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RESEARCH ARTICLE

Children treated for medulloblastoma and supratentorial primitive neuroectodermal tumor in Norway from 1974 through 2013: Unexplainable regional differences in survival

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Abbreviations: ASCT, autologous stem cell support; AT/RT, atypical teratoid rhabdoid tumor; CNS-PNET, supratentorial primitive neuroectodermal tumor; CRF, case report form; CSF, cerebrospinal fluid; CSI, cerebrospinal irradiation; CT, computed tomography; CTX, chemotherapy; EFS, event-free survival; EMA, epithelial membrane antigen; GFAP, glial fibrillary acidic protein; GTR, gross total resection; HR, high-risk medulloblastoma; HUH, Haukeland University Hospital; MB, medulloblastoma; OS, overall survival; OUH, Oslo University Hospital; RT, radiotherapy; SR, standard-risk medulloblastoma; St Olavs, St Olavs Hospital Trondheim University Hospital; UNN, University Hospital of North Norway; UR, uncertain-risk medulloblastoma; WHO, World Health Organization.

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Abstract

Background: A previous study based on Norwegian Cancer Registry data suggested regional differences in overall survival (OS) after treatment for medulloblastoma (MB) and supratentorial primitive neuroectodermal tumor (CNS-PNET) in Norway. The purpose of the present study was to confirm in an extended cohort whether there were regional differences in outcome or not, and if so try to identify possible explanations.

Material and methods: Data from patients aged 0–20 years diagnosed with and treated for MB/CNS-PNET at all four university hospitals in Norway from 1974 to 2013 were collected and compared.

Results: Of 266 identified patients, 251 fulfilled inclusion criteria. MB was diagnosed in 200 and CNS-PNET in 51 patients. Five-year OS and event-free survival (EFS) were 59% and 52%, respectively. There was a significant difference in five-year OS and EFS between MB and CNS-PNET patients; 62% versus 47% ($P = 0.007$) and 57% versus 35% ($P < 0.001$). In multivariable analysis, two factors were found to significantly contribute to improved five-year OS and EFS, whereas one factor contributed to improved five-year OS only. Gross total resection (GTR) versus non-GTR (hazard ratio [HR] 0.53, $P = 0.003$; HR 0.46, $P < 0.001$) and cerebrospinal irradiation (CSI) versus non-CSI (HR 0.24, $P < 0.001$; HR 0.28, $P < 0.001$) for both, and treatment outside Oslo University Hospital for OS only (HR 0.64, $P = 0.048$).

Conclusion: Survival was comparable with data from other population-based studies, and the importance of GTR and CSI was confirmed. The cause for regional survival differences could not be identified.

KEYWORDS
CNS-PNET, medulloblastoma, Norway, outcome, pediatric, survival

1 | INTRODUCTION

Medulloblastoma (MB) and supratentorial primitive neuroectodermal tumor (CNS-PNET) account for about 15%–20% and 2.5%, respectively, of malignant brain tumors in children. Altogether, these two comprise approximately 10%–15% of all pediatric brain tumors.[1–3] Both entities are embryonal tumors, MB arising in the infratentorial and CNS-PNET in the supratentorial brain. Until 2016, embryonal brain tumors were classified according to their histologic characteristics and encompassed MB, CNS-PNET, and atypical teratoid rhabdoid tumor (AT/RT). In the revised World Health Organization (WHO) classification from 2016, the term "medulloblastoma" was retained for posterior fossa tumors, but the term "CNS-PNET" was discarded, and tumors previously known as CNS-PNET were divided into several groups. Importantly, the revised WHO classification defines MB both histologically and genetically.[4–8] In this paper, we will use the term CNS-PNET due to the retrospective nature of the analysis.

Treatment for MB and CNS-PNET is currently based on a multidisciplinary and risk-stratified approach, involving surgery followed by adjuvant radiotherapy and/or chemotherapy.[9] Five-year survival data have been reported to be in the range of 40%–80% depending on disease characteristics.[10,11] These survival figures need to be viewed in conjunction with the sometimes detrimental late effects from treatment.[12,13]

Centralization of pediatric brain tumor treatment to improve survival has been discussed over the last decades, in Norway as well as worldwide.[14,15] In 2011, a Norwegian registry-based study raised concerns over this strategy, showing that MB/CNS-PNET patients living in so-called low-volume-providing health regions had better overall survival (OS) than those living in the high-volume-providing health region.[16] Outcome for Norwegian MB/CNS-PNET patients living in the high-volume-providing health region Oslo University Hospital (OUH) were published in 2017.[17] Data in the latter publication suggested a better OS than reported by Solheim et al,[16] but the data in the two publications were not directly comparable.

The primary objective of this retrospective study was to present a national real-world data cohort, and, based on the findings presented by Solheim et al,[16] confirm whether there have been regional differences in survival of children and adolescents with MB/CNS-PNET in favor of the three smaller regions compared with the largest. Furthermore, the purpose was to explore possible explanations for a potential difference. Relevant and detailed data were gathered on a national cohort through a detailed review of medical records, available tissue, and imaging data. We also sought to assess time trends in treatment and outcome.

2 | MATERIALS AND METHODS

2.1 | Patients

This study was designed as a multicenter national retrospective study including patients from three smaller (University Hospital of North Norway [UNN], St Olavs Hospital Trondheim University Hospital (St Olavs), Haukeland University Hospital [HUH]) and one larger regional unit OUH. A case report form (CRF) was prepared to collect data on Norwegian pediatric patients with MB or CNS-PNET (according to the 2007 WHO classification) from all centers treating these patients in Norway. Inclusion criteria were patient age younger than 20 years, a histologically confirmed diagnosis of MB/CNS-PNET, treatment at one of the four above-mentioned hospitals, and date of diagnosis between January 1974 and December 2013. Patients were identified using the archives of the four hospitals' pathological and neurosurgical departments, as well as using data from the Cancer Registry of Norway. Fourteen patients were found only in internal hospital registries, three were found only in the Cancer Registry of Norway, whereas the remaining patients were all registered in internal hospital databases as well in the Cancer Registry of Norway. Medical records were reviewed using the CRF to register detailed clinical data. October 15, 2017, was defined as the last date of follow-up.

2.2 | Histopathological diagnosis and review

Histopathological specimens from all patients were reviewed between 2012 and 2015, and classified according to the WHO 2007 classification of brain tumors by the authors AK, BK, HM, and KSM. In some of the oldest cases, the diagnosis was based solely on morphological characteristics in hematoxylin and eosin–stained as well as reticulin-stained sections. When necessary for making a diagnosis, supplementary immunohistochemical stainings were performed with antibodies against glial fibrillary acidic protein (GFAP), synaptophysin, NeuN, chromogranin A, neurofilament protein, INI-1, Ki-67, actin, desmin, smooth muscle actin, and epithelial membrane antigen (EMA). Patients for whom the revised histopathological diagnosis was different from MB or CNS-PNET were excluded from further analysis. In two cases, it was not possible to perform a reevaluation of the original pathological anatomical diagnosis, due to the lack of tumor material. Both cases were originally diagnosed as MB and were included in this study based on the original histopathological description. Due to various reasons, such as the retrospective nature of the study, old specimens, and sometimes sparse amounts of material of variable quality, it was not possible to determine MYC status, beta-catenin status, or molecular subgroup for all cases. However, when possible, molecular analysis was performed in newer cases when doubts regarding the diagnosis existed.

2.3 | Radiological imaging and review

The authors PD-T, SM, VM, JR, GCW, and ES reviewed all radiological reports and available imaging. Diagnostically, cerebral angiography and air ventriculography were regularly used until 1979 when the first computed tomography (CT) came into use at St Olavs, HUH, and OUH. CT was replaced by magnetic resonance imaging (MRI) from 1989. Until 2000, all radiological imaging performed at UNN, St Olavs, HUH, and OUH was routinely deleted 10 years after the imaging procedure. Thus, for many of the patients included in this study (i.e., those treated between 1974 and 2000), a detailed review of radiological imaging was not possible. For the latter patients, radiological reports and surgical notes were used for radiological and staging review.

2.4 | Risk group allocation of individual patients

One pediatric oncologist (ES) and one clinical oncologist (PB) categorized MB patients as standard risk (SR), high risk (HR), or uncertain risk (UR). SR was defined as minimal residual disease ($< 1.5\ cm^2$) postoperatively and no evidence of metastatic disease (M0). HR patients were defined as either M1-4 and/or residual disease ($> 1.5\ cm^2$) on postoperative imaging, anaplastic/large cell histology, and/or patients who did not receive cerebrospinal radiotherapy (i.e., children under the age of three–five years). The extent of resection was defined based on postoperative imaging when performed. If no postoperative imaging was performed, the extent of resection was determined based on the surgical note. If available data were insufficient for determining if a residual tumor and/or metastatic disease were present, the patient was classified as UR. The presence or absence of residual tumor was determined based on radiological imaging, radiological reports, and surgical notes. Metastatic disease was defined as positive lumbar cerebrospinal fluid (CSF) cytology and/or radiological evidence of multifocal disease. Neither histopathological nor molecular subgroup was used as a parameter to define patient risk status.

2.5 | Statistical methods for survival analysis

Time of recurrence was defined as date of the imaging procedure where recurrent tumor was confirmed, or date of the first patient record note with information on recurrence. To estimate event-free survival (EFS), date of primary surgery to date of death, date of recurrence, or to date of administrative censoring (October 15, 2017), whichever came first, was used. For OS, date from primary tumor, respectively, surgery or biopsy until date of death was registered. For EFS, only recurrence and death were defined as events. Comparisons of OS and EFS were done using Kaplan–Meier curves and corresponding log-rank tests. *P* values less than or equal to 0.05 were considered statistically significant. Regional comparisons of classification, treatment, and outcome were done between data from OUH and combined data from the three other university hospitals. In multivariable analyses, Cox proportional hazard regressions were estimated to analyze the possible impact of the following variables on OS and EFS: hospital (UNN, St Olavs, and HUH compared with OUH), gross total resection (GTR) versus non-GTR, cerebrospinal irradiation (CSI) versus non-CSI, CSF cytology performed or not, decades and clinical risk group (MB SR vs HR, UR, and CNS-PNET). These variables

were chosen because they are known risk factors for MB/CNS-PNET and because of the previous publication showing regional Norwegian survival differences.[16] The risk of secondary tumor was estimated using the Aalen-Johansen estimator,[18] treating death from all causes as a competing risk. Stata14 (StataCorp LP, 4905 Lakeway Drive, College Station, TX) was used for statistical analysis.

2.6 | Ethics statement

This protocol was approved by the Regional Committees for Medical and Health Research Ethics of the South-Eastern Norway Regional Health Authority (2016/1727 REK sør-øst D), and the Data Protection Officer at UNN, St Olavs, HUH, and OUH were notified about the study in writing and had no objections to it.

3 | RESULTS

3.1 | Patients

Between January 1, 1974, and December 31, 2013, 266 patients were diagnosed with MB or CNS-PNET at UNN, St Olavs, HUH, and OUH. For 13 patients, the revised histological diagnosis was not MB or CNS-PNET (see below). For two patients MB was diagnosed at autopsy. All these 15 patients were excluded from further analysis. An additional five patients received treatment at several university hospitals. These five patients were included in the national survival analysis, but they were not included in the comparison between the hospitals (Supporting Information Table S1). Thus, a total of 246 patients were available for further analysis (Table 1). No patients were lost to follow-up. Survival data for the whole cohort includes 10 patients who succumbed early postoperatively without receiving adjuvant therapy. Twenty-five patients were not treated according to a specific protocol; these were mostly teenagers/young adults. Five patients had a congenital genetic condition, confirmed by genetic testing. Symptoms, signs, and time from symptom debut until a neuroradiological diagnosis was determined for all 246 patients (Supporting Information Table S2).

3.2 | Histopathological diagnosis and review

Biopsy specimens from all 266 identified patients were reviewed and classified according to the WHO 2007 classification for brain tumors. For 13 of the initially identified 266 patients (4.9%), histopathological revision revealed a diagnosis different from MB or CNS-PNET and these were also excluded. The revised diagnoses were AT/RT in five patients, glioblastoma in three, germinoma in two, anaplastic astrocytoma in one, anaplastic ependymoma in one, and pontine glioma in one. Five patients were excluded from the comparative analysis because of treatment at several of the compared hospitals; all five had MB. Thus, the remaining cohort of 246 patients consisted of 196 cases of MB (80%) and 50 (20%) cases of CNS-PNET (13 of the CNS-PNET were pineoblastoma).

3.3 | Radiological imaging and review

Preoperative radiological imaging consisted of cerebral angiography and pneumoencephalography, a combination of CT and cerebral angiography, CT, MRI, or a combination of CT and MRI (Supporting Information Table S2). One hundred ninety patients (77%) had no radiological signs of metastatic disease at the time of primary diagnosis, 44 patients (18%) had metastatic disease, whereas in 12 patients (4.9%) it was impossible to retrospectively determine if they had metastatic disease or not.

3.4 | Risk group allocation

The risk group allocation pertains only to patients with MB and was hampered by several factors. First, the hospitals' policy to destroy radiological imaging 10 years after the imaging procedure made image review impossible for several patients and written reports were not always fully substantiating. Second, the CSF cytology part of disease staging was performed only in 96 cases (39%), it was not done in 139 cases (57%), and for nine patients (3.7%) it seems to have been performed without documentation of the result. Of the 196 MB patients, 44 patients (22%) were classified as SR, 66 patients (34%) as HR, and 86 patients (44%) as UR (Table 1).

3.5 | Surgery

All patients underwent surgery at the time of diagnosis. The median age at surgery was 7.0 years (range, two days to 19 years). GTR was achieved in 168 patients (68%) and subtotal resection (STR) in 76 patients (31%) (Table 1). Among the latter 76 patients, seven underwent biopsy only. Ninety-six patients (39%) required treatment for hydrocephalus in the postoperative period, 148 patients (60%) did not. Ten patients died before the start of adjuvant treatment, eight of them in the postoperative phase within 30 days from surgery. Two of these 10 patients were treated at UNN, St Olavs, and HUH, eight at OUH. Of the 116 patients (48%) who progressed during primary adjuvant treatment or recurred later (see below), 31 patients (26%) underwent new surgery and 85 (73%) did not (Table 1).

3.6 | Radiotherapy

Radiotherapy (RT) documentation from the earlier time periods did not allow us to retrospectively review RT target volumes and dose coverage of these. A total of 234 (95%) of 246 patients received adjuvant therapy and 195 received radiotherapy, whereof 188 received CSI (Table 1). The 39 patients (17%) who did not receive fractionated CSI were mostly young (< 3–5 years) and from the later time periods. The median time from surgery to start of radiotherapy for patients who did not receive sandwich chemotherapy (CTX) was 26 days (range, 5–248). For 19 patients (17%) radiotherapy started more than 40 days after surgery. At UNN, St Olavs, and HUH, the number was six patients (19%), and at OUH 13 patients (16%). The median duration of radiotherapy was 44 days (range, 28–107). Radiotherapy duration was below 40 days for 22 patients (11%), 40–48 days for 121 patients

TABLE 1 Patient characteristics

Parameter		Norway as a whole Number of patients *n* = 246 (SD/percentage/range)	UNN, St Olavs, and HUH Number of patients *n* = 89 (SD/percentage/range)	OUH Number of patients *n* = 157 (SD/percentage/range)
Sex	Female	97 (39%)	33 (37%)	64 (41%)
	Male	149 (61%)	56 (63%)	93 (59%)
	Ratio	1.5	1.7	1.5
Age at diagnosis	<3 years	51 (21%)	14 (16%)	37 (24%)
	3–5 years	33 (13%)	14 (16%)	19 (12%)
	>5 years	162 (66%)	61 (69%)	101 (64%)
	Median age	7.1 years	7.1 years	7.1 years
Hospital	UNN	4.8%	12	
	St. Olavs	16%	39	
	HUH	15%	38	
	OUH	64%		157
Time period	1974–1979	24 (9.9%)	5 (5.6%)	19 (12%)
	1980–1989	57 (23%)	14 (16%)	43 (27%)
	1990–1999	64 (26%)	26 (29%)	38 (24%)
	2000–2013	105 (43%)	44 (49%)	57 (36%)
Histological diagnosis				
	MB	***n* = 196 (80%)**	***n* = 73 (82%)**	***n* = 123 (78%)**
	Classic MB	148 (76%)	48 (66%)	100 (81%)
	Desmoplastic/nodular MB nodular MB	30 (15%)	16 (22%)	14 (11%)
	Extensive nodularity	1 (0.5%)	0	1 (0.8%)
	Anaplastic/large cell MB	10 (5.1%)	4 (5.6%)	6 (4.9%)
	MB/ CNS unspecified	7 (3.6%)	5 (6.8%)	2 (1.6%)
	CNS-PNET	***n* = 50 (20%)**	***n* = 16 (18%)**	***n* = 34 (22%)**
Surgical resection		***n* = 246**	***n* = 89**	***n* = 157**
	Gross total	168 (68%)	59 (66%)	109 (69%)
	Non gross total	76 (31%)	30 (34%)	46 (29%)
	Intraoperative death	2 (0.8%)		2 (1.3%)
CSF examination		***n* = 244**	***n* = 89**	***n* = 155**
	Not performed	139 (57%)	45 (51%)	94 (61%)
	Positive	24 (9.8%)	9 (10%)	15 (9.7%)
	Negative	72 (30%)	31 (35%)	41 (27%)
	Uncertain if performed	9 (3.7%)	4 (4.5%)	5 (3.22%)
Risk category (MB)[a]		***n* = 196**	***n* = 73**	***n* = 123**
	Standard risk	44 (22%)	14 (19%)	30 (24%)
	High risk	66 (34%)	29 (40%)	37 (30%)
	Uncertain risk	86 (44%)	30 (41%)	56 (46%)
First adjuvant treatment		***n* = 236**	***n* = 87**	***n* = 149**
	Radiotherapy	109 (46%)	32 (37%)	77 (52%)
	Chemotherapy	125 (53%)	55 (63%)	70 (47%)
	None	2 (0.9%)		2 (1.3%)
Relapse including progression during treatment		***n* = 236**	***n* = 87**	***n* = 149**
	Yes	116 (49%)	10 + 25 = 35 (40%)	26 + 55 = 81 (54%)
	No	120 (51%)	52 (60%)	68 (46%)

(Continues)

TABLE 1 (Continued)

Parameter		Norway as a whole Number of patients *n* = 246 (SD/percentage/range)	UNN, St Olavs, and HUH Number of patients *n* = 89 (SD/percentage/range)	OUH Number of patients *n* = 157 (SD/percentage/range)
Surgery at relapse		***n* = 116**	***n* = 35**	***n* = 81**
	Yes[b]	31 (27%)	9 (26%)	22 (27%)
	No[b]	85 (73%)	26 (74%)	59 (73%)
Radiotherapy as part of relapse treatment		***n* = 116**	***n* = 35**	***n* = 81**
	Yes[b]	29 (25%)	14 (40%)	14 (13%)
	No[b]	87 (75%)	21 (60%)	66 (57%)
Chemotherapy as part of relapse treatment		***n* = 116**	***n* = 35**	***n* = 81**
	Yes[b]	56 (48%)	23 (66%)	33 (41%)
	No[b]	60 (52%)	12(34%)	48 (59%)
Congenital genetic condition		***n* = 5**	***n* = 3**	***n* = 2**
	Gorlin syndrome	3 (60%)	3	
	Fanconi anemia	1 (20%)		1
	Nijmegen Breakage	1 (20%)		1

HUH, Haukeland University Hospital; OUH, Oslo University Hospital; St Olavs, St Olavs Hospital Trondheim University Hospital; UNN, University Hospital of North Norway.

[a]Only MB patients. SR cases include patients with localized disease, <1.5 cm^2 residual tumor postoperatively, and age >3–5 years (i.e., receiving CSI). HR cases include patients under the age of 3–5 years (i.e., not receiving CSI), patients with >1.5 cm^2 residual tumor postoperatively, anaplastic/large cell histology, and/or documented metastatic disease at the time of primary diagnosis. Patients for whom available data were insufficient for determining the presence or not of residual tumor and/or metastatic disease were classified as uncertain risk

[b]Either during primary treatment or after end of primary treatment.

(63%), and more than 48 days for 50 patients (26%). For the latter patient group, the cause for interruption(s) was not well documented, although leucopenia seemed to have been the most frequent cause. Twenty-six of the 50 patients (52%) with RT duration more than 48 days are alive, not significantly different from the rest of this material. Ninety-two patients (47%) received radiotherapy in line with their designated protocol, 80 patients (41%) did not, whereas 23 patients (12%) were not treated according to any specific protocol. Deviations include prescription of a too low dose to the brain, boost, or CNS axis, wrong fraction dose, too long time from surgery to start RT, and too long duration of RT. Thirty-seven (40%) of the 92 patients treated in line with their protocol are deceased, 55 patients (60%) are alive. Details for all hospitals (UNN, St Olavs, and HUH and OUH) are shown in Supporting Information Table S3.

Of the 80 patients (33%) who experienced tumor recurrence, the 36 patients progressing under primary treatment excluded, 25 patients (31%) received radiotherapy at the time of recurrence, and 55 patients (69%) did not. Of the first mentioned 25 patients, 20 had been treated with fractionated radiotherapy at the time of primary diagnosis, and six of these 25 patients are alive. Recurrence radiotherapy mostly consisted of palliative fractionation schedules such as 30 Gy in 10 fractions or single session gammaknife. Radiotherapy given at recurrence seemed to be more often used at UNN, St Olavs, and HUH compared with OUH (Table 1). Of the 80 experiencing recurrence, 73 are dead and seven alive; four without disease, two under treatment for disease, and one with stable disease.

3.7 | Chemotherapy

Thirty-nine of 234 patients (17%) did not have CTX as part of their adjuvant treatment. Protocols used are listed in Table 1. Sixteen of these 39 patients (41%) are alive, whereas 23 patients (59%) are dead. Eighty-three patients (42%) received CTX prior to radiotherapy (sandwich CTX), whereas 113 patients did not (58%). Seven patients (3.0%) were treated with high-dose CTX with autologous stem cell support (ASCT) as part of their primary treatment. For the 112 patients with modifications in their CTX, 33 patients (29%) relapsed, whereas 79 (71%) did not.

3.8 | Outcome

Survival figures are shown in Table 2 and Supporting Information Table S4. At the time of analysis, 115 of 251 patients (46%) were alive, whereas 136 were dead (54%). Five-year OS for MB and CNS-PNET altogether was 59%, for MB alone 62%, and for CNS-PNET alone 47% (Figure 1; Supporting Information Table S4), whereas five-year EFS for MB and CNS-PNET altogether was 52%, for MB 56%, and for CNS-PNET 35% (Figure 1; Supporting Information Table 4). In univariate analysis GTR (Figure S2) and CSI (Figure 3), but neither risk group (Supporting Information Figure S1) nor time period came across as significant for five-year OS and EFS (Supporting Information Table S5 and Figure S2). Sandwich chemotherapy yielded a significantly better five-year OS but not five-year EFS (Supporting Information Figure S3). For

TABLE 2 Outcome

	Norway	UNN, St. Olavs, and HUH	OUH
Complete Norwegian cohort[a]	***n* = 251**		
Alive	115 (46%)		
Dead	136 (54%)		
Five-year OS	59% (53–65%)		
Five-year EFS	52% (46–58%)		
Patients[b]	***n* = 246**	***n* = 89**	***n* = 157**
Alive	112 (46%)	50 (56%)	62 (39%)
Alive and disease free, never recurrence	106 (43%)	47 (53%)	59 (38%)
Alive and disease free, treated for recurrence	4 (1.6%)	2 (2.2%)	2 (1.3%)
Alive with disease	2 (0.8%)	1 (1.1%)	1 (0.6%)
Dead	134 (55%)	39 (44%)	95 (61%)
Dead of disease	115 (47%)	31 (35%)	84 (54%)
Dead of secondary tumor	7 (2.8%)	4 (4.5%)	3 (1.9%)
Dead of other cause	12 (4.9%)	4 (4.5%)	8 (5.1%)
Recurrence data	***n* = 236**	***n* = 87**	***n* = 149**
Recurrence	115 (49%)	35 (40%)	80 (54%)
Progression during treatment	36 (15%)	10 (12%)	26 (18%)
Local recurrence	21 (8.9%)	7 (6.9%)	14 (9.4%)
Distant recurrence	13 (5.5%)	3 (3.5%)	10 (6.7%)
Local and distant recurrence	45 (19%)	15 (17%)	30 (20%)

[a]All Norwegian patients, including the five treated at different university hospitals ($n = 251$).
[b]All Norwegian patients, excluding the five treated at different university hospitals ($n = 246$).

patients treated according to the PNET 4 protocol five-year OS was 82% (Supporting Information Table S4).

In univariable analysis, five-year OS, but not five-year EFS, for MB/CNS-PNET altogether was significantly better at UNN, St Olavs, and HUH compared with OUH (68% vs 54%, $P = 0.021$; Figure 4; Supporting Information Table S6). When broken down into MB and CNS-PNET separately, no significant survival differences were found between UNN, St Olavs, and HUH compared with OUH (Figure 5). Multivariable Cox regression analysis for all 246 patients identified GTR and CSI as strong independent favorable prognostic factors for five-year OS and EFS (HR 0.53, $P = 0.003$; HR 0.46, $P < 0.001$; HR 0.24, $P < 0.001$; HR 0.28, $P < 0.001$). Furthermore, treatment at OUH compared with UNN, St Olavs, and HUH came across as a significantly negative prognostic factor for five-year OS (HR 0.64, $P = 0.048$), but not for EFS (HR 0.70, $P = 0.075$), respectively, whereas neither the MB subgroup decade nor the performance of CSF examination or not was an independent prognostic factor (Table 3).

Most recurrences, both during and after primary treatment, were combined local and distal (Table 2). The median time from primary operation to relapse was 1.7 years (range, 0.28–23), and the median time from primary surgery to death from recurrent disease was 3.0 years (range, 0.46–23). A total of 49 second primary tumors in 34 patients were diagnosed (Supporting Information Table S7) with a median time for diagnosis after primary surgery of 20 years (range, 2.0–39). As registration of benign tumors such as meningioma is suspected not to be complete in Norway, the true incidence of second tumors might be higher. At the time of analysis, seven patients (2.8%) had succumbed to their secondary tumor: five from glioblastoma, one from anaplastic astrocytoma, and one from thyroid carcinoma. Nineteen patients (7.7%) died from other causes than MB/CNS-PNET without evidence of recurrent disease (Supporting Information Table 8 and Figure S4).

4 | DISCUSSION

Survival rates in the herein presented consecutive national Norwegian MB/CNS-PNET material were in line with a similar study from Sweden, but lower than results from other countries (Canada and France).[1,19–22] One possible explanation is that the Canadian work did not include patients from the period 1974–1990. Other possible causes include the suboptimal staging procedures and protocol deviations concerning RT and CTX in the Norwegian material. When compared with results obtained from clinical trials, the gap to our real-word data is large; results from PNET 4 gave a five-year OS of 87% in the standard fractionated radiotherapy group and 85% in the hyperfractionated radiotherapy (HFRT) group.[23] Parts of this difference can be explained by strict patient selections in trials, not least supported by the fact that OS of PNET 4 patients of 82% in the present material were similar to the international numbers. In addition, it has repeatedly been pointed out that inclusion of patients into clinical trials improves outcome when compared with populations treated outside clinical trials.[24,25]

Although data collection, data analysis, and histological review of the present patient material were demanding, the data set represents a consecutive, complete national cohort and as such is unique and offers valuable evidence on patient outcome. Notably, no patient was lost to follow-up. Due to the long and complete follow-up, the present study is able to document that five-year and even 10-year survival data do not tell the whole story in pediatric brain tumors, because there were many late deaths due to late recurrence, secondary neoplasms, and late effects of therapy. Limitations of the study are mainly issues related to the retrospective design and the long time span of inclusion. Examples are uncompleted radiological review due to condemned imaging and missing or uncertain description of the presence or absence of residual tumor. CSF cytological examination was only occasionally performed before the turn of the millennium. Furthermore, we were not able to perform molecular biological analyzes leading to a modern molecular subgrouping of tumors. Because of all these issues, risk stratification of patients was hard. This was reflected by the small proportion of only

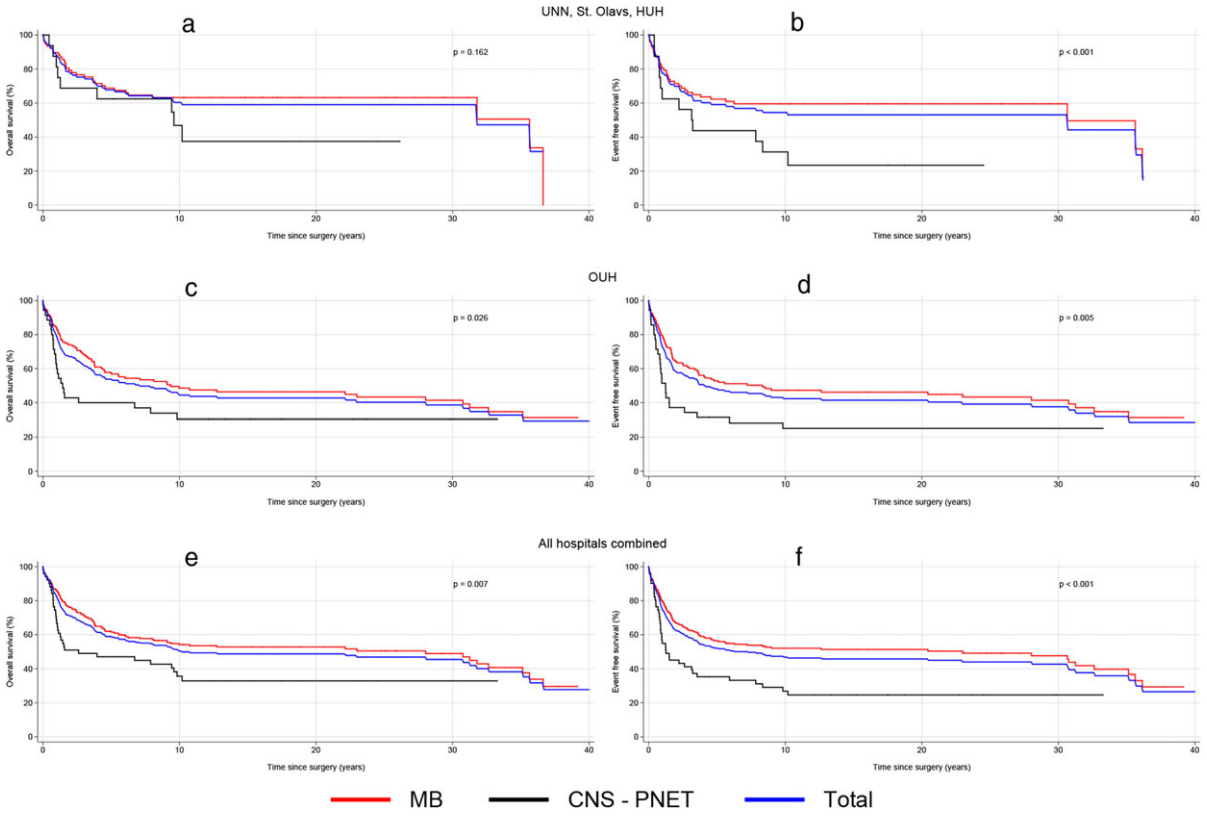


FIGURE 1 OS and EFS for MB and CNS-PNET patients altogether, for MB alone, and for CNS-PNET alone; a and b represent UNN, St Olavs, and HUH; c and d OUH; e and f national data. *P* values refer to comparison between MB and CNS-PNET

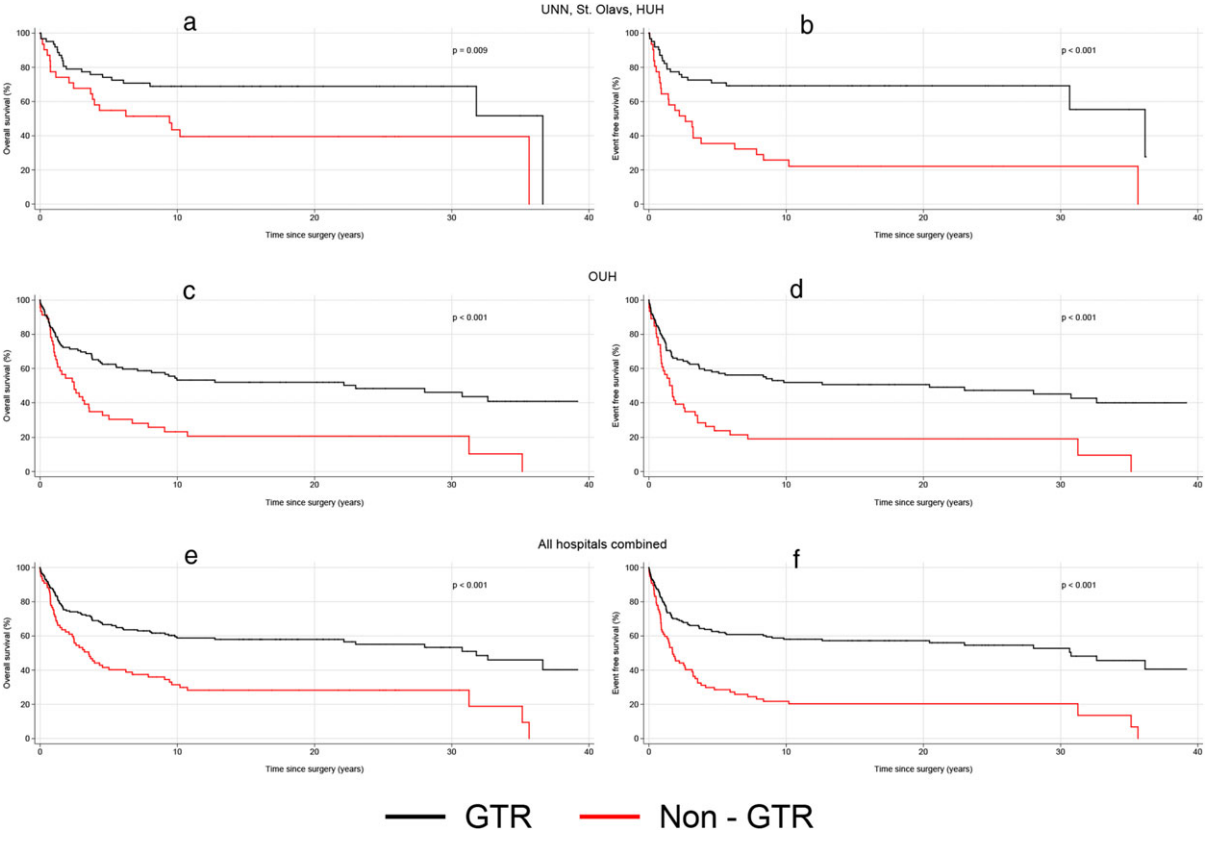


FIGURE 2 OS and EFS for MB and CNS-PNET patients stratified by resection grade (GTR vs non-GTR) at primary diagnosis; a and b represent UNN, St Olavs, and HUH; c and d OUH; e and f national data

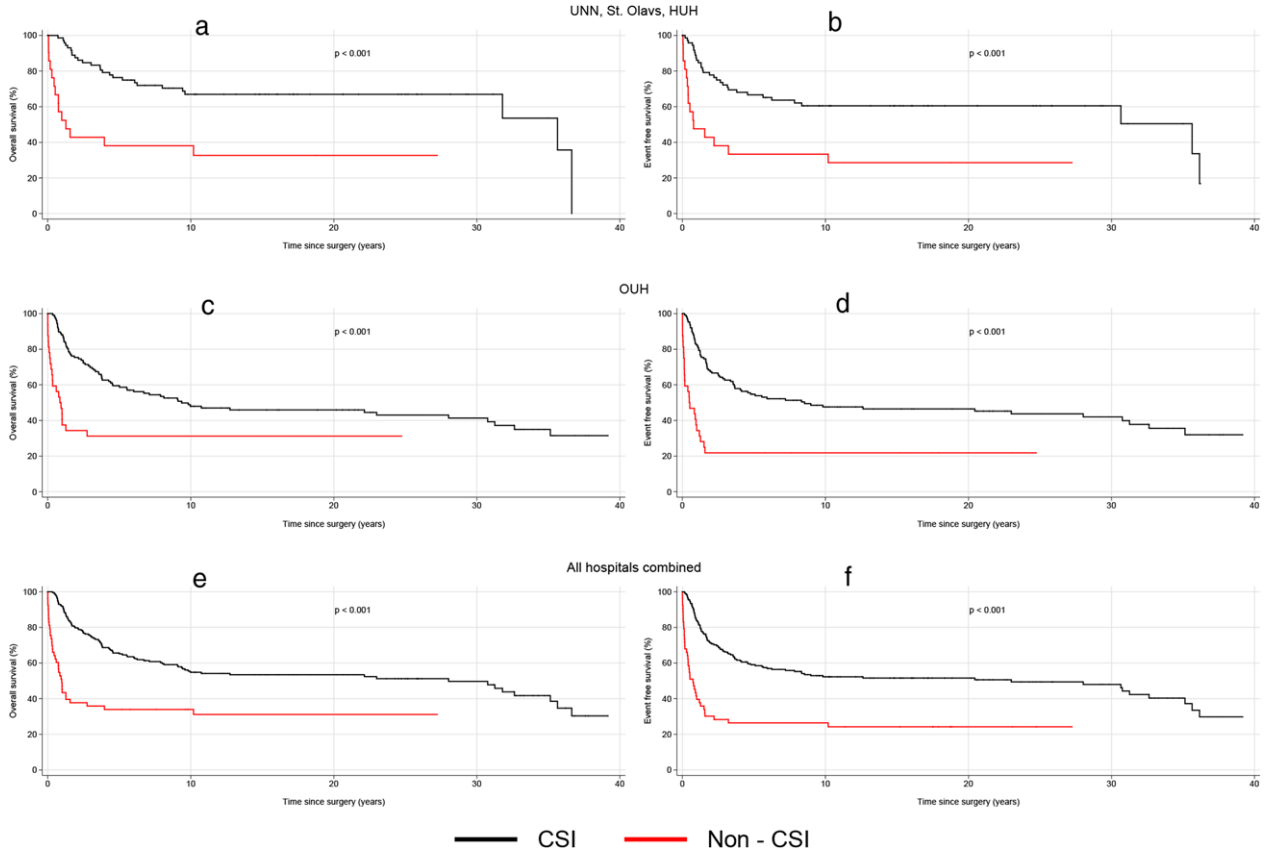
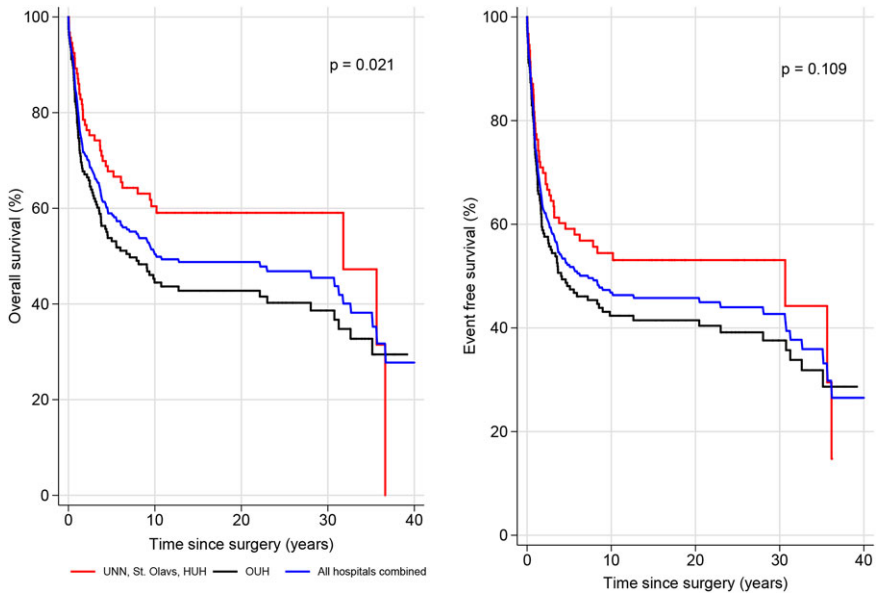


FIGURE 3 OS and EFS for MB and CNS-PNET patients stratified by radiotherapy including CSI or not at primary diagnosis; a and b represent UNN, St Olavs, and HUH; c and d OUH; e and f national data

FIGURE 4 OS and EFS for MB and CNS-PNET altogether stratified by treatment location



22% SR MB patients in this material, compared with about 70% in most previous publications, and by the large proportion of patients (44%) that were categorized as UR.

In multivariable analysis, three variables came across as positive prognostic factors. First, GTR was significantly better than non-GTR. Over the last decades, GTR has been regarded as a favorable prognostic factor for MB/CNS-PNET patients. However, a study in 2016 questioned this, indicating that the prognostic benefit of GTR for patients with MB was attenuated if molecular subgrouping was taken into account.[26] As stated above, this retrospective material did not allow for molecular subgrouping analyses. Second, patients treated with CSI had better OS than those treated without CSI, firmly

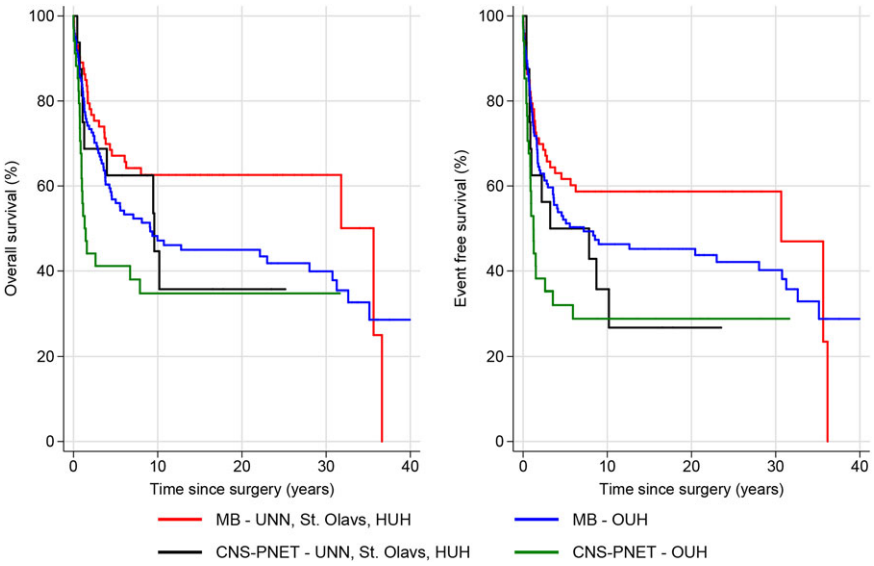


FIGURE 5 OS and EFS for MB and CNS-PNET patients stratified by entity and treatment location

TABLE 3 Multivariable Cox regression analysis: five-year overall and EFS

	Overall survival			EFS		
Parameter	Hazard ratio	95% CI	*P*	Hazard ratio	95 % CI	*P*
GTR vs non-GTR	0.53	0.34–0.81	$P = 0.003$	0.46	0.31–68	$P < 0.001$
CSI vs non-CSI	0.24	0.14–0.42	$P < 0.001$	0.28	0.17–0.46	$P < 0.001$
SR vs HR MB	0.90	0.42–10.9	$P = 0.78$	1.1	0.53–2.2	$P = 0.85$
SR vs UR MB	0.54	0.23–1.2	$P = 0.14$	0.91	0.42–2.0	$P = 0.81$
CSF examination, yes vs no	0.74	0.60–1.7	$P = 0.99$	1.1	0.68–1.7	$P = 0.77$
UNN, St. Olavs, and HUH vs OUH	0.64	0.42–1.0	$P = 0.048$	0.70	0.47–1.0	$P = 0.08$
Decades						
1970s vs 80s	0.84	0.44–1.6	$P = 0.61$	0.85	0.44–1.6	$P = 0.62$
1970 vs 90s	0.45	0.21–0.96	$P = 0.039$	0.60	0.29–1.2	$P = 0.15$
1970 vs 20s	0.28	0.12–0.66	$P = 0.004$	0.43	0.19–0.94	$P = 0.034$

CI, confidence interval; CSF, cerebrospinal fluid; CSI, cerebrospinal irradiation; GTR, gross total resection; HR, high risk; HUH, Haukeland University Hospital; OUH, Oslo University Hospital; SR, standard risk; St Olavs, St Olavs Hospital Trondheim University Hospital; UNN, University Hospital of North Norway; UR, uncertain risk.

supporting current knowledge. Interestingly, although it is generally accepted that radiotherapy duration more than 48 days is prognostically unfavorable,[27–29] our findings did not support this. A detailed review of radiotherapy target volumes and fields for patients experiencing recurrence would have been of considerable interest, but this was not feasible as we did not have adequate radiotherapy documentation for early years (up until a few years past the turn of the millennium). Third, patients treated at UNN, St Olavs, and HUH fared significantly better than those treated at OUH. This is in accordance with previously published data, although that data set covered a shorter time period and did not include histopathological revision.[16]

We have not succeeded in our efforts to identify possible explanations for the survival differences, in spite of a thorough review of diagnostic work-up, surgery, RT, and CTX. Especially, the identified suboptimal diagnostic procedures including lack of CSF cytology and proper radiological work-up seemed to have been similar throughout the country. The frequency of CTX modifications and RT protocol adherence did not differ significantly across the regions throughout the country. The relative high frequency of CTX modification was not unexpected because CTX for MB/CNS-PNET is often associated with toxicity, especially when used in combination with CSI. There is now an ongoing project at OUH trying to characterize MB/CNS-PNET from 2005 and onward, to explore if there might be molecular biological factors that might explain the regional OS difference.

Another important finding was the occurrence of late and very late events. Secondary malignancies, including incurable disease such as glioblastoma, were observed as early as three years but also as late as 37 years following the primary diagnosis of MB/CNS-PNET. The risk of recurrence has been reported to be highest within the first 5 to 10 years following diagnosis. Our data support this, but also clearly show that later recurrences do occur, and there should be an increased awareness related to this. It is therefore important to focus on late treatment complications as well as late recurrences in this patient group. This is in accordance with previously published data[17,30–32] and

reminds us that survival should not be the only parameter looked upon when cancer treatment success is measured.

5 | CONCLUSION

Norwegian survival data for MB and CNS-PNET are comparable to international data, but inferior to survival rates obtained in international clinical trials. This retrospective study corroborated the importance of GTR and CSI for survival and showed that survival for the MB/CNS-PNET patient group as a whole differed between regions. Unfortunately, we were not able to identify any explanation for this difference. We also conclude that awareness toward both late recurrences and late treatment-related effects is important.

CONFLICTS OF INTEREST

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REFERENCES

1. Fairley L, Picton SV, McNally RJ, Bailey S, McCabe MG, Feltbower RG. Incidence and survival of children and young people with central nervous system embryonal tumours in the North of England, 1990–2013. *Eur J Cancer*. 2016;61:36-43.
2. Smoll NR, Drummond KJ. The incidence of medulloblastomas and primitive neurectodermal tumours in adults and children. *J Clin Neurosci*. 2012;19(11):1541-1544.
3. Patel S, Bhatnagar A, Wear C, et al. Are pediatric brain tumors on the rise in the USA? Significant incidence and survival findings from the SEER database analysis. *Childs Nerv Syst*. 2014;30(1):147-154.
4. Taylor MD, Northcott PA, Korshunov A, et al. Molecular subgroups of medulloblastoma: the current consensus. *Acta Neuropathol*. 2012;123(4):465-472.
5. Northcott PA, Korshunov A, Pfister SM, Taylor MD. The clinical implications of medulloblastoma subgroups. *Nat Rev Neurol*. 2012;8(6):340-351.
6. Ramaswamy V, Taylor MD. Medulloblastoma: from myth to molecular. *J Clin Oncol*. 2017;35(21):2355-2363.
7. Mellinghoff IK, Gilbertson RJ. Brain tumors: challenges and opportunities to cure. *J Clin Oncol*. 2017;35(21):2343-2345.
8. Northcott PA, Robinson GW, Kratz CP, et al. Medulloblastoma. *Nat Rev Dis Primers*. 2019;5(1):11.
9. Laprie A, Hu Y, Alapetite C, et al. Paediatric brain tumours: a review of radiotherapy, state of the art and challenges for the future regarding protontherapy and carbontherapy. *Cancer Radiother*. 2015;19(8):775-789.
10. Ramaswamy V, Remke M, Adamski J, et al. Medulloblastoma subgroup-specific outcomes in irradiated children: who are the true high-risk patients. *Neuro Oncol*. 2016;18(2):291-297.
11. Goschzik T, Schwalbe EC, Hicks D, et al. Prognostic effect of whole chromosomal aberration signatures in standard-risk, non-WNT/non-SHH medulloblastoma: a retrospective, molecular analysis of the HIT-SIOP PNET 4 trial. *Lancet Oncol*. 2018;19(12):1602-1616.
12. Oeffinger KC, Mertens AC, Sklar CA, Kawashima T, Hudson MM, Meadows AT, et al. Chronic health conditions in adult survivors of childhood cancer. *N Engl J Med*. 2006;355(15):1572-1582.
13. Fay-McClymont TB, Ploetz DM, Mabbott D, et al. Long-term neuropsychological follow-up of young children with medulloblastoma treated with sequential high-dose chemotherapy and irradiation sparing approach. *J Neurooncol*. 2017;133(1):119-128.
14. Birkmeyer JD, Siewers AE, Finlayson EV, et al. Hospital volume and surgical mortality in the United States. *N Engl J Med*. 2002;346(15):1128-1137.
15. Begg CB, Cramer LD, Hoskins WJ, Brennan MF. Impact of hospital volume on operative mortality for major cancer surgery. *JAMA*. 1998;280(20):1747-1751.
16. Solheim O, Salvesen O, Cappelen J, Johannesen TB. The impact of provider surgical volumes on survival in children with primary tumors of the central nervous system–a population-based study. *Acta Neurochir (Wien)*. 2011;153(6):1219-1229. discussion 29.
17. Stensvold E, Krossnes BK, Lundar T, et al. Outcome for children treated for medulloblastoma and supratentorial primitive neuroectodermal tumor (CNS-PNET) – a retrospective analysis spanning 40 years of treatment. *Acta Oncol*. 2017;56(5):698-705.
18. Aalen Odd O, Soren J. An empirical transition matrix for non-homogeneous Markov chains based on censored observations. *Scand J Statist*. 1978;5:141-150.
19. Lannering B, Sandstrom PE, Holm S, et al. Classification, incidence and survival analyses of children with CNS tumours diagnosed in Sweden 1984–2005. *Acta Paediatr*. 2009;98(10):1620-1627.
20. Desandes E, Guissou S, Chastagner P, Lacour B. Incidence and survival of children with central nervous system primitive tumors in the French National Registry of Childhood Solid Tumors. *Neuro Oncol*. 2014;16(7):975-983.
21. Tulla M, Berthold F, Graf N, et al. Incidence, trends, and survival of children with embryonal tumors. *Pediatrics*. 2015;136(3):e623-32.
22. Johnston DL, Keene D, Kostova M, et al. Survival of children with medulloblastoma in Canada diagnosed between 1990 and 2009 inclusive. *J Neurooncol*. 2015;124(2):247-253.
23. Lannering B, Rutkowski S, Doz F, et al. Hyperfractionated versus conventional radiotherapy followed by chemotherapy in standard-risk medulloblastoma: results from the randomized multicenter HIT-SIOP PNET 4 trial. *J Clin Oncol*. 2012;30(26):3187-3193.
24. Mathew RK, O'Kane R, Parslow R, et al. Comparison of survival between the UK and US after surgery for most common pediatric CNS tumors. *Neuro Oncol*. 2014;16(8):1137-1145.
25. Vivekanandan S, Breene R, Ramanujachar R, et al. Reply to comment on: The UK experience of a treatment strategy for pediatric metastatic medulloblastoma comprising intensive induction chemotherapy, hyperfractionated accelerated radiotherapy, and response-directed high-dose myeloablative chemotherapy or maintenance chemotherapy (Milan strategy). *Pediatr Blood Cancer*. 2016;63(6):1125-1126.
26. Thompson EM, Hielscher T, Bouffet E, et al. Prognostic value of medulloblastoma extent of resection after accounting for molecular subgroup: a retrospective integrated clinical and molecular analysis. *Lancet Oncol*. 2016;17(4):484-495.
27. Kann BH, Park HS, Lester-Coll NH, et al. Postoperative radiotherapy patterns of care and survival implications for medulloblastoma in young children. *JAMA Oncol*. 2016;2(12):1574-1581.
28. Burki TK. Postoperative radiotherapy for paediatric medulloblastoma. *Lancet Oncol*. 2016;17(9):e381.
29. Paulino AC, Jaboin JJ. Radiotherapy deferral in medulloblastoma. *JAMA Oncol*. 2016;2(12):1582.

30. Olsen JH, Moller T, Anderson H, et al. Lifelong cancer incidence in 47,697 patients treated for childhood cancer in the Nordic countries. *J Natl Cancer Inst*. 2009;101(11):806-813.
31. Goldstein AM, Yuen J, Tucker MA. Second cancers after medulloblastoma: population-based results from the United States and Sweden. *Cancer Causes Control*. 1997;8(6):865-871.
32. Ning MS, Perkins SM, Dewees T, Shinohara ET. Evidence of high mortality in long term survivors of childhood medulloblastoma. *J Neurooncol*. 2015;122(2):321-327.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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