European Journal of Cancer 115 (2019) 120–127

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

The European study on centralisation of childhood cancer treatment

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Received 27 February 2019; received in revised form 25 March 2019; accepted 2 April 2019
Available online 24 May 2019

KEYWORDS
Childhood cancers;
Rare cancers;
Survival;
Hospital;
Centralised treatment

Abstract ***Background:*** It is generally agreed to centralise treatment of childhood cancers (CCs). We analysed (1) the degree of centralisation of CCs in European countries and 2) the relations between centralisation and survival.

Patients and methods: The analysis comprised 4415 CCs, diagnosed between 2000 and 2007 and followed up to the end of 2013, from Belgium, Bulgaria, Finland, Ireland, the Netherlands and Slovenia. All these countries had national population-based cancer registries and were able to provide information on diagnosis, treatment, treatment hospitals, and survival. Each case was then classified according to whether the patient was treated in a high- or a low-volume hospital among those providing CC treatment. A Cox proportional hazard model was used to calculate the relation between volume category and five-year survival, adjusting by age, sex and diagnostic group.

Results: The number of hospitals providing treatment for CCs ranged from six (Slovenia) to slightly more than 40 (the Netherlands and Belgium). We identified a single higher volume hospital in Ireland and in Slovenia, treating 80% and 97% of cases, respectively, and three to five major hospitals in the other countries, treating between 65% and 93% of cases.

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https://doi.org/10.1016/j.ejca.2019.04.024
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Outcome was significantly better when primary treatment was given in high-volume hospitals compared to low-volume hospitals for central nervous system tumours (relative risk [RR] = 0.71), haematologic tumours (RR = 0.74) and for all CC combined (RR = 0.83).
Conclusion: Treatment centralisation is associated with survival benefits and should be further strengthened in these countries. New plans for centralisation should include ongoing evaluation.
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1. Introduction

Childhood cancers (CCs) are a group of heterogeneous rare cancers. Because the diagnosis and treatment for CCs are complex, there is general agreement that management of these patients with cancer should be concentrated in specialised multidisciplinary centers. A few studies [1] have demonstrated a relationship between outcome and hospital centralisation for these cancers. The project 'Information Network on Rare Cancer' (RARECAREnet), funded by the European Commission, addressed the question of centralisation of patients with rare tumours in six European population–based cancer registries (CRs) [2], providing information about the hospital of treatment. The present study considered all children diagnosed with cancer under 15 years of age with the aims of (1) describing the degree of centralisation of CCs in the participating countries and (2) analysing the relation between centralisation and five-year survival.

2. Children and methods

We analysed individual data regarding 4415 rare cancers diagnosed in children aged less than 15 years during the period 2000–2007 and vital status up to the end of 2013. The data were received in the framework of the RARECAREnet project [2], from six national CRs: Belgium, Bulgaria, Finland, Ireland, the Netherlands and Slovenia; selected as routinely collecting the required information on referral, diagnosis, treatment, treatment hospitals and outcome for all CCs diagnosed in each country. We used the following information: sex, date of birth, date of diagnosis, topography (site) and morphology codes according to the third edition of the International Classification of Diseases for Oncology (ICD-O-3), vital status, date of the last follow-up or date of death.

We analysed only malignant cases; therefore, we excluded benign, in situ and borderline tumours. We also considered the following data for up to five hospitalisation events in the 12 months after diagnosis: hospital blind code, date of admission and type of treatment (surgery, chemotherapy, hormonal therapy, targeted therapy, radiotherapy, other therapy and unknown). Data from Belgium were limited to the period of diagnosis 2004–2007, those from Bulgaria and the Netherlands to 2005–2007.

The estimation of hospital of treatment and hospital volumes was carried out from all the CC cases included in the RARECAREnet database, that, however, did not include [2] cases diagnosed with tumours of poorly defined morphology and/or topography or common cancers (at paediatric ages, the only relevant one is non-Burkitt Non Hodgkin Lymphoma).

For each cancer case, a main treating hospital (primary treatment) was established. This was the hospital providing the first chemotherapy for haematological cancers and the first surgery for solid tumours. Otherwise, we counted the hospital where the first treatment was given.

The annual volume for each hospital was calculated separately for each of the ten International Classification of Childhood Cancers (ICCC) diagnostic groups below defined dividing the total number of treatments for cancers belonging to that group by the number of years of diagnosis, contributed by the registry.

For each country, we ranked all hospitals treating cancers of the same diagnostic group by annual volume. Then, we identified a country-specific cut-off separating high-volume from low-volume hospitals. As a first option, a cut-off corresponded to the volume for the hospital—proceeding from the top to the bottom of the ranked list—that treated at least twice the number of cases as the next one down. If no such gap was seen, the cut-off was taken as the volume of the top hospitals treating at least half the cases of the given diagnostic group in that country. Each cancer case was then classified according to whether the patient received the main treatment in a higher or a lower volume hospital among those providing treatment for the given diagnostic group. During the study period, there were no hospitals renamed or units being transferred to a new hospital; thus, there was no misleading in classifying hospital volume.

Sixteen cancers defined by the ICCC were considered for survival analyses: Ia-b (leukaemias both myeloid and lymphoblastic) and IIa, IIc (Hodgkin lymphoma and Burkitt lymphoma); IIIa-d (ependymomas and choroid plexus tumours, astrocytomas, intracranial and

Table 1
Childhood cancer cases, population of children, hospitals of first treatment and 5-year survival in six European countries.

Country	Belgium	Bulgaria	Finland	Ireland	The Netherlands	Slovenia	Total
Years of diagnosis	2004–07	2005–07	2000–07	2000–07	2005–07	2000–07	
Population[a]	1.8	1	0.9	1	2.9	0.3	7.9
Cases in the database	1052	395	714	802	1152	300	4415
ICCC diagnostic group selected for survival analysis	798	337	590	669	941	239	3574
Ia Lymphoid leukaemias	268	145	294	234	332	75	1348
Ib Acute myeloid leukaemias	50	21	48	55	68	20	262
IIa Hodgkin lymphomas	63	26	36	43	44	21	233
IIc Burkitt lymphoma	32	6	8	8	37	6	97
IIIa Ependymomas and choroid plexus tumour	31	10	12	19	25	6	103
IIIb Astrocytomas	51	16	9	46	38	23	183
IIIc Intracranial and intraspinal embryonal tumours	47	22	24	33	64	17	207
IIId Other gliomas	30	6	2	28	39	5	110
V Retinoblastoma	40	11	22	23	66	6	168
VIa Nephroblastoma and other epithelial renal tumours	70	19	58	57	88	21	313
VIIa Hepatoblastoma	4	2	9	14	15	4	48
VIIIa Osteosarcomas	22	11	18	19	30	7	107
VIIIc Ewing tumour	38	6	5	24	28	4	105
IXa Rhabdomyosarcomas	36	20	21	46	44	16	183
IXb Fibrosarcomas	3	4	7	5	12	3	34
Xc Gonadal germ cell tumours	13	12	17	15	11	5	73
Cases with H[b]	711	312	585	669	834	233	3344
Haematologic	368	181	382	340	442	117	1830
All solid	343	131	203	329	392	116	1514
Treated in:							
1 hospital	622	238	549	468	775	173	2825
2 hospitals	81	68	36	160	58	59	462
3-5 hospitals	8	6	0	41	1	1	57
5-year survival	81.8	68.5	84.9	79.2	80.9	80.7	80.3

ICCC, International Classification of Childhood Cancers.
[a] Millions.
[b] Cases with information on hospital.

intraspinal embryonal tumours and other gliomas), called CNS tumours; V retinoblastoma, VIa nephroblastoma, VIIa hepatoblastoma, VIIIa, VIIIc (osteosarcomas, Ewing tumours and other related sarcomas) grouped in malignant bone tumours; IXa-b (rhabdomyosarcomas and fibrosarcomas) grouped into soft tissue sarcomas (STSs) and Xc malignant gonadal germ cell tumours. The entities from Ia to IIc were grouped into Haematological Tumours, all the other entities in the group of Solid Tumours.

Five-year absolute survival was estimated as an outcome measure by country, volume category, cancer, both individually and grouped into haematological and solid cancers. A Cox proportional hazard model [3] was used to calculate the relation between the volume category and survival, adjusting by age (0, 1–4, 5–9, 10–14 years) sex and ICCC diagnostic group (I-X) to account for differences in case mix. The same model was used to analyse the volume/survival relationship in the pool of the six countries, after including also country as an adjustment covariate.

We also repeated survival analyses using the hospital volume cut-off of 30 cases of any CC treated per year (Over30), as defined by the European Standards of Care for Children with Cancer [4].

3. Results

Hospital volume was estimated on the 4415 cases included in the database. Depending on the size of the population, the numbers of cases varied widely from 300 in Slovenia to 1152 in the Netherlands (Table 1). For survival analysis, 3574 cases, diagnosed with the 16 selected cancers, were considered. Table 1 provides the distribution of ICCC entities by registries. In all, 6% of cases (230) had no information on hospital of treatment, ranging from 0 to 11% across the registries. Eighty-four percent of children were treated in only one hospital, ranging from 70% in Ireland to 94% in Finland (Table 1).

Fig. 1 shows the distribution of hospital volume by country. The annual number of cancer cases treated by each hospital is reported on the Y axis, separately for haematological (light grey) and solid tumours (grey). The treatment hospitals are represented as categories on the X axis, ranked from the highest to the lowest annual

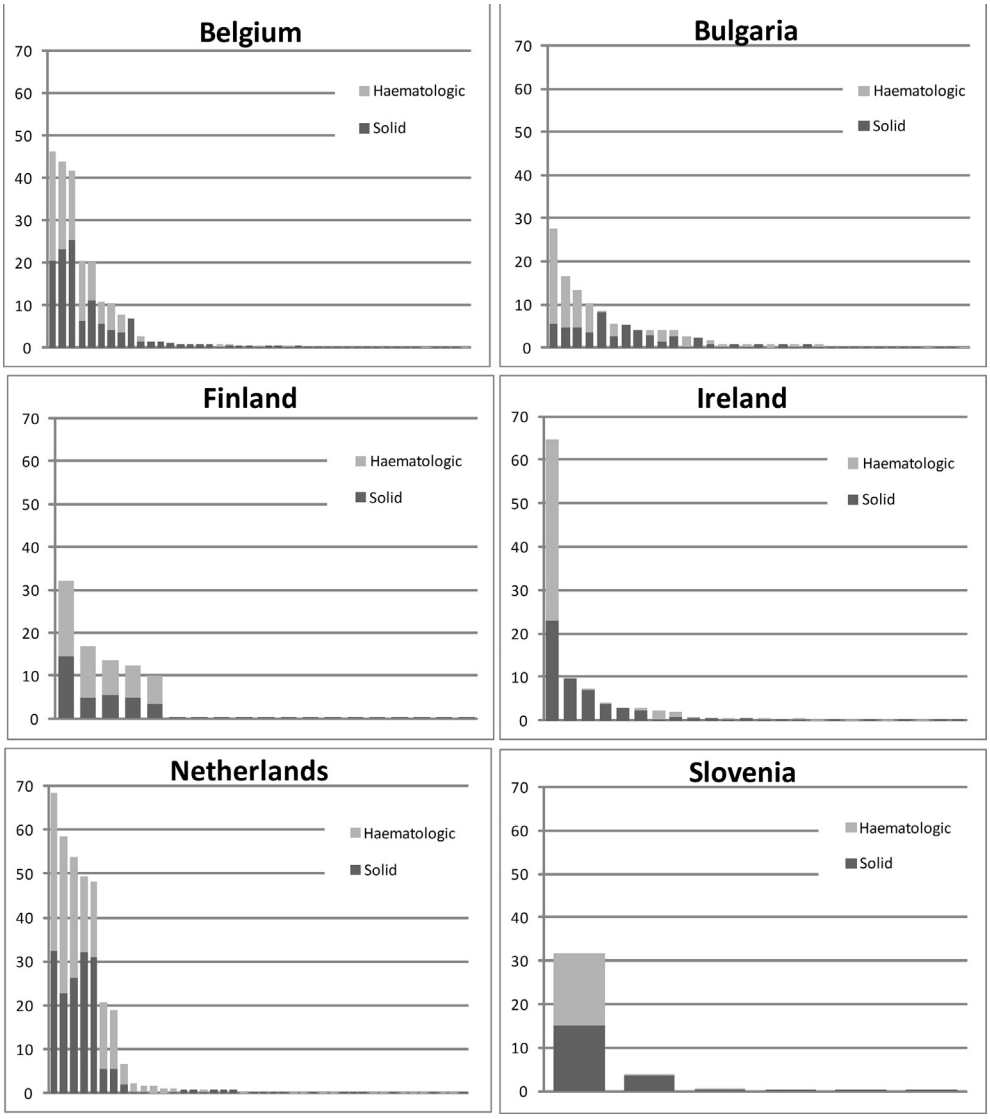

Fig. 1. All childhood cancers together, number of annual cases (y) by hospital (x) in the six European countries.

volume for all cancers combined. The number of hospitals providing treatment for CC ranged from six (Slovenia) to slightly more than 40 (the Netherlands and Belgium). The Figure shows in each country the hospitals treating more than 30 cases/year. Three hospitals fulfilled the Over30 criterion in Belgium, 1 in Ireland and Slovenia, 5 in the Netherlands and none in Bulgaria. High-volume hospitals treated both haematological and solid tumours in all countries.

Table 2 shows (columns 2–5) the numbers of higher volume hospitals, cases treated in higher and in lower volume hospitals and the level of centralisation of primary treatment in higher volume hospitals, by country and cancer type. The proportion of treatments in higher volume hospitals ranged between 46% for STS in Bulgaria and 100% in Ireland and Finland for nephroblastoma and haematologic tumours, respectively. For all cancers combined, centralisation was the highest in Finland and Slovenia and the lowest in Belgium. Table 2 also provides (columns 6–9) the model-based relative risks (RRs) of dying after primary treatment in major higher versus lower volume hospitals, adjusted by age and sex and presented according to country. Countries with 10 cases or less in lower volume hospitals were not included in cancer-specific models. The RRs for haematological tumours, also adjusted by the tumour group (leukaemias and lymphomas), ranged from 0.87 in Belgium to 0.66 in Ireland. RRs for CNS tumours treated in higher volume hospitals were significantly protective in Belgium and the Netherlands.

Treatment of nephroblastoma was highly centralised in all countries, and only for Belgium, we could estimate a (non-significant) better outcome in higher versus lower volume hospitals. Also for bone sarcomas, even if not significant, survival was better in higher volume hospitals. An inverse, but not statistically significant, relation was found for STS. Considering all the solid tumours included in this analysis, excluding CNS, for the strong

Table 2
Numbers of higher volume hospitals treating childhood cancers, numbers and percentages of cases treated in higher and lower volume hospitals; adjusted risks of dying (RR), their corresponding 95% confidence intervals (95% CI) and p values (p), in higher versus lower volume hospitals in six European countries, by 7 groups of paediatric cancers.

Group of cancer/country	Number of higher volume hospitals	Cases in lower volume hospitals	Cases in higher volume hospitals	Centralisation in higher volume hospitals (%)	RR[a]	95% CI	p
Haematologic							
Belgium	3	154	214	58	**0.87**	**0.51–1.48**	0.60
Bulgaria	4	41	140	77	**0.75**	**0.38–1.49**	0.42
Finland	5	0	382	100	-		–
Ireland	1	37	303	89	**0.66**	**0.33–1.35**	0.26
The Netherlands	3	189	253	57	**0.67**	**0.43–1.06**	0.09
Slovenia	1	2	115	98	-		–
CNS							
Belgium	5	32	96	75	**0.51**	**0.29–0.91**	0.02
Bulgaria	3	20	32	62	**0.79**	**0.38–1.64**	0.52
Finland	5	1	45	98	-		–
Ireland	1	58	68	54	**1.20**	**0.71–2.03**	0.50
The Netherlands	5	11	87	89	**0.27**	**0.12–0.59**	0.00
Slovenia	1	1	50	98	-		–
Nephroblastoma							
Belgium	4	12	55	82	**0.73**	**0.07–7.95**	0.79
Bulgaria	3	2	16	89	-		–
Finland	4	4	54	93	-		–
Ireland	1	0	57	100	-		–
The Netherlands	4	3	85	97	-		–
Slovenia	1	1	20	95	-		–
Bone sarcoma							
Belgium	3	21	36	63	**0.81**	**0.26–2.56**	0.72
Bulgaria	2	7	8	53	-		–
Finland	1	10	13	57	-		–
Ireland	1	21	22	51	**0.34**	**0.11–1.04**	0.06
The Netherlands	5	3	55	95	-		–
Slovenia	1	1	10	91	-		–
Soft tissue sarcoma							
Belgium	4	13	25	66	**n.e.**[b]		–
Bulgaria	5	13	11	46	**1.82**	**0.27–12.45**	0.54
Finland	1	14	14	50	**1.13**	**0.31–4.08**	0.86
Ireland	2	10	41	80	-		–
The Netherlands	2	23	33	59	**1.34**	**0.39–4.65**	0.64
Slovenia	2	1	18	95	-		–
All solid excluding CNS							
Belgium	3	62	153	71	**1.40**	**0.57–3.45**	0.47
Bulgaria	4	32	47	59	**0.94**	**0.41–2.16**	0.88
Finland	5	40	117	75	**0.87**	**0.30–2.50**	0.80
Ireland	1	39	164	81	**1.01**	**0.46–2.25**	0.97
The Netherlands	5	39	255	87	**0.77**	**0.28–2.10**	0.61
Slovenia	1	3	62	95	**0.36**	**0.03–3.93**	0.40
All selected cancers							
Belgium	3	248	463	65	**0.82**	**0.57–1.17**	0.27
Bulgaria	4	93	219	70	**0.90**	**0.58–1.38**	0.73
Finland	5	41	544	93	**0.70**	**0.25–1.95**	0.50
Ireland	1	134	535	80	**0.98**	**0.67–1.44**	0.93
The Netherlands	5	239	595	71	**0.61**	**0.42–0.88**	0.01
Slovenia	1	6	227	97	**0.37**	**0.10–1.31**	0.12

Bold value signifies RR and their 95% CI. RR, relative risk.
[a] Adjusted by age and sex and, for haematologic and all cancers, also case mix.
[b] Not estimable: all cases treated in lower volume hospitals survived.

effect of centralisation, a favourable effect (also accounting for case mix) was found in all countries, excluding Belgium and Ireland; however, no risks were significant. When considering all cancers combined, RRs adjusted by age, sex and case mix varied between 0.98 and 0.37 across countries, with a significant positive effect of volume only in the Netherlands (RR = 0.61). To provide more stable outcome results, we analysed the pool of CC cases from all six countries. Risks were adjusted by age, sex, country and tumour type. In view of the more marked effect seen on CNS tumours, we separated them from the other solid tumours. Then, we

assessed the risks for four groups of CC: all tumours combined, haematologic, solid other than CNS and CNS (Table 3). For three groups, the adjusted RRs of cases treated in higher versus lower volume hospitals were significantly less than one, ranging from 0.83 (all CC combined) to 0.71 (CNS). Similar results were found using the Over30 criteria to classify the hospitals, with the RRs significantly less than one for solid, CNS tumours and all CC combined.

4. Discussion

This is the largest population-based study on the volume effect in paediatric oncology, carried out on more than 4000 CC cases diagnosed during the period 2000–2007 in six small- to medium-sized European countries. Our results provide a baseline from which further healthcare reorganisations can be assessed and which are ongoing in several of the countries who took part.

The volume indicator, in terms of annual number of hospital admissions, is an absolute measure that depends not only on cancer care organisation but also on the number of cases diagnosed annually and on the population size in each country. To outline the organisational aspects, we derived from registry data the volume distribution in each country and classified each hospital as higher or lower volume, using a relative definition that was country and cancer group specific. We compared the results with those based on an absolute volume threshold of 30 cases per year, suggested as a European standard [4].

The upper age limit for paediatric as opposed to adult oncological care was not younger than age 15 years in all the countries in the study. This indicates the no dispersion is expected of older children among the more numerous hospitals providing adult oncology services.

More than 70% of the CC included in the database had their initial (primary) treatment in a limited number of high-volume hospitals. This proportion, however, varied widely, from 97% in Finland to 65% of all children in Belgium (see Table 2).

When considering centralisation, the number of cases treated in major hospitals alone is not an indicator of success or failure and did not explain the geographical differences in outcome. Other factors may influence outcomes on the national level, such as multidisciplinary teams, audit, use of agreed protocols or the existence of a formal or informal network in the country. We found very similar five-year survival estimates for paediatric tumours in Slovenia and Finland even though Slovenia had only one high-volume hospital, while Finland had five. There were also no important survival differences for (all combined) CCs between the six countries, ranging from 79% to 85%, as reported in Table 1, with the sole exception of Bulgaria (69%).

The Bulgarian health service has had a system of care introduced in the early 2000s that involves only three accredited CC treatment centers. These three hospitals were all classified as 'higher volume' and treated (data not shown) 54% of children, including 60% of patients with haematological cancer, but a minority of cases diagnosed with brain cancers (39%), bone (30%) or STS (43%). The data provided by the national registry suggest that in Bulgaria for the years covered by the study (2005–07) not all patients with paediatric cancer were treated in those accredited hospitals, but also in other specialised hospitals from the existing healthcare network in the country. However, since 2012, there is a national society for paediatric haematology and oncology which is working to assure a network of care across these three centres and improve the quality of data provided to the national CR.

We estimated a significant 17% lower risk of dying for children diagnosed with all CCs who received their primary treatment in higher versus lower volume hospitals. The corresponding reductions were, respectively, 26% and 29% for haematological and CNS. We estimated no effect for the other solid tumours but a strong and significant protection in hospitals treating more than 30 cases/year.

Unfortunately, we cannot adjust the model with further prognostic factors because our database did not include sufficiently complete information on grading, dimension and stage of the tumour.

The effect of centralisation on CNS survival was marked in all the analysed countries, with Ireland being the only (not significant) exception, that presented the lowest proportion (54%) of centralised treatments. In order to explore a possible artefact due to case mix, we selected the lethal CNS tumours (anaplastic astrocytoma, glioblastoma, gliomatosis cerebri, atypical teratoid/rhabdoid tumours) and we found that their treatment was equally distributed between higher and lower volume hospitals. A recent report from the Netherlands, for the diagnostic period 2004–2013,

Table 3
Adjusted risks of dying (RR[a]), their corresponding 95% confidence interval (95% CI) and p values (p), for higher versus lower volume hospitals and over versus under 30[b]: pool of six European countries for haematologic, solid, CNS cancers and all selected cancers.

	N	Hospital volume category	RR[a]	95% CI	p
Haematologic	2075	higher/lower	**0.74**	0.56–0.98	0.03
		over/under 30[b]	**0.87**	0.65–1.16	0.34
CNS	518	higher/lower	**0.71**	0.52–0.98	0.04
		over/under 30[b]	**0.69**	0.48–0.99	0.04
All solid excluding CNS	1526	higher/lower	**1.00**	0.70–1.44	0.99
		over/under 30[b]	**0.64**	0.44–0.94	0.02
All selected cancers	4119	higher/lower	**0.83**	0.70–0.99	0.04
		over/under 30[b]	**0.82**	0.69–0.99	0.04

Bold value signifies RR and their 95% CI. RR, relative risk.
[a] RR adjusted by sex, age, country and case mix.
[b] According to the cut-off of the European Standards of Care for Children [4].

stated that 30 children with a CNS tumour died within one week of diagnosis and about half of them were not known at the paediatric oncology center [5]. A Canadian study on medulloblastoma showed a double—significantly higher—risk of dying for cases treated in low-volume hospitals compared to the University Center Hospital. The risk was lower and became non-significant after adjustment for stage, extent of resection, meningitis and sex, suggesting that the cases treated in minor hospitals were complicated or more advanced [6]. Only two studies considered in the Knops review, on the effect of hospital volume in CC outcome [1], included a complete collection of stage [6,7]. They found a slightly more advanced stage at diagnosis for medulloblastoma and Wilms tumours in low-volume hospitals than high-volume hospitals.

Country-specific results generally confirmed a lower risk of dying for children treated in higher volume hospitals, but this did not reach statistical significance, except for the Netherlands with CNS, bone sarcomas and all CCs and Belgium and Slovenia with CNS tumours. One of the main reasons for the lack of significance is that in most countries only very small numbers of cases were treated in lower volume hospitals, thus underpowering any comparisons with higher volume hospitals. For children with Wilms tumour, surgery was so highly centralised that survival in higher and lower volume hospitals could not be even compared, apart for Belgium [8].

A review of the volume effect on paediatric oncology [1] showed that it was more evident for tumours involving surgery. This is partly borne out by our findings, mainly for CNS, with the highest reduction of risk (see Table 3). For STS in three countries, we observed a disadvantage—not statistically significant—for children treated in higher volume hospitals. This could be because patients with more aggressive and/or complicated disease are more often referred to major hospitals. An anatomic site is a prognostic factor for rhabdomyosarcoma [9], which represents more than 80% of our STS cases. We found that 60% of rhabdomyosarcomas treated in lower and only 44% of those treated in higher volume hospitals were located in favourable sites (orbit, head and neck and genitourinary tract). For these cancers, in any case, centralisation was fairly limited, ranging between 46% (Bulgaria) and 59% (Netherlands).

Our analysis involved several steps, each one being a possible source of incompleteness or bias. The selection of cases in analysis was partially affected by the proportion of unspecified cases within each ICCC diagnostic group. Table 1 shows marked deficits of Burkitt lymphoma in Bulgaria, Finland and Ireland and of astrocytoma and other gliomas in Finland. In the original data, the deficit of Burkitt lymphoma corresponded to a high number non-Hodgkin, Hodgkin and unspecified lymphomas, respectively, in the three countries. The deficit of astrocytoma and glioma in Finland can be explained by coding to tumour NOS, as ICD-O-3 was not used in the Finnish CR during the study period. Our procedure for analysing hospital volume involved several steps, each one being a possible source of incompleteness or bias. Information on hospital of treatment was missing for an appreciable proportion of patients in some registries, such as Bulgaria (7%), the Netherlands and Belgium (11%), against an average of 6.4% for the whole sample. Cases with the hospital missing were more frequent among CNS tumours (17%) and lymphomas (12%) and less among leukaemias (4%) and other solid tumours (3%). They had similar survival in Belgium (81% versus 82%) but lower survival in Bulgaria (56% versus 68%) and overall (71% versus 80%). We could not analyse the survival of cases with hospital missing in the Netherlands because follow-up information was also missing.

As there is no unambiguous definition of primary treatment, we took the first hospital reporting chemotherapy for haematological cancers, surgery for solid tumours or the first hospital reporting an alternative treatment as the main treatment hospital. This may not always be true, however, particularly when the information on treatments is incomplete. CRs collect data on primary treatment in the first year; therefore, whenever a case is assigned a treatment and treatment hospital, data are usually correct and valid. On the whole, completeness of treatment data was high at 93%. The specific definitions of hospital of diagnosis and treatment were agreed in the study protocol among the six registries, so a hospital where diagnostic biopsies were taken should not be misclassified as the hospital of primary surgery.

For complex treatments, the decision on the most appropriate hospital may not be straightforward, but in most cases, no such decision was required. We analysed up to five different treatment hospitals per child, and only 16% of children were treated in more than one hospital (Table 1). This proportion drops to 8% when removing the subgroup of patients who underwent radiotherapies. In 75% of cases, radiotherapy followed the surgical or systemic treatment.

The results could also be influenced by how we defined higher and lower volume hospitals. There was no clear cut-off in several countries. For example, both in Belgium and the Netherlands, two intermediate-size hospitals were grouped among lower only to respect the common criterion, but they could also have been grouped among the higher volume hospitals. Such a shift, however, would not have substantially altered the sense of the results, leading to new RRs for all cancers combined of 0.72 instead of 0.82 in Belgium and again of 0.61 in the Netherlands (Table 2).

We also analysed centralisation and relative outcome using the cut-off of 30 cases per year suggested by the European standard for care of children with cancer [4]. Compared to the first definition of hospitals, we obtained similar results for CNS tumours and all CC combined, slightly higher RRs for the haematologic tumours and a lower and significant RR for solid (non-

CNS) cancers. In any case, hospital volumes and the distinction between higher and lower volume hospitals may be sensitive for the completeness and validity of treatment data in our study.

To conclude, we found better survival and significantly fewer deaths when primary treatment was given in high-volume hospitals for the haematological malignancies, CNS tumours and for all CC combined.

Many CCs are curable; standardised guidelines are available, and inclusion of children in clinical studies for improving patient stratification for treatment is quite routine in paediatric oncology. The dispersion of treatment in several hospitals (Fig. 1) in high-survival countries such as Belgium, Finland and the Netherlands suggests there was existing collaboration for treating CCs in the time period analysed. Thus, patients treated in low-volume hospitals might have been advised by consultants from major hospitals or even treated locally by leading experts. This could also have an impact on our survival comparison between higher and lower volume hospitals.

For relatively rare diseases with complex treatments, such as CCs, a large enough number of cases must be treated to gain optimal expertise. Indeed, with this aim in mind, the Netherlands centralised treatment of all CCs into a single new CC hospital in 2018 [5]. Participation in international networks is vital when the numbers of cases are low on account of the rarity of the disease and/or the country's small population. Bulgaria—like other eastern countries, as already stated [10]—requires and is putting in place collaborative programs to help narrow the survival gaps in Europe, taking advantage of the European Commission's call for twinning programs [11]. The implementation and extension of the European directive on cross-border healthcare [12] is also important for small European countries.

Funding

This work was supported by the European Commission through the Consumers, Health, Agriculture and Food Executive Agency (Chafea), 'Information network on rare cancers'—RARECARENet [grant number: 2000111201] and European Union's Health Programme (2014-2020) [Grant No. 724161]. Project title 'Joint Action on rare Cancers'—JARC.

Conflict of interest statement

None declared.

Acknowledgements

The authors thank J D Baggott for editing, Lucia Buratti for technical support and Prof Rob Pieters and Prof Dobrin Konstantinov, for critical review of the manuscript.

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