European Journal of Cancer 208 (2024) 114209

Contents lists available at ScienceDirect

European Journal of Cancer

journal homepage: www.ejcancer.com

Original research

The survival disparity between children and adolescents and young adults (AYAs) with Ewing sarcoma in the Netherlands did not change since the 1990s despite improved survival: A population-based study

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ARTICLE INFO

Keywords:
Adolescents and young adults
AYAs
Children
Disease stage
Epidemiology
Ewing sarcoma
Relative survival

ABSTRACT

Background: Adolescents and young adults (AYAs) with Ewing sarcoma have a worse prognosis than children. Population-based survival evaluations stratifying findings by important clinical factors are, however, limited. This Dutch population study comprehensively compared survival of children and AYAs with Ewing sarcoma over three decades considering diagnostic period, tissue of origin, tumor site, and disease stage.

Methods: Data on all children (0–17 years, N = 463) and AYAs (18–39 years, N = 379) diagnosed with Ewing sarcoma in the Netherlands between 1990–2018 were collected from the Netherlands Cancer Registry with follow-up until February 2023. Five-year relative survival was calculated using the cohort method. Multivariable analyses were conducted through Poisson regression.

Results: Children with Ewing sarcoma had a significantly higher 5-year relative survival than AYAs (65 % vs. 44 %). An increasing trend in survival was noted reaching 70 % in children and 53 % in AYAs in 2010–2018. Results were similar for Ewing bone sarcoma and extraosseous Ewing sarcoma. AYAs had a poorer prognosis than children for most tumor sites and regardless of disease stage. Survival probabilities were 60 % vs. 78 % for localized disease and 20 % vs. 33 % for metastatic disease. Multivariable-regression analysis, adjusted for follow-up time, diagnostic period, sex, disease stage, and tumor site, confirmed increased excess mortality among AYAs compared with children (excess HR: 1.7, 95 % CI: 1.3–2.1).

Conclusions: Despite survival improvements since the 1990s, AYAs with Ewing sarcoma in the Netherlands continue to fare considerably worse than children. This survival disparity was present irrespective of tissue of origin, tumor site, and disease stage

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https://doi.org/10.1016/j.ejca.2024.114209
Received 3 May 2024; Received in revised form 28 June 2024; Accepted 3 July 2024
Available online 6 July 2024

1. Introduction

Ewing sarcoma is a highly aggressive type of cancer originating in the bone or soft tissues that typically affects children and adolescents and young adults (AYAs). Ewing sarcoma of bone is the second most commonly diagnosed primary bone malignancy in these age groups [1–4]. In roughly 25 % of the patients, Ewing sarcoma arises in soft tissues [1,5]. Recent Ewing sarcoma trials conducted among patients aged up to 50 years reported 5-year survival of approximately 70 % overall [6] and > 85 % for standard-risk localized disease [7]. The prognosis of patients with extrapulmonary metastases at diagnosis was dismal, with a 5-year survival of around 30 % [8].

Age at diagnosis is inversely associated with the prognosis of Ewing sarcoma [4,9,10] and AYAs with Ewing sarcoma were reported to have a worse outcome than children in both the European and US population [11–13]. In the EUROCARE-5 study (2000–2007), children with Ewing sarcoma had a 5-year survival of 67 % compared with 49 % for AYAs [12]. Likewise, 5-year survival estimates were 77 % for children and 54 % for AYAs using US SEER data (2002–2006) [11]. The survival disparity between children and AYAs with Ewing sarcoma may be related to variability in tumor biology, treatment (adherence), pharmacodynamics and -kinetics, clinical trial participation, and social aspects [14]. Tumor site of Ewing sarcoma has been shown to be age-dependent, with the less favorable axial and pelvic locations being more frequent among AYAs. Additionally, AYAs are more likely to have metastases at diagnosis and primary extraosseous tumors [3,4,9,14]. While metastatic disease at diagnosis is the strongest adverse prognostic factor for Ewing sarcoma [3,9], the prognostic significance of tissue of origin remains inconclusive [15,16]. Despite the potential differences, previous population-based studies evaluating survival of children and AYAs with Ewing sarcoma did generally not specify their findings by these important clinical factors.

The aim of the present study was to compare population-based survival of children and AYAs with Ewing sarcoma in the Netherlands, while considering diagnostic period, tissue of origin, tumor site, and disease stage. Findings for the Netherlands can likely be extrapolated to other developed countries with compulsory health insurance and complete coverage of costs of anti-cancer therapies.

2. Patients and methods

2.1. Data collection

Data on all children (0–17 years) and AYAs (18–39 years) diagnosed with Ewing sarcoma in the Netherlands between 1990–2018 were obtained from the population-based Netherlands Cancer Registry (NCR), which has been nationwide since 1989 (completeness ≥96 %) [17,18]. Case notification occurs through the Nationwide Network and Registry of Histopathology and Cytopathology (PALGA) and the National Registry of Hospital Discharges, and is followed by retrospective medical records review to collect relevant information. Vital status is updated yearly by linkage with the nationwide Personal Records Database (last linkage: February 1, 2023). Patients with Ewing sarcoma were identified using International Classification of Diseases for Oncology (3rd edition, ICD-O-3) morphology codes: 8803, 9260, and 9364–9368. Tissue of origin (bone, extraosseous) and primary site were derived from the ICD-O-3 topography codes (Supplementary Table S1). Stage at diagnosis was categorized as localized [Extent of Disease (EoD)= 2–5 or M0/X], metastatic (EoD=6 or M+), or unknown. Metastatic site has been completely registered in the NCR since 2008 and was categorized as no metastases, lung only (including pleura), extrapulmonary, or unknown. Site of treatment was considered to be a university medical center (UMC) if any therapy had taken place at a UMC or the Princess Máxima Center for pediatric oncology in the Netherlands. Six patients who underwent either surgery or all treatments abroad were excluded from the analyses. Patients were followed from diagnosis to death (i.e., event) or censoring (i.e., emigration or February 1, 2023). There were no autopsy diagnoses or deaths on the day of diagnosis.

2.2. Statistical analyses

Descriptive statistics were used to characterize the study population. Statistical significance of differences between children and AYAs was determined by Pearson's X^2 or Fisher's Exact tests.

Relative survival portrays the excess mortality related to the cancer diagnosis and was calculated through dividing the patients' observed survival by the expected survival of an age-, sex-, and period-matched cohort from the general population [19]. The Ederer II method was applied to compute the expected survival from Dutch population life tables [20]. Five- and 10-year relative survival were calculated using traditional cohort-based analysis, with the exception of 10-year relative survival for the latest diagnostic period which was estimated using period-based analysis [21] because of incomplete follow-up. Changes in 5-year relative survival over time were evaluated by including diagnostic period (1990–1999, 2000–2009, 2010–2018) as a continuous term in Poisson regression models using the strs command in Stata [19]. The same modelling approach was employed to analyze the association of age with excess mortality from Ewing sarcoma within 5 years of diagnosis. To this end, multivariable models were created which were adjusted for follow-up time, diagnostic period, sex, disease stage, and tissue-specific tumor site. Site of treatment was not included in the final model since it was not significantly associated with excess mortality from Ewing sarcoma and did not affect the excess hazard ratios (HR) of the other variables. Because immortal time bias could potentially have influenced outcome for specific treatment groups, primary treatment was not taken into account in the multivariable analyses.

All analyses were performed using Stata 17 (StataCorp LLC, College Station, TX). Two-sided p-values < 0.05 were considered statistically significant. Statistical significance of differences in relative survival was judged based on the 95 % confidence intervals (95 % CI).

3. Results

3.1. Patient characteristics

From 1990–2018, 463 children (0–17 years, median age: 12 years) and 379 AYAs (18–39 years, median age: 24 years) were diagnosed with Ewing sarcoma in the Netherlands (Table 1). Ewing sarcoma originated in the bone in 77 % of the children compared with 55 % of the AYAs (p < 0.001). No age-dependent differences in tumor site were noted for Ewing bone sarcoma. However, for extraosseous Ewing sarcoma, extremity tumors seemed more prevalent among AYAs at the expense of head and neck tumors (Supplementary Fig. S1). Additionally, AYAs more commonly presented with metastases at diagnosis than children (35 % vs. 28 %, p = 0.046) and metastases in AYAs were less likely to be isolated to the lungs. The percentage of children and AYAs with metastases at diagnosis increased over time resulting from a decrease in unknown disease stage, while the prevalence of localized disease remained constant (Supplementary Fig. S2). Although treatment at a non-UMC was more frequent among AYAs in earlier periods, in 2010–2018 almost all patients were cared for in a UMC regardless of age (data not shown). Differences in initial therapy existed between children and AYAs independent of disease stage, but were particularly pronounced in the metastatic setting (Supplementary Fig. S3). The percentage of children and AYAs receiving chemotherapy without local therapy decreased over time for both disease stages. In 2010–2018, only AYAs with metastatic disease still relatively commonly received this type of treatment (35 %).

3.2. Relative survival and excess mortality

Overall, the 5-year relative survival of children and AYAs with Ewing

sarcoma in the Netherlands was 56 % between 1990–2018 (Table 2). Children had a statistically significantly higher survival than AYAs (65 % vs. 44 %) (Fig. 1). Survival improved over time to a similar extent in both age groups, from 56 % to 70 % in children and from 37 % to 53 % in AYAs. Survival estimates were comparable for men and women. Overall, outcome did also not depend on tissue of origin (Table 2). Extraosseous tumors seemed nonetheless to have a lower survival in the 1990s, particularly in children (Fig. 1). Ewing bone tumors located at the pelvis had a worse prognosis than tumors located at other axial sites or the extremities (5-year relative survival: 41 % vs. 61–66 %). Among AYAs with extraosseous Ewing sarcoma, head and neck tumors seemed to be associated with a favorable outcome compared with the other sites (5-year relative survival: 82 % vs. 41–43 %), though numbers were small. Inferior survival of AYAs compared with children was observed for all tumor sites, except for bone tumors in the upper limb and extraosseous tumors in the head and neck. Moreover, AYAs had a worse outcome regardless of disease stage; survival probabilities were 60 % vs. 78 % for localized disease and 20 % vs. 33 % for metastatic disease. Site of metastases did not affect survival of patients diagnosed since 2008. Survival estimates by primary treatment are included in Supplementary Table S2. These findings should, however, be interpreted with caution because of the risk of immortal time bias. Detailed analyses showed a superior 5-year relative survival of 78 % for children aged 0–4 years (Figure 2). In subsequent age groups, survival gradually decreased, plateauing at 40–50 % in AYAs aged 18 years or older. Similar patterns were observed for localized and metastatic disease in stage-specific analyses.

Multivariable-regression analysis adjusting for follow-up time, diagnostic period, sex, disease stage, and tissue-specific tumor site confirmed higher excess mortality within 5 years of diagnosis for AYAs compared with children (excess HR, 95 % CI: 1.7, 1.3–2.1; Table 3). Using 0–4 year-olds as reference, statistically significantly increased excess HR were obtained for older children aged 15–17 years (excess

Table 1
Characteristics of children (0–17 years) and AYAs (18–39 years) diagnosed with Ewing sarcoma in the Netherlands between 1990–2018.

	All Ewing sarcoma						
	Total		Children		AYAs		
Characteristics	N	%	N	%	N	%	P(Chi^2)[a]
Overall	842		463		379		
Period of diagnosis							**0.01**
1990-1999	263	31.2	128	27.7	135	35.6	
2000-2009	300	35.6	163	35.2	137	36.2	
2010-2018	279	33.1	172	37.2	107	28.2	
Median age at diagnosis in years, IQR	16	(12-23)	12	(8-15)	24	(20-30)	
Sex							0.29
Male	483	57.4	258	55.7	225	59.4	
Female	359	42.6	205	44.3	154	40.6	
Microscopically verified	842	100	463	100	379	100	
Tissue of origin							**<0.001**
Bone	566	67.2	357	77.1	209	55.2	
Extraosseous	276	32.8	106	22.9	170	44.9	
Tumor site - bone[b]							0.53
Axial - pelvic	144	25.4	84	23.5	60	28.7	
Axial - other	182	32.2	116	32.5	66	31.6	
Extremity - upper limb	59	10.4	36	10.1	23	11.0	
Extremity - lower limb	179	31.6	119	33.3	60	28.7	
Not specified	2	0.4	2	0.6	0	0.0	
Tumor site - extraosseous[b]							**0.04**
Head & neck	27	9.8	16	15.1	11	6.5	
Trunk	156	56.5	62	58.5	94	55.3	
Extremity	85	30.8	25	23.6	60	35.3	
Other & not specified	8	2.9	3	2.8	5	2.9	
Stage at diagnosis							**0.046**
Localized	540	64.1	314	67.8	226	59.6	
Metastatic	262	31.1	130	28.1	132	34.8	
Unknown	40	4.8	19	4.1	21	5.5	
Metastatic site[c]							**0.01**
No metastases	213	62.5	134	66.0	79	57.3	
Lung only[d]	46	13.5	32	15.8	14	10.1	
Extrapulmonary	78	22.9	36	17.7	42	30.4	
Unknown	4	1.2	1	0.5	3	2.2	
Site of treatment							**<0.001**
Non-UMC	78	9.3	22	4.8	56	14.8	
UMC	764	90.7	441	95.3	323	85.2	
Primary treatment							**<0.001**
Surgery and/or RT	33	3.9	11	2.4	22	5.8	
Surgery only	25	3.0	9	1.9	16	4.2	
RT only	3	0.4	1	0.2	2	0.5	
Surgery & RT	5	0.6	1	0.2	4	1.1	
CT only	119	14.1	40	8.6	79	20.8	
CT & surgery and/or RT	676	80.3	406	87.7	270	71.2	
Other	3	0.4	0	0.0	3	0.8	
No treatment/unknown[e]	11	1.3	6	1.3	5	1.3	

Abbreviations: AYAs, adolescents and young adults; IQR, interquartile range; UMC, university medical center; RT, radiation therapy; CT, chemotherapy; ICD-O-3, International Classification of Diseases for Oncology, 3rd edition.

[a] Fisher's Exact test was used instead of Pearson's X^2 test when $N \leq 5$ in one or more categories.

[b] The ICD-O-3 topography codes included are listed for each tumor site in Supplementary Table S1.

[c] Metastatic site was only completely registered for patients diagnosed in 2008 or later.

[d] Includes metastases of the pleura.

[e] Numbers of patients with "unknown" treatment were 1 overall, 0 for children, and 1 for AYAs.

Table 2
Five-year relative survival[f] of children (0–17 years) and AYAs (18–39 years) diagnosed with Ewing sarcoma in the Netherlands between 1990–2018.

	All Ewing sarcoma								
	Total			Children			AYAs		
Characteristics	$N_{at\ risk}$	5-yr RS	95 % CI	$N_{at\ risk}$	5-yr RS	95 % CI	$N_{at\ risk}$	5-yr RS	95 % CI
Overall	842	55.5	(52.1-58.8)	463	64.7	(60.2-68.9)	379	44.3	(39.2-49.3)
Period of diagnosis									
1990-1999	263	46.3	(40.2-52.3)	128	56.3	(47.3-64.4)	135	36.8	(28.7-44.9)
2000-2009	300	56.0	(50.1-61.4)	163	65.5	(57.6-72.3)	137	44.6	(36.2-52.7)
2010-2018	279	63.7	(57.7-69.0)	172	70.2	(62.7-76.5)	107	53.3	(43.3-62.2)
P-trend		**< 0.001**			**0.01**			**0.01**	
Sex									
Male	483	55.7	(51.1-60.0)	258	66.6	(60.4-72.0)	225	43.2	(36.6-49.6)
Female	359	55.4	(50.1-60.4)	205	62.4	(55.4-68.7)	154	46.0	(37.9-53.6)
Tissue of origin									
Bone	566	58.0	(53.8-62.0)	357	65.7	(60.5-70.4)	209	44.9	(38.0-51.5)
Extraosseous	276	50.4	(44.4-56.2)	106	61.4	(51.4-69.9)	170	43.6	(36.1-50.9)
Tumor site - bone[g]									
Axial - pelvic	144	41.3	(33.2-49.2)	84	49.4	(38.2-59.6)	60	30.0	(19.0-41.8)
Axial - other	182	65.9	(58.4-72.3)	116	72.4	(63.3-79.7)	66	54.1	(41.3-65.4)
Extremity - upper limb	59	66.1	(52.5-76.7)	36	63.8	(45.9-77.2)	23	69.7	(46.7-84.4)
Extremity - lower limb	179	61.0	(53.4-67.7)	119	71.5	(62.4-78.7)	60	40.1	(27.7-52.2)
Not specified	2	NA		2	NA		0	NA	
Tumor site - extraosseous[g]									
Head & neck	27	74.2	(53.3-86.9)	16	68.9	(40.5-85.8)	11	82.0	(44.8-95.3)
Trunk	156	47.5	(39.5-55.1)	62	58.1	(44.9-69.2)	94	40.5	(30.6-50.3)
Extremity	85	49.4	(38.4-59.5)	25	64.1	(42.3-79.5)	60	43.3	(30.6-55.4)
Other & not specified	8	NA		3	NA		5	NA	
Stage at diagnosis									
Localized	540	70.2	(66.1-73.9)	314	77.7	(72.6-81.9)	226	59.7	(53.0-65.8)
Metastatic	262	26.3	(21.1-31.7)	130	32.8	(24.9-41.0)	132	19.7	(13.4-26.9)
Unknown	40	50.1	(33.9-64.3)	19	68.5	(42.9-84.5)	21	33.4	(14.9-53.2)
Metastatic site[h]									
No metastases	213	77.9	(71.7-83.0)	134	81.3	(73.6-87.0)	79	72.2	(60.9-80.8)
Lung only[i]	46	34.1	(20.8-47.9)	32	45.8	(27.9-62.1)	14	7.2	(0.5-27.6)
Extrapulmonary	78	33.2	(23.1-43.7)	36	41.5	(25.4-56.9)	42	26.1	(14.0-40.0)
Unknown	4	NA		1	NA		3	NA	
Site of treatment									
Non-UMC	78	44.9	(33.7-55.6)	22	68.3	(44.7-83.5)	56	35.7	(23.5-48.2)
UMC	764	56.6	(53.0-60.1)	441	64.5	(59.9-68.8)	323	45.8	(40.3-51.2)

NA: Estimation of a reliable survival probability was not possible because of $N_{at\ risk} < 10$.
Abbreviations: AYAs, adolescents and young adults; 5-yr RS, 5-year relative survival; 95 % CI, 95 % confidence interval; UMC, university medical center; ICD-O-3, International Classification of Diseases for Oncology, 3rd edition.
[f] Expected probabilities of survival were estimated using the Ederer II method.
[g] The ICD-O-3 topography codes included are listed for each tumor site in Supplementary Table S1.
[h] Metastatic site was only completely registered for patients diagnosed in 2008 or later.
[i] Includes metastases of the pleura.

HR: 2.2) and all AYAs (excess HR: 2.7–3.4). Furthermore, associations seemed stronger for localized disease than metastatic disease (excess $HR_{children\ vs.\ AYAs}$: 2.1 vs. 1.4; both $p < 0.05$).

Finally, 10-year relative survival was estimated as a sensitivity analysis. Although 10-year relative survival was slightly lower than 5-year relative survival, results were comparable (Figure 3). Between 1990–2018, 10-year relative survival increased from 51 % to 64 % in children and from 33 % to 48 % in AYAs. Again, estimates did not differ for Ewing bone sarcoma vs. extraosseous Ewing sarcoma and worse prognosis of AYAs was observed for both localized and metastatic disease.

4. Discussion

This comprehensive population-based study revealed that despite survival improvements since the 1990s, AYAs with Ewing sarcoma in the Netherlands still have an inferior outcome compared with children. The survival gap did not change over time and AYAs had a worse prognosis irrespective of tissue of origin, tumor site, and disease stage.

The approximately 20 %-point lower 5-year relative survival of AYAs with Ewing sarcoma in the Netherlands matches international data. In the US population, 5-year survival estimates of children and AYAs were 77 % vs. 54 % overall [11] and 79 % vs. 64 % for non-metastatic disease [13]. Similarly, a large European population study observed an 18 %-point lower 5-year relative survival for AYAs [12]. Inferior survival of AYAs compared with children was also demonstrated using population-based data from the Nordic countries [22], Ireland [23], and Japan [24].

The survival disparity between children and AYAs with Ewing sarcoma might be attributed to diversity in patient characteristics, treatment and therapy-related factors, and tumor biology across the age spectrum. Site of the primary tumor has been shown to be age-dependent. Pelvic primaries are increasingly common with age and are associated with less favorable outcome [4,25–27]. Although the proportion of pelvic bone tumors was somewhat higher in AYAs in our cohort as well, age was not significantly related to tumor site. Additionally, it has consistently been shown that older patients with Ewing sarcoma are more likely to have metastases at diagnosis, which is the strongest adverse prognostic factor [3,4,9,10,13,25]. In our study, 5-year relative survival of patients with metastatic disease was only 26 % compared with 70 % for localized disease, though improvements were visible over time. Stratified analysis demonstrated nevertheless that AYAs had worse survival regardless of the presence of metastases. According to the literature, the higher proportion of advanced disease among AYAs may be the result of the prolonged interval between symptom onset and diagnosis in this age group due to delayed patient presentation and recognition by health care professionals owing to a lack of awareness [28–31]. It remains, however, uncertain whether this

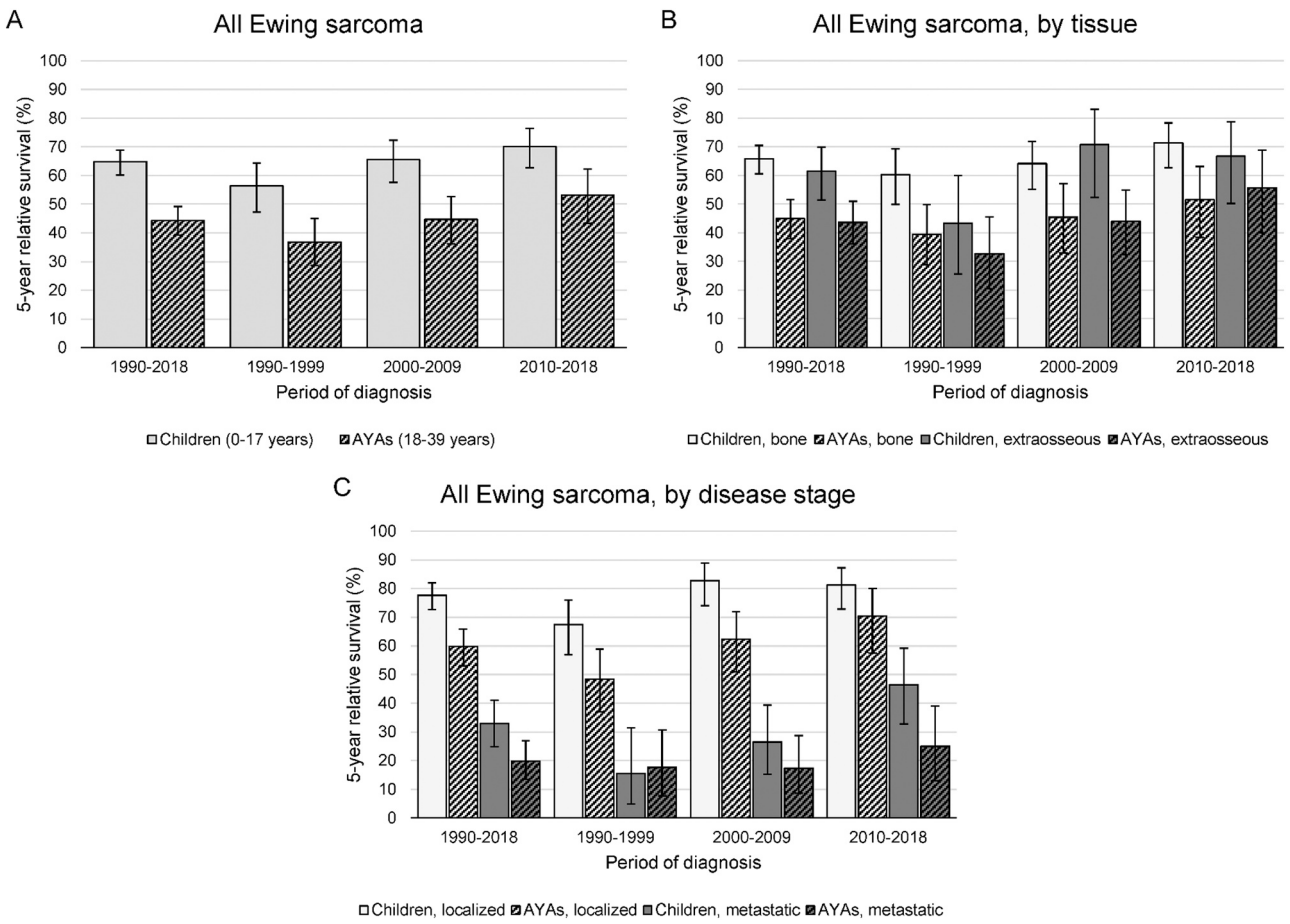

Fig. 1. Five-year relative survival of children (0–17 years) and AYAs (18–39 years) diagnosed with Ewing sarcoma in the Netherlands between 1990–2018, overall (A), by tissue (B), and by disease stage (C). The error bars depict 95 % confidence intervals of the survival estimates. Abbreviation: AYAs, adolescents and young adults.

diagnostic delay is related to survival outcome [28–30,32,33]. Besides differential patient characteristics, variation may exist between children and AYAs in treatment, toxicity, and other therapy-related factors. Ewing sarcoma trials have been open for both pediatric and AYA patients during the majority of our study period. In the Netherlands, children and AYAs with Ewing sarcoma were generally treated according to (European Intergroup) Cooperative Ewing's Sarcoma Study protocols CESS-86 [34], EICESS-92 [35], EURO-E.W.I.N.G.99 [36], EWING-2008 [37], or EURO EWING 2012 [6] (personal communication and [38–40]). Before the EURO-E.W.I.N.G.99 protocol, treatment of children with extraosseous Ewing sarcoma was variable consisting of regimens for Ewing bone sarcoma and soft tissue sarcoma [41]. Also, it is uncertain whether AYAs with extraosseous Ewing sarcoma received full treatment as various perspectives existed concerning the optimal management of this patient group. Despite concerns that AYAs may tolerate intense therapy less well than children, a safety analysis of the EURO-E.W.I.N.G.99 study including 224 AYAs (19–50 years) reported that the frequency of severe adverse reactions generally decreased with age [36]. It is unknown whether this finding points towards a biological effect or can be explained by differences in treatment tolerability, dose adaptations, or therapy compliance [4,36]. Similarly, lower rates of severe toxicity among AYAs have been observed in pediatric rhabdomyosarcoma trials [42]. Treatment of bone sarcoma in the Netherlands has been centralized in four expert centers in the past two decades. The percentage of patients treated at an expert center rose between 2000–2009 and 2010–2018 from 76 % to 83 % for children and from 51 % to 79 % for AYAs, which might have contributed to the increasing survival trend that we reported together with improvements and developments in diagnostics, local and systemic therapy, and supportive care. Since centralization of care took place from around 2000 while our study covered the time span from 1990–2018, we did not examine treatment at an expert center in the main analyses of our paper but used treatment at a UMC instead. Underinsurance of AYAs is no issue in the Netherlands where costs of anti-cancer therapy are completely covered by the obligatory standard health insurance. Finally, age-related differences in tumor biology may have played a role in the survival disparity. Ewing sarcoma is characterized by *FET::ETS* gene fusions, most commonly *EWSR1::FLI1* [1,3]. Since molecular analysis to detect the fusion gene was not routine in the Netherlands during the 1990s, we were not able to distinguish morphologically similar "Ewing-like" sarcomas without *FET::ETS* fusions, such as *BCOR*-rearranged, *CIC*-fused, and *NFATC2* sarcomas [3]. The predilection for certain gene fusion types in Ewing(-like) sarcoma varies with age [43]. Tsuda *et al.* [43] showed a higher median age at diagnosis for fusions involving the *FEV* and *NFATC2* genes than *EWSR1::FLI1*. Three-year overall survival was 91 % for *EWSR1::FLI1* compared with 60 % for alternative fusions. Furthermore, *BCOR*-rearranged and *CIC*-fused sarcomas are mostly diagnosed in teenagers and older AYAs, respectively [44]. While *BCOR*-rearranged sarcomas have a similar prognosis as "classic" Ewing sarcoma, the outcome of *CIC*-fused sarcomas is less favorable [3,44].

The relatively large number of patients analyzed and the use of nationwide population-based data promote the representativeness of our findings. Additionally, we were able to evaluate the impact of tissue of origin, tumor site, and disease stage, which has not often been done before. In the Netherlands, children younger than 18 years at diagnosis are managed by pediatric oncologists, whereas adult oncologists take

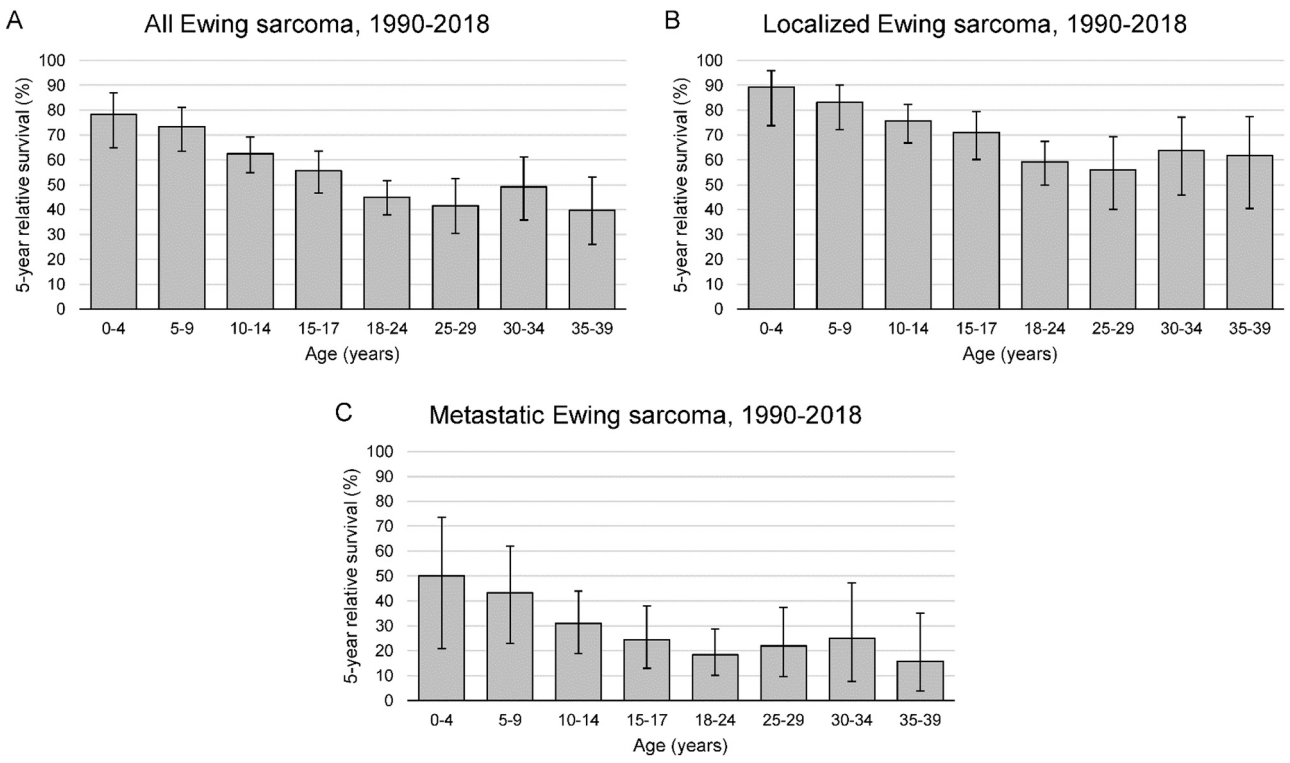

Fig. 2. Age-specific 5-year relative survival of children and AYAs (0–39 years) diagnosed with Ewing sarcoma in the Netherlands between 1990–2018, overall (A) and by disease stage (B,C). The error bars depict 95 % confidence intervals of the survival estimates. Abbreviation: AYAs, adolescents and young adults.

Table 3
Multivariable-adjusted associations[j] of age with excess mortality due to Ewing sarcoma within 5 years of diagnosis in children and AYAs (0–39 years) diagnosed in the Netherlands between 1990–2018, overall and by disease stage.

	All Ewing sarcoma				**Localized Ewing sarcoma**[k]				**Metastatic Ewing sarcoma**[k]			
	$N_{at\ risk}$	Excess HR	95 % CI	P-value	$N_{at\ risk}$	Excess HR	95 % CI	P-value	$N_{at\ risk}$	Excess HR	95 % CI	P-value
Age												
Children (0-17 years)	463	1.0 (ref)			314	1.0 (ref)			130	1.0 (ref)		
AYAs (18-39 years)	379	1.7	(1.3-2.1)	**< 0.001**	226	2.1	(1.5-3.0)	**< 0.001**	132	1.4	(1.0-2.0)	**0.03**
Age (years)												
0-9	153	1.0 (ref)			108	1.0 (ref)			35	1.0 (ref)		
10-17	310	1.7	(1.2-2.4)	**0.01**	206	1.8	(1.0-3.1)	**0.047**	95	1.5	(0.9-2.5)	0.15
18-29	272	2.4	(1.6-3.4)	**< 0.001**	164	3.3	(1.9-5.7)	**< 0.001**	97	1.9	(1.1-3.2)	**0.02**
30-39	107	2.5	(1.6-3.8)	**< 0.001**	62	3.0	(1.5-6.0)	**0.001**	35	2.0	(1.1-3.7)	**0.02**
Age (years)[l]												
0-4	55	1.0 (ref)										
5-9	98	1.3	(0.6-2.7)	0.46								
10-14	176	1.9	(1.0-3.5)	0.06								
15-17	134	2.2	(1.1-4.2)	**0.02**								
18-24	196	2.8	(1.5-5.3)	**0.001**								
25-29	76	2.8	(1.4-5.4)	**0.003**								
30-34	59	2.7	(1.3-5.3)	**0.01**								
35-39	48	3.4	(1.7-6.9)	**0.001**								

Abbreviations: AYAs, adolescents and young adults; Excess HR, excess hazard ratio; 95 % CI, 95 % confidence interval.

[j] All models were adjusted for follow-up time (years), diagnostic period (1990–1999; 2000–2009; 2010–2018), sex (male; female), disease stage (localized; metastatic; unknown), and tumor site (bone, axial - pelvic; bone, axial - other; bone, extremity - upper limb; bone, extremity - lower limb; bone, not specified; extraosseous, head & neck; extraosseous, trunk; extraosseous, extremity; extraosseous, other & not specified).

[k] The stage-specific models were not adjusted for disease stage.

[l] For this variable, multivariable-adjusted analyses were not performed stratified by disease stage because of insufficient numbers.

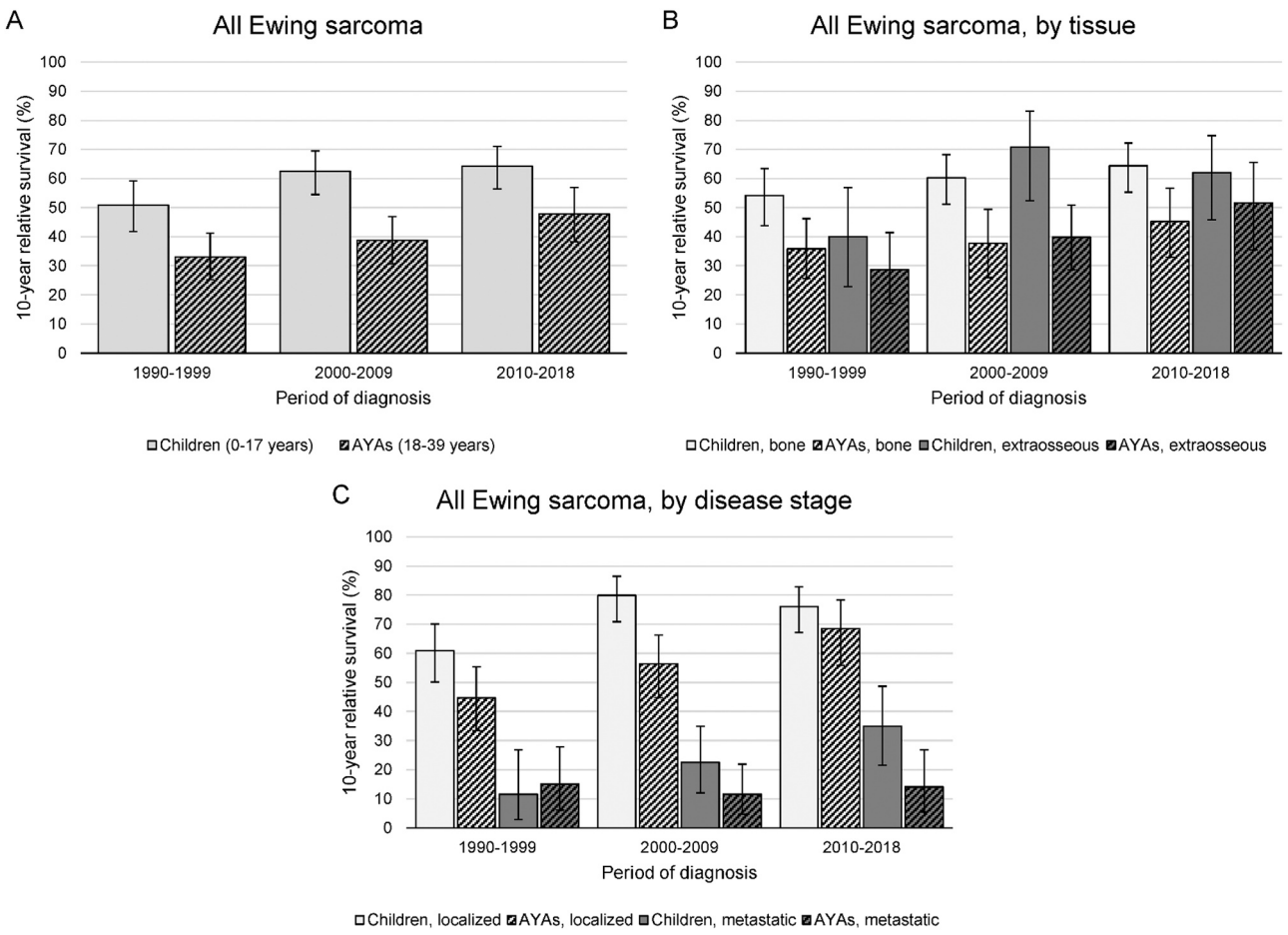

Fig. 3. Ten-year relative survival of children (0–17 years) and AYAs (18–39 years) diagnosed with Ewing sarcoma in the Netherlands between 1990–2018, overall (A), by tissue (B), and by disease stage (C). The error bars depict 95 % confidence intervals of the survival estimates. Ten-year relative survival for the period 2010–2018 has been estimated using period-based survival analysis because follow-up was complete until February 1, 2023. Abbreviation: AYAs, adolescents and young adults.

care of AYAs who were defined using the age range 18–39 years [45]. The latter slightly deviates from the internationally accepted definition of 15–39 years [12,46]. However, comparable results were obtained when we used an age cutoff of 15 years (data not shown). Changes in the diagnosis (i.e., introduction of molecular techniques and new imaging modalities) and classification of Ewing sarcoma over time may have influenced our findings [47]. Due to improvements in diagnostic techniques, the percentage of patients with unknown disease stage in our cohort almost decreased to zero, while an increase was observed in metastatic disease for both children and AYAs. Moreover, as mentioned earlier, the present analysis included "Ewing-like" sarcomas which have different clinical behavior and are no longer recognized as histological variants of Ewing sarcoma [3]. Furthermore, our definition encompassed peripheral primitive neuroectodermal tumors (pPNET) that were in past studies sometimes considered a separate entity. The inclusion of pPNET is reflected in the relatively large proportion of extraosseous Ewing sarcoma that we reported, as pPNET primarily originates from soft tissue. Although treatment of children and AYAs with Ewing sarcoma in the Netherlands became increasingly homogenized during our study period with the designation of four bone sarcoma expert centers, our data did indicate some treatment differences between children and AYAs with the same disease stage, especially in the presence of metastases. However, the available treatment information was very broad and individual therapy details lacked preventing the formulation of any strong conclusions about its influence on the survival disparity. Detailed treatment information as well as data regarding tumor size/volume, chemotherapy response, molecular features, clinical trial participation, cause of death, and recurrences would be of high value in future investigations.

Notwithstanding that AYAs with Ewing sarcoma in the Netherlands are treated according to the same protocols as children, they continue to fare considerably worse. The survival discrepancy was consistent across subgroups based on tissue of origin, tumor site, and disease stage, and did not diminish over the past three decades despite survival improvements. Though metastatic Ewing sarcoma was more frequent among AYAs, its outcome was dismal regardless of age at diagnosis and urgently requires the development of novel treatment strategies. Recently, the EURO EWING 2012 trial [6] showed that the US interval-compressed VDC (vincristine, doxorubicin, cyclophosphamide) plus IE (ifosfamide, etoposide) induction was associated with better survival, less toxicities, and shorter duration than the European VIDE (vincristine, ifosfamide, doxorubicin, etoposide) induction. As a result, VDC plus IE has been adopted as the new standard first-line treatment for children and AYAs with Ewing sarcoma in the Netherlands (and most of Europe), which will hopefully further improve outcomes in both age groups and resolve the currently persisting survival gap.

Ethics statement

According to the Central Committee on Research Involving Human Subjects (CCMO), this observational study does not require approval from a local ethics committee in the Netherlands. Use of anonymous data for our study was approved by the Privacy Review Board of the NCR and the Biobank and Data Access Committee of the Princess Máxima

Center for pediatric oncology.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CRediT authorship contribution statement

Lizz van der Heijden: Writing – review & editing. **Suzanne EJ Kaal:** Writing – review & editing. **Maya Schulpen:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Conceptualization. **Lianne M Haveman:** Writing – review & editing. **Jacco J de Haan:** Writing – review & editing. **Laura S Hiemcke-Jiwa:** Writing – review & editing. **Jos AM Bramer:** Writing – review & editing. **Henrike E Karim-Kos:** Writing – review & editing, Supervision, Methodology, Data curation, Conceptualization. **Raquel Davila Fajardo:** Writing – review & editing. **Hendrik WB Schreuder:** Writing – review & editing. **Jacqueline M Tromp:** Writing – review & editing. **Simone AJ ter Horst:** Writing – review & editing. **Paul C Jutte:** Writing – review & editing. **Hans Gelderblom:** Writing – review & editing. **Johannes HM Merks:** Writing – review & editing, Supervision, Conceptualization. **Winette TA van der Graaf:** Writing – review & editing. **Michiel AJ van de Sande:** Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

The data used in our study are available on request from the NCR. To obtain data of children diagnosed with cancer in the Netherlands since 2014, an additional permission from the Biobank and Data Access Committee of the Princess Máxima Center for pediatric oncology is required. Further information is available from the corresponding author.

Acknowledgements

The authors would like to thank the registration team of the Netherlands Comprehensive Cancer Organization (IKNL) for the collection of data for the NCR. Additionally, the authors acknowledge Dr Otto Visser (director of registration IKNL) for his help with the patient selection, and for sharing his expertise regarding the NCR data and registration practices. This work was generated within the European Reference Networks for pediatric oncology (ERN PAEDCAN) and rare adult solid cancers (EURACAN).

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2024.114209.

References

[1] Balamuth NJ, Womer RB. Ewing's sarcoma. Lancet Oncol 2010;11(2):184–92.
[2] Rainusso N, Wang LL, Yustein JT. The adolescent and young adult with cancer: state of the art – bone tumors. Curr Oncol Rep 2013;15(4):296–307.
[3] Grunewald TGP, Cidre-Aranaz F, Surdez D, Tomazou EM, de Alava E, Kovar H, et al. Ewing sarcoma. Nat Rev Dis Prim 2018;4(1):5.
[4] Worch J, Ranft A, DuBois SG, Paulussen M, Juergens H, Dirksen U. Age dependency of primary tumor sites and metastases in patients with Ewing sarcoma. Pedia Blood Cancer 2018;65(9):e27251.
[5] Ghandour M, Lehner B, Klotz M, Geisbusch A, Bollmann J, Renkawitz T, et al. Extraosseous ewing sarcoma in children: a systematic review and meta-analysis of clinicodemographic characteristics. Child (Basel) 2022;9(12).
[6] Brennan B, Kirton L, Marec-Berard P, Gaspar N, Laurence V, Martin-Broto J, et al. Comparison of two chemotherapy regimens in patients with newly diagnosed Ewing sarcoma (EE2012): an open-label, randomised, phase 3 trial. Lancet 2022;400(10362):1513–21.
[7] Koch R, Haveman L, Ladenstein R, Brichard B, Jurgens H, Cyprova S, et al. Zoledronic acid add-on therapy for standard-risk ewing sarcoma patients in the Ewing 2008R1 Trial. Clin Cancer Res 2023;29(24):5057–68.
[8] Koch R, Gelderblom H, Haveman L, Brichard B, Jurgens H, Cyprova S, et al. High-dose treosulfan and melphalan as consolidation therapy versus standard therapy for high-risk (metastatic) ewing sarcoma. J Clin Oncol 2022;40(21):2307–20.
[9] Duchman KR, Gao Y, Miller BJ. Prognostic factors for survival in patients with Ewing's sarcoma using the surveillance, epidemiology, and end results (SEER) program database. Cancer Epidemiol 2015;39(2):189–95.
[10] Gaspar N, Hawkins DS, Dirksen U, Lewis IJ, Ferrari S, Le Deley MC, et al. Ewing sarcoma: current management and future approaches through collaboration. J Clin Oncol 2015;33(27):3036–46.
[11] Keegan TH, Ries LA, Barr RD, Geiger AM, Dahlke DV, Pollock BH, et al. Comparison of cancer survival trends in the United States of adolescents and young adults with those in children and older adults. Cancer 2016;122(7):1009–16.
[12] Trama A, Botta L, Foschi R, Ferrari A, Stiller C, Desandes E, et al. Survival of European adolescents and young adults diagnosed with cancer in 2000-07: population-based data from EUROCARE-5. Lancet Oncol 2016;17(7):896–906.
[13] Chen I, Pasalic D, Fischer-Valuck B, Frangoul H, DeWees T, Shinohara ET, et al. Disparity in outcomes for adolescent and young adult patients diagnosed with pediatric solid tumors across 4 decades. Am J Clin Oncol 2018;41(5):471–5.
[14] Wilhelm M, Dirksen U, Bielack SS, Whelan JS, Lewis IJ, Jurgens H, et al. ENCCA WP17-WP7 consensus paper on teenagers and young adults (TYA) with bone sarcomas. Ann Oncol 2014;25(8):1500–5.
[15] Cash T, McIlvaine E, Krailo MD, Lessnick SL, Lawlor ER, Laack N, et al. Comparison of clinical features and outcomes in patients with extraskeletal versus skeletal localized Ewing sarcoma: a report from the Children's Oncology Group. Pedia Blood Cancer 2016;63(10):1771–9.
[16] Lynch AD, Gani F, Meyer CF, Morris CD, Ahuja N, Johnston FM. Extraskeletal versus Skeletal Ewing Sarcoma in the adult population: controversies in care. Surg Oncol 2018;27(3):373–9.
[17] Schouten LJ, Hoppener P, van den Brandt PA, Knottnerus JA, Jager JJ. Completeness of cancer registration in Limburg, The Netherlands. Int J Epidemiol 1993;22(3):369–76.
[18] van der Sanden GA, Coebergh JW, Schouten LJ, Visser O, van Leeuwen FE. Cancer incidence in The Netherlands in 1989 and 1990: first results of the nationwide Netherlands cancer registry. Coordinating Committee for Regional Cancer Registries. Eur J Cancer 1995;31A(11):1822–9.
[19] Dickman PW, Coviello E. Estimating and modeling relative survival. Stata J 2015;15(1):186–215.
[20] Ederer F., Heise H. Instructions to IBM 650 programmers in processing survival computations. Methodological note No.10. End Results Evaluation Section. Bethesda MD: National Cancer Institute; 1959.
[21] Brenner H, Hakulinen T. Advanced detection of time trends in long-term cancer patient survival: experience from 50 years of cancer registration in Finland. Am J Epidemiol 2002;156(6):566–77.
[22] Rostgaard K, Hjalgrim H, Madanat-Harjuoja L, Johannesen TB, Collin S, Hjalgrim LL. Survival after cancer in children, adolescents and young adults in the Nordic countries from 1980 to 2013. Br J Cancer 2019;121(12):1079–84.
[23] Alken S, Owens C, Gilham C, Grant C, Pears J, Deady S, et al. Survival of childhood and adolescent/young adult (AYA) cancer patients in Ireland during 1994-2013: comparisons by age. Ir J Med Sci 2020;189(4):1223–36.
[24] Fukushima T, Ogura K, Akiyama T, Takeshita K, Kawai A. Descriptive epidemiology and outcomes of bone sarcomas in adolescent and young adult patients in Japan. BMC Musculoskelet Disord 2018;19(1):297.
[25] Cotterill SJ, Ahrens S, Paulussen M, Jurgens HF, Voute PA, Gadner H, et al. Prognostic factors in Ewing's tumor of bone: analysis of 975 patients from the European Intergroup Cooperative Ewing's Sarcoma Study Group. J Clin Oncol 2000;18(17):3108–14.
[26] Gupta AA, Pappo A, Saunders N, Hopyan S, Ferguson P, Wunder J, et al. Clinical outcome of children and adults with localized Ewing sarcoma: impact of chemotherapy dose and timing of local therapy. Cancer 2010;116(13):3189–94.
[27] Marina N, Granowetter L, Grier HE, Womer RB, Randall RL, Marcus KJ, et al. Age, tumor characteristics, and treatment regimen as event predictors in ewing: a children's oncology group report. Sarcoma 2015;2015:927123.
[28] Ferrari A, Miceli R, Casanova M, Meazza C, Favini F, Luksch R, et al. The symptom interval in children and adolescents with soft tissue sarcomas. Cancer 2010;116(1):177–83.
[29] Ferrari A, Gasparini P, Gill J, Gorlick R. Challenges of clinical management of adolescent and young adults with bone and soft tissue sarcoma. Cancer J 2018;24(6):301–6.
[30] Soomers V, Husson O, Young R, Desar I, Van der Graaf W. The sarcoma diagnostic interval: a systematic review on length, contributing factors and patient outcomes. ESMO Open 2020;5(1).
[31] Younger E, Husson O, Asare B, Benson C, Judson I, Miah A, et al. Metastatic soft tissue sarcomas in adolescents and young adults: a specialist center experience. J Adolesc Young– Adult Oncol 2020;9(6):628–38.
[32] Brasme JF, Chalumeau M, Oberlin O, Valteau-Couanet D, Gaspar N. Time to diagnosis of Ewing tumors in children and adolescents is not associated with

metastasis or survival: a prospective multicenter study of 436 patients. J Clin Oncol 2014;32(18):1935–40.
[33] Goedhart LM, Gerbers JG, Ploegmakers JJ, Jutte PC. Delay in diagnosis and its effect on clinical outcome in high-grade sarcoma of bone: a referral oncological centre study. Orthop Surg 2016;8(2):122–8.
[34] Paulussen M, Ahrens S, Dunst J, Winkelmann W, Exner GU, Kotz R, et al. Localized Ewing tumor of bone: final results of the cooperative Ewing's Sarcoma Study CESS 86. J Clin Oncol 2001;19(6):1818–29.
[35] Paulussen M, Craft AW, Lewis I, Hackshaw A, Douglas C, Dunst J, et al. Results of the EICESS-92 Study: two randomized trials of Ewing's sarcoma treatment–cyclophosphamide compared with ifosfamide in standard-risk patients and assessment of benefit of etoposide added to standard treatment in high-risk patients. J Clin Oncol 2008;26(27):4385–93.
[36] Juergens C, Weston C, Lewis I, Whelan J, Paulussen M, Oberlin O, et al. Safety assessment of intensive induction with vincristine, ifosfamide, doxorubicin, and etoposide (VIDE) in the treatment of Ewing tumors in the EURO-E.W.I.N.G. 99 clinical trial. Pedia Blood Cancer 2006;47(1):22–9.
[37] Whelan J, Le Deley MC, Dirksen U, Le Teuff G, Brennan B, Gaspar N, et al. High-dose chemotherapy and blood autologous stem-cell rescue compared with standard chemotherapy in localized high-risk ewing sarcoma: results of Euro-E.W.I.N.G.99 and Ewing-2008. J Clin Oncol 2018;36(31). JCO2018782516.
[38] Kerst JM, Van Coevorden F, Peterse J, Haas RL, Linn SC. Young adults with Ewing's sarcoma. Ned Tijdschr Geneeskd 2004;148(27):1355–8 (in Dutch).
[39] Smorenburg CH, van Groeningen CJ, Meijer OW, Visser M, Boven E. Ewing's sarcoma and primitive neuroectodermal tumour in adults: single-centre experience in The Netherlands. Neth J Med 2007;65(4):132–6.
[40] Bosma SE, van der Heijden L, Sierrasesumaga L, Merks H, Haveman LM, van de Sande MAJ, et al. What Do We Know about survival in skeletally premature children aged 0 to 10 years with ewing sarcoma? A multicenter 10-year follow-up study in 60 patients. Cancers (Basel) 2022;14(6).
[41] van den Berg H, Heinen RC, van der Pal HJ, Merks JH. Extra-osseous Ewing sarcoma. Pedia Hematol Oncol 2009;26(4):175–85.
[42] Ferrari A, Chisholm JC, Jenney M, Minard-Colin V, Orbach D, Casanova M, et al. Adolescents and young adults with rhabdomyosarcoma treated in the European paediatric Soft tissue sarcoma Study Group (EpSSG) protocols: a cohort study. Lancet Child Adolesc Health 2022;6(8):545–54.
[43] Tsuda Y, Zhang L, Meyers P, Tap WD, Healey JH, Antonescu CR. The clinical heterogeneity of round cell sarcomas with EWSR1/FUS gene fusions: Impact of gene fusion type on clinical features and outcome. Genes Chromosomes Cancer 2020;59(9):525–34.
[44] Hesla AC, Papakonstantinou A, Tsagkozis P. Current status of management and outcome for patients with Ewing Sarcoma. Cancers (Basel) 2021;13(6).
[45] ⟨https://ayazorgnetwerk.nl/⟩ (accessed March 2024, in Dutch).
[46] US Department of Health and Human Services, US National Institutes of Health, US National Cancer Institute, Adolescent and Young Adult Oncology Progress Review Group. Closing the gap: research and care imperatives for adolescents and young adults with cancer. 2006.
[47] Zollner SK, Amatruda JF, Bauer S, Collaud S, de Alava E, DuBois SG, et al. Ewing Sarcoma-diagnosis, treatment, clinical challenges and future perspectives. J Clin Med 2021;10(8).