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Original research

Incidence and survival of European adolescents and young adults diagnosed with sarcomas: EUROCARE-6 results

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ABSTRACT

Background: Epidemiological data for sarcoma in adolescents and young adults (AYAs) and across age groups are limited. We aim to: 1) update sarcoma incidence, survival, and changes over time in European AYAs; 2) provide an updated comparison of sarcoma survival in AYAs versus children and mature adults.
Methods: We calculated crude incidence rates (IR) per 100,000 European population per year from 2006 to 2013. Using the period approach, we calculated 5-year relative survival (RS) for the follow-up period 2010–2014. We estimated changes in incidence and survival for bone sarcoma (BS) and soft tissue sarcoma (STS) subtypes in AYAs in the years 2000–2013.

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Findings: In European AYAs, the IR was 0.81/100,000 for BS and 1.45/100,000 for STS. Five-year RS was 69 % and 65 % for BS and STS, respectively. Compared to children, AYAs had poorer survival for Ewing sarcoma of bone, synovial sarcoma, Ewing sarcoma of soft tissue and rhabdomyosarcoma. Compared to mature adults, AYAs had higher 5-year RS for all BS and for most of the STS subtypes. In AYAs, incidence increased for a few bone and soft tissue subtypes. Survival increased mainly for BS.
Interpretation: The reason for the better survival observed in AYAs compared to mature adults is probably multifactorial. The limited improvement of STS survival in AYAs may reflect the relative absence of new drugs for STS during the study period. The increase in RS for BS might relate to general improvements in radiological and surgical approaches and radiotherapy techniques.

1. Introduction

Sarcomas are rare tumours of mesenchymal origin. They can be divided into dozens of histological subtypes and can occur in virtually any anatomical site [1]. This complex interaction between anatomical site and histology leads to a wide heterogeneity of clinical entities, which also differ across age classes. In adolescents and young adults (AYAs, 15–39 years) [2], sarcomas include subtypes typical of children and adults as they progress from adolescence to early adulthood [3–5]. The heterogeneity and rarity of this family of tumours mean that data, including epidemiological data, are limited. Thus, routine statistics [6,7] either do not include sarcomas or are not histotype-specific [8,9]. Using the most recent data available in the EUROCARE-6 database, we aimed to update the incidence, survival, and changes over time in European AYAs, unveiling the heterogeneity of sarcoma subtypes in this age group [10].

Specifically, although survival has increased for many cancers in AYAs, the previous EUROCARE-5 study showed worse survival for most cancers in AYAs compared to children, and better survival compared to adults [10]. We will describe sarcoma subtypes across age groups (from children to mature adults i.e. between the ages of 40 and 69 years) and provide an updated comparison of sarcoma survival in AYAs versus children and mature adults by selecting sarcoma subtypes common to each age group.

2. Methods

2.1. Study design and data collection

We used the EUROCARE-6 database, which houses data from 108 population-based cancer registries (CRs) from 29 European countries, as previously described [11]. Registries provided information on the site and morphology of each diagnosed cancer, coded according to the International Classification of Disease for Oncology, Third Edition, first update (ICD-O-3.1) [12]. Only malignant tumours (/3) are registered and therefore included in the analyses. We used ICD-O-3 codes to define the most common malignant primary bone (BS) and soft tissue sarcomas (STS) in AYAs (Supplementary Material, Table S1). We excluded sarcomas of the skin because data were incomplete.

2.2. Incidence 2006-2013

We calculated crude incidence rates (IR) per 100,000 individuals per year in the European population from 2006 to 2013. We only included general CRs in the incidence analyses, excluding CRs specialising solely in specific tumour groups. A total of 95 CRs across Europe contributed to this study, covering about 57 % of the European population (EU27 + Switzerland, UK, Norway, and Iceland).

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Table 1
Crude incidence rate (IR) of bone and soft tissue sarcomas in European adolescents and young adults (aged 15–39 years) and in different age groups (15–19, 20–29, 30–39 years) by subtype, in 2006–2013, reported with 95 % confidence intervals (95 %CI) and number of cases (N). IR x 100,000.

	AYA (15–39 years)				15–19 years				20–29 years				30–39 years			
	N	IR	95 % CI		N	IR	95 % CI		N	IR	95 % CI		N	IR	95 % CI	
Bone sarcomas	5693	0.81	0.79	0.83	1816	1.44	1.38	1.51	2048	0.73	0.70	0.76	1829	0.62	0.59	0.65
Osteosarcoma	1982	0.28	0.27	0.30	898	0.71	0.67	0.76	638	0.23	0.21	0.25	446	0.15	0.14	0.17
Chondrosarcoma	1352	0.19	0.18	0.20	136	0.11	0.09	0.13	458	0.16	0.15	0.18	758	0.26	0.24	0.28
Ewing sarcoma of bone	1401	0.20	0.19	0.21	608	0.48	0.45	0.52	570	0.20	0.19	0.22	223	0.08	0.07	0.09
Soft tissue sarcomas	10,150	1.45	1.42	1.48	1386	1.10	1.04	1.16	3243	1.16	1.12	1.20	5521	1.87	1.82	1.92
Desmoplastic small round-cell tumour	123	0.02	0.01	0.02	22	0.02	0.01	0.03	60	0.02	0.02	0.03	41	0.01	0.01	0.02
Synovial sarcoma	449	0.06	0.06	0.07	84	0.07	0.05	0.08	180	0.06	0.06	0.07	185	0.06	0.05	0.07
Malignant peripheral nerve sheath tumour	621	0.09	0.08	0.10	88	0.07	0.06	0.09	265	0.09	0.08	0.11	268	0.09	0.08	0.10
Liposarcoma	1452	0.21	0.20	0.22	69	0.05	0.04	0.07	325	0.12	0.10	0.13	1058	0.36	0.34	0.38
Epithelioid sarcoma	218	0.03	0.03	0.04	28	0.02	0.01	0.03	83	0.03	0.02	0.04	107	0.04	0.03	0.04
Leiomyosarcoma	1138	0.16	0.15	0.17	52	0.04	0.03	0.05	243	0.09	0.08	0.10	843	0.29	0.27	0.31
Clear-cell sarcoma	150	0.02	0.02	0.03	24	0.02	0.01	0.03	68	0.02	0.02	0.03	58	0.02	0.01	0.03
Alveolar soft part sarcoma	132	0.02	0.02	0.02	30	0.02	0.02	0.03	64	0.02	0.02	0.03	38	0.01	0.01	0.02
Angiosarcoma	291	0.04	0.04	0.05	24	0.02	0.01	0.03	88	0.03	0.03	0.04	179	0.06	0.05	0.07
Undifferentiated high-grade pleomorphic sarcoma	259	0.04	0.03	0.04	22	0.02	0.01	0.03	86	0.03	0.02	0.04	151	0.05	0.04	0.06
Rhabdomyosarcoma	816	0.12	0.11	0.12	349	0.28	0.25	0.31	274	0.10	0.09	0.11	193	0.07	0.06	0.08
Rhabdomyosarcoma, not otherwise specified / Embryonal / Alveolar	744	0.11	0.10	0.11	336	0.27	0.24	0.30	247	0.09	0.08	0.10	161	0.05	0.05	0.06
Pleomorphic rhabdomyosarcoma	44	0.01	0.00	0.01	2	0.00	0.00	0.01	20	0.01	0.00	0.01	22	0.01	0.00	0.01
Ewing sarcoma of soft tissue	663	0.09	0.09	0.10	187	0.15	0.13	0.17	284	0.10	0.09	0.11	192	0.07	0.06	0.08
Other soft tissue sarcomas	3838	0.55	0.53	0.57	407	0.32	0.29	0.36	1223	0.44	0.41	0.46	2208	0.75	0.72	0.78
Ewing sarcoma of bone and soft tissue	2064	0.29	0.28	0.31	795	0.63	0.59	0.68	854	0.30	0.28	0.33	415	0.14	0.13	0.16

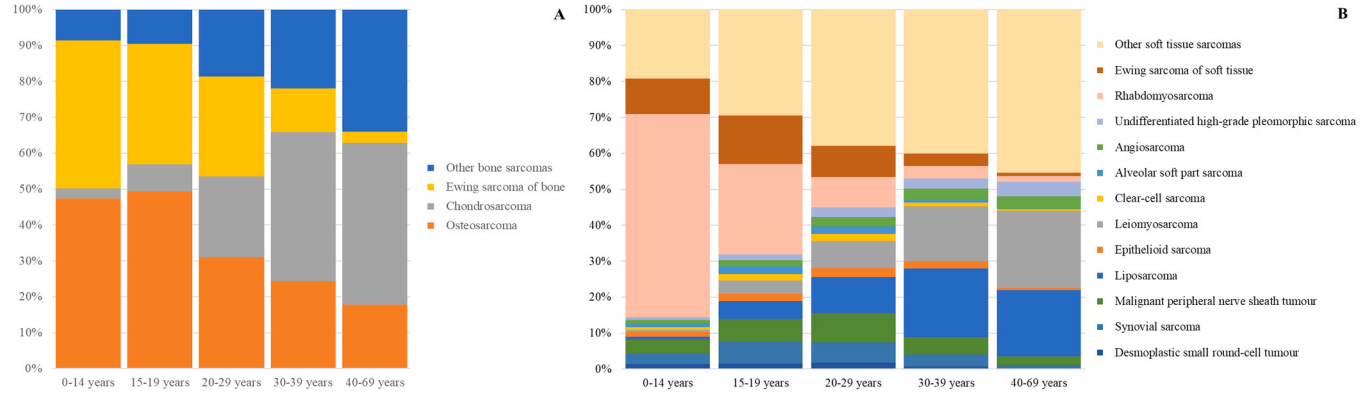

Fig. 1. Percentage distribution of bone (A) and soft tissue (B) sarcomas subtypes in children (aged 0–14 years), AYA age groups (15–19, 20–29, 30–39 years) and mature adults (40–69 years).

2.3. Survival 2010-2014

Using the period approach, we calculated 5-year relative survival (RS) for the follow-up period 2010–2014, based on cases diagnosed in 2006–2013, followed up for vital status to December 31st, 2014, in the same 95 CRs [13]. We used RS, which is the ratio of observed to expected survival in the general population of the same age, calendar year, registry, and sex, to correct for deaths from causes other than sarcoma. We estimated expected survival by the Ederer II method [14], censoring individuals who had not experienced the event by the end of the study or were lost to follow-up.

We reported incidence for the most common BS and STS subtypes for AYAs and across AYA age groups. Furthermore, we compared both incidence and survival of AYAs vs children and mature adults in selected sarcoma subtypes common to both age groups being considered. In the analysis, leiomyosarcomas (LMS) were described as either uterine- or non-uterine-LMS, as evidence suggests they exhibit different biology and clinical behaviour [15]. Liposarcomas were divided into the subtypes myxoid, well- and de-differentiated, and pleomorphic liposarcoma, as they are specific entities, each featuring adipocytic differentiation but with distinct pathology, clinical history, and treatment [1].

Ewing sarcomas, which occur in both bone and soft tissue, were examined separately by site of origin and combined as a single entity. We excluded cases aged over 70 years since major comorbidities and old age have a significant impact on treatment and survival, limiting the value of comparison with AYAs. We required a minimum of 40 cases of each sarcoma subtype to present and compare incidence and RS estimates across age groups.

2.4. Variation over time

We estimated changes over time in incidence and survival for BS and STS subtypes in AYAs. We estimated changes in incidence from 2000 to 2013 using the Incidence Rate Ratio (IRR) i.e. the ratio between the IR in 2009–13 and 2000–04. We used the F-Intervals p-value to evaluate IRR differences over time [16].

We analysed changes in 5-year RS, using the difference in survival between two follow-up periods: 2010–2014 (of the cohort diagnosed in 2006–2013) and 2004–2006 (of the cohort diagnosed in 2000–2006). We used the Z-test to assess relevant survival differences over time.

Of the 95 participating CRs, 69 provided data covering at least the period of diagnosis 2001–2010, which contributed to the survival and

Table 2
Crude incidence rate (IR) of bone and soft tissue sarcomas in European adolescents and young adults (aged 15–39 years), children (0–14 years) and mature adults (40–69 years) by subtype common to each age group being compared, in 2006–2013, reported with 95 % confidence intervals (95 % CI) and number of cases (N). IR x 100,000.

	0–14 years				AYA (15–39 years)				40–69 years			
	N	IR	95 % CI		N	IR	95 % CI		N	IR	95 % CI	
Bone sarcomas	2323	0.69	0.66	0.72	5693	0.81	0.79	0.83	8139	1.00	0.98	1.02
Osteosarcoma	1100	0.33	0.31	0.35	1982	0.28	0.27	0.30	1452	0.18	0.17	0.19
Chondrosarcoma	66	0.02	0.02	0.02	1352	0.19	0.18	0.20	3673	0.45	0.44	0.47
Ewing sarcoma of bone	958	0.28	0.27	0.30	1401	0.20	0.19	0.21	253	0.03	0.03	0.04
Other bone sarcomas	199	0.06	0.05	0.07	958	0.14	0.13	0.15	2761	0.34	0.33	0.35
Soft tissue sarcomas	2702	0.80	0.77	0.83	10,150	1.45	1.42	1.48	50,329	6.17	6.12	6.22
Synovial sarcoma	80	0.02	0.02	0.03	449	0.06	0.06	0.07	538	0.07	0.06	0.07
Malignant peripheral nerve sheath tumour	102	0.03	0.02	0.04	621	0.09	0.08	0.10	1196	0.15	0.14	0.16
Liposarcoma	-	-	-	-	1452	0.21	0.20	0.22	9266	1.14	1.11	1.16
Myxoid liposarcoma	-	-	-	-	735	0.10	0.10	0.11	1903	0.23	0.22	0.24
Pleomorphic liposarcoma	-	-	-	-	69	0.01	0.01	0.01	723	0.09	0.08	0.10
Liposarcoma, well differentiated, not otherwise specified	-	-	-	-	243	0.03	0.03	0.04	2548	0.31	0.30	0.32
Dedifferentiated liposarcoma	-	-	-	-	66	0.01	0.01	0.01	1194	0.15	0.14	0.15
Well differentiated and Dedifferentiated liposarcoma	-	-	-	-	309	0.04	0.04	0.05	3742	0.46	0.44	0.47
Epithelioid sarcoma	-	-	-	-	218	0.03	0.03	0.04	327	0.04	0.04	0.04
Leiomyosarcoma	-	-	-	-	1138	0.16	0.15	0.17	10,846	1.33	1.30	1.35
Uterine Leiomyosarcoma	-	-	-	-	292	0.04	0.04	0.05	4011	0.49	0.48	0.51
Non uterine Leiomyosarcoma	-	-	-	-	846	0.12	0.11	0.13	6835	0.84	0.82	0.86
Clear-cell sarcoma	-	-	-	-	150	0.02	0.02	0.03	144	0.02	0.01	0.02
Alveolar soft part sarcoma	21	0.01	0.00	0.01	132	0.02	0.02	0.02	53	0.01	0.00	0.01
Angiosarcoma	-	-	-	-	291	0.04	0.04	0.05	1782	0.22	0.21	0.23
Undifferentiated high-grade pleomorphic sarcoma	-	-	-	-	259	0.04	0.03	0.04	2007	0.25	0.24	0.26
Rhabdomyosarcoma	1525	0.45	0.43	0.48	816	0.12	0.11	0.12	862	0.11	0.10	0.11
Rhabdomyosarcoma, not otherwise specified / Embryonal / Alveolar	1508	0.45	0.43	0.47	744	0.11	0.10	0.11	561	0.07	0.06	0.07
Pleomorphic rhabdomyosarcoma	-	-	-	-	44	0.01	0.00	0.01	266	0.03	0.03	0.04
Ewing sarcoma of soft tissue	268	0.08	0.07	0.09	663	0.09	0.09	0.10	453	0.06	0.05	0.06
Ewing sarcoma of bone and soft tissue	1226	0.36	0.34	0.38	2064	0.29	0.28	0.31	706	0.09	0.08	0.09

incidence trend analyses.

3. Results

3.1. Incidence

We analysed 5693 and 10,150 AYAs diagnosed with BS and STS in 2006–2013, respectively (Table 1). The IR was 0.81/100,000 for BS and 1.45/100,000 for STS, corresponding to 1 % and 2 %, respectively, of AYA malignant tumours (excluding non-melanoma skin lesions). The IR for Ewing sarcoma of bone and soft tissue was 0.29/100,000.

The distribution of sarcoma subtypes differed within the AYA age groups. Among BS, osteosarcoma and Ewing sarcoma were more common in adolescents, while chondrosarcoma was more frequent in 30–39-year-olds. Among the STS, liposarcoma and LMS were the most common in those aged 30–39 years, and rhabdomyosarcoma (RMS) was the most frequent in adolescents (15–19 years), followed by synovial sarcoma and malignant peripheral nerve sheath tumour (MPNST) (Table 1). More details of the incidence of AYA sarcoma subtypes presented by 5-year age groups are reported in the Supplementary Material, Table S2.

Differences in the incidence of specific sarcoma subtypes within the AYA age groups mirrored differences between major age groups. Ewing sarcoma of bone and osteosarcoma were predominant among children (41 % and 47 %, respectively) and decreased with increasing age (Figure 1A). Among STS, RMS accounted for 56 % of childhood cases (0–14 years). Liposarcoma and LMS were predominant in mature adults (18 % and 22 % of STS, respectively) (Figure 1B).

Table 2 presents the IR of sarcoma subtypes common to children and AYAs or AYAs and mature adults. Among the liposarcomas, myxoid liposarcoma represented 51 % of liposarcomas in AYAs and 21 % in mature adults. Well-differentiated and dedifferentiated liposarcomas corresponded to 21 % and 40 % of liposarcomas in AYAs and mature adults, respectively. Regarding LMS, non-uterine were more common than uterine LMS in both AYAs and mature adults; however, the IR of uterine LMS was higher in mature adults than in AYAs. As regards RMS, in children and AYAs embryonal RMS was the most common across age groups, while pleomorphic RMS IR was higher in mature adults than in AYAs. Noteworthily, the heterogeneous availability of molecular testing for alveolar RMS may have led to misdiagnoses or non-specific diagnoses such as RMN, not otherwise specified.

3.2. Survival

Table 3 reports the 5-year RS for BS and STS subtypes in AYAs, children, and mature adults.

In AYAs, 5-year RS was 69 % and 65 % for BS and STS, respectively. Ewing sarcoma of bone and soft tissue had a 5-year RS of 52 %. Regarding BS, chondrosarcoma had the highest survival (87 %) followed by osteosarcoma (64 %) and Ewing sarcomas (51 %). Among the STS, liposarcoma showed the highest (86 %) survival, followed by LMS (74 %) and synovial sarcoma (66 %). The poorest prognosis was observed for RMS and angiosarcoma (41 % and 33 %, respectively).

Compared to children, AYAs had similar 5-year RS for BS overall but poorer survival for Ewing sarcoma of bone. AYAs showed poorer survival for STS overall and specifically poorer for synovial sarcoma, Ewing sarcoma, and RMS. AYAs had worse survival than children also for Ewing sarcoma of bone and soft tissue.

Compared to mature adults, AYAs had higher 5-year RS for BS and the related subtypes and higher survival for STS overall and for most of the STS subtypes (synovial sarcoma, liposarcoma, epithelioid sarcoma, uterine and non-uterine leiomyosarcoma, alveolar soft part sarcoma, undifferentiated pleomorphic sarcoma [UPS], and RMS).

3.3. Variation over time

In BS in AYAs, IR slightly increased over time for chondrosarcoma and Ewing sarcoma (by 16 % and 14 %, respectively from about 0.17–0.2/100,000). In STS in AYAs, IR slightly increased for four subtypes (synovial sarcoma, liposarcoma, LMS, clear-cell sarcoma). The incidence of UPS decreased (-40 %, Figure 2).

Table 3
Five-year relative survival (RS) for bone and soft tissue sarcomas in European adolescents and young adults (aged 15–39 years), in children (0–14 years) and mature adults (40–69 years) by subtype common to each age group being compared, reported with 95 % confidence intervals (95 %CI) and number of cases (N). Follow-up period 2010–2014, based on cases diagnosed in 2006–2013.

	0–14 years				AYA (15–39 years)				40–69 years			
	N	RS	95 % CI		N	RS	95 % CI		N	RS	95 % CI	
Bone sarcomas	1170	70.2 %	67.4 %	72.8 %	2824	69.0 %	67.2 %	70.7 %	4003	63.6 %	62.0 %	65.2 %
Osteosarcoma	558	66.9 %	62.8 %	70.6 %	986	64.2 %	61.1 %	67.2 %	741	45.9 %	42.1 %	49.6 %
Chondrosarcoma	34	90.0 %	71.4 %	96.7 %	678	86.6 %	83.7 %	89.0 %	1861	74.5 %	72.2 %	76.6 %
Ewing sarcoma of bone	478	69.4 %	64.9 %	73.4 %	710	51.1 %	47.2 %	54.8 %	126	32.1 %	23.9 %	40.5 %
Soft tissue sarcomas	1350	72.6 %	70.1 %	75.0 %	5034	65.4 %	64.0 %	66.7 %	25,199	60.2 %	59.6 %	60.9 %
Synovial sarcoma	40	97.3 %	81.6 %	99.6 %	223	66.1 %	59.5 %	71.9 %	275	52.4 %	46.1 %	58.4 %
Malignant peripheral nerve sheath tumour	50	59.4 %	44.1 %	71.7 %	315	48.3 %	42.5 %	53.8 %	592	47.1 %	42.8 %	51.3 %
Liposarcoma	-	-	-	-	723	85.6 %	82.7 %	88.1 %	4661	77.6 %	76.2 %	78.9 %
Myxoid liposarcoma	-	-	-	-	366	90.9 %	87.2 %	93.5 %	948	81.5 %	78.6 %	84.1 %
Pleomorphic liposarcoma	-	-	-	-	35	65.6 %	47.1 %	79.0 %	361	53.8 %	48.2 %	59.1 %
Liposarcoma, well differentiated, not otherwise specified	-	-	-	-	122	95.1 %	88.8 %	97.9 %	1323	93.3 %	91.3 %	94.9 %
Dedifferentiated liposarcoma	-	-	-	-	34	64.2 %	45.7 %	77.9 %	595	53.9 %	49.6 %	58.0 %
Well differentiated and Dedifferentiated liposarcoma	-	-	-	-	154	87.8 %	81.1 %	92.2 %	1902	80.4 %	78.3 %	82.3 %
Epithelioid sarcoma	-	-	-	-	114	63.0 %	53.2 %	71.2 %	176	45.2 %	37.1 %	52.9 %
Leiomyosarcoma	-	-	-	-	567	74.0 %	70.1 %	77.6 %	5410	52.1 %	50.7 %	53.5 %
Uterine Leiomyosarcoma	-	-	-	-	146	72.2 %	63.6 %	79.0 %	2013	43.4 %	41.2 %	45.6 %
Non uterine Leiomyosarcoma	-	-	-	-	422	74.6 %	70.1 %	78.6 %	3403	57.4 %	55.6 %	59.2 %
Clear-cell sarcoma	-	-	-	-	75	51.2 %	38.6 %	62.4 %	73	47.2 %	34.3 %	59.1 %
Alveolar soft part sarcoma	-	-	-	-	65	65.0 %	51.7 %	75.4 %	28	31.5 %	13.7 %	51.1 %
Angiosarcoma	-	-	-	-	144	32.6 %	24.8 %	40.5 %	904	28.3 %	25.3 %	31.4 %
Undifferentiated high-grade pleomorphic sarcoma	-	-	-	-	130	67.4 %	58.0 %	75.1 %	995	54.7 %	51.2 %	58.0 %
Rhabdomyosarcoma	771	69.2 %	65.8 %	72.4 %	401	40.9 %	36.0 %	45.7 %	440	27.3 %	23.1 %	31.7 %
Rhabdomyosarcoma, not otherwise specified / Embryonal / Alveolar	760	68.8 %	65.3 %	72.1 %	365	40.0 %	34.9 %	45.1 %	292	26.8 %	21.6 %	32.2 %
Pleomorphic rhabdomyosarcoma	-	-	-	-	-	-	-	-	133	26.7 %	19.6 %	34.3 %
Ewing sarcoma of soft tissue	132	69.2 %	60.3 %	76.4 %	335	53.7 %	48.0 %	59.0 %	228	41.5 %	34.5 %	48.3 %
Ewing sarcoma of bone and soft tissue	609	69.4 %	65.5 %	73.0 %	1043	51.9 %	48.8 %	55.0 %	351	38.3 %	32.9 %	43.7 %

In BS in AYAs, 5-year RS increased, notably for chondrosarcoma (by 8 % from 77 % to 85 % from 2004 to 2014). Improvements in survival were reported also for Ewing sarcoma of bone and soft tissue. For STS in AYA, we observed a 1.4 % increase, which seemed also consistent and, possibly, clinically relevant, albeit not statistically significant (Figure 3).

4. Discussion

Two major findings of our study were: (1) that survival in AYAs was lower for synovial sarcoma, RMS, and Ewing sarcoma of both soft tissue and bone compared to children, and that survival only slightly improved by 1.4 % over time for STS but increased by 4.4 % for BS. Moreover, (2) for most STS and all BS subtypes AYAs had better 5-year RS than mature

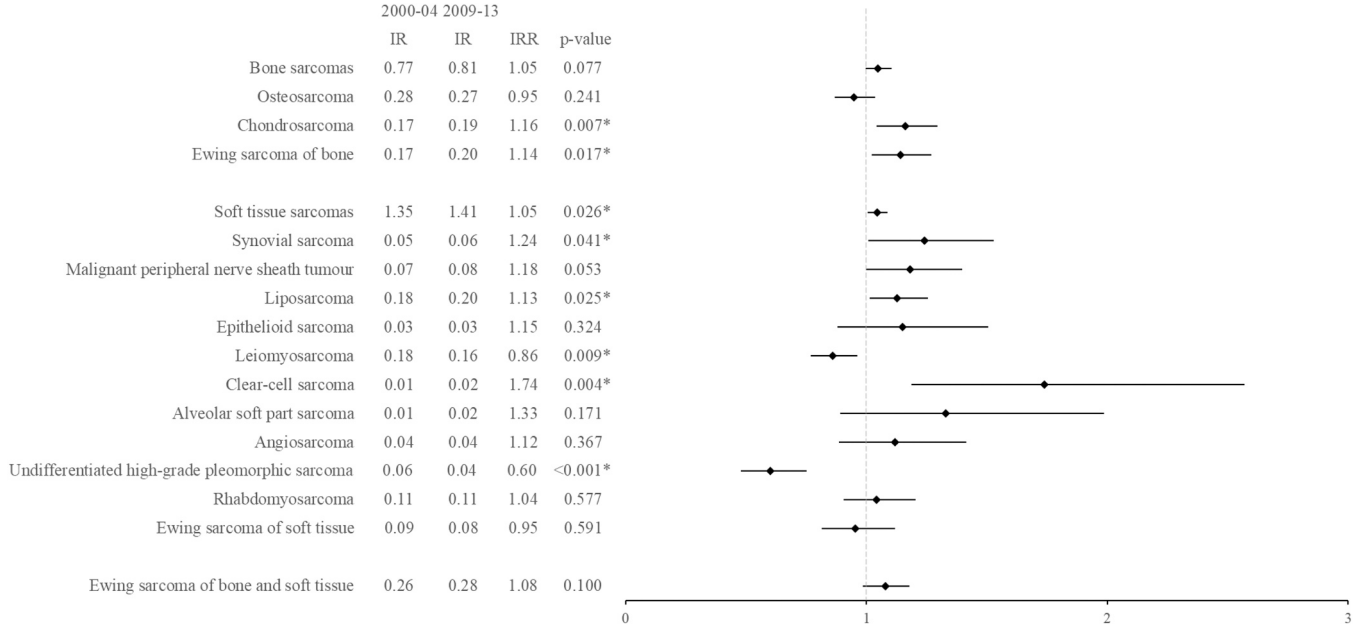

Fig. 2. Bone and soft tissue sarcomas: incidence rate ratios (IRR) in incidence rates over time (2009–2013 vs 2000–2004) in European adolescents and young adults (aged 15–39 years), by subtype, reported with p-value and the incidence rate (IR) in 2000–2004 and 2009–2013.

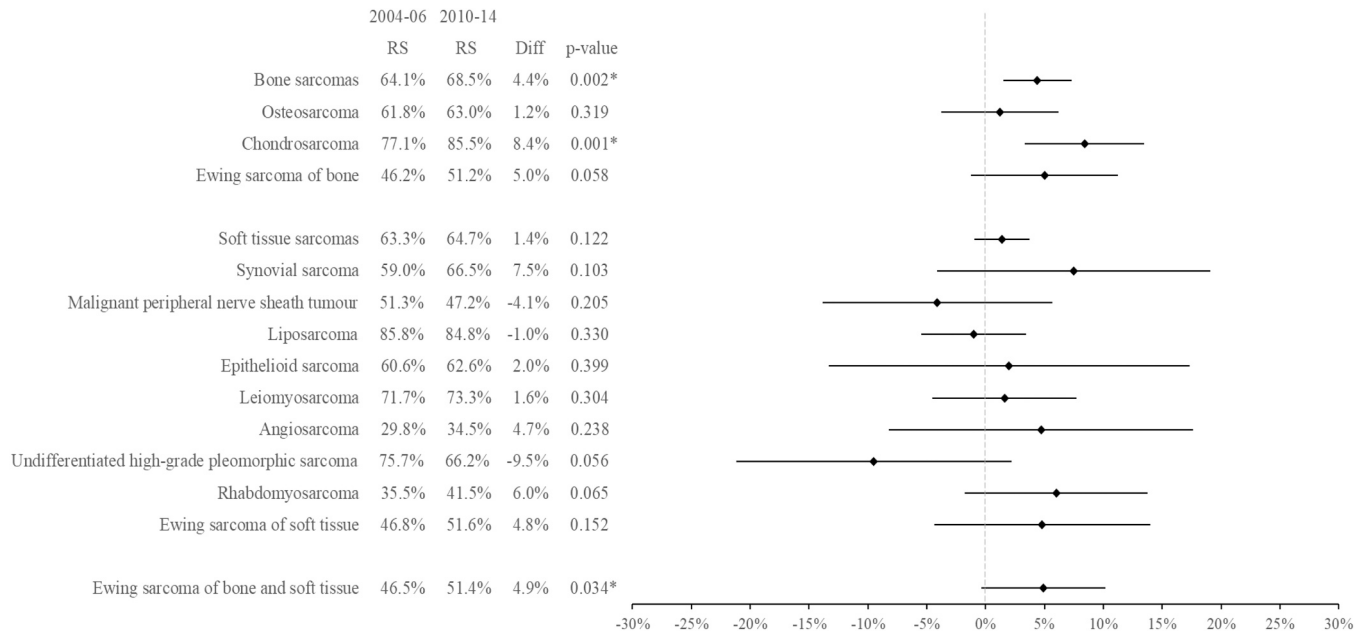

Fig. 3. Bone and soft tissue sarcomas: five-year relative relative survival (RS) differences over time, comparing period 2004–2006 (cohort diagnosed 2000–2006) to 2010–2014 (cohort diagnosed 2006–2013), in European adolescents and young adults (aged 15–39 years), by subtype, reported with 5-year relative survival (RS), survival difference (Diff) and Z-test p-value.

adults.

Previous studies reported poorer survival of AYA patients compared to children [17–20]. The survival gap was previously considered related, at least in part, to differences in clinical management. Various studies showed that AYA patients with RMS had better outcomes when treated with a multidisciplinary approach aligned with the paediatric strategy [21–23]. However, more recent studies have shown that treatment results in AYAs seem to remain less effective even when they receive the same treatment as paediatric patients [24]. This evidence suggests that the prognostic gap may be attributable in part to biological differences in RMS arising in different age groups [25]. It is currently well recognised, for example, that two recently identified RMS subtypes (spindle cell-sclerosing RMS with MYOD1 mutation and TFPC2 gene fusions) typically occur in AYAs and are characterised by poor response to chemotherapy and poorer prognosis as compared to the classic paediatric-type RMS [26–28]. A possible correlation between intrinsic differences in cancer biology in AYAs and their worse outcome compared to children has also been seen in other types of sarcoma: in synovial sarcoma, for example, higher genomic instability is frequent in adult but rare in paediatric cases, and correlates with the risk of metastatic spread [29]. Finally, the survival gap has also been attributed to lower recruitment rates of AYA in clinical trials [30].

The reason for the better survival observed in AYAs compared to mature adults is probably multifactorial. Biological heterogeneity within the same entity may also play a part in this outcome. However, treatment tolerability and compliance may also decline with advancing age. Finally, as multidisciplinary networks and policies to treat sarcomas in adults are not as embedded across Europe as in the paediatric setting, we cannot exclude that this has a role. This is important because survival differences between European countries have been observed for both STS and BS, with BS having one of the highest survival differences between countries (42 %) [11]. Sarcomas are rare and complex to treat and treatment should be centralized in expert centres or networks including expert centres. Therefore, implementing clinical networks around expert centres with a dedicated AYA program could help increase AYA survival and reduce geographic disparities.

For BS, our analysis showed that compared to children, AYA patients had no significant differences in outcome overall but had lower survival for Ewing sarcomas [31]. Survival decreases for patients older than 40 years. The similarity in outcome between AYAs and children for BS overall may be related to the long-term trans-age treatment protocols for osteosarcoma and Ewing sarcoma in Europe, which enrol patients of different ages who are managed cooperatively between paediatric and adult oncologists [32–36]. The differences in outcome, i.e. in children versus AYA patients with Ewing and overall in mature adults, may also be associated with increased intolerability rates for intensive treatments as age increases [37,38].

For AYAs with STS, the limited improvement in survival over time may reflect the relative absence of new drugs for STS during the study period [39]. Although the spectrum of potentially effective novel therapies for sarcomas has grown, few drugs have become available. Even immunotherapy has limited, histotype-specific efficacy in STS.

For AYAs with BS, RS increased over time for the whole group: this improvement might be related to general improvements in radiological and surgical approaches (as observed in chondrosarcoma in particular), in addition to radiotherapy techniques. It may also be associated with the progressive intensification of Ewing sarcoma treatments in appropriately selected cases.

We also confirmed that sarcoma subtypes vary, within both AYA and other age groups (young children, AYAs, mature adults), especially regarding STS. Within the AYA age range, differences in the incidence of sarcoma subtypes were evident, with adolescents tending to develop STS more similar to those of children and young adults (20–39 years) tending to develop STS more similar to those of mature adults. The interface cases and shared challenges add to the reasons to enhance collaboration between paediatric and adult sarcoma specialists and teams.

Between 2000 and 2013, increases in IR in AYAs were observed in BS for chondrosarcoma and Ewing sarcoma, and in STS for synovial sarcoma, liposarcoma, LMS, and clear-cell sarcoma. It is difficult to determine what caused this increase. It may be related to improved diagnostic accuracy. The histotypes with increasing IR are all characterised by specific molecular alterations: over the years the wider use of more accurate diagnostic tests could (in principle) have led to a relative increase in these diagnoses which in the past were potentially classified as undifferentiated or sarcomas ‘not otherwise specified [NOS]’; (we

observed a decrease in sarcoma NOS diagnoses from 7 % to 5 %). The term malignant fibrous histiocytoma has declined, most likely because this diagnostic label has been replaced by the newer category of 'undifferentiated high-grade pleomorphic sarcoma,' in acknowledgement of the growing emphasis on combined histological and molecular diagnosis.

Our study has a number of limitations, including the lack of details on molecular characterisation, tumour stage at diagnosis, treatments received, and information of health status at diagnosis. In addition, the rarity of sarcomas hinders detailed analyses of specific histotypes, due to the small number of cases. An additional limitation includes the relatively old diagnostic period and the end of the follow-up used for the analyses. Finally, the quality of a CR inevitably depends on the local healthcare environment and the available sources of information. Inappropriate pathological diagnoses will result in misclassification in CRs. Sarcomas are particularly exposed to discrepancies in quality of care. Furthermore, the histological classification of sarcomas has changed over time thus we cannot rule out some misclassification in sarcoma subtypes (e.g., well-differentiated and dedifferentiated liposarcoma). However, these data are the most current real data (as different from projections or hypothetical models) available in Europe.

Despite these limitations, the study offers updated data on the incidence and survival of AYA patients with sarcomas in Europe, providing important comparisons with the adjacent age categories (i.e. children and mature adults) and an evaluation of the trends over time, thereby improving knowledge of the epidemiology and clinical history of BS and STS by age-group at onset. Given the complexity of the clinical management of AYAs with sarcoma, combined with the need for specific expertise and multidisciplinary approaches, the international paediatric and adult sarcoma communities have recently started to build joint collaborative programmes. The upcoming Network of Expertise (https://jane-project.eu) on AYA-onset cancer in particular aspires and is detailing plans to play an important role in this. Converging toward a common strategy should be the goal, leading to improvements in research (including integrated age-related biological, immunological and genomic studies) and age-adapted treatment strategies. This should include increasingly timely, detailed epidemiological data, pan-age clinical trials where host physiology and tumour biology so suggest, and clinical trials in new biologically defined entities, removing barriers to access to clinical trials from early drug development phases [40].

Data access

Annalisa Trama had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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CRediT authorship contribution statement

Francesco Cerza: Writing – review & editing. **Winette van der Graaf:** Writing – review & editing. **Seyed Mohsen Mousavi:** Writing – review & editing. **Martin G McCabe:** Writing – review & editing. **Andrea Ferrari:** Writing – review & editing, Writing – original draft, Conceptualization. **Lucy Metayer:** Writing – review & editing. **Laura Botta:** Writing – review & editing, Methodology. **Nathalie Gaspar:** Writing – review & editing. **Christina Schindera:** Writing – review & editing. **Dan Stark:** Writing – review & editing. **Ana María Vizcaíno Batllés:** Writing – review & editing. **Annalisa Trama:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Funding acquisition, Conceptualization. **Luigino Dal Maso:** Writing – review & editing. **Paolo Lasalvia:** Writing – review & editing, Writing – original draft, Software, Methodology, Formal analysis, Data curation. **Rosalia Ragusa:** Writing – review & editing. **Salvatore Provenzano:** Writing – review & editing, Writing – original draft, Conceptualization. **Sandra J Strauss:** Writing – review & editing. **Damien Bennett:** Writing – review & editing. **Marcela Guevara:** 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.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2024.115212.

Data Availability

We analysed pseudonymised data collected from 108 population-based cancer registries, after approval by the Ethics Committee of the National Cancer Institute of Milan (INT73/16; April 21, 2016). We hold these data in trust from each participating registry for the statistical analyses agreed in the EUROCARE-6 protocol, available at http://www.eurocare.it. We are not allowed to share individual data. Aggregated level data, in the form of counts, rates, or survival proportions, can be only shared after express permission from the participating registries. These data should be requested by contacting the corresponding author.

References

[1] WHO Classification of Tumours Editorial Board. Soft Tissue and Bone Tumours WHO Classification of Tumours, 5th Edition, 3. France: IARC; 2020.
[2] Closing the gap: research and care imperatives for adolescents and young adults with cancers. Report of the Adolescent and Young Adult Oncology Progress Review Group. 2006 available at https://www.cancer.gov/types/aya/research/ayao-august-2006.pdf accessed 8th October 2024.
[3] Ferrari A, Sultan I, Huang TT, et al. Soft tissue sarcoma across the age spectrum: a population-based study from the surveillance, epidemiology, and end results database. Pedia Blood Cancer 2011;57:943–9.
[4] Corey RM, Swett K, Ward WG. Epidemiology and survivorship of soft tissue sarcomas in adults: a national cancer database report. Cancer Med 2014;3:1404–15.
[5] Whelan J, McTiernan A, Cooper N, et al. Incidence and survival of malignant bone sarcomas in England 1979–2007. Int J Cancer 2012;131:E508–17.
[6] ECIS - European cancer information system available at: http://ecis.jrc.ec.europa.eu/en accessed 8th October 2024.
[7] Globocan data available at: https://gco.iarc.fr/today/en accessed 8th October 2024.
[8] Toro JR, Travis LB, Wu HJ, Zhu K, Fletcher CD, Devesa SS. Incidence patterns of soft tissue sarcomas, regardless of primary site, in the surveillance, epidemiology and end results program, 1978-2001: An analysis of 26,758 cases. Int J Cancer 2006;119(12):2922–30. https://doi.org/10.1002/ijc.22239.
[9] Pizzato M, Collatuzzo G, Santucci C, Malvezzi M, Boffetta P, Comandone A, Levi F, La Vecchia C, Bertuccio P, Negri E. Mortality patterns of soft-tissue sarcomas worldwide up to 2018, with predictions for 2025. Eur J Cancer Prev 2023;32(1):71–80. https://doi.org/10.1097/CEJ.0000000000000768.
[10] Trama A, Botta L, Foschi R, 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.
[11] Trama A, Botta L, Stiller C, et al. Survival of European adolescents and young adults diagnosed with cancer in 2010-2014. Eur J Cancer 2024;202:113558.

[12] Fritz A, Percy C, Jacl A, Shanmugaratnam K, Sobin L, Parkin DM, Whelan S. International classification of disease for oncology. 3rd edition. WHO; 2000. First Revision (ICD-O-3.1).
[13] Brenner H, Söderman B. Hakulinen T. Use of period analysis for providing more up-to-date estimates of long-term survival rates: empirical evaluation among 370,000 cancer patients in Finland. Int J Epidemiol 2002;31(2):456–62.
[14] Ederer F, Axtell LM, Cutler SJ. The relative survival rate: a statistical methodology. Natl Cancer Inst Monogr 1961;6:101–21.
[15] George S, Serrano C, Hensley M, Ray-Coquard I. Soft tissue and uterine leiomyosarcoma. J Clin Oncol: J Am Soc Clin Oncol 2018 2018;36(2):144–50. https://doi.org/10.1200/JCO.2017.75.9845.
[16] Fay MP, Tiwari RC, Feuer EJ, Zou Z. Estimating average annual percent change for disease rates without assuming constant change. Biometrics 2006;62(3):847–54. https://doi.org/10.1111/j.1541-0420.2006.00528.x.
[17] Sultan I, Qaddoumi I, Yaser S, Rodriguez-Galindo C, Ferrari A. Comparing adult and pediatric rhabdomyosarcoma in the surveillance, epidemiology and end results program, 1973 to 2005: an analysis of 2,600 patients. J Clin Oncol 2009;27(20):3391–7.
[18] Sultan I, Rodriguez-Galindo C, Saab R, Yasir S, Casanova M, Ferrari A. Comparing children and adults with synovial sarcoma in the surveillance, epidemiology, and end results program, 1983 to 2005: an analysis of 1268 patients. Cancer 2009;115:3537–47.
[19] Van Gaal JC, Van der Graaf WT, Rikhof B, et al. The impact of age on outcome of embryonal and alveolar rhabdomyosarcoma patients. A multicenter study. Anticancer Res 2012;32:4485–97.
[20] Children, teenagers and young adults UK cancer statistics report 2021 – National Disease Registration Service available at: https://digital.nhs.uk/ndrs/data/data-outputs/cancer-publications-and-tools/ctya-uk-cancer-statistics-report-2021 accessed 8th October 2024.
[21] Ferrari A, Dileo P, Casanova M, et al. Rhabdomyosarcoma in adults: a retrospective analysis of 171 patients treated at a single institution. Cancer 2003;98:571–80.
[22] Bergamaschi L, Bertulli R, Casanova M, et al. Rhabdomyosarcoma in adults: analysis of treatment modalities in a prospective single-center series. Med Oncol 2019;36:1–8.
[23] Ferrari A, Bernasconi A, Bergamaschi L, et al. Impact of rhabdomyosarcoma treatment modalities by age in a population-based setting. J Adolesc Young– Adult Oncol 2021;10:309–15.
[24] Ferrari A, Chisholm JC, Jenney 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;6:545–55.
[25] Ferrari A, Gatz SA, Minard-Colin V, et al. Shedding a light on the challenges of adolescents and young adults with rhabdomyosarcoma. Cancers 2022;14(24):6060. https://doi.org/10.3390/cancers14246060.
[26] Watson S, Perrin V, Guillemot D, et al. Transcriptomic definition of molecular subgroups of small round cell sarcomas. J Pathol 2018;245:29–40.
[27] Agaram NP, Zhang L, Sung YS, et al. Expanding the spectrum of intraosseous rhabdomyosarcoma: correlation between 2 distinct gene fusions and phenotype. Am J Surg Pathol 2019;43:695–702.
[28] Xu B, Suurmeijer A, Agaram NP, et al. Head and neck rhabdomyosarcoma with TFCP2 fusions and ALK overexpression: a clinicopathological and molecular analysis of 11 cases. Histopathology 2021;79:347–57.
[29] Lagarde P, Przybyl J, Brulard C, et al. Chromosome instability accounts for reverse metastatic outcomes of pediatric and adult synovial sarcomas. J Clin Oncol 2013;31:608–15.
[30] Ferrari A, Trama A, De Paoli A, Bergeron C, Merks JHM, Jenney M, Orbach D, Chisholm JC, Gallego S, Glosli H, De Salvo GL, Botta L, Gatta G, Bisogno G. RARECAREnet Working Group. Pedia Blood Cancer 2017;64(6). https://doi.org/10.1002/pbc.26348.
[31] Klingberg D, Bae S, Zhou DD, Sim HW, Cai R, Anazodo A, Grimison P, Lewis C, Lee YC. Association of chemotherapy dose intensity and age with outcomes in patients with Ewing's family sarcoma. Asia Pac J Clin Oncol 2023. https://doi.org/10.1111/ajco.13998.
[32] Brennan B, Kirton L, Marec-Bérard P, Gaspar N, Laurence V, Martín-Broto J, Sastre A, Gelderblom H, Owens C, Fenwick N, Strauss S, Moroz V, Whelan J, Wheatley K. 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. https://doi.org/10.1016/S0140-6736(22)01790-1.
[33] Koch R, Haveman L, Ladenstein R, Brichard B, Jürgens H, Cyprova S, van den Berg H, Hassenpflug W, Raciborska A, Ek T, Baumhoer D, Egerer G, Kager L, Renard M, Hauser P, Burdach S, Bovee JVMG, Hong AM, Reichardt P, Kruseova J, Streitbürger A, Kühne T, Kessler T, Bernkopf M, Butterfaß-Bahloul T, Dhooge C, Bauer S, Kiss J, Paulussen M, Bonar F, Ranft A, Timmermann B, Rascon J, Vieth V, Kanerva J, Faldum A, Hartmann W, Hjorth L, Bhadri VA, Metzler M, Gelderblom H, Dirksen U. Zoledronic acid add-on therapy for standard-risk ewing sarcoma patients in the ewing 2008R1 Trial. Clin Cancer Res 2023;29(24):5057–68. https://doi.org/10.1158/1078-0432.CCR-23-1966.
[34] Gaspar N, Occean BV, Pacquement H, et al. Results of methotrexateetoposide-ifosfamide based regimen (M-EI) in osteosarcoma patients included in the French OS2006/sarcome-09 study. Eur J Cancer 2018;88:57–66.
[35] Grier HE, Krailo MD, Tarbell NJ, et al. Addition of ifosfamide and etoposide to standard chemotherapy for Ewing's sarcoma and primitive neuroectodermal tumor of bone. N Engl J Med 2003;348:694–701.
[36] Womer RB, West DC, Krailo MD, et al. Randomized controlled trial of interval-compressed chemotherapy for the treatment of localized Ewing sarcoma:a report from the Children's Oncology Group. J Clin Oncol 2012;30:4148–54.
[37] Janeway KA, Barkauskas DA, Krailo MD, et al. Outcome for adolescent and young adult patients with osteosarcoma: a report from the Children's Oncology Group. Cancer 2012;118:4597–605.
[38] Collins M, Wilhelm M, Conyers R, et al. Benefits and adverse events in younger versus older patients receiving neoadjuvant chemotherapy for osteosarcoma: findings from a meta-analysis. J Clin Oncol 2013;31:2303–12.
[39] van der Graaf WT, Blay JY, Chawla SP, Kim DW, Bui-Nguyen B, Casali PG, Schöffski P, Aglietta M, Staddon AP, Beppu Y, Le Cesne A, Gelderblom H, Judson IR, Araki N, Ouali M, Marreaud S, Hodge R, Dewji MR, Coens C, Demetri GD, Fletcher CD, Dei Tos AP, Hohenberger P. EORTC Soft Tissue and Bone Sarcoma Group; PALETTE study group. Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet 2012;379(9829):1879–86. https://doi.org/10.1016/S0140-6736(12)60651-5.
[40] Gaspar N, Marshall LV, Binner D, Herold R, Rousseau R, Blanc P, et al. Joint adolescent-adult early phase clinical trials to improve access to new drugs for adolescents with cancer: proposals from the multi-stakeholder platform-ACCELERATE. Ann Oncol 2018;29(3):766–71. https://doi.org/10.1093/annonc/mdy002.