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Survival of children with soft-tissue sarcoma in Europe since 1978: results from the EUROCARE study

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Abstract

Soft-tissue sarcomas account for 5–8% of all childhood cancers in European countries. In the EUROCARE childhood cancer study, there were 2163 registrations from 17 countries for soft-tissue sarcomas in patients aged 0–14 years during 1978–1989. Of this total, three-quarters were contributed by childhood cancer registries in Germany and the UK. Age-standardised 5-year survival rates of children diagnosed during 1985–1989 were 65% (95% confidence interval (CI) 56–72) for rhabdomyosarcoma, 68% (95% CI 58–77) for fibrosarcoma, 78% (95% CI: 64–87) for other specified soft-tissue sarcomas except Kaposi's and 51% (95% CI 37–65) for 'unspecified' soft-tissue sarcomas. Survival rates increased steadily throughout the 12-year study period for all soft-tissue sarcomas combined, but the increase took place predominantly in the early 1980s for rhabdomyosarcoma. Improvements in survival which had previously been reported from individual countries and in clinical series are confirmed as having taken place throughout much of Europe on a population basis. In a supplementary analysis, there was little indication of a further improvement during 1990–1992.

Keywords: Population-based survival; Cancer registries; Survival trends; Children; Europe; Rhabdomyosarcoma; Fibrosarcoma; Soft-tissue neoplasms

1. Introduction

Soft-tissue sarcomas account for 5–8% of all cancers occurring among children aged 0–14 years in most European countries [1]. The most common histological type is rhabdomyosarcoma, accounting for 50–65% of cases in many countries. This tumour is diagnosed throughout childhood, but around half of the incidence occurs in the first 5 years of life. Fibrosarcoma, neurofibrosarcoma and other fibromatous neoplasms typically account for 10–20% of childhood soft-tissue sarcomas. There are two age peaks of incidence, in infancy and at age 10–14. Kaposi's sarcoma is hardly ever seen in European children. The heterogeneous subgroup of 'other specified' soft-tissue sarcomas accounts for 10–25% of cases; the most frequent morphologies are peripheral primitive neuroectodermal tumour (PNET), leiomyosarcoma and synovial sarcoma. The remaining cases are 'unspecified' soft-tissue sarcomas, usually 5–10% of the total.

In this paper, we describe the pattern of survival from childhood soft-tissue sarcomas diagnosed in European populations during 1978–1989. Trends in survival are also assessed in a multivariate analysis of data from a selection of registries for the period 1978–1992.

2. Patients and methods

Soft-tissue sarcomas were defined as all diagnoses in Group IX of the International Classification of Childhood Cancer (ICCC) [2]. As the classification is based on morphology, all primary sites were included. This is in contrast to the EUROCARE analyses of soft-tissue

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sarcoma in adults, for which the ICD was used to define diagnostic groups and only those cases with a primary site of connective tissue were included [3].

In total, 2163 children with soft-tissue sarcomas diagnosed during 1978–1989 were identified in the EUROCARE childhood cancer database. Table 1 shows the distribution of all soft-tissue sarcomas, rhabdomyosarcoma and fibrosarcoma between countries and by age, gender and period of diagnosis. Rhabdomyosarcomas accounted for 61% of registrations, the fibrosarcoma group for 15%, Kaposi's sarcoma for less than 1% (3 cases), 'other specified' soft-tissue sarcomas for 17% (358 cases) and 'unspecified' soft-tissue sarcomas for 8% (173 cases). In the Nordic countries, the fibrosarcoma group had a higher relative frequency of 30%. There was a rather high proportion of 'other specified' in Slovakia (35%). Table 2 shows indicators of data quality overall and by country. Unspecified histological types accounted for 25% of cases in Estonia and 22% in France. 'Unspecified' sarcomas were relatively common in the first year of life, when they accounted for 13% of all soft-tissue sarcomas. Losses to follow-up were 2% of the data base, but 5% in Germany. In order to check that cases of unspecified histology had not been included in the ICCC Group XIIb (unspecified malignant neoplasms), the 19 registrations for this category with a connective tissue primary site were retrieved from the database. Six of these were from England and Wales, while the proportionately largest number was in Finland, with 4 cases; if these were all in fact soft-tissue sarcomas, unspecified histology would still only account for 15% (11/72) of Finnish registrations. Some registries also contributed data for the period 1990–1992, enabling 548 extra cases from six countries to be included in an analysis of trends in survival up to 1992.

Survival rates were calculated by the actuarial method. Age-standardised survival rates were calculated for countries with cases in all three age-groups 0–4, 5–9

Table 1
Numbers of childhood soft-tissue sarcoma cases in the EUROCARE childhood cancer database for 1978–1989

Country	Total		Rhabdomyosarcoma	Fibrosarcoma
	1978–1989 *n* (%)	1985–1989 *n* (%)	*n* (%)	*n* (%)
Northern Europe				
Denmark	89 (4)	47 (5)	38 (3)	27 (9)
Finland	68 (3)	28 (3)	31 (2)	18 (6)
Iceland	11 (0.5)	2 (0.2)	4 (0.3)	4 (1)
Sweden[a]	26 (1)	9 (0.9)	15 (1)	9 (3)
UK				
England and Wales	843 (39)	371 (36)	561 (43)	117 (37)
Scotland	88 (4)	29 (3)	55 (4)	9 (3)
Western and Central Europe				
Austria[a]	4 (0.2)	4 (0.4)	2 (0.2)	0
France[a]	27 (1)	14 (1)	16 (1)	3 (1)
Germany	681 (31)	374 (36)	430 (33)	81 (26)
Switzerland[a]	7 (0.3)	2 (0.2)	5 (0.4)	1 (0.3)
The Netherlands[a]	19 (0.9)	8 (0.8)	11 (0.8)	1 (0.3)
Southern Europe				
Italy[a]	113 (5)	53 (5)	71 (5)	14 (4)
Spain[a]	16 (0.7)	16 (2)	7 (0.5)	1 (0.3)
Eastern Europe				
Estonia	24 (1)	8 (0.8)	8 (0.6)	4 (1)
Poland[a]	11 (0.5)	6 (0.6)	7 (0.5)	1 (0.3)
Slovakia	119 (6)	48 (5)	42 (3)	23 (7)
Slovenia	17 (0.8)	17 (2)	12 (0.9)	1 (0.3)
Age (years)				
0–<1	227 (10)	114 (11)	116 (9)	46 (15)
1–4	676 (31)	349 (34)	536 (41)	40 (13)
5–9	590 (27)	255 (25)	381 (29)	83 (26)
10–14	670 (31)	318 (31)	282 (21)	145 (46)
Sex				
Boys	1225 (57)	562 (54)	764 (58)	164 (52)
Girls	938 (43)	474 (46)	551 (42)	150 (48)
Total	2163 (100)	1036 (100)	1315 (100)	314 (100)

[a] <20% of the national population is covered.

and 10–14 years [4]. Overall (European) survival was estimated as the weighted average of survival in individual countries, with weights proportional to the total childhood population of each country, assuming that survival of patients included in the study for each country was representative of survival at the national level. Because of the very small numbers of cases contributed by registries from some of the larger countries, the weighted European average survival rates [4] had very wide confidence intervals. We therefore also present unweighted overall survival rates in this paper.

Univariate survival analysis was carried out on two overlapping subsets of cases for rhabdomyosarcomas, fibrosarcomas, 'other specified' soft-tissue sarcomas (excluding Kaposi's) and 'unspecified' soft-tissue sarcomas. The first contained cases diagnosed throughout 1978–1989, but was restricted to those registries whose contribution to the database covered at least the whole of the period 1981–1986 and included enough cases for calculation of age-adjusted rates. The second consisted of all cases diagnosed during 1985–1989.

Two Cox proportional hazards analyses were done for each group of rhabdomyosarcomas, fibrosarcomas and all soft-tissue sarcomas combined. The first was designed to investigate trends in survival during 1978–1989 taking into account the varying distributions of age at diagnosis, gender and country. The total calendar period was divided into the three sub-periods, 1978–1981, 1982–1985 and 1986–1989. This analysis was confined to countries with 30 cases (rhabdomyosarcoma, all soft-tissue sarcomas) or at least 15 cases (fibrosarcoma) and with registrations included in all three 4-year periods. The second analysis covered the period 1978–1992, with 1990–1992 as a fourth sub-period. It was limited to countries with cases from all four sub-periods and with the same minimum numbers as before.

Table 2
Data quality for soft-tissue sarcoma cases in the EUROCARE childhood cancer database for 1978–1989

Country	Total cases	% IXe	% MV	% Lost to follow-up
Northern Europe				
Denmark	89	8	95	0
Finland	68	10	93	0
Iceland	11	9	100	0
Sweden[a]	26	8	100	0
UK				
England and Wales	843	7	99	1
Scotland	88	14	99	2
Western and Central Europe				
Austria[a]	4	0	100	0
France[a]	27	22	96	0
Germany	681	7	100	5
Switzerland[a]	7	0	100	14
The Netherlands[a]	19	11	95	16
Southern Europe				
Italy[a]	113	5	97	3
Spain[a]	16	19	100	0
Eastern Europe				
Estonia	24	25	100	4
Poland[a]	11	0	100	0
Slovakia	119	10	100	0
Slovenia	17	6	100	0
Age (years)				
0–<1	227	13	96	4
1–4	676	6	96	2
5–9	590	7	97	3
10–14	670	9	95	2
Sex				
Boys	1225	8	96	2
Girls	938	9	97	2
Total	2163	8	96	2

IXe, International Classification of Childhood Cancer, Group IXe, 'unspecified' soft-tissue sarcomas; MV, morphologically verified; NA, not available.

[a] <20% of the national population is covered.

3. Results

3.1. Univariate analysis

Table 3 shows age-standardised 5-year survival rates for the two study periods where there were sufficient cases for analysis. Survival from rhabdomyosarcoma for 1978–1989 was much lower in Slovakia than in any other country reported here, and the second lowest survival rate was observed in Finland, but both confidence intervals were wide and contained the average. In Finland, survival for 1985–1989 was slightly lower than for the whole study period 1978–1989, implying a recent decline in prognosis. Scotland had a similar survival rate to the average in 1978–1989 as a whole, but a lower survival in 1985–1989. Germany had high survival rates with fairly narrow confidence limits at or above the average for the European registries in both periods. The fact that Germany did not supply data for 1978–1979 may partly explain the result for the longer time period.

Patients with fibrosarcoma had a higher survival rate than those with rhabdomyosarcoma. As this diagnosis is less common, few individual countries had sufficient cases for separate analysis and the average for the European registries was well within all of the confidence intervals. For 'other specified' soft-tissue sarcomas, survival rates were relatively high in Germany and lower in England and Wales and especially low in Slovakia. These results are difficult to interpret, however, as this diagnostic group is very heterogeneous and the relative frequencies of histological types varied between regis-

Table 3
Age-standardised 5-year survival rates (95% confidence limits) for childhood soft-tissue sarcomas, 1978–1989 and 1985–1989[a]

	1978–1989	1985–1989
Rhabdomyosarcoma		
Denmark	69 (53–82)	65 (43–82)
England and Wales	55 (50–59)	60 (54–66)
Finland	52 (34–69)	40 (18–66)
Germany	62 (57–67)	69 (63–75)
Italy[b]	65 (53–75)	64 (47–78)
Scotland	54 (41–68)	52 (31–73)
Slovakia	43 (27–60)	–
Slovenia	–	80 (33–97)
Europe (unweighted)	57 (54–60)	62 (58–66)
Europe (weighted)	56 (50–62)	65 (56–72)
Fibrosarcoma		
England and Wales	68 (59–76)	74 (61–85)
Germany	70 (58–79)	77 (62–87)
Europe (unweighted)	71 (66–76)	75 (68–82)
Europe (weighted)	62 (54–70)	68 (58–77)
Other specified (except Kaposi's)		
Denmark	–	75 (42–93)
England and Wales	60 (50–69)	70 (55–82)
Germany	75 (67–82)	80 (70–88)
Italy[b]	–	64 (39–83)
Slovakia	49 (33–65)	52 (27–76)
Europe (unweighted)	66 (61–71)	75 (68–80)
Europe (weighted)	61 (53–68)	78 (64–87)
Unspecified		
England and Wales	46 (34–58)	44 (28–61)
Germany	35 (23–48)	31 (17–50)
Europe (unweighted)	47 (39–54)	50 (39–60)
Europe (weighted)	42 (33–52)	51 (37–65)

[a] Results for individual countries only reported when there were at least 30 cases (1978–1989) or at least 10 cases (1985–1989).
[b] < 20% of the national population is covered.

tries. Survival from 'unspecified' soft-tissue sarcomas was lower than for any other diagnostic subgroup.

Fig. 1 shows survival of children in the four age groups with rhabdomyosarcoma diagnosed during 1985–1989, based on the unweighted pooled data. Infants aged 0–< 1 year and older children aged 10–14 years had a poorer prognosis. Among infants this was established during the first year following diagnosis, whereas the poorer survival of the 10–14 years age group only emerged in the second year. Similar patterns were observed in England and Wales and in Germany (data not shown). The poorer prognosis for infants was not evident in the weighted pooled estimates, but these gave large weights to some countries with very small numbers of cases (data not shown).

3.2. Multivariate analysis

Table 4 shows the results of the Cox proportional hazards analyses. The results for age, gender and country relating to 1978–1992 were very similar to those for 1978–1989 (data not shown). Girls had a lower survival rate than boys from rhabdomyosarcomas, fibrosarcomas and all soft-tissue sarcomas combined. For rhabdomyosarcomas, children aged 10–14 years had a worse prognosis than younger patients. There was a trend towards improving survival with the more recent year of diagnosis throughout the period 1978–1989 both for rhabdomyosarcomas and for all soft-tissue sarcomas. For fibrosarcoma, there was little difference between 1978–1981 and 1982–1985, but survival was higher in 1986–1989. The supplementary analysis including data from 1990 to 1992 showed no further improvement in the most recent time period for all soft-tissue sarcomas or for either diagnostic subgroup.

4. Discussion

The results presented here show that there was a sustained improvement in survival from childhood soft-tissue sarcomas throughout much of Europe over the whole of the study period. This corroborates the results that have previously been published from population-based analyses in a few individual countries and from the principal clinical trials. Table 5 shows population-based survival data from other industrialised countries outside Europe. The results for childhood soft-tissue sarcomas in Europe are broadly similar to those reported from the USA and Australia. Among adults in the EUROCARE II study, survival has been found to be somewhat lower in Eastern Europe [3]. In the present study, survival was worse than average in Slovakia (where data was available), although still quite similar to that observed in Japan. In contrast, Slovenia had a high survival rate for rhabdomyosarcoma in the time period of 1985–1989.

The treatment of childhood soft-tissue sarcomas in Europe has, as elsewhere in the world, been based largely upon strategies developed for, and evaluated in, rhabdomyosarcoma as this is the most common individual diagnosis. The importance of multi-agent chemotherapy has been clearly demonstrated for rhabdomyosarcoma as part of a co-ordinated multimodality treatment and cure rates have improved from approximately 25% in the early 1970s when combination chemotherapy was first implemented. The role of chemotherapy has since been explored in a series of multi-centre clinical trials in both North America and Europe and the drugs most commonly used are alkylating agents in combination with vincristine and actinomycin D. Strategies have evolved which match the intensity of treatment against known prognostic factors. Site, stage and pathological subtype are universally recognised as the factors of the greatest prognostic significance in rhabdomyosarcoma [5]. The influence of the primary site is particularly responsible for the complex-

ity of the treatment schedules which have evolved to stratify treatment intensity according to good or poor predicted outcomes.

Within Europe, three major collaborative study groups have emerged which, although functioning independently, have evolved a degree of collaboration, particularly in recent years. The International Society of Paediatric Oncology (SIOP) Malignant Mesenchymal Tumour (MMT) committee opened its first study, RMS 75, in 1975. This was only for patients with rhabdomyosarcoma. Two further studies followed during the era of the EUROCARE study, both of which recruited all types of soft-tissue sarcoma. These were MMT 84 and MMT 89, open during 1984–1989 and 1989–1995, respectively. The German Cooperative Soft-tissue Sarcoma (CWS) Group and the Italian Cooperative Group (ICG) have traditionally cooperated closely, organising parallel studies and, latterly, joint protocols. Trials undertaken during the era of the EUROCARE study included CWS 81, CWS 86, ICG 79 and ICG 88 [6].

Despite improvements in survival, the outlook for certain groups of patients remains poor, whilst some anxieties have emerged about the possible over-treatment of patients shown to have good prospects for cure. In this context, some important differences in treatment philosophy have emerged between the major collaborative groups within Europe, as well as with the Intergroup Rhabdomyosarcoma Study (IRS) Group in North America. The major controversy relates to local tumour control and specifically to the method and timing of local treatment, particularly to the place of radiotherapy in guaranteeing local control for patients who appear to achieve complete remission with chemotherapy and, sometimes, surgery. In the SIOP studies, unlike those of the IRS Group and, to some extent, those of the German and Italian Co-operative Groups, radiotherapy is not used systematically except at some sites of disease. Local relapse rates are generally higher in the SIOP studies than those experienced elsewhere although a significant number of patients who relapse may be cured with alternative treatments [7]. The impact of this philosophy on overall survival has not yet been fully assessed but a judgement needs to be made about the relative acceptability of any reduction in survival against the benefits which may result in sparing patients late *sequelae* of treatment.

The earliest SIOP studies (RMS 75 and MMT 84) were largely supported by France as well as by The Netherlands and Belgium. United Kingdom patients were not recruited until MMT 89, and since then they have been a major contributor to the SIOP studies together with Spain, some of the Nordic Countries and selected centres in several other European countries. Treatment centres in Austria and Switzerland, as well as those in some other European countries (Sweden, Poland) have been recruited into the German studies.

Before 1989, most treatment centres in the UK, like many elsewhere in the world, based their treatment on IRS protocols and the UK Children's Cancer Study Group (UKCCSG) was an official partner with the IRS Group in IRS III (1984–1991), although only a minority of centres actually entered patients [8]. The philosophy

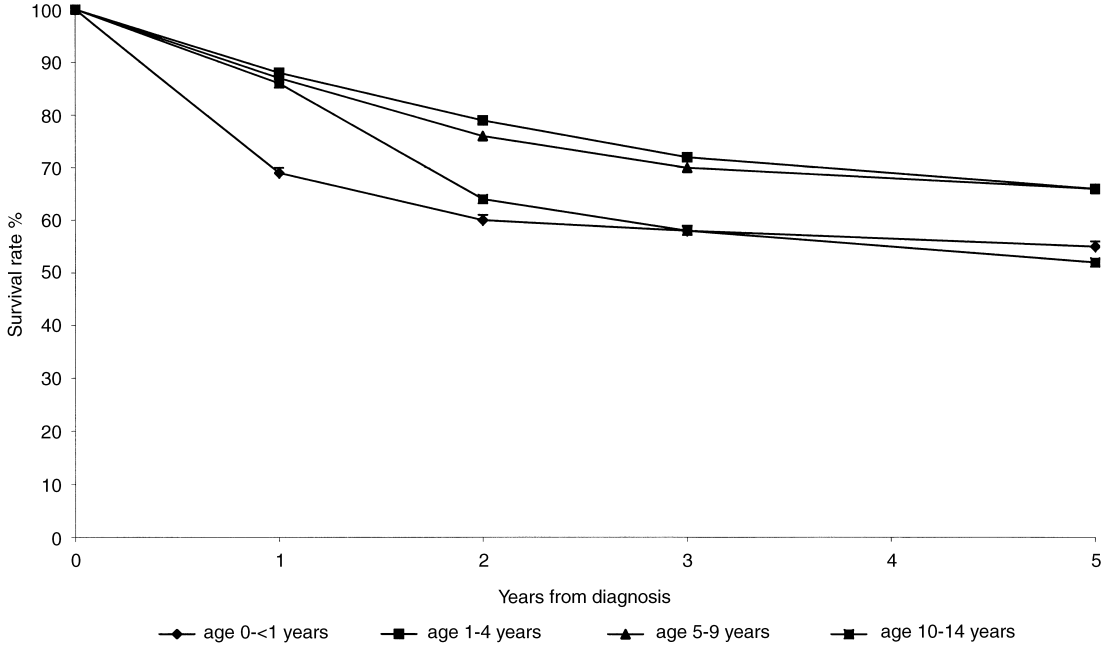

Fig. 1. Survival rates by age at diagnosis for children with rhabdomyosarcoma diagnosed in 1985–1989. Results from unweighted European pooled data.

Table 4
Results of Cox proportional hazards analyses for soft-tissue sarcoma

	Rhabdomyosarcoma RR (95% CI)	Fibrosarcoma RR (95% CI)	All soft-tissue sarcomas RR (95% CI)
1978–1989[a]			
Sex			
Male	1 (reference)	1 (reference)	1 (reference)
Female	1.19 (1.01–1.41)	1.26 (0.82–1.94)	1.14 (1.00–1.30)
Age (years)			
0–4	1 (reference)	1 (reference)	1 (reference)
5–9	0.92 (0.75–1.12)	1.31 (0.72–2.36)	0.90 (0.76–1.07)
10–14	1.18 (0.96–1.45)	1.31 (0.78–2.20)	1.02 (0.87–1.20)
Period			
1978–1981	1 (reference)	1 (reference)	1 (reference)
1982–1985	0.76 (0.62–0.93)	0.87 (0.52–1.44)	0.83 (0.71–0.98)
1986–1989	0.66 (0.54–0.82)	0.49 (0.27–0.88)	0.68 (0.58–0.81)
Country			
Denmark	0.60 (0.34–1.04)	0.58 (0.24–1.40)	0.64 (0.44–0.93)
Finland	1.09 (0.67–1.79)	0.67 (0.26–1.74)	0.69 (0.46–1.04)
Germany	0.78 (0.64–0.95)	1.06 (0.64–1.77)	0.81 (0.69–0.95)
Italy[c]	0.82 (0.55–1.22)	–	0.97 (0.71–1.32)
Slovakia	1.68 (1.12–2.50)	1.54 (0.78–3.03)	1.32 (1.02–1.71)
England and Wales	1 (reference)	1 (reference)	1 (reference)
Scotland	1.12 (0.77–1.63)	–	0.80 (0.57–1.11)
1978–1992[b]			
Period			
1978–1981	1 (reference)	1 (reference)	1 (reference)
1982–1985	0.74 (0.60–0.91)	0.89 (0.54–1.47)	0.83 (0.70–0.98)
1986–1989	0.67 (0.54–0.83)	0.51 (0.28–0.92)	0.69 (0.58–0.83)
1990–1992	0.68 (0.54–0.85)	0.63 (0.32–1.21)	0.72 (0.59–0.87)

RR, relative risk; 95% CI, 95% confidence interval.
[a] 1978–1989 countries with too few cases (see text) or not covering at least 1981–1986 are excluded.
[b] 1978–1992 countries with too few cases (see text) or not covering at least 1981–1990 are excluded.
[c] <20% of the national population is covered.

of this study was much closer to that of the German and Italian groups than to that of the SIOP studies (then or since) and it is interesting, therefore, that results of treatment both for rhabdomyosarcoma and for all soft-tissue sarcoma were not as good in the UK as in Germany and Italy during this period. Nevertheless, the survival rates for rhabdomyosarcoma in the UK have continued to improve since 1989, when UK centres have been major contributors to the more recent MMT studies. The lack of registrations from France in the EUROCARE database means that a potentially interesting comparison reflecting on the possible differences in outcome between the different philosophies of the earlier MMT studies and the German and Italian studies is unobtainable.

Table 5
5-year survival rates (%) (95% CI where known) for rhabdomyosarcoma in EUROCARE and other population-based studies

Europe 1978–1989	57 (54–60)
Europe 1985–1989	62 (58–66)
USA (SEER) 1983–1987 [10]	68
Australia (Victoria) 1980–1989 [11]	57
Japan (Osaka) 1980–1984 [12]	42

The impact of age on outcome for rhabdomyosarcoma is well recognised and most recent collaborative studies now show that prognosis is worse for patients aged over 10 years at diagnosis. The adverse impact of older age is partly explained by an association between age and site of disease. For example, more patients with limb primaries are aged over 10 years; this is a less favourable site of disease and also associated with an increased risk of unfavourable (alveolar) histology.

Management of non-rhabdomyosarcoma soft-tissue sarcomas tends to emphasise early local treatment because of evidence that this heterogeneous and sometime difficult to classify group of tumours are less chemosensitive than rhabdomyosarcoma. This is not a consistent finding and the chemosensitivity of some of these diagnoses (such as synovial sarcoma) may be greater in children than when diagnosed in adults. Recruitment of non-rhabdomyosarcoma MMT into treatment trials is very variable and there is some evidence that where such patients are recruited there is bias towards the inclusion of patients with certain diagnoses.

For example, although fibrosarcoma and related fibrous neoplasms represent up to 20% of patients with all forms of soft-tissue sarcoma in the EUROCARE database, in the MMT studies (which since MMT 84 have been open to the recruitment of most forms of non-rhabdomyosarcoma MMT as well as rhabdomyosarcoma) PNET/extra-osseous Ewing's sarcoma is the most common diagnosis after rhabdomyosarcoma representing approximately 25% of the non-rhabdomyosarcoma cases, followed by synovial sarcoma (15%), whilst fibrous tumours account for only 10% of the non- rhabdomyosarcoma tumours [9]. This probably reflects the pathological diversity of fibrosarcoma and related tumours as well as the lesser role for chemotherapy (and hence, perhaps, for paediatric oncologists) in some of these tumour sub-types.

The wide variation in the relative frequencies of 'other specified' and 'unspecified' soft-tissue sarcomas in the EUROCARE data base may result from international differences in pathology practice or registry coding policies rather than underlying variations in risk. The markedly higher proportions in some countries of subgroups other than rhabdomyosarcoma, especially the fibrosarcoma group, could indicate a greater tendency to register tumours of borderline malignancy.

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