Original article

Highlights

- Degree of centralization of childhood cancers varied across six European countries
- Survival was higher for children treated at high volume hospitals, especially for CNS tumours.
- Centralisation of treatment should be improved
- Plan of centralisation, including evaluation, are needed

The European study on centralisation of childhood cancers treatment

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Abstract

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

Patients and methods. The analysis comprised 4,415 CC, diagnosed between 2000-2007 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 CC ranged from six (Slovenia) to slightly more than 40 (Netherlands and Belgium). We identified a single higher volume hospital in Ireland and in Slovenia, treating respectively 80% and 97% of cases, and three -five major

hospitals in the other countries, treating between 65% to 93% of cases. Outcome was significantly better when primary treatment was given in high compared to low volume hospitals for CNS tumors (RR=0.71), hematologic 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.

Key words

Childhood cancers, rare cancers, survival, hospital, centralized treatment

Introduction

Childhood cancers (CC) are a group of heterogeneous rare cancers. Because the diagnosis and treatment for CC are complex, there is general agreement that management of these cancer patients 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 tumors 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 CC in the participating countries and 2) analysing the relation between centralisation and five-year survival.

Children and methods

We analysed individual data regarding 4,415 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, Netherlands and Slovenia; selected as routinely collecting the required information on referral, diagnosis, treatment, treatment hospitals and outcome for all CC 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 last followup 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 hospitalization events in the 12 months after diagnosis: hospital blind code, date of admission, type of treatment (surgery, chemotherapy, hormonal therapy, targeted therapy, radiotherapy, other therapy, 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 NHL).

For each cancer case, a main treating hospital (primary treatment) was established. This was the hospital providing the first chemotherapy for hematological cancers, and the first surgery for solid tumors. 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 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 volume hospital.

Sixteen cancers defined by the International Classification of Childhood Cancers (ICCC) were considered for survival analyses: Ia-b (leukaemias both myeloid and lymphoblastic) and IIa, IIc (Hodgkin lymphoma and Burkit lymphoma); IIIa-d (ependimomas and choroid plexus tumours, astrocytomas, intracranial and 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 (STS) 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 hematological and solid cancers. A Cox proportional hazard model [4] was used to calculate the relation between 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

Results

Cancer [3].

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). 3,574 cases, diagnosed with the 16 selected cancers, were considered for survival analysis. 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).

Figure 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 hematological (light grey) and solid tumors (grey). The treatment hospitals are represented as categories on the X axis, ranked from the highest to the lowest annual volume for all cancers combined. The number of

hospitals providing treatment for CC ranged from six (Slovenia) to slightly more than 40 (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 hematological and solid tumors 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 soft tissue sarcoma 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 cancerspecific models. The RRs for hematological tumors, also adjusted by tumor group (leukemias and lymphomas), ranged from 0.87 in Belgium to 0.66 in Ireland. RRs for CNS tumors treated in higher volume hospitals were significantly protective in Belgium and the Netherlands.

Treatment of nephroblastoma was highly centralized 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 effect of centralisation, a

favourable effect (also accounting for case mix) was found in all countries, excluding Belgium and Ireland, however no risks was 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 tumor type. In view of the more marked effect seen in CNS tumors, we separated them from the other solid tumors. Then we assessed the risks for four groups of CC: all tumors combined, hematologic, 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.

Discussion

This is the largest population-based study on the volume effect in pediatric oncology, carried out on more than 4,000 CC cases diagnosed during the period 2000-2007 in six small to mediumsized 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.

Volume indicator, in terms of annual number of hospital admissions, is an absolute measure that depends not only on cancer care organization, but also on the number of cases diagnosed annually and on the population size in each country. To outline the organizational 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 [3].

The upper age limit for paediatric as opposed to adult oncological care was not younger than age 15 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 pediatric tumors 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) CC 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 haematological cancer patients, 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 paediatric cancer patients 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 cancer registry.

We estimated a significant 17% lower risk of dying for children diagnosed with all CC 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 tumors, but a strong and significant protection in hospitals treating more than 30 cases/year.

Unfortunately, we cannot adjust the model with further prognostic factors, since our database did not include sufficiently complete information on grading, dimension and stage of the tumor. The effect of centralization on CNS survival was marked in all the analysed countries, with the only (not significant) exception of Ireland, that presented the lowest proportion (54%) of centralized treatments. In order to explore a possible artefact due to case-mix, we selected the lethal CNS tumours (anaplastic astrocytoma, glioblastoma, gliomatosi cerebri, atypical teratoid/rabdoid 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, stated that 30 children with a CNS tumor died within one week of diagnosis and about half of them were not known at the pediatric 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 childhood cancer outcome [1], included a complete collection of stage [6,7]. They found a slightly more advanced stage at diagnosis for medulloblastoma and Wilms tumors in low 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 CC and Belgium, Slovenia for the 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 under-powering any comparisons with higher volume hospitals. For children with Wilms tumor 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 in pediatric oncology [1] showed that it was more evident for tumors 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. 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 was 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 of non-Hodgkin, of Hodgkin, and of unspecified lymphomas, respectively in the three countries. The deficit of astrocytoma and glioma in Finland can be explained by coding to tumour NOS, as ICDO-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 tumors (17%) and lymphomas (12%), and less among leukemias (4%) and other solid tumors (3%). They had similar survival in Belgium (81% vs. 82%), but lower survival in Bulgaria (56% vs. 68%) and overall (71%) vs.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 hematological cancers, surgery for solid tumors, 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. Cancer registries collect data on primary treatment in the first year, so whenever a case is assigned a treatment and treatment hospital, data is 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 that 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 [3]. Compared to the first definition of hospitals, we obtained similar results for CNS tumors and all CC combined, slightly higher RRs for the hematologic tumors, 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 hematological malignancies, CNS tumours and for all CC combined.

Many childhood cancers are curable; standardised guidelines are available and inclusion of children in clinical studies for improving patient stratification for treatment is quite routine in pediatric oncology. The dispersion of treatment in several hospitals (Figure 1) in high-survival countries like Belgium, Finland and the Netherlands suggests there was existing collaboration for treating CC 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 CC, 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 childhood cancers into a single new childhood cancer 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.

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Conflict of Interest statement

Declarations of interest: none

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