

The impact of provider surgical volumes on survival in children with primary tumors of the central nervous system—a population-based study

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Abstract

Background Provider volume is often a central topic in debates about centralization of procedures. In Norway, there is considerable variation in provider volumes of the neurosurgical centers treating children. We sought to explore long-term survival after surgery for central nervous system tumors in children in relation to regional provider volumes.

Method Based on data from the Norwegian Cancer Registry we analyzed survival in all reported central nervous system tumors in children under the age of 16 treated over two decades, between March 1988 and April 2008; a total of 816 patients with histologically confirmed disease.

Results There was no overall difference in survival between regions. In the subgroup of PNET/medulloblastomas, both living in the high-provider volume health region and receiving treatment in the high-volume region was significantly associated with inferior survival.

Conclusions In this population-based study of children operated over a period of two decades, we found no evidence of improved long-term survival in the high-provider volume region. Surprisingly, a subgroup analysis indicated that survival in PNET/medulloblastomas was significantly better if living outside the most populated health region with the highest provider volumes. One should, however, be careful of interpreting this directly as a symptom of quality of care, as there may be unseen confounders. Our study demonstrates that provider case volume may serve as an axiom in debates about centralization of cancer surgery while perhaps much more reliable and valid but less quantifiable factors are important for the final results.

Keywords Brain neoplasms · Child · Hospital mortality/trends · Survival analysis

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Introduction

It has been demonstrated that high-volume centers and surgeons may be associated with lower perioperative mortality after major cancer surgery and a range of other procedures [7], but the relative importance of volume varies markedly in different publications and according to the type of surgery [9, 13]. Moreover, several limitations are common in such studies. Frequent limitations are failure to control for potential confounders, lack of validated, long-term end-points, and lack of analysis based on surgeons' individual surgical volumes. Further, interest-bias may be associated with such studies as publications mostly originate from high-volume centers. Finally, as the majority of the available studies are American, the results may not necessarily directly apply to countries where health care is

organized differently. A recent systematic review and meta-analysis of 101 publications found that one-third of the included studies did not find an effect of volume on mortality. The heterogeneity of results made the authors question the value of case volume as a proxy for care quality [12].

Norway has a population of 4.7 million people and a socialized health care system having quite evenly distributed resources and uniform training and licensing for medical professionals. Due to considerable regional differences in provider volumes, a centralization of pediatric neurosurgery has been debated for years. However, so far, surgery is provided by pediatric neurosurgeons at four different university hospitals, each serving a separate geographical health region. As the southeastern region is by far the most populated, approximately half of all pediatric neurosurgical cases are treated at one center, while the other patients are treated at the other three centers. Consequently, hospital provider volumes of pediatric neurosurgery are quite low for three out of the four treating hospitals.

To explore a possible effect of provider volume on long-term outcome, we analyzed population-based data from the Norwegian Cancer Registry and compared outcome after surgery for central nervous system tumors diagnosed over two decades, between March 1988 and April 2008.

Materials and methods

The Norwegian Cancer Registry

Reports to the Norwegian Cancer Registry are compulsory. All neoplasms and certain precancerous lesions are to be registered. The cancer registry receives data from three sources: (1) Copies of all pathology and autopsy reports from all Norwegian laboratories, (2) Clinical registration forms from treating doctors, and (3) Information from Statistics Norway about cause of death notified on death certificates as well as vital status of all registered persons in the cancer registry (if they are alive, dead, or have emigrated). The compliance of the different data sources is generally good. The unique 11-digit personal identification numbers assigned to all Norwegian citizens ensure tracking of patients and limit the risk of duplicate registrations. From 1998, the cancer registry has also acquired data files with discharge diagnoses (ICD-10 C or D) on all patients treated for neoplastic disease in every Norwegian hospital and outpatient clinic. When C- or D-diagnoses are used in patients that are not registered in the cancer registry, the clinician will receive reminders. The completeness of patient registration has improved over the years, and there are presumably no systematic biases in the

registered data. If patients undergo repeated surgery, or if an autopsy is performed, the database is continuously updated through submission of additional histological reports. The Norwegian population of 4.7 million is stable with very little migration. A study on the completeness of data demonstrated that 93.8% of all central nervous system tumors, including non-histologically verified cases [15].

Norwegian health regions, provider volumes, and adjuvant treatment

Norway is divided into four geographical and administrative so-called health regions (South-East, West, Middle, and North) with one serving, university hospital with a complete neurosurgical department offering pediatric neurosurgery in each region. According to Statistics Norway, there were 975,125 children under the age of 16 in Norway by January 1, 2009. Of these, 529,290 (54.3%) live in the South-Eastern health region. Consequently, the case volumes of pediatric tumors is about half the national volume in one high-volume center while the other three centers share the rest of the caseload. There are 1–3 neuropathologists at each university hospital, with extensive collaboration between centers and frequent use of second opinion reviews by the neuropathologist in other hospitals. Adjuvant chemotherapy or radiotherapy is decided by pediatric oncologists at the respective university hospitals. However, there are national and/or international treatment protocols for all malignant pediatric nervous system entities, so there are presumably no major regional differences in adjuvant treatment. Since 1998, there have been regular national meetings between neuropathologists, pediatric neurosurgeons, and pediatric oncologists to exchange experience and ensure common practice.

Included patients and variables

The study aimed to include all children below the age of 16 operated for central nervous system tumors in Norway in the 20-year period between March 1988 and April 2008. In this period of two decades, 946 children below the age of 16 were diagnosed with central nervous system tumors in Norway. Of these, patients diagnosed only based on clinical examination or radiological methods were excluded (127 cases) together with patients where CNS tumor was mentioned solely on the death certificate without further documentation (0 cases). Cases diagnosed incidentally by autopsy were excluded (three cases), leaving 816 patients with histologically confirmed tumors. All patients were followed until death or until April 30, 2009. Seven patients emigrated and their data were censored at the time they left the country. No patients were otherwise lost to follow-up. Follow-up thus ranged from 1 to 21 years.

The outcome parameter was long-term survival. We sought to make comparative analyses between the high-volume center and low-volume centers. Data from the three low-volume centers, i.e., low-volume health regions, was analyzed together.

Limitations in classifications of provider volume data

Data was analyzed based on both the health region where the surgery was performed and on the geographical health region the patient belonged to. This was done as both methods are associated with some limitations due to cross-over. Analyses based on the geographical origin of patients is the most conservative approach and is equivalent to intention-to-treat analyses in randomized controlled trials, while analyses based on treating hospital is equivalent to as-treated-analyses. In registry data, several prognostic variables are unavailable. There is therefore a theoretical potential for skewed distribution of prognostic factors that cannot be controlled for. The risk of suffering from a brain tumor with an unfavorable prognosis per se is, however, presumably not dependent on one's address. The conservative method of analyses based on a patient's address reduces the power to detect a statistical difference between regions when there is cross-over, but this is of no concern if statistical tests reveal a difference. Some patients were for logistic reasons or due to local or regional hospital referral traditions treated in a different center than they geographically belong to. Seventy-two patients from the low volume had their surgery in the high-volume hospital. There are several reasons for this cross-over in our study. Of these cross-over patients, 48 (62%) belong geographically to the county of Rogaland. The densely populated Stavanger region in Rogaland County has traditionally referred all neurosurgical patients to the National Hospital in Oslo instead of Bergen, to which their patients geographically belong. This has historical, logistical, as well as political reasons. Also, 19 of the cross-over patients (26%) were living in the three northernmost counties and were operated in Oslo instead of Tromsø. The department in Tromsø was established as late as 1986, only 2 years before the beginning of our inclusion period. For historical reasons, some doctors in the northernmost counties continued for years to refer their neurosurgical patients to Oslo instead of Tromsø. Due to transportational logistics, it is also easier for many patients to travel to Oslo instead of Tromsø. The fact that epilepsy surgery is centralized to the high-volume south-eastern health region may also have implications on where some lesions are treated. In addition, from 2001 patients have been allowed to choose themselves where to be operated. However, very few decide to be operated in a different health region than their own. If patients were operated more than once and at different centers or

geographical health regions, data from the first operation was used in the classification into high or low-volume providers for the long-term survival analysis. One limitation in the attempt to classify surgical volumes based on health regions is the fact that until 1998, some children in the South-Eastern region were also operated at a second University Hospital in the South-Eastern region. The patients from this low-volume center are thus analyzed together with the high-volume data from Rikshospitalet University Hospital.

Histopathological classification

In the Norwegian Cancer Registry, tumors were classified according to ICD-7 until 1993. Thereafter, ICD-O-2 has been used. Based on the ICD codes, we grouped the operated tumor types into major groups in coherence with the WHO classification of central nervous system tumors [17].

Subgroup analyses

Most histopathological subgroups were too small to perform any meaningful subgroup analysis. Benign lesions or low-grade (WHO I or II) neuroepithelial tumors are for the most part not associated with a significant medium-term mortality rate. High-grade neuroepithelial tumors were, however, analyzed separately as survival is dependent on resection grades for these lesions [21], and as the overall mortality is considerable.

Survival in the largest malignant histopathological subgroup, namely PNET/medulloblastomas, is very much dependent on remaining tumor mass after resection [1, 25, 27]. It was therefore of interest to conduct a separate subgroup analysis for these tumors.

Ethics

The study was approved by the Regional Ethics Committee.

Statistics

Statistical significance level was set to 0.05. Data was analyzed using SPSS 14.0 for Windows and R version 2.9.0. Cohen's Kappa was used for assessing agreement between the two classifications of provider volumes (by geographical region or by health region in charge of the initial treatment). Fisher's exact test and Chi-square test were used in the analysis of significance in contingency tables. Log-rank (Mantel-Cox) test was used for comparison of overall survival between the two provider volumes. A statistician (ØS) verified the results of the presented analyses. Multivariate Cox regression analysis with age as a

covariate was preformed in the largest malignant subgroup, namely PNET/medulloblastomas.

Results

Characteristics of low- and high-volume providing health regions

Table 1 shows that the three smaller health regions counted together have a lower surgical volume of pediatric central nervous system tumors than the most populated health region, both when analyzed by residential address of the patient and when analyzed by region where the initial treatment was given. It is further seen that some patients are treated in a different health region than they geographically belong to. Cohen's kappa for agreement between the geographical health region of residency and health region providing the actual, initial treatment was 0.79, demonstrating a substantial (but not perfect) agreement [14]. It may also be deduced from Table 1 that the high-volume health region seems to provide surgery for more central

nervous system tumors than expected from the number of patients belonging to this region geographically. The histopathological subgroups were for the most part quite evenly distributed between the high- and low-volume regions. However, choroid plexus tumors were more frequently seen in patients living in the high-volume region ($p = 0.004$).

Overall survival

As seen in Fig. 1, there were no overall differences in survival between the low- and high-volume regions. An overall statistical comparison between the two volume groups with log-rank (Mantel–Cox) test resulted in $p=0.953$ when analyzed by geographical belonging or $p=0.587$ when analyzed by health region providing initial surgery.

As seen in Table 2, 1-, 3-, and 5-year survival in children operated for central nervous system tumors is very similar in high- and low-volume regions. The wide 95% confidence intervals reflect the limited power of these analyses.

Table 1 Distribution of histopathological subgroups by geographical region or by health region providing the initial treatment

Histopathology	Belonging to which geographical health region; <i>n</i> , (%)		Initial treatment in which health region; <i>n</i> , (%)	
	Low-volume regions	High-volume region	Low-volume regions	High-volume region
Pilocytic astrocytomas	74 (19.9)	77 (17.3)	66 (22.0)	85 (16.5)
Grade II astrocytomas	35 (9.4)	56 (12.6)	30 (10.0)	61 (11.8)
Anaplastic astrocytomas	4 (1.1)	5 (1.1)	4 (1.3)	5 (1.0)
Glioblastomas	14 (3.8)	11 (2.5)	14 (4.7)	11 (2.1)
Oligodendrogliomas	5 (1.3)	8 (1.8)	4 (1.3)	9 (1.7)
Mixed gliomas	10 (2.7)	16 (3.6)	9 (3.0)	17 (3.3)
Ependymal cell tumors	20 (5.4)	22 (5.0)	18 (6.0)	24 (4.7)
PNET/medulloblastomas	66 (17.7)	59 (13.3)	54 (18.0)	71 (13.8)
Other gliomas	14 (3.8)	15 (3.4)	12 (4.0)	17 (3.3)
Neuroepithelomatous neoplasms	23 (6.2)	30 (6.8)	17 (5.7)	36 (7.0)
Choroid plexus tumors	3 (0.8)	19 (4.3)	1 (0.3)	21 (4.1)
Pineal parenchymal tumors	8 (2.2)	2 (0.5)	7 (2.3)	3 (0.6)
Nerve sheath tumors	4 (1.1)	0 (0)	4 (1.3)	0 (0)
Meningiomas	8 (2.2)	3 (0.7)	7 (2.3)	4 (0.8)
Blood vessel tumors	5 (1.3)	2 (0.5)	4 (1.3)	3 (0.6)
Other mesenchymal non-meningothelial tumors	13 (3.5)	30 (6.8)	3 (1.0)	40 (7.8)
Primary intracranial adenomas/adenocarcinomas	5 (1.3)	10 (2.3)	5 (1.7)	10 (1.9)
Craniopharyngiomas	15 (4.0)	20 (4.5)	12 (4.0)	23 (4.5)
Germ cell tumors	1 (0.3)	2 (0.5)	1 (0.3)	2 (0.4)
Other tumors	35 (9.4)	39 (8.8)	24 (8.0)	50 (9.7)
Unspecified tumors	10 (2.7)	18 (4.1)	4 (1.3)	23 (4.5)
Total	372 (100)	444 (100)	300 (100)	516 (100)

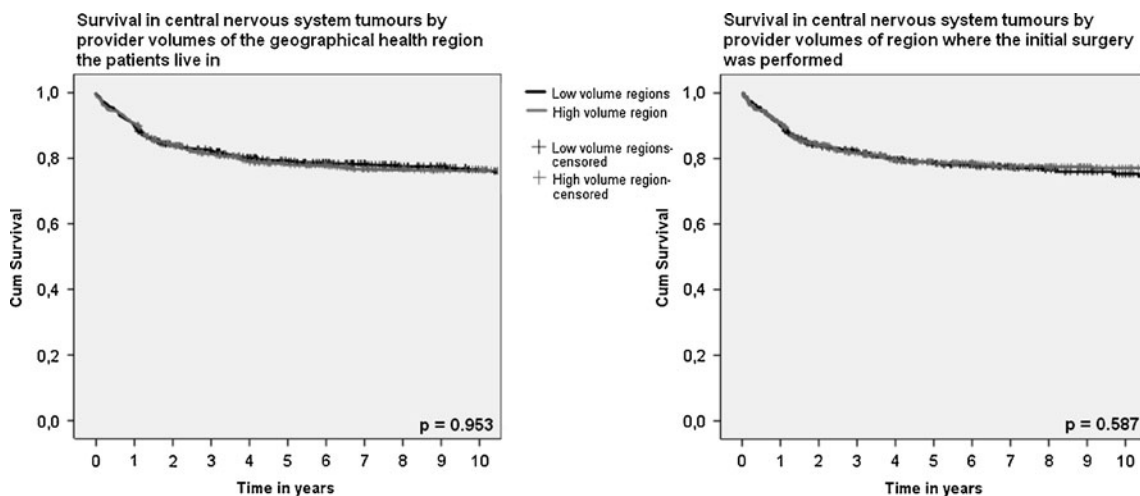


Fig. 1 Kaplan–Meier curves displaying cumulative survival in the 816 children with central nervous system tumors

Subgroup analyses

As seen in the subgroup analysis of high-grade neuroepithelial tumors displayed in Fig. 2, a comparison between the two volume groups with log-rank (Mantel–Cox) test resulted in $p=0.178$ when analyzed by geographical health region residency or $p=0.043$ when analyzed by health region providing initial surgery.

Figure 3 shows the Kaplan–Meier curves of survival in PNET/medulloblastomas. There seems to be a survival advantage both for patients living in or operated in the low-volume health regions, $p=0.042$ and 0.023 , respectively. Estimated 5-year overall survival rates were $65\pm 6\%$ when living in a low provider volume region versus $42\pm 7\%$ when the patients' addresses were in the high-provider-volume region. As the prognosis of PNET/medulloblastomas is highly dependant on age, we also performed an analysis of survival of PNET/medulloblastomas in a multiple Cox regression model, correcting for age. In the national protocols for treatment in the 20-year period of inclusion, full-dose adjuvant therapy has generally only been given to children older than 4 years old. Age was therefore analyzed as a categorical variable; less than 4 years, or 4 years or older. The results are shown in

Table 3. Age less than 4 years was to no surprise an independent risk factor for shorter survival, $p=0.001$. The adjusted hazard ratio comparing mortality in children less than 4 years versus older children was 2.533, 95% CI (1.491, 4.305). Provider volume of the geographical health region the patient lived in was a significant factor in the unadjusted analysis, $p=0.045$. The adjusted hazard ratio was 1.798, 95% CI (1.057, 3.059) when the patient lived in the high-volume health region as compared to the low-volume regions, $p=0.030$. As presented in Table 4, the data was also analyzed by the health region where the patient received initial surgery. An age less than 4 years was still an independent negative risk factor for survival, $p<0.001$. The adjusted hazard ratio comparing mortality in children less than 4 years versus older children was 2.572, 95% CI (1.512, 4.373). Provider volume of health region where the patient received initial surgery was a significant, independent risk factor for survival, $p=0.015$. The adjusted hazard ratio was 2.012, 95% CI (1.145, 3.533) when the initial surgery was performed in the high-volume health region compared to elsewhere.

We also repeated all analyses after excluding the 72 patients that for some reason were centralized, i.e., operated in the high-volume region while living in a low-volume

Table 2 Overall survival after 1, 3, and 5 years, analyzed by which geographical health region the patients belong to or received initial treatment in

Survival proportion and CI (95%) after	Address in which geographical region		Initial treatment in which region	
	Low-volume regions	High-volume region	Low-volume regions	High-volume region
1 year	91 [88 to 94] %	91 [88 to 94] %	90 [87 to 93] %	91 [86 to 93] %
3 years	82 [78 to 85] %	81 [77 to 85] %	82 [78 to 86] %	82 [79 to 85] %
5 years	79 [75 to 83] %	78 [74 to 82] %	79 [74 to 83] %	79 [75 to 82] %

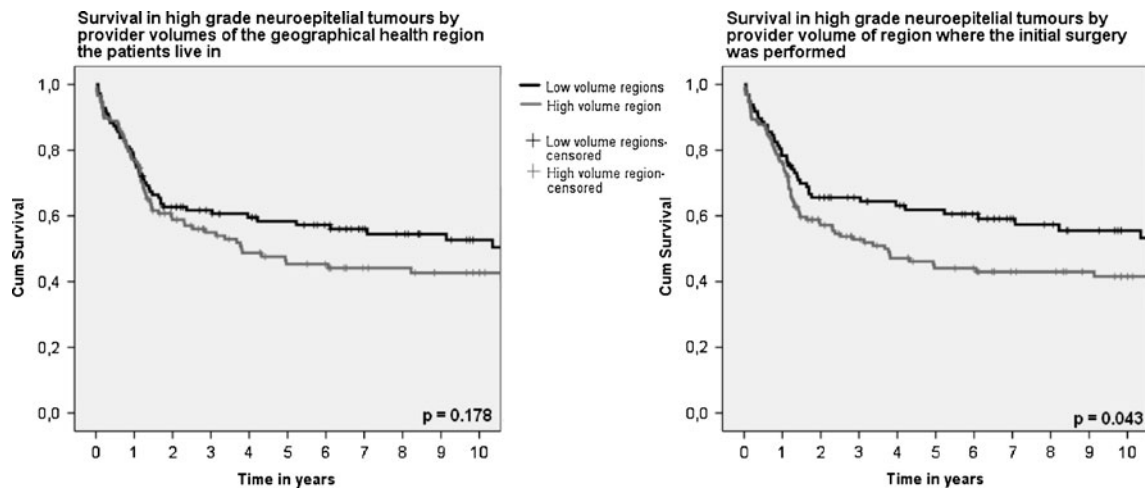


Fig. 2 Kaplan–Meier curves displaying cumulative survival in the 230 children with high-grade neuroepithelial tumors

region. This was done to further explore if more difficult lesions, contrary to our belief, are in fact already to some extent centralized today. Data from these analyses is not shown as hazard ratios and significance levels were practically unchanged.

Since requested in the review process of this paper, we also attempted to explore survival in pure medulloblastomas separately. Before 1993, medulloblastomas and other PNETS have been classified together according to the ICD-7 classification system, not allowing for an identification of the pure medulloblastomas. From 1993, location of lesions has been registered according to the ICD-O2, enabling a separation of supratentorial PNETS, overlapping PNETS and unspecified/unclassified PNETS from the pure medulloblastomas affecting the cerebellum or brain stem. Sixty-seven pure medulloblastomas that were registered since 1993 were identified in our data set. In this small subgroup of tumors, we still observed a tendency towards a survival advantage if patients were living in the low-volume health regions ($n=34$),

$p=0.062$. In a Cox regression model, the patient's address was an independent risk factor for survival, after correcting for age and location of lesion (pure medulloblastoma vs. other), HR 2.2, $p=0.015$. Curiously, we did not observe a statistically significant difference in survival between “pure” medulloblastomas and other PNETS in Norway treated since 1993, ($p=0.492$).

Discussion

Surgical volumes of pediatric tumors in the Norwegian neurosurgical departments vary markedly as one of the centers has higher surgical volumes than the other three treating departments counted together. Inspired by an ongoing national debate about centralizing surgery for central nervous system tumors in children, we conducted an analysis of long-term survival in low-volume regions versus the high-volume region. We observed no overall

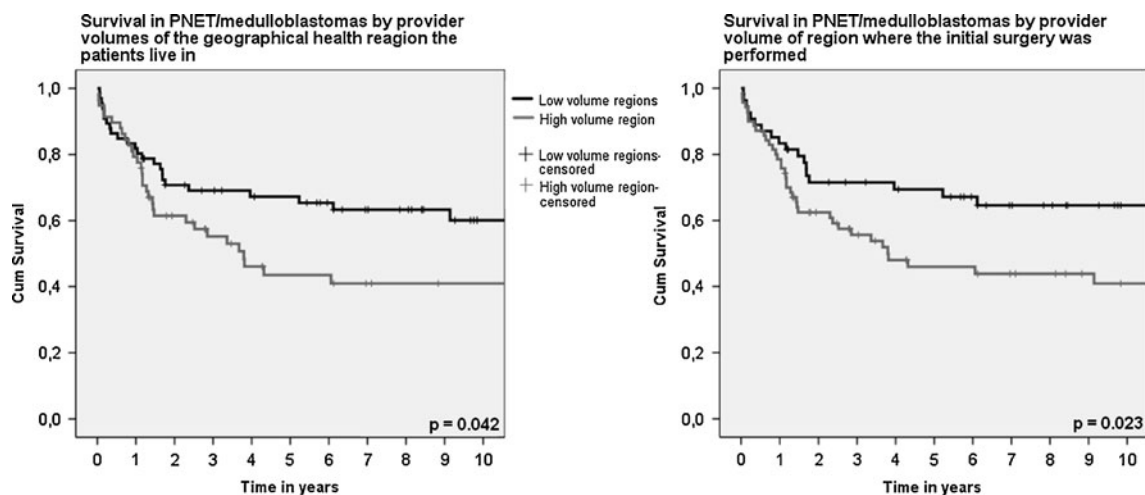


Fig. 3 Kaplan–Meier curves displaying cumulative survival in the 125 children with PNET/medulloblastomas

Table 3 Cox regression analysis of age and patient address as a predictor for survival. Hazard ratios (HR) and 95% confidence intervals (CI) are shown

Variables in the regression model	Unadjusted HR	95% CI	<i>p</i> value	Adjusted HR	95% CI	<i>p</i> value
Age less than 4 years	2.455	1.446 to 4.167	0.001	2.533	1.491 to 4.305	0.001
Address in the high-volume health region	1.722	1.012 to 2.931	0.045	1.798	1.057 to 3.059	0.030

survival advantage associated with high surgical volumes. This may of course be a type II error due to lack of statistical power. However, as the analysis presumably included practically all central nervous system tumors of children treated in Norway over a period of two decades, this power problem is not solvable. The subgroup analysis in high-grade neuroepithelial tumors revealed an unexpected tendency of lower survival associated with the high-provider-volume region. The largest subgroup of malignant brain tumors in children, namely PNET/medulloblastomas, was analyzed separately. Living in and/or receiving treatment in the high-provider-volume health region was independently associated with inferior survival in these patients. Estimated 5-year overall survival rates were $65 \pm 6\%$ versus $42 \pm 7\%$, when analyzed by geographical belonging. A study from the National Cancer Institute's Surveillance Epidemiology and End Results (SEER) database reports of 56% 5-year survival in PNET/medulloblastomas in patients less than 20 years old treated in the period between 1985 and 1998 [19]. However, after the developments in chemotherapy in the later years, survival rates have improved considerably [20]. Published studies often use different inclusion criteria in terms of patient age, tumor location, and risk stratification, making comparisons of results difficult. Generally, few modern series report of 5-year survival rates of less than 50%.

The role of the volume–outcome relationship is much discussed in surgery as the true nature of the volume–outcome relationship is not yet fully understood. The “practice-makes-perfect” hypothesis [18] is supported by numerous studies of many procedures that report an overall tendency toward better outcome if treated in high-volume hospitals or by high-volume surgeons. Another explanation of the observed volume–outcome relationship is the “selective-referral hypothesis” [18], which suggests that health care institutions or surgeons with better outcomes may receive higher patient volumes due to an increase in referrals. Or likewise, high-volume hospitals may have a

greater tendency to attract surgeons who are receiving better results. It is, however, also known that there may be considerable variability in patient outcome, even among high-volume surgeons [8]. Further, several low-volume surgeons or hospitals report excellent outcomes. Higher case volumes may therefore not automatically result in better outcome, and case volume may perhaps serve as a surrogate marker for several interacting factors in complex medical settings. By analyzing data based on geographical belonging, there is no concern for referral bias in our study.

Several limitations are common in studies of provider volume and outcome in brain tumor surgery. Available studies are almost exclusively American [3–6, 10, 11, 16, 22] and tend to utilize many of the same administrative data sources with the same strengths and limitations. Frequent weaknesses are failure to control for potential confounders, lack of validated, long-term end-points, and lack of analysis based on surgeons' individual surgical volumes. Further, interest bias may affect such publications as publications mostly originate from high-volume centers. Results may also not necessarily apply to countries where health care is organized differently. Little is also known about how regional differences in common outcome measurements such as in-hospital mortality and early morbidity affect long-term results. Further, it is not known if reasonable patient volumes are associated with poorer results than very high patient volumes, or if the benefit of surgical experience reaches a plateau. One American study reports that pediatric neurosurgeons are more likely than general neurosurgeons to extensively remove malignant pediatric brain tumors [2]. However, the pediatric neurosurgeons all had practiced for a number of years to obtain the subspecialty, while there was a wider spectrum of experience among the general neurosurgeons in the study. Thus, the observed difference may be a result of differences in neurosurgical experience, and not necessarily due to differences in experience with pediatric cases. Many of the general neurosurgeons in the study also had very low

Table 4 Cox regression analysis of age and treating health region as a predictor for survival. Hazard ratios (HR) and 95% confidence intervals (CI) are shown

Variables in the regression model	Unadjusted HR	95% CI	<i>p</i> value	Adjusted HR	95% CI	<i>p</i> value
Age less than 4 years	2.455	1.446 to 4.167	0.001	2.572	1.512 to 4.373	<0.001
Treated in the high-volume health region	1.900	1.082 to 3.336	0.025	2.012	1.145 to 3.533	0.015

volumes. Another American study reports that perioperative mortality was lower when craniotomies in children were performed at high-volume hospitals and by high-volume surgeons [22]. However, 25% of the hospitals treated only 1–4 pediatric brain tumors annually and 22% of the surgeons only operated one pediatric case per year. Conversely, a survival analysis of children with primary malignant brain tumors in England and Wales found no regional differences [24].

Pediatric intracranial tumors are very diverse both in locations and histopathology, thereby limiting the possibility of obtaining extensive personal surgical experience for most entities, even in the larger centers. Further, as both clinical and part-time academic positions often are more prevalent in the larger centers, the higher institutional volumes may not always be reflected in the personal experience of the individual surgeons. Thus, even if one may believe in a potential volume–outcome relationship in most medical procedures, it may still not be a significant factor in pediatric brain tumor operations, since personal volumes (and thereby “practice”) is difficult to obtain due to the diversity and rarity of such lesions. As seen in Table 1, there was for example only 35 craniopharyngiomas in children in treated Norway over a period of 20 years, or only 1.75 cases per year nationally. Thus, for many pediatric neurosurgical tumors, the operating surgeon often presumably needs to rely more on “transferable skills” based on experience from operations in the same anatomical region or cases with similar histopathology, rather than recent and direct experience from exact similar cases. Hydrocephalus is by far the most common pediatric neurosurgical condition in terms of the number of operations. Perhaps a neurosurgeon primarily engaged in difficult adult tumors and various infratentorial procedures who also operates a few pediatric tumors may achieve results as good as a pediatric neurosurgeon who performs a lot of shunt surgeries in addition to a fair amount of pediatric tumor resections.

Several factors and professions contribute to the final result for children with brain tumors (skill of neuroradiologists, surgical technique, surgical skills, frequency of complications, treatment of medical and surgical complications, anesthesiological skills, intensive-care treatment, adherence to adjuvant treatment protocols, quality of the rehabilitation service, closeness of follow-up, frequency of repeated surgery, accuracy of neuropathologists, etc). Most factors are not easily quantifiable, but may still affect outcome and even survival. We believe that the potential importance of surgical case volumes may be greatly overshadowed by all the other factors that are important for the results in these patients. As exemplified in our results, just counting the number of operations at a center, as often is the case in debates about centralization, is not necessarily a valid measure for quality of treatment.

In our study, we observed no benefit from living in the most populated health region or receiving treatment in the health region with the highest case volumes. On the contrary, a subgroup analysis of PNET/medulloblastomas surprisingly indicated that both living in and receiving treatment in the high-volume region was associated with inferior survival. Theoretically, there may be several explanations for the observed differences in our study: differences in adjuvant therapy, differences in histopathological classifications due to inter-observer variability, differences in surgical skills or surgical technique, unknown differences in tumor biology, for example due to differences in ethnical compositions of treated populations, or simply due to statistical chance. As seen from the *p* values, the likelihood of the discrepancy in medulloblastoma/PNET survival to be a result of mere statistical chance is in the range between 1.5 and 4.5%. Adjuvant chemotherapy or radiotherapy is decided by pediatric oncologists at the respective university hospitals. However, there are national or international treatment protocols for malignant pediatric entities so there are presumably no significant regional differences in adjuvant treatment. Still, adherence to protocols may theoretically vary. For more than a decade, there have been regular national meetings between neuropathologists, pediatric neurosurgeons, and pediatric oncologists to exchange experience and ensure common practice. Divergence in treatment strategies or tumor classification is very seldom. There is an extensive collaboration between centers and frequent use of second-opinion reviews by neuropathologists from other centers to ensure agreement in classifications. Still, to be acknowledged, unknown variations in classification represent a potential significant threat to our subgroup analyses, since there was no uniform microscopic review of included patients. Controversies relating to the pathobiology and classification of central nervous system primitive neuroectodermal tumors have plagued neuropathologists for years. Even though differences in molecular genetics and prognosis are reported, given that PNETS and medulloblastomas are histologically identical, it is for now recommended that studies provide analyses for the two entities combined to reduce the bias of misclassification [19]. We nevertheless attempted to also analyze a recent cohort of “pure” medulloblastomas separately, since a location variable was available in the later years. Curiously, we did not find a statistical significant difference in survival between “pure” medulloblastomas and other PNETS in Norway treated since 1993. This could perhaps be due to the lack of power associated with the small sample sizes in such subgroup analyses. We observed a tendency towards regional differences in survival in pure medulloblastomas treated since 1993, but these were statistically just non-significant. In a regression model, patient address was however an independent, significant

factor when correcting for site of lesion and age in this subgroup. It therefore seems unlikely that skewed distributions in the site are responsible for the regional differences in survival observed in PNETs/medulloblastomas. Still, since the Norwegian Cancer Registry has no information about tumor sizes, actual resection grades, or other factors associated with survival, it is not known that the compared groups are completely balanced. However, the analysis based on the patients' addresses is quite conservative, and would presumably ensure a balanced composition of patient groups, presupposing that incidence rates are not geographically unbalanced. As seen in Table 1, the size of the medulloblastoma/PNET group is slightly bigger in the low-volume regions, suggesting a possible variance in classification between centers. However, the subgroup analysis in high-grade neuroepithelial tumors, a subgroup where all true medulloblastomas and other PNETS presumably are included, also indicated a tendency towards inferior survival in the health region with higher case volumes. Nevertheless, due to the above-mentioned factors, especially the potential for misclassification bias, we suggest that the finding in the medulloblastoma/PNET group should be interpreted with caution. Even so, these results call for that tumor classification and patient outcome should be evaluated on a national level in these patients.

A weakness of our study is the potential for skewed distributions of histopathological subgroups due to inter-observer variability among the different neuropathologists. This could naturally affect results from subgroup analyses, as already discussed. We observed an unexpected skewed distribution of choroid plexus tumors between the health regions in the Norwegian Cancer Registry data. We cannot explain this finding, but is possibly due to differences in reporting to the cancer registry since in some instances these tumors may have been classified as non-reportable blood vessel tumors. Other causes could be statistical chance (and multiple significance testing), variance in classification, or due to differences in initial treatment strategy (expectancy, gamma knife treatment, shunt surgery, or resection/biopsy). We only included histologically confirmed tumors in our study. Excluding the five malignant choroid plexus tumors in the data did alter the p values in the high-grade neuroepithelial tumor cohorts, but not much. The p value changed to $p=0.064$; thus still a tendency towards a better outcome if high-grade neuroepithelial tumors were treated in the low-volume centers. However, to be acknowledged, the patient material of 816 quite diverse cases may be vulnerable due to its limited power. The tendency of inferior survival in high-grade neuroepithelial tumors treated in the high-volume center is eliminated if PNET/medulloblastomas are excluded from the analysis; thus leaving the difference

in PNETS/medulloblastoma survival as the only unexplained finding.

The strength of our study is the high-quality data from the Norwegian Cancer Registry. Very few studies on provider volumes and outcome can provide population-based data with high degree of inclusion, and long-term follow-up. Surgical case series without adequate controls from single institutions are flourishing in the neurosurgical literature. Yet, it is known that studies with excellent outcome are more likely to be published. Evaluation of own data may further be associated with bias. It has for example been reported that the true surgical mortality rates are much higher than published in operative series [23]. Thus, community-based prospective registration of all patients who underwent surgery, providing a sampling frame free from publication and sampling bias is encouraged [26]. The unselected population-based inclusion in our study ensures high external validity and unbiased selection of patients. Still to be acknowledged, population-based studies may be associated with some difficulties as several prognostic variables often are unavailable. However, as data was also analyzed by patients' geographical belonging, large variations in prognostic factors between the two provider volume groups are not likely. We still adjusted for age and in part for tumor location in the analysis of results in PNETs/medulloblastomas. Preferably, we should also have been able to correct for other known prognostic factors such as tumor size, prevalence of micro-metastases, adherence to adjuvant treatment protocols, re-operation rates, histopathological features, etc. Unfortunately, such variables were not available to us.

The main weakness of our study is the relatively low power, which is due to small population of Norway. As mentioned in the Materials and methods section, pediatric neurosurgery was also performed at a second university hospital in the South-East region up until 1998. This pollutes the high-volume health region in our analysis with some operations from this lower-volume hospital. However, the tendency in the results is not different in the last 10 years as compared to the first 10 years of the study period (data not shown). Thus, this weakness in data classification is presumably of no major concern for the conclusion. Like most studies, we were unable to analyze data based on operating volumes of the individual surgeons. Some may argue that the case volume of the largest Norwegian neurosurgical center is still quite low. Our conclusions may therefore not be valid in countries where pediatric neurosurgeons have much higher caseloads. However, for most histopathological subgroups and tumor sites, the volume per pediatric neurosurgeon is low at any center in the world, due to the low incidence and the diversity of such lesions.

Despite some weaknesses, it seems safe to conclude that provider volume is no proxy for quality of care in pediatric central nervous system tumors in Norway. Some may believe that data aggregated from hundreds of neurosurgical centers would have demonstrated a trend towards better long-term outcome in high-volume centers. However, such possible findings may not necessarily be extrapolated across national borders or to small regions with only a few centers. There are many outliers in pooled analysis of data on provider volumes, and surgical case volume is only one of many potential factors that may influence patient outcome.

Conclusions

Inspired by an ongoing debate about centralization, we aimed to explore if the low-volume neurosurgical centers are associated with inferior survival in children with central nervous system tumors. In this population-based study of all central nervous system tumors in children operated over a period of two decades, we found no evidence of improved long-term survival in the high-provider-volume region. On the contrary, a subgroup analysis found that survival in PNET/medulloblastomas was significantly better if treated elsewhere than in the most populated health region with the highest case volumes. We have no explanation for this finding. One should, however, be careful of interpreting this directly as a symptom of quality of care, as there may be unseen confounders. Our study demonstrates that provider case volume may serve as an axiom in debates about centralization of cancer surgery while perhaps much more reliable and valid but less quantifiable factors are important for the final results.

Conflicts of interest None.

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Comment

This is an interesting study looking to see if outcomes of CNS tumors in children correlate with the caseload in Norway. The data is quite solid because it is based on a very organized and reliable reporting system.

The conclusions are probably contrary to what was to be expected. There was no demonstrable advantage of being operated or having adjuvant neuro-oncological treatments performed in higher-volume centers. There was actually a slight opposite tendency.

The authors underscore most difficulties with the study. Degree of resection and differences in surgical skills all seem to be attenuated in

a study of this span. Diverse tumor biology based on ethnical grounds is possible but not plausible. How are we then to interpret these findings and what should be made relevant? Pediatric neurosurgery has been an organized subspecialty in neurosurgery for many years now and one which requires an extra period of training beyond what is currently comprised within general residency training. This may justify an average longer surgical experience for pediatric neurosurgeons as compared to across-the-board general neurosurgeons. This being the case, this factor may contribute to dilute differences between higher- and lower-volume centers. Also, high- and low-volume needs necessarily to be defined especially for pediatric CNS tumors. It should be defined not only for centers but also for single surgeons performing surgery. Factors such as resident training (and the part we let them play in surgery), which usually occurs in higher-volume centers may also be a consideration (as for other types of surgery). Thirdly, outcomes must also be tied up with the types of tumors treated. The authors have justly opted to separately analyze the group of PNET/medulloblastomas, a group where degree of resection is of the utmost importance. We have, however, no information regarding this issue. The type of surgery, or else the difficulty of each surgical act as it relates to the underlying tumor, is also a factor that is not possible to factor in. Resection of a medulloblastoma is of extreme importance but usually a less difficult task than the resection of a craniopharyngioma or the odd pineal region tumor.

All in all, what the study seems to point at is that the sheer number of cases done per year is certainly not the single variable influencing operative and treatment outcomes for these and other nosological entities. It is also not known for each specific area of expertise within neurosurgery what the boundary is that draws the line between a surgical practice self-sufficient to comply to the state-of-the-art numbers of M&M and one which does not meet these caseload criteria.

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