The volume effect in paediatric oncology: a systematic review

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Background: For several adult cancer types, there is evidence that treatment in high volume hospitals, high case volume providers, or in specialised hospitals leads to a better outcome. The aim of this study is to give an overview of the existing evidence regarding the volume effect in paediatric oncology related to the quality of care or survival.

Materials and methods: An extensive search was carried out for studies on the effect of provider case volume on the quality of care or survival in childhood cancer. Information about study characteristics, comparisons, results, and quality assessment were abstracted.

Results: In total, 14 studies were included in this systematic review. Studies with a low risk of bias provide evidence that treatment of children with brain tumours, acute lymphoblastic leukaemia, osteosarcoma, Ewing’s sarcoma, or children receiving treatment with allogenic bone marrow transplantation in higher volume hospitals, specialised hospitals, or by high case volume providers, is related with a better outcome.

Conclusions: This systematic review provides support for the statement that higher volume hospitals, higher case volume providers, and specialised hospitals are related to the better outcome in paediatric oncology. No studies reported a negative effect of a higher volume.

Key words: childhood cancer, paediatric oncology, quality of care, volume

introduction

Childhood cancer is the leading cause of death from illness in children in high income countries [1]. However, the improvement of childhood cancer therapies has led to a considerable rise of survival rates. In Western countries, the overall 5-year survival rate for children diagnosed with cancer has risen from 44% in the 1970s to 81% in the early 2000s [2, 3].

The care for patients with cancer is complex [4]. In addition, childhood cancer is a rare disease. All types of childhood cancer are acknowledged as orphan diseases [5], and only 1% of all cancers are diagnosed in children [2]. Both complexity and rarity make it a challenge to optimise the quality of care and thus survival of children with cancer.

For several adult cancer types, there is evidence that treatment in high volume hospitals or by high case volume providers leads to a better outcome compared with low volume hospitals or low case volume providers [6, 7]. As an explanation for this positive correlation, the ‘practice makes perfect’ effect has been used; a greater supply of patients will give physicians and their teams more experience and will consequently lead to the improvement of care [8]. Another explanation of this volume effect is the phenomenon of selective referral, which means a physician or hospital with a reputation of excellent care will attract more patients [8].

The use of provider case volume as a quality measure receives a growing amount of interest of care givers and policy makers [9]. To give an overview of the existing evidence regarding the volume effect in paediatric oncology, we systematically reviewed the association between hospital volume, provider case volume, and/or specialised hospitals and quality of care or survival in childhood cancer.

methods

search strategy for identification of studies

The objective of the literature search was to identify the available evidence on the effect of provider case volume on the quality of care or survival in childhood cancer. The databases of Medline/PubMed (from 1966 to November 2010) and The Cochrane Library (issue 4, 2010) were searched for potentially relevant articles. The search strategy combined controlled vocabulary and text word terms for volume, outcome, and childhood cancer. The complete search strategy is presented in supplementary File S1.

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available at Annals of Oncology online. In addition, the bibliographies of all included reviews and included studies were searched for additional references, which were not registered in the above mentioned databases. Experts in the field of childhood cancer were also asked to supply additional articles.

**selection of articles**

Selection of articles was based on title and abstract and carried out by two independent reviewers. The following inclusion criteria were used: (i) study population of more than 100 patients treated for childhood cancer, (ii) comparison between high and low volume hospitals, or high and low case volume providers, or specialised and non-specialised hospitals, or teaching and non-teaching hospitals, (iii) outcome given as a quality of care or survival, (iv) written in English, Dutch, German, or French. Each article had to meet all four criteria for inclusion. There were no restrictions regarding study design. The following two criteria were used to exclude articles: if only a comparison was made between trial and non-trial patients, or a comparison between treatment in paediatric and adult facilities. Articles were examined in the full text for more detailed information if the abstract was not electronically available or if the information of the abstract of the article was insufficient. All retrieved articles were examined in full text by two reviewers to ensure that they met the inclusion criteria. In the case of disagreement about the selection of articles between the two reviewers, the abstracts and articles were re-examined and discussed until consensus was reached. If disagreement persisted, a third author (LCMK) was asked for advice.

**data extraction**

From each included study, information about country, design, study population, comparisons, results, and quality assessment were abstracted. Although there is no consensus about a threshold in paediatric oncology that indicates the transition from low volume providers to high volume providers, for this review we defined the treatment of more than five cases per year per provider (i.e. either hospital or physician) as ‘high volume’. This definition of high volume was made after reading the selected studies and based on the encountered volume numbers. Data extraction was carried out by one reviewer and checked by another reviewer. In the case of disagreement, a third author (LCMK) was asked for advice.

**quality assessment of the included studies**

Quality assessment of the included studies was done by two independent reviewers and based on Evidence-Based medicine criteria [10, 11]. Evaluation of the quality of the included studies was based on the following criteria. First, the selection of the study population was evaluated (i.e. the risk of selection bias). The study population was defined as representative for the underlying population if it consisted of >90% of eligible childhood cancer patients. The risk of selection bias was considered to be low when selection was based on regional or national registries, taking into consideration that these registries are not always complete. Secondly, the risk of attrition or follow-up bias was evaluated. The follow-up was defined as complete if the outcome was assessed at the end of the study for >90% of the study population. Thirdly, we checked if the data analysis took the stage of disease and other confounding factors, like age, gender, demographics, and treatment variables, into consideration. Fulfilment of each quality criterion was awarded with a ‘+’. In the case of uncertainty, due to the lack of information, the quality criterion was awarded a ‘-’. In the case of disagreement, a third author was asked for advice. The quality assessment results of each study were interpreted according to their level of research in which the quality assessment scores and fulfilment of our high volume definition were incorporated (level B = <3 ‘+’, level A2 = ≥3 ‘+’). This was based on the manual of the Dutch Evidence Based Guideline Development platform (EBRO platform) [12], which was adjusted for the purpose of this study (Table 1).

**data analysis**

Results were considered to be significant, only if a level of $P \leq 0.05$ was reached. An interpretation of the results was based on the level of conclusion (Table 2), which was also based on the EBRO platform and adjusted for the purpose of this study [12]. A pooled analysis of the data was not carried out since the studies were very heterogeneous regarding design, study population, definitions, and quality. Therefore, we summarised the results descriptively.

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**results**

**selection of articles**

The search in Medline/PubMed and The Cochrane Library identified a total of 731 potentially eligible articles. Screening of the titles and abstracts of these articles excluded 710 studies. The remaining 21 articles, consisting of 16 original studies and 5 reviews, were retrieved in the full text for more detailed examination. Hand searching the reference lists of the reviews resulted in four other potentially eligible articles, which were also retrieved for full-text appraisal. Eight of the retrieved articles met all inclusion criteria. In addition to the search in the two databases, 20 potentially eligible articles were supplied by experts. Six of these studies met the inclusion criteria after full-text appraisal. Between the two reviewers was disagreement regarding one of these six studies. After consulting a third author, this study was also included in this systematic review. Thus, in total, 14 articles were included in this systematic review (Figure 1).

**general characteristics of the included studies**

The characteristics, results, and quality assessment of each study are presented in supplementary File S2, available at *Annals of Oncology* online. The studies are reported separately because of differences in study population, tumour groups, comparisons, and outcome measures. A short summary of the results per study is presented in supplementary File S3, available at *Annals of Oncology* online. All but one study [13] had a retrospective design. In 12 of the 14 studies, the outcome measure was survival. The other two studies evaluated the quality of care. In one study, the quality of care depended on the performance of a radiotherapy protocol [13] and, in another study, the quality of care was defined as the extent of central nervous system (CNS)-tumour resection and its complications [14]. Seven studies were carried out in the UK [15–21], five in the USA [13, 14, 22–24], one in Canada [25], and one used data that were derived from international collaborations [26]. The study population consisted in six studies of patients with CNS or solid tumours [14, 21–25], and in six studies of patients with haematological tumours [13, 17–20, 26]. One of the studies on haematological tumours was mainly directed at the treatment with allogenic bone marrow transplantation [26]. In two studies, the study population consisted of a mix of patients of both solid and haematological tumours [15, 16]. The two studies carried out by Gutierrez et al. [22, 23] used the same study population. Three studies described a mixed study population of children and adults [19, 21, 26]. Two of these three studies took age into account in their analysis [21, 26]. The remaining 11 studies described only children. Three studies did not meet our definition of high volume (greater than or equal to five cases per year) [19, 22, 23] and, in three studies, the volume was unclear [15, 16, 18].

**quality assessment of the included studies**

The quality assessment of each study is also presented in supplementary File S2, available at *Annals of Oncology* online. The study population was well defined in all studies, and we considered the risk of selection bias as low. We considered the risk of follow-up bias to be low in 8 of the 14 studies [13–15, 17–21]. Four studies also appeared to have a low risk of follow-up bias, but this was not specifically mentioned [16, 24–26]. The two remaining studies seemed to have a complete follow-up, but because the authors mentioned the possibility of an overestimation of survival by 5%–10%, this is not certain [22, 23]. Six of the 14 studies carried out a multivariate analysis correcting for possible confounding factors [21–26]. Information about the stage of disease was provided in 3 of the 14 studies [22, 23, 25]. Three studies provided incomplete data about the stage of disease [15, 21, 24]. Six studies gave no information about the stage of disease [14, 16–20]. In the remaining two studies, staging of disease was not applicable to the tumour type [13, 26]. According to our definitions of research levels, 10 studies met the criteria for level A2 [13, 14, 17, 20–26] and 4 met the criteria for level B [15, 16, 18, 19].

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**Figure 1.** Selection of articles.
general conclusion of the results

The results per tumour type (including the study on allogeneic bone marrow transplantation [26]) and their level of conclusion are shown in supplementary File S3, available at *Annals of Oncology* online. According to conclusion level 1, it has been demonstrated that children with brain tumours treated in high volume hospitals have a lower mortality rate compared with low volume hospitals [24, 25]. Particularly, the lower mortality risk for children younger than 2 years stands out [24].

According to conclusion level 2, it is likely that children with acute lymphoblastic leukaemia (ALL) [15], children/adults with osteosarcoma [21], Ewing’s sarcoma [21], or those with leukaemia who were treated with allogeneic bone marrow transplantation [26] have a better survival in high volume hospitals. For patients with neuroblastoma [23], Wilms’ tumour [23], or AML [16, 18], it is likely that treatment in specialised hospitals benefits survival. It is also likely that children with medulloblastoma, primitive neuroectodermal tumour, or high-grade glioma have a better survival [24] and a better extent of tumour resection [14] when they are operated on by high case volume providers.

According to conclusion level 3, there are indications that rhabdomyosarcoma patients have a better survival in specialised hospitals [16].

For other tumour types, there are non-significant results, suggesting that treatment in high volume hospitals or more specialised hospitals benefits survival (supplementary File S4, available at *Annals of Oncology* online) [13, 20, 22, 24]. No study suggests a negative effect for high volume hospitals or high case volume providers. There is no clear threshold for the number of patients with childhood cancer that indicates the transition from low volume providers to high volume providers.

discussion

The best available evidence in paediatric oncology provides support for the notion that higher volume hospitals, higher case volume providers, and specialised hospitals provide care with a better outcome. No studies reported a negative effect of a higher volume in paediatric oncology. The threshold that indicates the number of childhood cancer patients needed to treat to benefit from the volume cannot be established from the available data.

The included studies of this systematic review were very heterogeneous regarding design, study population, definitions, and quality. This complicates the analysis of the results and limits the possibility of performing a meta-analysis and/or making generalised conclusions. Therefore, we evaluated the quality of each study and also defined the level of research of each study. By integrating the quality assessment into the evaluation of the results, we made it possible to combine some results and to reach a level of conclusion. In general, there is a positive correlation between higher volume hospitals, higher case volume providers, or specialised hospitals and survival in paediatric oncology. The volume effect is more evident for tumour types in which surgery is involved in the treatment. However, most included studies compared different hospital volumes, and only two studies looked at the volume of patients treated per surgeon. All studies reported a positive or a non-significant positive effect of higher volume. None of the included studies reported a negative effect of higher volume or specialised hospitals.

The differences in outcome between high versus low volume hospitals, high versus low case volume providers, and specialised versus non-specialised hospitals are relatively small. A confounding factor could be that more complicated patients are primarily being treated in high volume hospitals, specialised hospitals, or by high case volume providers.

As explanations for the positive correlation between outcome and volume, the concepts of ‘practice makes perfect’ and ‘selective referral’ have been used [8]. The reviewed studies do not further reflect on this matter. Most likely, both concepts play a role in paediatric oncology.

A limitation of this systematic review is that the presence of language bias cannot be completely ruled out. Although we included all studies reported in English, Dutch, German, or French, studies reported in other languages may have been missed.

In contrast to adult oncology, the number of studies that investigated the volume effect in paediatric oncology is limited. A large body of research is available on the volume effect in ‘adult healthcare’, which has been systematically reviewed and favours the outcome in high volume centres [7]. Systematic reviews investigating volume in adult cancer care also favoured the outcome in high volume centres [6, 27]. A meta-analysis in adult gastrointestinal cancers calculated that to prevent one volume-associated death between 10 and 50 patients per year have to be moved from a low volume hospital to a high volume hospital [6].

Unlike adult cancer care, the organisation of care for children with cancer has already seen some form of concentration and specialisation. In addition, most care for childhood cancer is highly protocolised and carried out by specialised caregivers [22]. The volume effect could also be of benefit to this standardised form of care.

In adult cancer types, as oesophageal and colon cancer the threshold hospital volume above which mortality is lower seems to lie between 16 and 32 cases per year [6]. Breast cancer patients have a better survival if their clinician treats over 30 new cases per year [28]. This systematic review did not find evidence for a volume threshold for paediatric malignancies above which the mortality rate is lower. More studies in a greater number of children with the same tumour type have to be carried out to provide this evidence.

The studies in this systematic review used different cut-off points to indicate ‘high volume’. Due to the rareness of childhood cancer volumes of more than 30 cases, as mentioned in breast cancer care [28], are almost never met in paediatric oncology. Some of the included studies used definitions of high volume of even less than five cases. The fact that the volume effect seems to be present in this relatively small amount of patients could also imply that the current ‘large’ volumes in paediatric oncology are still in the range of the steep slope of the volume–outcome relationship curve. This would imply that increasing volume to ‘adult’ volumes would lead to continuous increase in outcome. Therefore, patient volumes in paediatric oncology should be increased by further concentrating care and/or selective referral of children with cancer to high
volume hospitals, high case volume providers, or specialised hospitals.

Survival is considered as the most obvious and important outcome measure. Most of the included studies in this systematic review had survival as outcome measure, but the performance of a radiotherapy protocol or the extent of tumour resection was also measured in some studies. Besides the possible effects on survival, these other outcome measures can also lead to severe late adverse effects and may have an effect on quality of life. For example, complications during Wilms’ tumour surgery do not worsen survival, because higher dosed chemotherapy and radiotherapy schemes will salvage the otherwise lower survival rate [29]. However, due to these intensified therapies, the possibility for severe adverse late effects rises and quality of life decreases [30]. So, it is important not to overlook other measures of outcome, as they can determine the quality of life during and after treatment.

Conclusion
This systematic review provides support for the statement that higher volume hospitals, higher case volume providers, and specialised hospitals are related to the better outcome in paediatric oncology. No studies reported a negative effect of a higher volume. The threshold that indicates the number of childhood cancer patients needed to treat to benefit from the volume effect remains unclear. More studies including a greater number of children with the same tumour type have to be carried out to provide this evidence.

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