeloproliferative	Myelodysplastic	Myeloid and lymphoid	Total
Total	**40**	**10**	**0**	**3**	**0**	**53**
Race						
White	37.0 (92.5%)	-	0.00	2.00 (66.7%)	0.00	49 (92.5%)
Black	0.00 (0.0%)	-	0.00	0.00 (0.0%)	0.00	0.00 (0.0%)
Others	3.00 (7.5%)	0.00(0.0%)	0.00	1.00 (33.3%)	0.00	4.00 (7.5%)
Unknown	0.00(0.0%)	0.00 (0.0%)	0l00	0.00 (0.0%)	0.00	0.00 (0.0%)
Marital status						
Single	34 (85.0%)	7 (70.0%)	0.00	3.00 (100.0%)	0.00	44 (83.0%)
Married	6 (15.0%)	3 (30.0%)	0.00	0.00 (0.0%)	0.00	9.00 (17.0%)
Unknown	0.00 (0.0%)	0.00 (0.0%)	0.00	0.00 (0.0%)	0.00	0.00 (0.0%)
Year of diagnosis						
2000–2009	10 (25.0%)	2 (20.0%)	0.00	0.00 (0.0%)	0.00	12.0 (22.6%)
2010–2019	26 (65.0%)	7 (70.0%)	0.00	3.00 (100.0%)	0.00	36.0 (67.9%)
2020 +	4.00 (10.0%)	1.00 (10.0%)	0.00	0.00 (0.0%)	0.00	5.0 (9.4%)
Gender						
Male	18(45.0%)	7 (70%)	0.00	0.00	0.00	0.00
Female	22(55%)	3.00(30%)	0.00	3.00 (100%)	0.00	0.00
Age						
<25	32 (80.0%)	6.00 (60.0%)	0.00	3.00 (100.0%)	0.00	41 (77.4%)
25–64	8.00 (20.0%)	3.00 (30.0%)	0.00	0.00 (0.0%)	0.00	11.0 (20.8%)
>65	0.00 (0.0%)	1.00 (10.0%)	0.00	0.00 (0.0%)	0.00	1.00 (1.9%)
Chemotherapy						
No/unknown	7.00 (17.5%)	2.00 (20.0%)	0.00	3.00 (100.0%)	0.00	12.0 (22.6%)
Yes	33 (82.5%)	8.00 (80.0%)	0.00	0.00 (0.0%)	0.00	41.0 (77.4%)
Surgery						
No	1.00 (100.0%)	5.00 (83.3%)	0.00	0.00	0.00	6.00 (85.7%)
Yes	0.00 (0.0%)	1.00 (16.7%)	0.00	0.00	0.00	1 .00(14.3%)
Unknown	0.00 (0.0%)	0.00 (0.0%)	0.00	0.00	0.00	0.00 (0.00%)
Radiotherapy						
No	38 (95.0%)	9.00 (90.0%)	0.00	3 (100.0%)	0.00	50 (94.3%)
Yes	2.00 (5.0%)	1.00 (10.0%)	0.00	0.00 (0.0%)	0.00	3.00 (5.7%)
SEER stage						
In situ	0.00 (0.0%)	0.00 (0.0%)	0.00	0.00 (0.00%)	0.00	0.00 (0.00%)
Localized	1.00 (2.6%)	1.00 (11.1%)	0.00	0.00 (0.00%)	0.00	2.00 (4.0%)
Regional	0.00 (0.0%)	0.00 (0.0%)	0.00	0.00 (0.00%)	0.00	0.00 (0.00%)
Distant	37 (97.4%)	8.0 (88.9%)	0.00	3.00 (100.0%)	0.00	48 (96.0%)
Unknown	0 (0.0%)	0.00 (0.0%)	0.00	0.00 (0.00%)	0.00	0.00 (0.0%)
Grade						
Grade I	0.00 (0.0%)	0.00 (0.0%)	0.00	0.00 (0.0%)	0.00	0.00 (0.0%)
Grade II	0.00 (0.0%)	0.00 (0.0%)	0.00	0.00 (0.0%)	0.00	0.00 (0.0%)
Grade III	0.00 (0.0%)	0.00 (0.0%)	0.00	0.00 (0.0%)	0.00	0.00 (0.0%)
Grade IV	0.00 (0.0%)	0.00 (0.0%)	0.00	0.00 (0.0%)	0.00	0.00 (0.0%)
Unknown	38 (100.0%)	3.00 (100.0%)	0.00	3.00 (100.0%)	0.00	44.0 (100.0%)

demographic factors that influence the risk and the importance of personalized monitoring strategies.

There was a higher risk of SPMs among ES survivors agreeing with other studies[15,16]. This underscores the need for practices aimed at preventing the development of SPMs[17]. Leukemia is the most frequent SPM reported in the literature[15]. This highlights the serious long-term complications of intensive chemotherapy regimens, such as topoisomerase II inhibitors, on hematopoietic system health[18]. A higher SPM risk of bones and joints, soft tissue, endocrine system, and skin cancers was noted in this study, which has been discussed in earlier studies[7,15–17]. Many studies mentioned increased AL risk associated with the type of chemotherapy, radiotherapy dose, depending on the stage and tumor site, including agents such as ifosfamide, vincristine, and etoposide[16]. Unfortunately, the rapid expansion of cancerous cells was studied as acceptable collateral damage, as it may increase the SPM risk[18].

The time-related risk of leukemia as an SPM, reaching a maximal point of 5 years from the time of diagnosis, has been discussed by Caruso *et al*[15,17]. To this end, there is a need to carry out monitoring over this important period. The decreased leukemia risk after 10 years may indicate that chemotherapy effects are transient, while other SPMs emerged between 5 years and10 years later. These results highlight the importance of long-term follow-up in patients with ES, as solid SPMs can occur many years after the initial diagnosis. The

Table 3

Baseline characteristics of patients with hematological malignancy after ES diagnosis

Variable	Observed	O/E	(95%CI)	Mean age at event
Race				
White	36.0	71.11*	49.81–98.45	22.83
Black	0.00	0.00	0.00–316.02	
Others	3.00	105.40*	21.74–308.03	14.39
Unknown	0.00	0.00	0.00–1917.97	
Year of diagnosis				
2000–2009	10.0	75.25*	36.08–138.38	21.93
2010–2019	29.0	78.75*	52.74–113.09	22.26
Year of diagnosis Gender				
2020 +	0.00	0.00	0.00–78.30	
Male	19.0	52.94*	31.87–82.67	19.27
Female	20.0	105.62*	64.52–163.12	24.93
Age				
<25	30.0	92.61*	62.48–132.21	15.05
25–64	9.00	53.42*	24.43–101.41	45.92
Age Chemotherapy				
>65	0.00	0.00	0.00–66.01	
No /Unknown	1.00	28.34	0.72–157.88	22.42
Yes	38.0	74.07*	52.42–101.67	22.17
Surgery				
No	19.0	125.73*	75.70–196.35	23.57
YES	20.0	51.37*	31.38–79.33	20.85
Surgery Radiotherapy				
Unknown	0.00	0.00	0.00–1346.24	
No	14.0	49.35*	26.98–82.79	22.71
Yes	25.0	98.14*	63.51–144.87	21.88
Stage				
Localized	10.0	67.13*	32.19–123.46	
Regional	7.00	51.34*	20.64–105.78	
Distal	14.0	165.39*	90.42–227.50	
Unknown	3.00	150.01*	30.94–438.41	
Grade				
Grade I	1.00	559.92*	14.18–3119.70	17.50
Grade II	0.00	0.00	0.00–1428.65	
Grade III	0.00	0.00	0.00–100.05	
Grade IV	6.00	56.13*	20.60–122.16	26.82
Unknown	32.0	79.97*	54.70–112.90	21.45

*$P < 0.05$ is considered significant

results of this study also showed a proportionality between the total SIRs and the stage at the time of first diagnosis, indicating the need for appropriate follow-up management depending on the primary disease stage.

In terms of demographics, similar to the earlier studies on ES, the majority of subjects affected with this disease were males[1,17]. Elsewhere, the study also addressed racial disparities related to the risk of SPMs. While the White race consistently showed higher risks for leukemia SPM, bone/joint SPMs, and skin SPMs, Black patients had a lower overall risk. However, they had a distinct increased risk of pancreatic SPMs. This disparity underscores the need for further research into potential contributing factors, such as socioeconomic and environmental influences. The study also identifies a significantly elevated risk of non-lymphocytic leukemia in American Indian/AK White and Asian/Pacific Islander populations, a new discovery that requires further investigation and focused interventions. Thus, the prospective adoption of monitoring plans based on such factors as age, clinical history, family history, and other parameters is essential for detection of potential SPMs among ES survivors.

Strength and weakness

The study had both notable strengths and inherent limitations. One of the primary limitations is its retrospective nature, suggesting that the findings may necessitate further validation through large randomized controlled trials. The use of the SEER database introduces certain constraints, particularly regarding unavailable variables, including specific surgical procedures, surgical margins, types of chemotherapy administered, and molecular pathological characteristics of ES and AML. Despite these limitations, the demographic characteristics examined in this study reflect diverse factors, and the large sample size enhances the strength of the findings. However, the SEER database presents challenges, particularly with intervention modalities. Furthermore, the presence of a substantial portion of the population with unknown parameters can negatively affect the overall robustness of the cohort. Despite these shortcomings, the SEER database remains a valuable resource for studying rare tumor entities, such as those examined in this investigation. It offers a wealth of data that can facilitate research into cancer populations, ultimately contributing to a better understanding of these diseases with very long follow-up periods. In conclusion, while the limitations of this study warrant consideration, its strengths, particularly the diversity of demographics and large sample size, provide a solid foundation for further exploration and analysis in future research endeavors.

Conclusion

Hematological SPMs are more common among the White race, pediatrics, and young adults. This disparity underscores the need for further research into potential contributing socioeconomic and environmental factors. Chemotherapy was

Table 4

Risk of hematological second primary malignancies after Ewing sarcoma diagnosis across different follow-up time intervals

	1 year		1–5 years		5–10 years		+10 years	
Hematological malignancy	O/E (95%CI)	ER	O/E (95%CI)	ER	O/E (95%CI)	ER	O/E (95%CI)	ER
Acute leukemia	32.83 (6.77–95.93)	11.72	146.37 (99.45–207.76)	49.21	36.74 (11.93–85.74)	11.07	71.13 (50.58–97.24)	23.45
Chronic leukemia	0.00 (0.00–96.54)	–0.15	0 (0.00—45.48)	–0.13	0 (0.00–55.67)	–0.15	0 (0.00–13.60)	–0.17
Myeloma	0.00 (0.00–126.85)	–0.12	0 (0.00–65.73)	–0.09	0 (0.00–83.36)	–0.10	0 (0.00–19.09)	–0.12
Lymphoma	9.98(1.21–36.07)	7.25	6.27 (1.29–18.34)	4.03	2.61 (0.07–14.55)	1.40	4.83 (1.94–9.95)	3.39
Aleukemic, subleukemia	0.00(0.00–1281.42)	–0.01	0 (0.00–579.52)	–0.01	0.00 (0.00–749.95)	–0.01	0.00 (0.00–181.66)	–0.01

ER: excess risk per 10, 000

*$P < 0.05$ is considered significant

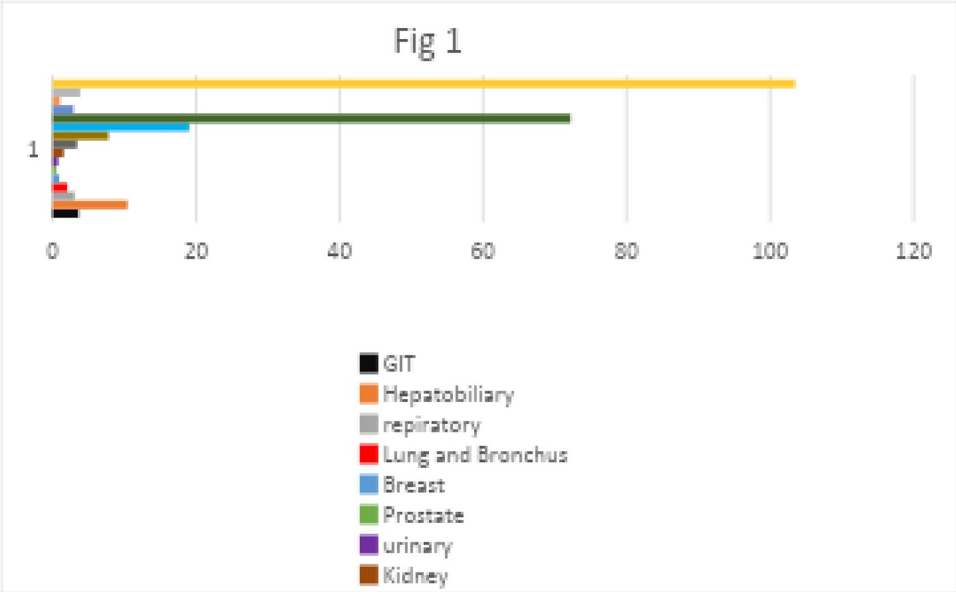

Figure 1. Distribution and risk of second primary malignancies (SPMs) among Ewing sarcoma patients in SEER database. The overall SPM risk is increased compared to the general population, particularly for leukemia, bone and joint tumors, soft tissue malignancies, and skin cancers.

associated with increased risk, especially with AL and lymphoma SPMs, which can persist for a decade or more following initial diagnosis with ES, which demonstrates the importance of tailored follow-up for this vulnerable population. Moreover, our study demonstrated the demographic and treatment factors affecting the occurrence of SPM. Variables such as age, race, treatment modality, and tumor stage at diagnosis should be considered when designing individualized survivorship care plans to enhance long-term outcomes. It is crucial to conduct further research, maintain close monitoring, and implement proactive strategies, including lifestyle adjustments and advancements in targeted therapies for ES patients.

Ethical approval

No ethical approval was required as the data used are publicly available and personal data are concealed.

Consent

Written informed consent was not required for this study as it is a SEER-based study.

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Author contributions

A.E. and M.Z. designed the study methodology. A.E. and M.Z. contributed to the data analysis using the SEER database. B.A., M.E., S.J.E., and E.H.H. contributed to the process of tables and figures creation, revision, and results interpretation. M.E. wrote the introduction. S.M.M.Z. wrote the method section. A.F.A. wrote the discussion and liaised between members. N.A.A. wrote the results section and revised the discussion section. A.E., M.Z., and A.F.A. revised the final version. All authors contributed to the manuscript writing and revised the final version. A.F revised the final version of the manuscript. All authors approved the submitted version of the manuscript.

Conflicts of interest disclosure

The authors have no relevant financial or non-financial interests to disclose.

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Provenance and peer review

Not invited.

Data availability statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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