

ORIGINAL ARTICLE



Epithelioid sarcoma: half a century later

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ABSTRACT

Background and objectives: Epithelioid sarcoma (ES) is an aggressive malignancy scarcely reported on due to its rarity. This study is a review of its traits and features of prognosis and survival by analyzing both the literature and a national cancer database.

Methods: Data were acquired from both the Survival, Epidemiology, and End Results database and literature. 1, 5, and 10-year Disease Specific Survival rates and hazard ratios (HR) were determined. Data were split into pre-2000 (<2000) and post-2000 (>2000) groups. Overall survival, recurrence, and metastasis rates were obtained.

Results: Ninety hundred and ninety eight and 992 cases of ES were identified from the database and literature, respectively. Age, anatomical site, grade, TNM staging, treatment modality and year of diagnosis were demonstrated to be independent predictors of survival. Overall 5- and 10-year survival were 60.4% and 50.2%, respectively. Overall recurrence and metastasis rates were 63.4% and 40.3%. Using cases diagnosed prior to 2000 as reference, those diagnosed after 2000 had a worse prognosis (HR: 1.55).

Conclusions: We report using the largest cohort of ES to date. Despite ES's often dismal prognosis, there are factors associated with better outcomes. A worsening survival over the years warrants further investigation into this sarcoma.

Abbreviations: ES: Epithelioid Sarcoma; SEER: Survival Epidemiology, and End Results (SEER); DSS: Disease Specific Survival; HR: Hazard Ratio; 2000: pre-2000; 2000: post-2000; AJCC: American Joint Committee on Cancer; TNM: T: size/extent of tumor; N: extent of spread to lymph nodes; M: presence of metastasis

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Introduction

Epithelioid sarcoma (ES) is a rare yet high-grade and highly aggressive soft tissue neoplasm of indeterminate histogenesis first identified by Enzinger in 1970 [1,2]. These mesenchymal malignancies display multidirectional differentiation that is primarily epithelial and make up approximately 1% of all soft tissue sarcomas [3]. While ES is not associated with any specific genetical changes, numerous identified cases reveal recurring abnormalities in the 22q region and the loss of SMARCB1 protein expression [1,4]. Typical morphology is characterized by the presence of firm, small, and if cutaneous, potentially ulcerated nodules that may be alone or within clusters [3]. Microscopic findings of ES include central necrosis, an eosinophilic-staining cytoplasm, occasional mitoses, and spindling cells in the periphery [4]. ES is subdivided into two subtypes – the distal and proximal-type variants – though it has been suggested that rather than being distinct entities, the two subtypes of ES are on opposite ends of a histological continuum [5].

Classically, ES affects the distal extremities of young adults and adolescents of the male gender in association with tendons or aponeuroses, though ES is not limited to these and can affect anyone anywhere [6]. Nearly a quarter of cases of

ES are suspected to have an association with skin penetration, prior trauma, or scar tissue [7]. ES's indolent nature and slow growth over the years grant it a falsely benign appearance and may contribute in explaining why it is often misdiagnosed by clinicians on first encounter [4]. This cancer's high previously reported recurrence and metastasis rates (around 70% and 50%, respectively) and semblance to other entities such as granuloma annular, vascular epithelioid tumors, and synovial sarcoma are additional factors owing to ES's poor prognosis [4].

The survival rate of ES reported in the literature varies, with 5-year survival rates ranging from as low as 25% to as high as 92% [8–10]. Much of what is known about survival rates of ES and factors associated with better or worse outcomes is from the numerous, isolated investigations conducted by institutions reporting on their own experiences with this cancer [11–13]. Given ES's scarcity, high recurrence and metastasis rates, wide variance in reported survival, mimicry of other entities, and poor prognosis, an accurate description of associated factors and outcomes is of necessity.

The Surveillance, Epidemiology, and End Results (SEER) Database is a large cancer registry that represents nearly 30% of the United States population [14,15]. By combining

Table 1. (SEER) Demographic and clinicopathologic traits.

Total # of cases: 998					
Mean age of diagnosis: 45.8 ± 21.5					
	N	%		N	%
Age category ^a			Anatomical region ^a		
Elderly (>80)	61	6.2	Upper limb	275	34.9
Old-adult (56–79)	272	27.5	Lower limb	193	24.5
Mid-adult (36–55)	312	31.6	Head and neck	51	6.5
Young-adult (18–35)	235	23.8	Abdomen	41	5.2
Pediatric (<18)	108	10.9	Trunk	36	4.6
Gender ^a			Thorax	55	7
Male	546	55.3	Pelvis	138	17.5
Female	442	44.7	Unknown	209	–
Race ^a			Grade ^a		
White	795	79.6	I–II	62	13.7
Black	117	11.8	III	194	42.7
Other	86	8.6	IV	198	43.6
Year of diagnosis: grouping #1 ^a			T-staging ^a		
Pre-2000	217	22	T1 (<5 cm)	191	49.5
Post-2000	771	78	T2, T3, T4 (>5 cm)	195	50.5
Year of diagnosis: grouping #2 ^a			N-staging ^a		
1973–2005	458	46.4	N0	375	64.2
2006–2015	530	53.6	N1 + N2	209	35.8
Treatment			M-staging ^a		
S–/R–	196	19.8	M0	381	77.6
S+/R–	458	46.4			
S+/R+	287	29	M1	110	22.4
S–/R+	12	1.2			
Unknown	35	3.5			

^aUnknown values excluded from respective % contribution.

cases of ES obtained from SEER (November 2017 release) with those which are reported in the literature, we hope to use the largest ever combined cohort of ES cases to report statistically sound demographic, clinicopathologic, and survival information on ES as well as on possible changes in survival over the decades. Moreover, we seek to appraise the previously posed idea that survival of ES has decreased over the years [16].

By identifying trends and predictive factors of survival for ES, we hope to provide clinicians with the most accurate information on ES for outcome expectation, assistance in risk-stratification, and therapy management.

Methods

Patient population #1: SEER database

The SEER database contains millions of patient cases ranging from 1973 to 2015 that represent approximately 30% of the United States population. These cases are derived from 18 local cancer registries, chosen with national population representation in mind. SEER's validity has been studied strenuously. As all patient information within SEER is de-identified, this study has been exempted from institutional review board approval, as per the standing policy of Rutgers New Jersey Medical School (Newark, NJ, USA). The *International Classification of Disease for Oncology, Third Edition* was used to select for patients diagnosed with ES using morphological code 8804/3. Variables of interest included age at diagnosis (subdivided into 5 groupings), gender, race, anatomical site affected, grade, American Joint Committee on Cancer (AJCC) TNM (T: size/extent of tumor, N: extent of spread to lymph nodes, and M: presence of metastasis) soft tissue sarcoma

cancer staging, treatment modality, and year of diagnosis (subdivided into two different groupings). These two groupings included Grouping #1: pre- and post-2000, and Grouping #2: where the number of cases was divided nearly equally (near 50:50 frequency split).

Patient population #2: cases from the literature

The literature (PubMed, EBSCO, Ovid) was searched for cases of ES with varying combinations of 'AND', 'OR', and 'NOT' using the following search queries: 'epithelioid sarcoma', 'epithelioid', 'sarcoma', 'recurrence', and 'treatment'. Articles identified were sub-divided into two groupings by publication date: the pre-2000 (<2000) and post-2000 (>2000) cohorts. All articles referenced in the bibliographies of identified or related papers were evaluated for potential inclusion. The 'Similar Articles' feature was also utilized to expand articles included. The local medical school library was utilized to access articles unavailable online. Sample size, 5-year survival, 10-year survival, recurrence rate, and metastasis rate were recorded, when available. Articles that failed to provide at least one of these variables aside from sample size were excluded. Articles not written in English were excluded. Articles that were solely case reports or with populations of ES < 5 were excluded. Articles that were ultimately inaccessible were excluded. Overall, 24 articles consisting of a total 992 cases of ES were identified from the literature search.

SEER cases statistical analysis

In total, 998 cases of ES were identified from the SEER database. Using the Pearson's chi-square and Cox regression tests, univariate analyses were carried out to determine the presence of any relationships among demographic and clinicopathologic characteristics with survival. 1-, 5-, and 10-year Disease Specific Survival (DSS) rates were determined through Kaplan-Meier survival curve analysis and hazard ratios (HR) through Cox regression by different significant categories. Multivariable analyses via Cox regression were then conducted to determine the presence of any independent predictors of survival from those significant on univariate analysis.

Decades-based analysis

Cases from both patient populations were divided into <2000 and >2000 cohorts. SEER cases were split by years of diagnosis. Cases attained from the literature were split by article publication date. <2000 and >2000 5- and 10-year survival, recurrence, and metastasis rates were determined. Less than 2000 and >2000 5- and 10-year survival rates were determined for cases from the SEER database. All values were weighted accordingly by their sample sizes and combined. An unpaired independent t-test was then performed to determine if any of the differences among the four categories were significant between the two groups (>2000 vs. <2000).

Table 2. (SEER) Traits – univariate cox regression and Kaplan-Meier analysis.

Cox regression hazard ratio analysis		Kaplan-Meier survival analysis		
	HR	1-Year DSS %	5-Year DSS %	10-Year DSS %
Age category ^a				
Elderly (>80)	Ref.	38.3	14.3	–
Old-adult (56–79)	0.52	55.1	37.3	36.4
Mid-adult (36–55)	0.27	76.9	58.9	52.4
Young-adult (18–35)	0.24	86.9	64.8	52.5
Pediatric (<18)	0.13	89.1	77.1	72.7
Year of diagnosis: grouping #1 ^a				
Pre-2000	Ref.	83.9	65.7	59
Post-2000	1.54	70.9	52.5	46
Year of diagnosis: grouping #2 ^a				
1973–2005	Ref.	76.6	60	53.3
2006–2015	1.29	71.5	50.6	44.6
Grade ^a				
I-II	Ref.	96	91.6	73.4
III	4.43	65.1	45.3	42
IV	5.32	56.9	38.7	33.4
T-staging ^a				
T1	Ref.	94.8	84.2	83
T2	1.54	64	36	29
T3-T4	12.33	22.2	–	–
N-staging ^a				
N0	Ref.	83.3	65	59.8
N1	2.72	53.5	31.2	25.7
M-staging ^a				
M0	Ref.	87.4	67.6	61.4
M1	5.98	33	9.7	5.8
Anatomical region ^a				
Abdomen	Ref.	49.7	25.2	–
Lower limb	0.32	83.5	61.2	57.1
Upper limb	0.21	93.1	77.2	66.5
Trunk	0.26	78.1	71	66.6
Pelvis	0.41	75.9	56	47.7
Treatment ^a				
S–/R–	Ref.	31.1	8.5	5.7
S+/R–	0.14	85.4	71	64.3
S+/R+	0.18	86.8	63.8	54.7

^aVariables without significance excluded from table.

Joined cases analysis

Survival rates of 5- and 10-year from SEER were weighted by case numbers and added with the overall 5- and 10-year survival rates obtained from the literature. Overall recurrence and metastasis rates from the literature were also determined.

Results

SEER database

In total, 998 cases of ES were identified from the SEER database (Table 1). Average age of diagnosis among patients extracted from SEER was 45.8 years (SD: 21.5). Patients were predominantly white (79.6%), male (55.3%), and fell within the three middle age categories (cumulatively 82.9%). The majority of cases were also diagnosed after the year 2000 (78.0%).

In 59.4% of cases, the location of the tumor was in a proximal location (upper or lower extremity) and 86.3% of cases was high grade (III or IV – Table 1). Nearly half (49.5%) of the tumors were ≤ 5 cm and approximately a third (35.8%) presented with nodal involvement. Metastasis was present in 22.4% of cases at diagnosis while the most

Table 3. (SEER) Traits – multivariate cox regression hazard ratio analysis.

Cox regression hazard ratio analysis		HR	p Value
Age category ^a			
Mid-adult (36–55)		Ref.	
Elderly (>80)		3.31	<.001
Old-adult (56–79)		1.89	<.001
Young-adult (18–35)		0.80	>.05
Pediatric (<18)		1.12	>.05
Year of diagnosis: grouping #1 ^a			
Pre-2000		Ref.	
Post-2000		1.55	.006
Grade ^a			
I-II		Ref.	
III		4.34	<.001
IV		4.28	<.001
T-staging			
T1 (<5 cm)		Ref.	
T2 (>5 cm)		2.75	<.001
M-staging (at diagnosis) ^a			
M0		Ref.	
M1		2.32	<.001
Anatomical region ^a			
Abdomen (proximal)		Ref.	
Lower limb (distal)		0.51	.01
Upper limb (distal)		0.45	.003
Treatment ^a			
S–/R–		Ref.	
S+/R–		0.23	<.001
S+/R+		0.27	<.001

^aVariables without significance excluded from table (except for age category). Values that are bolded indicate possession of statistical significance.

commonly employed treatment method was surgery without radiation (S+/R–, $n = 458$, 46.4%).

Varying 1-, 5-, and 10-year DSS rates were obtained via Kaplan-Meier analysis (Table 2). Overall 1-, 5-, and 10-year DSS rates were 74%, 55.7%, and 49.3%. The variable groups that had the highest 1-year DSS rates were Grade I-II (96%), T1 staging (94.8%), and upper limb primary tumor site (93.1%). Those with the lowest 1-year DSS rates were T stages 3–4 (22.2%) and radiation only treatment (S–/R+ – 22.2%). Factors with the best 5-year DSS rates were Grade I-II (91.6%), T1 staging (84.2%), and pediatrics age group (77.1%). Factors with the worst 5-year DSS rates were M1 (9.7%), and no treatment (S–/R – 8.5%). Factors with the best 10 -year DSS rates were Grade I-II (73.4%), T1 staging (83.0%), and pediatrics age group (72.7%).

On univariate analysis, younger age was significantly associated with better outcomes (Table 2). The best outcome was associated with the pediatrics age category (HR: 0.13), with subsequently increasing HRs with increasing age categories. However, no significant differences were found among pediatrics, young adult, and mid-adult age groups. No significance in effect on survival was found for gender and race. For cases diagnosed post-2000 (Year of Diagnosis: Grouping #1), a worse survival was seen (HR: 1.55). For Year of Diagnosis: Grouping #2, a worse survival was also seen for later years of diagnosis (2006–2015 – HR: 1.29). Higher TNM staging values were associated with worse survival, with the greatest HRs seen in Grade IV (HR: 5.32), T stage 3–4 (HR: 12.33), and M1 (metastasis – HR: 5.98). Certain anatomical locations were also associated with better and worse outcomes. With abdomen (proximal body part) as reference, the upper limb (HR: 0.21), lower limb (HR: 0.32), trunk (HR: 0.26),

and pelvis (HR: 0.41) were associated with better outcomes. With S-/R- as reference, S+/R- and surgery with radiation (S+/R+) had better outcomes (HRs: 0.14 and 0.18, respectively).

Multivariate analysis via Cox regression revealed several independent factors to be associated with outcomes (Table 3). Ages <56 are independently associated with better outcomes as the Old-Adult and Elderly age categories had significant HRs of 1.89 and 3.31, respectively. The performance of surgery was shown to be associated with better outcomes, regardless of whether treatment was S+/R+ (HR: 0.27) or S+/R- (HR: 0.23). Higher tumor grade was also identified as an independent worse predictor, with Grade III having a HR of 4.34 and Grade IV having a HR of 4.28. Tumor size of >5 cm and the presence of metastasis were also independent negative predictors of survival (T stage 2 HR: 2.75 and M1 HR: 2.32). With abdomen as reference for anatomical region, both the upper (HR: 0.51) and lower extremities (HR: 0.45) were independent positive factors. Lastly, having a year of diagnosis post-2000 was another negative independent predictor of survival (HR: 1.55).

SEER and the literature

Overall, 24 articles consisting of a total 992 cases of ES were identified from the literature search. Of these identified articles, 6 articles ($n=411$) were published prior to the year 2000 and 18 after ($n=581$). Table 4 compares the overall >2000 and <2000 5- and 10-year survival, recurrence, and metastasis rates obtained from combining values from SEER and the literature. The cumulative 5-year survival of ES based on all pre-2000 cases from the literature and pre-2000 SEER cases was determined to be 67.7% ($n=628$). The pre-2000 10-year survival was determined to be 59.1% ($n=349$). The cumulative pre-2000 recurrence rate was 68.2% ($n=338$). Overall pre-2000 metastasis rate was 44.9% ($n=360$). In contrast, cumulative 5-year survival for post-2000 cases was 56.5% ($n=1253$). Post-2000 10-year survival was 47.2% ($n=1152$). Post-2000 recurrence and metastasis rates were 56.9% ($n=248$) and 33.8% ($n=253$), respectively. For the values of all four of these rates, the differences between the two groups (pre-2000 vs. post-2000) were statistically significant ($p<.0001$ – Table 4) based on the results of the unpaired t-test.

Table 5 presents 5- and 10-year survival, recurrence, and metastasis rates for the literature (<2000 and >2000), SEER, and overall (SEER and literature combined). The comprehensive 5-year survival rate for ES from all accumulated available cases was shown to be 60.4% ($n=1891$). The comprehensive 10-year survival rate for ES was found to be 50.2% ($n=1511$). The comprehensive recurrence rate was determined to be 63.4% ($n=586$). The comprehensive metastasis rate was determined to be 40.3% ($n=613$).

Discussion

ES, a belligerent neoplasm with an unpromising prognosis, compromises about 1% of all STS yet is the most common

among this class of cancers to affect the hand [17]. Its prevalence is higher among children, with reports of representation ranging from 5% to 8% among nonrhabdomyosarcoma STS [18]. For these reasons, ES should have its place on any clinician's differential when dealing with a young patient or one who presents with a mass on his or her hand. Nearly 50 years have passed since ES was first described and to the present there is no study reported in the literature on a cohort of ES patients that approaches $n=500$ [2]. By utilizing the largest number of gathered ES cases ($n=1990$), we sought to report on the most statistically sound demographic and clinicopathologic traits, favorable and adverse associations, prognosis, and any other trends of ES.

The literature varies in its description of ES's age distribution, but many studies claim a majority of cases can be expected to fall between 10 and 35 years of age [6,19]. However, this range is below the average age of diagnosis obtained from SEER. In fact, more than half (65.2%) of cases in SEER are patients older than 35 years of age, suggesting that our previous understanding of ES's age distribution may have been lacking. Though there are reports in the literature that show age has no impact on survival, we have identified a negative, independent association with ages >55 [17,19]. Our data also confirms the male-dominant distribution attributed to ES (55.3%) but challenges the previously posed idea that the female gender is a protective factor [2,6,13].

Livi et al. have previously shown anatomical site to be an important prognostic factor, which reflects the results we have obtained [9,13]. More distal tumors such as those on the extremities offer better chance of survival. A greater rate of survival has also been shown to be associated with the more common of the two histological ES subtypes: the distal-type [20]. Distal ES is often seen in the extremities while proximal ES typically affects the trunk, axilla, and groin among other proximal sites [21]. Debate on whether the proximal-type is inherently worse than distal ES or whether it is due to their associations with the affected site persists [1,4]. As the SEER database does not differentiate cases between the two, no analysis of subtype was provided.

Both SEER data and literature review demonstrate the importance of surgery for survival, as it has remained the mainstay treatment of ES and often includes amputation [3]. Steinberg et al.'s study showed that the wider the surgical margin, the better the outcome [22]. Based on our analysis of SEER, whether radiation was performed or not did not matter as long as surgery was undertaken. However, numerous studies have suggested the benefit of adjuvant high-dose radiation therapy in reducing the risk of recurrence, maintaining functionality, and improving overall outcomes [19]. Chemotherapy's role in treatment of ES is far less adequately defined than surgery and radiation. SEER's inadequate coding of chemotherapy is one of its limitations, while the literature varies on its results with one study claiming that it may be associated with worse survival and others that it offers little benefit [8,23].

The use of grading for ES has previously been debated [18,24]. It is possible this dispute is reflected in the cases inputted into SEER as 54% of cases were missing values for

Table 4. Pre- and post-2000 rates comparison – SEER and the literature combined.^{a,b}

	5 Year survival rate	10 Year survival rate	Recurrence rate	Metastasis rate
<i>Prior to 1/1/2000 (cumulative)</i>				
Rate	67.7	59.1	68.2	44.9
n/(SD)	628/5.50	349/10.89	338/17.7	360/2.05
<i>After 1/1/2000 (cumulative)</i>				
Rate	56.5	47.2	56.9	33.8
n/(SD)	1253/19.97	1152/22.01	248/21.4	253/11.9
Significance	Yes	Yes	Yes	Yes
p value	$p < .0001$	$p < .0001$	$p < .0001$	$p < .0001$

^aRates weighted by respective *n* counts per article/database.^bOverall pre- and post-2000 values compared by combining cases from SEER and the literature.**Table 5.** Overall SEER and literature rates.^a

	5 Year survival	10 Year survival	Recurrence rate	Metastasis rate
<i>Prior to 1/1/2000 (literature)</i>				
Rate	68.8	59.2	68.2	44.9
n (# of ES cases)	n = 441	n = 132	n = 338	n = 360
n (# of articles)	n = 6	n = 3	n = 4	n = 5
<i>After 1/1/2000 (literature)</i>				
Rate	63.0	49.5	56.9	33.8
n (# of ES cases)	n = 482	n = 381	n = 248	n = 253
n (# of articles)	n = 15	n = 12	n = 9	n = 8
<i>SEER database</i>				
Rate	55.7	49.3	–	–
n (# of ES cases)	n = 998	n = 998		
<i>Overall</i>				
Rate	60.4	50.2	63.4	40.3
n (# of ES cases)	n = 1891	n = 1511	n = 586	n = 613

^aSeparate literature (pre-2000 and post-2000), separate SEER, and overall (SEER and literature combined) values presented.

Grade ($n = 534$). The majority of cases with reported values were high grade (either III or IV: 86.7%). These two high grades also had high HRs on multivariate Cox regression (4.38 and 4.28, respectively) and therefore may contribute in explaining why ES has such a poor prognosis. The potential association of ES survival with the three different variables that are a part of the AJCC's TNM soft tissue sarcoma staging has previously been explored [1,4,7,25]. The majority of papers on the topic suggest worse outcomes with tumor sizes >5 cm. This is in line with our attained results as tumors marked as >5 cm in SEER had a significantly worse HR on multivariate analysis (HR: 2.75). The literature describes ES to be unique among STS due to its natural tendency for lymph nodal spreading, which was once more in accordance with our results (35.8% nodal involvement) [6]. While the effect nodal involvement has on survival has been debated, we found no demonstrated association of significance. Meanwhile, the presence of metastasis has repeatedly been shown to lead to worse outcomes and was significant on our multivariate Cox regression analysis [7,12,26].

A previous ES SEER study that had less than half of the cases ($n = 441$) currently registered in the November 2017 SEER submission report identified a solely univariate significant association of year of diagnosis with survival [16]. Though Jawad et al. did not find significance on multivariate analysis, it must be acknowledged that they employed a smaller sample size. The 5- and 10-year survival rates reported by this study were 68% and 61%, respectively. The survival results we obtained from the updated SEER database that added 10 more years (2006–2015) and many more cases ($n = 557$) were lower than these rates (55.7% and 49.3%,

respectively), suggesting a recent dip in survival. Our results also showed a significant HR on multivariate analysis to be associated with diagnosis after the year 2000 (HR: 1.55). To determine the validity of this database finding, we compared rates compiled from the literature (pre-2000 vs. post-2000) to each other. Six articles were identified as published prior to the year 2000 [7,19,26–29], and eighteen after [8–13,18,23,25,30–38]. The significance of the difference ($p < .0001$) found between the two groups for all four variables (5-year survival, 10-year survival, recurrence rate, metastasis rate) whether pre- and post-2000 SEER cases were factored in or not suggests that survival of ES may have in fact decreased over the last two decades. The results from the data acquired from the literature supported this SEER finding, indicating that large databases have the potential to be very powerful tools in discerning changes over time that would otherwise have been difficult to perceive. Our updated SEER rates also seemed to level toward the overall comprehensive rates that were calculated.

The large population of ES patients assembled through different methods of inclusion proffer this study the ability to be an authority on reporting rates, associations, and trends of ES. The attained comprehensive rates of ES suggest that at 5-years after diagnosis, three of five diagnosed patients can expect to survive, and at 10-years after diagnosis, one of two patients. More than half of all reported cases in the literature were marked by recurrence (63.4%). Recurrence is often noted to occur after wide surgical margins and even amputation [22]. Nearly two of every five people diagnosed with ES develop metastasis (40.3%), a very important factor to consider in ES's prognosis. A potential explanation as to why pre-2000 recurrence and metastasis rates were higher than the post-2000 group is the inability to include the SEER cases as they do not report on such variables. Because more than half of our cases (998 of 1990) are immediately excluded from inclusion into analysis of recurrence and metastasis, true pre- and post-2000 values for recurrence and metastasis may be different. This explanation may be taken further as 78% of the SEER cases were diagnosed after 2000; therefore, the vast majority of our >2000 cases are not included and may explain why the >2000 recurrence and metastasis rates seen in Table 4 are less than <2000 's rates despite a worse survival.

While a trend of decreasing survival has been identified, an explanation remains to be found. While it was significant on multivariate analysis, it is possible that improper variable grouping may have had a role. This may be explained by an

increasing age-population, increasing use of radiation for palliative as opposed to curative therapy, or even chemotherapy's ambiguous role in ES treatment. Regardless, ES remains marked by many unfavorable factors such as high chances of recurrence, metastasis, and misdiagnosis. Given this and a potentially worsening survival rate, the need for a search for novel treatment modalities is understated and as such is the clinical takeaway from our finding. ES patients may benefit from the future promises of personalized medicine that bring with it targeted and immune-based therapies [20].

As all research studies are, this study is in possession of several limitations. First, it is confined in all the ways large database studies are. For surgical treatment reported in SEER, extent of surgery was missing. A great proportion of SEER cases were missing information on grade as well as TNM stages. No accurate data on chemotherapy was reported in SEER. No differentiation between the two ES subtypes is made in SEER. No consistent information on recurrence and metastasis is reported on in SEER. A potential selection bias may exist regarding treatment as the cases with high TNM staging or grade may have been the ones to have received chemotherapy or surgery with radiation. It is possible that there may have been an overlap of cases both described in the literature and inputted into SEER that may have impacted our data analysis. A potential pitfall of our study design may be the improper categorization of articles from the literature for pre or post-2000. While an article may have been published after the year 2000, it may include cases of ES diagnosed prior to 2000. Another potential limitation is the relatively fewer number of accessible publications prior to the year 2000. Future studies should devote efforts toward comparing the two different subtypes of ES and the role of chemotherapy using a large population size of ES patients that may be possible with multi-institutional collaboration. Novel methods of treatment such as immunotherapy should be explored as conventional treatment modalities have done little in ways of preventing the drop or stagnancy of ES survival over the last 50 years.

Conclusion

ES is a rare but belligerent STS that poses a serious challenge to clinicians and patients alike. A poor prognosis can be expected with overall 5- and 10-year survival rates of 60% and 49%, respectively. It has high overall rates of recurrence (63%) and metastasis (42%) and is recurrently misdiagnosed. Positive independent prognostic factors include peripheral anatomical site, diagnosis age < 55, and surgical treatment. Negative independent prognostic factors include tumor size > 5 cm, presence of metastasis, higher grade (III or IV), and diagnosis after the year 2000. Survival of ES over the last 20 years has stagnated and may have even fallen, suggesting that conventional treatment methods of ES should be reevaluated.

Synopsis

This is a combined database and literature review on the rare yet highly aggressive malignancy ES. Using the largest cohort of ES cases ($n = 1990$), this article reports on its demographic and clinicopathologic traits, prognosis, trends, and features of survival.

Disclosure statement

No potential conflict of interest was reported by the authors.

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Data availability statement

The data that support the findings of this study are available upon request in the Surveillance, Epidemiology, and End Results Program Database [<https://seer.cancer.gov/data/>].

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