Unmet rehabilitation needs in 86% of Norwegian paediatric embryonal brain tumour survivors

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Aim: To study incidence, types and degrees of late effects in a geographical cohort of paediatric medulloblastoma and central nervous system primitive neuroectodermal tumour (CNS-PNET) survivors, and identify the need for rehabilitation.

Methods: Between 1974 and 2013, 63 patients survived treatment for paediatric medulloblastoma and CNS-PNET at Oslo University Hospital, Norway. Of these, 50 accepted invitation and were included in this study.

Results: Median follow-up was 20 years (range 3.2-41), and 96% of participants had developed late effects. Cognitive impairment was found in 72%, reduced hearing in 68%, endocrine deficits in 66%, epilepsy in 32% and another 30% had been diagnosed with one or more second primary neoplasms. Radiotherapy significantly increased risk of secondary primary neoplasms and endocrinological deficits, chemotherapy risk of ototoxicity and endocrinological deficits, and epilepsy was found significantly more often in CNS-PNET than medulloblastoma patients. Epilepsy was the main cause of cognitive impairments (full-scale IQ) in our study. 86% of participants had an unmet rehabilitation need.

Conclusion: Significant late effects and unmet rehabilitation needs were documented in the large majority of survivors after treatment for paediatric medulloblastoma and CNS-PNET.

Keywords: central nervous system peripheral neuroectodermal tumour, cognitive impairments, late effects, medulloblastoma, rehabilitation need.

Abbreviations: CNS-PNET, central nervous system supratentorial primitive neuroectodermal tumour; CI, confidence interval; HR, hazard ratio; IQ, intelligence quotient; SD, standard deviation.

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INTRODUCTION

Medulloblastoma and central nervous system primitive neuroectodermal tumour (CNS-PNET) are embryonal tumours arising in the infratentorial and supratentorial brain, respectively, and represent 10%-15% of paediatric brain tumours. These neoplasms are classified according to the 2016 version of the World Health Organization classification of tumours of the CNS. The nomenclature PNET has been replaced by several new embryonal tumour categories. In this paper, we use the term CNS-PNET because all patients were treated before 2016. Five-year overall survival for standard-risk medulloblastoma, high-risk medulloblastoma and CNS-PNET is >80%, 40%-60% and 50%-70%, respectively. Because of the high risk of leptomeningeal disease dissemination, standard postoperative treatment for medulloblastoma and CNS-PNET includes craniospidal irradiation and chemotherapy. All these treatment modalities are associated with long-term sequelae and morbidity affecting cognition, hearing, hormonal status, second primary neoplasms and quality of life. Knowledge related to these long-term or late effects occurring many months to years after antineoplastic treatment has risen in later years, and focus has moved from survival only to also include quality of life. Nonetheless, only very few studies have reported follow-up of more than 10 years and rehabilitation need for medulloblastoma and CNS-PNET patient cohorts. We hypothesised that a high percentage of medulloblastoma and CNS-PNET survivors experience late effects and that the resulting rehabilitation need is largely unmet. This study therefore aimed at determining the frequency of unwanted late effects in medulloblastoma and CNS-PNET survivors, focusing on cognition, hearing, endocrinology, epilepsy, second primary neoplasms, cerebrovascular and cardiovascular status, vision and the severity of these late effects. The secondary aim was to define the frequency of patients with unmet rehabilitation needs.

MATERIALS AND METHODS

Participants

Oslo University Hospital is a tertiary university hospital in southern Norway covering 3.0 (57%) of the 5.3 million Norwegian inhabitants. Between January 1, 1974, and December 31, 2013, a total of 123 paediatric medulloblastoma and 34 paediatric CNS-PNET patients were treated at Oslo University Hospital. All 63 survivors were invited to participate and 50 (79%) consented, whereof 42 had been treated for medulloblastoma (84%) and eight (16%) for CNS-PNET. Patient characteristics are summarised in Table 1. The 13 non-participant survivors did not differ from the participants in terms of age at time of first surgery, gender, histology and whether or not they had received radiotherapy (Table S1). A tissue-based reclassification beyond histopathological review of participants’ neoplasms was not possible, because many survivors were treated several years ago and only sparse amounts of material with poor quality because of older fixation procedures were available.

Procedure

The follow-up examination was performed between 2016 and 2018, lasted for two days and included interviews, physical examination, audiometry, basal endocrinological laboratory tests, neuropsychological assessment and medical record review. Severity of adverse events was graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0, except for cognitive evaluation and audiometry. Grade 1 late effects were not recorded.

Measures and definitions

All participants underwent individual neuropsychological assessment. Measures included tests of intelligence, verbal and visual memory, attention, processing speed and executive functions (Table S2). Cognitive impairment was defined as a test result two standard deviations (SD) or more below the age mean, which means a standardised score at or below 70.

Hearing loss was graded from 1 to 4 according to International Society of Paediatric Oncology (SIOP) Boston Ototoxicity Scale, based on the ear with the lowest grade. Pure-tone audiograms were used to assess hearing thresholds. Frequencies from 125 to 8,000 Hz were tested and measured in decibel hearing level. Bone conduction thresholds were obtained to rule out a conductive component of any hearing impairment. Audiometry data were collected without the participants using hearing aids.

Disturbances in hormonal regulation requiring hormone replacement therapy were defined as a clinically significant lack of the...
production of either thyroxine, growth hormone, gonadal hormones
and/or cortisone.

Medical record review was used to extract information on endocrinologically relevant data. Basal endocrinological tests used are listed in Table S3. Sitting and standing height for participants over 18 years at time of study assessment were measured. Measurements 2 SD or more below expected values, based on published data from the Netherlands\textsuperscript{11} and Norway,\textsuperscript{12} were registered as abnormal.

Epilepsy was defined according to the official International League Against Epilepsy criteria.\textsuperscript{13}

Second primary neoplasms were registered based on participant interviews, clinical examination, medical record review and the Cancer Registry of Norway.

**TABLE 1** Participant and treatment characteristics (n = 50)

| Parameter                                  | Number/median/years (SD/percentage/range) |
|--------------------------------------------|-------------------------------------------|
| Sex                                        |                                           |
| Female                                     | 25 (50%)                                  |
| Male                                       | 25 (50%)                                  |
| MB                                         |                                           |
| Female                                     | 19 (45%)                                  |
| Male                                       | 23 (55%)                                  |
| CNS-PNET                                   |                                           |
| Female                                     | 6 (75%)                                   |
| Male                                       | 2 (25%)                                   |
| Histology and risk groups                  |                                           |
| Medulloblastoma                            | 42 (84%)                                  |
| Classic                                    | 35 (83%)                                  |
| Desmoplastic/nodular                       | 6 (14%)                                   |
| Anaplastic/large cell                      | 1 (2.4%)                                  |
| Medulloblastoma risk groups                |                                           |
| Standard-risk                              | 14 (33%)                                  |
| High-risk                                  | 15 (36%)                                  |
| Uncertain-risk\textsuperscript{a}          | 13 (31%)                                  |
| CNS-PNET                                   | 8 (16%)                                   |
| CNS embryonal tumour, NOS                  | 5 (63%)                                   |
| Pineoblastoma                              | 1 (13%)                                   |
| Ependymoblastoma                           | 1 (13%)                                   |
| Embryonal tumour with multilayered rosettes, NOS | 1 (13%)                                  |
| Time period of primary treatment           |                                           |
| 1974-1979                                  | 2 (4%)                                    |
| 1980-1989                                  | 13 (26%)                                  |
| 1990-1999                                  | 12 (24%)                                  |
| 2000-2013                                  | 23 (46%)                                  |
| Age at diagnosis                           |                                           |
| Median                                     | 7.1 y (2.0 mo-19 y)                       |
| <5 y                                       | 18 (36%)                                  |
| 6-10 y                                     | 22 (44%)                                  |
| 11-20 y                                    | 10 (20%)                                  |
| Median, MB                                 | 7.9 (0.9 mo-19 y)                         |
| Median, CNS-PNET                           | 3.8 (0.2 mo-6.5 y)                        |
| Age at study                               |                                           |
| Median                                     | 26 y (5.5-52)                             |
| 5-10 y                                     | 3 (6.0%)                                  |
| 11-18 y                                    | 13 (26%)                                  |
| >18 y                                      | 34 (68%)                                  |
| Median, MB                                 | 27 (5.5-52)                               |
| Median, CNS-PNET                           | 15 (6.4-27)                               |
| Time since first surgery                   |                                           |
| Median                                     | 20 y (3.2-41)                             |

**TABLE 1** (Continued)

| Parameter                                                  | Number/median/years (SD/percentage/range) |
|------------------------------------------------------------|-------------------------------------------|
| Hydrocephalus (before primary surgery)                     | 50                                        |
| Present                                                    | 43 (86%)                                  |
| Absent                                                     | 7 (14%)                                   |
| Surgery                                                    | 50                                        |
| GTR                                                        | 43 (86%)                                  |
| Non-GTR                                                    | 7 (14%)                                   |
| Hydrocephalus (after primary surgery)                      | 50                                        |
| Present                                                    | 17 (34%)                                  |
| Absent                                                     | 33 (66%)                                  |
| Epilepsy                                                   |                                           |
| Yes                                                        | 16                                        |
| No                                                         | 34                                        |
| MB                                                         |                                           |
| Yes                                                        | 12                                        |
| No                                                         | 30                                        |
| CNS-PNET                                                   |                                           |
| Yes                                                        | 4                                         |
| No                                                         | 4                                         |
| Adjuvant treatment                                         | 50                                        |
| Only radiotherapy                                          | 8 (16%)                                   |
| Only chemotherapy                                          | 6 (12%)                                   |
| Radiotherapy and chemotherapy                              | 36 (72%)                                  |
| Radiotherapy dose, n = 44\textsuperscript{b}                |                                           |
| Craniocpspine dose                                         | 35.0 Gy (23.4-36.0)                       |
| Tumour bed boost                                           | 20.0 Gy (14.4-54.0)                       |
| Total                                                      | 54.0 Gy (45.0-56.7)                       |

Abbreviations: CNS-PNET, central nervous system primitive neuroectodermal tumour; GTR, gross total resection; Gy, Gray; NOS, not otherwise specified; SD, standard deviation.

\textsuperscript{a}Uncertain risk; if available data were insufficient for determining if a residual tumour and/or metastatic disease were present, the patient was classified as uncertain risk.

\textsuperscript{b}One participant received only local fractionated radiotherapy to parts of the left hemisphere without cerebrospinal irradiation.
Ophthalmological late effects were defined as either impaired vision or blindness and were registered based on participants interviews and medical chart review.

A disturbance of blood supply to the brain or heart caused by thrombosis or embolism of an artery resulting in either neurologic or cardiac damage, as well as disease in aortic and or pulmonary valve function or structure, was defined as cerebrovascular and cardiovascular late effects.

An unmet rehabilitation need was defined in accordance with WHO criteria: one or more symptoms or signs necessitating further follow-up or intervention that the patient was not receiving at the time of study assessment. The decision to state unmet rehabilitation need(s) was made by the first author based upon objective study results. Participants who had abnormal findings either at cognitive examination, on audiometry, at cardiac auscultation and or uncertain dermatological lesions were categorised as with unmet rehabilitation need. Also, participants who had been treated with radiotherapy and were not followed by an endocrinologist were categorised in this group.

### 2.4 Ethics statement

The study was approved by the Regional Committees for Medical and Health Research Ethics of the South-Eastern Norway Regional Health Authority (#2015/2362) and The Data Protection Officer at Oslo University Hospital. Informed consent was obtained from all participants and or their parents/guardians. The study was registered in ClinicalTrials.gov (NCT02851355). Ethical standards of the Declaration of Helsinki were followed.

### 2.5 Statistics

Descriptive data are presented as mean and SD for normally distributed variables or median and range for non-normal continuous variables. To compare results in different cognitive domains, paired sample t tests were computed. One-way analysis of variance, with Tukey's tests to control for multiple comparisons, was used to compare differences in means between groups of participants. Second primary neoplasms, audiometric,
TABLE 3  Standardised neuropsychological test scores for (A) all participants, and comparison between participants (B) with medulloblastoma and CNS-PNET, (C) having received radiation treatment or not, (D) with and without epilepsy and (E) hydrocephalus at any time or not

(A)

| Cognitive domain            | Mean (SD) | Min-max score | N (%) of participants with scores two or more standard deviations below the age mean |
|-----------------------------|-----------|---------------|-------------------------------------------------------------------------------------|
| Full-scale IQ (N = 50)      | 86.7 (21.5) | 25-125        | 11 (22%)                                                                            |
| Verbal IQ (N = 50)          | 85.4 (20.3) | 25-123        | 10 (20%)                                                                            |
| Performance IQ (N = 50)     | 89.6 (21.0) | 25-126        | 9 (18%)                                                                             |
| Verbal memory (N = 47)      | 87.5 (19.0) | 27-134        | 7 (15%)                                                                             |
| Visual memory (N = 43)      | 66.3 (27.3) | 27-115        | 20 (47%)                                                                            |
| Memory span (N = 47)        | 85.7 (15.3) | 55-115        | 9 (19%)                                                                             |
| Processing speed (N = 44)   | 90.4 (18.4) | 40-123        | 7 (16%)                                                                             |
| Inattentiveness (N = 44)    | 91.1 (19.0) | 40-109        | 7 (16%)                                                                             |
| Impulsiveness (N = 44)      | 87.3 (15.8) | 57-124        | 6 (14%)                                                                             |
| Flexibility (N = 43)        | 89.2 (18.5) | 55-115        | 9 (21%)                                                                             |

(B)

| Cognitive domain            | Medulloblastoma Mean (SD) | CNS-PNET Mean (SD) | Sign. |
|-----------------------------|---------------------------|--------------------|-------|
| Full-scale IQ (N = 42, 8)   | 87.8 (22.2)               | 81.1 (17.2)        | t(48) = 0.805, P = .425 |
| Verbal IQ (N = 42, 8)       | 86.7 (20.9)               | 78.3 (16.5)        | t(48) = 1.085, P = .283 |
| Performance IQ (N = 42, 8)  | 90.2 (21.8)               | 86.8 (17.0)        | t(48) = 0.421, P = .676 |
| Verbal memory (N = 40, 7)   | 88.5 (17.4)               | 82.2 (27.7)        | t(45) = 0.800, P = .428 |
| Visual memory (N = 36, 7)   | 65.3 (27.2)               | 71.4 (29.5)        | t(41) = -0.535, P = .595 |
| Memory span (N = 40, 7)     | 86.6 (15.3)               | 80.7 (15.1)        | t(45) = 0.945, P = .350 |
| Processing speed (N = 38, 6) | 92.6 (17.0)              | 76.5 (22.2)        | t(42) = 2.068, P = .045* |
| Inattentiveness (N = 38, 6) | 92.0 (17.5)               | 85.5 (27.8)        | t(42) = 0.775, P = .443 |
| Impulsiveness (N = 38, 6)   | 83.6 (13.0)               | 110.5 (12.7)       | t(42) = -4.737, P < .001** |
| Flexibility (N = 38, 5)     | 88.4 (19.1)               | 95.0 (12.7)        | t(41) = -0.743, P = .462 |

(C)

| Cognitive domain            | Radiation treatment Mean (SD) | No radiation treatment Mean (SD) | Sign. |
|-----------------------------|-------------------------------|----------------------------------|-------|
| Full-scale IQ (N = 44, 6)   | 85.2 (21.4)                  | 98.3 (19.4)                      | t(48) = 1.425, P = .161 |
| Verbal IQ (N = 44, 6)       | 84.0 (20.4)                  | 95.8 (18.3)                      | t(48) = 1.355, P = .182 |
| Performance IQ (N = 44, 6)  | 88.1 (21.1)                  | 101.2 (18.1)                     | t(48) = 1.449, P = .154 |
| Verbal memory (N = 42, 5)   | 85.2 (17.3)                  | 107.7 (23.2)                     | t(45) = 2.656, P = .011* |
| Visual memory (N = 38, 5)   | 63.3 (27.4)                  | 89.2 (10.8)                      | t(41) = 2.074, P = .044* |
| Memory span (N = 42, 5)     | 85.4 (14.9)                  | 89.0 (19.8)                      | t(45) = 0.501, P = .619 |
| Processing speed (N = 39, 5) | 89.8 (18.2)                 | 94.6 (21.4)                      | t(42) = 0.541, P = .592 |
| Inattentiveness (N = 39, 5) | 91.8 (17.9)                  | 85.3 (28.0)                      | t(42) = -0.723, P = .474 |
| Impulsiveness (N = 39, 5)   | 86.1 (15.4)                  | 96.4 (17.8)                      | t(42) = 1.387, P = .173 |
| Flexibility (N = 38, 5)     | 88.3 (19.1)                  | 96.0 (12.9)                      | t(41) = 0.873, P = .388 |

(D)

| Cognitive domain            | Epilepsy Mean (SD) | No epilepsy Mean (SD) | Sign. |
|-----------------------------|--------------------|-----------------------|-------|
| Full-scale IQ (N = 15, 35)  | 73.2 (23.2)        | 92.5 (18.1)           | t(48) = 3.181, P = .003** |
| Verbal IQ (N = 15, 35)      | 72.0 (21.3)        | 91.1 (17.2)           | t(48) = 3.351, P = .002** |

(Continues)
cardiovascular and cerebrovascular outcomes were analysed from time of first surgery to time of the event of interest. If the late effect event did not occur, participants were censored at the date of last clinical examination. In multivariable analyses, Cox proportional hazard regressions were estimated to analyse the possible impact of the following variables on endocrinology, second primary neoplasms, reduced hearing and epilepsy: medulloblastoma versus CNS-PNET, age at time of first surgery, irradiation versus no irradiation, sex, and chemotherapy versus no chemotherapy. Hazard ratio (HR) and their associated 95% confidence intervals (CI) were used to assess the effect of the chosen covariates on outcome. P-values < .05 were considered statistically significant. For statistical analyses, IBM SPSS Statistics version 25.0 (2018, International Business Machines Corporation, Statistical Package for the Social Sciences, Armonk, New York, USA) and Stata15 (StataCorp LP, 4905 Lakeway Drive, College Station, Texas 77845-4512, USA) were used.

### RESULTS

#### 3.1 Antineoplastic treatment

Among participants, median age at time of first surgery was 7.1 years (range two months-19 years), median follow-up was 20 years (range 3.2-41 years) and median age at study examination was 26 years (range 5.5-52 years, Table 1). All participants had gone through tumour resection at the time of primary diagnosis, and 42 had received radiotherapy as part of primary treatment, 41 of these including craniospinal irradiation. There were eight participants that due to low age had not received radiotherapy as part of primary treatment; five of these had medulloblastoma and three CNS-PNET. Of these eight, two had received craniospinal irradiation at time of recurrence. Thus, a total of 43 participants (88%) received craniospinal irradiation. Except age, there

| Cognitive domain | Hydrocephalus at any time Mean (SD) | No hydrocephalus Mean (SD) | Sign. |
|------------------|-------------------------------------|-----------------------------|-------|
| Full-scale IQ (N = 46, 4) | 86.0 (21.4) | 95.8 (23.3) | t(48) = 0.873, P = .387 |
| Verbal IQ (N = 46, 4) | 84.8 (20.1) | 92.3 (25.2) | t(48) = 0.701, P = .487 |
| Performance IQ (N = 46, 4) | 88.8 (21.1) | 99.0 (20.1) | t(48) = 0.928, P = .358 |
| Verbal memory (N = 43, 4) | 88.5 (17.3) | 77.3 (35.1) | t(45) = −1.127, P = .266 |
| Visual memory (N = 39, 4) | 66.8 (26.5) | 61.8 (38.2) | t(41) = −0.347, P = .730 |
| Memory span (N = 39, 4) | 85.0 (14.1) | 93.8 (26.6) | t(45) = 0.525, P = .602 |
| Processing speed (N = 40, 4) | 90.9 (18.4) | 85.8 (19.8) | t(42) = −0.175, P = .862 |
| Inattentiveness (N = 40, 4) | 91.3 (17.7) | 89.5 (33.2) | t(42) = 3.238, P = .002** |
| Impulsiveness (N = 39, 4) | 85.0 (14.2) | 109.4 (15.7) | t(42) = 3.238, P = .002** |
| Flexibility (N = 40, 3) | 88.3 (18.7) | 101.7 (2.7) | t(41) = 1.218, P = .230 |

Note: Independent samples t test, equal variances assumed.
* P<.05.
** P<.01.

### TABLE 4  Time from first surgery to late effect (y)

|                      | All late effects | Endocrinological late effects | Ophthalmological late effects | Second primary neoplasms | Cerebrovascular and cardiovascular late effects |
|----------------------|------------------|-------------------------------|-------------------------------|--------------------------|-----------------------------------------------|
| Median time (y)      | 6.2              | 3.6                           | 15                            | 21                       | 33                                            |
| SD (range)           | 11 (1.1-39)      | 8.1 (1.2-34)                  | 11 (3.3-35)                   | 9.9 (3.4-39)             | 13 (1.7-39)                                   |
### Table 5: Multivariable Cox regression analyses on late effects

| Parameter                          | Endocrinological deficits | Second Primary Neoplasms |
|-----------------------------------|---------------------------|--------------------------|
|                                   | HR  | 95% CI      | P-value | HR  | 95% CI      | P-value |
| CNS-PNET vs medulloblastoma       | 2.2 | 0.70-6.9    | P = .18 | 0.61| 0.75-5.1    | P = .65 |
| Radiotherapy vs no radiotherapy   | NA  | NA          | NA      | NA  | NA          | NA      |
| Girls vs boys                     | 0.98| 0.45-2.1    | P = .97 | 5.9 | 1.1-31.5    | P = .04 |
| Age at time of first surgery      | 0.98| 0.91-1.1    | P = .65 | 0.93| 0.79-1.1    | P = .31 |
| Chemotherapy vs no chemotherapy   | 3.9 | 1.1-14.6    | P = .042| 1.0 | 14-7.7      | P = .97 |

| Parameter                          | Reduced hearing | Epilepsy |
|-----------------------------------|----------------|---------|
|                                   | HR  | 95% CI      | P-value | HR  | 95% CI      | P-value |
| CNS-PNET vs medulloblastoma       | 0.98| 0.21-4.5    | P = .97 | 7.1 | 1.7-29.9    | P = .008 |
| Radiotherapy vs no radiotherapy   | 1.6 | 0.20-13.5   | P = .64 | NA  | NA          | NA      |
| Girls vs boys                     | 0.73| 0.33-1.6    | P = .44 | 1.9 | 0.58-6.0    | P = .29 |
| Age at time of first surgery      | 1.1 | 0.96-1.2    | P = .26 | 0.92| 0.78-1.1    | P = .32 |
| Chemotherapy vs no chemotherapy   | 3.8 | 1.2-11.8    | P = .023| 0.93| 0.18-4.8    | P = .93 |

Abbreviations: CI, confidence interval; CNS-PNET, central nervous system primitive neuroectodermal tumour; HR, hazard ratio; NA, not applicable.

No events in the no radiotherapy group.

**Figure 1** Full-scale IQ from Wechsler Abbreviated Scale of Intelligence (WASI), according to age at time of first surgery: A, differences between survivors with medulloblastoma and CNS-PNET, B, differences between participants receiving radiation treatment or not, and C, differences for patients with and without epilepsy. Reference lines represent age mean (IQ 100) and ± two standard deviations. IQ scores below 70 represent cognitive impairments.
were no differences between participants that had or had not received radiotherapy. Survivors from the 1990s and onwards were more likely to have received chemotherapy, including platinum and alkylating agents, compared with survivors from 1970s to 1980s.

### 3.2 Late effects

Most of our participants were followed by the general practitioner only. We found that 48 participants (96%) had developed late effects (Tables 2 and 3). Median time from time of first surgery to late effect was 6.2 years (SD 11, range 1.1-39 years; Table 4). For 17 (35%) of these 48 participants, their late effects were diagnosed 10-30 years after time of first surgery. Endocrinological late effects were the first to appear, whereas cerebrovascular and cardiovascular were the last. Radiotherapy, chemotherapy and epilepsy all came across as risk factors for late effects, details below and in Tables 3 and 5.

A total of 43 participants (86%) were defined to have one or several unmet rehabilitation needs. These 43 individuals were referred to neurologist (n = 9), otorhinolaryngologist (n = 34), ophthalmologist (n = 3), endocrinologist (n = 17), plastic surgeon or dermatologist (n = 9), and or cardiologist (n = 3). Most participants referred to neurologist had mild cognitive deficits and should preferably have been referred to adult habilitation, but no such service was available.

### 3.3 Cognition

Neuropsychological findings are presented in Table 3 and Figure 1. Cognitive impairment was found in 72%, and nine of the remaining 14 participants had scores below 85 on at least one of the domains assessed. Thus, only five participants (10%) showed absolutely no signs of cognitive impairment in any of the domains assessed (all results >85). Three of these five had received radiotherapy including cerebrospinal irradiation, all were medulloblastoma survivors, there were 4 males and 1 female, age at first time surgery spanned from 0.9 to 16 years, and follow-up time ranged from 4.6 to 36 years. The mean full-scale intelligence quotient (IQ) for all participants was 86.7. Mean test results for other cognitive domains were between 85.7 and 91.1, with the exception of visual memory where the mean score was 66.3. There was large variability in IQ scores among the participants (range 25-125), and 25 participants (50%) had a full-scale, verbal and or performance IQ below 85. Of these, 11 had full-scale IQ scores ranging from 25 to 70. Performance IQ was significantly higher than verbal IQ, \( P = .003 \). There were eighteen participants (36%) treated between two and seven years of age, and these eighteen had significantly lower full-scale IQ than participants treated before two years of age \( (n = 6) \) or after seven years of age \( (n = 26) \). \( F(2,47) = 8.052, P = .001 \). All participants older than seven years and 17 of 18 (94%) between two and six years of age at time of first surgery had received radiotherapy, whereas only one of six participants (17%) younger than two years had received radiotherapy. Medulloblastoma survivors had a significantly better processing speed but a higher grade of impulsivity than CNS-PNET participants, \( P = .045 \) and <.001, respectively. Radiotherapy significantly affected verbal and visual memory, \( P = .011 \) and .044, respectively. Participants who never had experienced hydrocephalus—neither at time of first surgery nor postoperatively—showed less impulsivity than participants diagnosed with hydrocephalus either at time of first surgery and or postoperatively, \( P = .002 \) (Table 3). Participants with epilepsy had significantly lower IQ scores in six of ten domains (Table 3).

### 3.4 Audiometry

Audiometry was performed in 48 participants (96%). Two participants were not able to perform audiometry because of neurological and cognitive impairments. Reduced hearing was found in 34 of 48 survivors (68%). Two participants were deaf, diagnosed 2 and 32 years from time of first surgery, respectively. In 22 participants, hearing loss was known but without proper follow-up. Unfortunately, it was not possible to determine the time of diagnosis for hearing loss in most of these 22 survivors. The latter 10 patients with sensorineural hearing loss were diagnosed based on audiometric findings in this study. Multivariable Cox regression analysis showed that hearing loss (ototoxicity higher than SIOP grade 2) was significantly more common in participants that had received chemotherapy, \( P = .023 \). Tumour entity, radiotherapy, sex and age at time of first surgery did not significantly affect hearing (Table 5).

### 3.5 Endocrinology

Endocrinological disturbances requiring hormone replacement therapy were found in 33 participants (66%, Table 2); all had been diagnosed before this study and all had received radiotherapy. Panhypopituitarism was seen in 13 participants (26%), sole hypothyroidism was observed in eight participants (16%), a combination of hypothyroidism and growth hormone deficiency in eight participants (16%), and sole growth hormone deficiency in four participants (8.0%). None had sole gonadotropic or corticotropic failure. Median time from first surgery to endocrinological event was 3.6 years (Table 4). The order of appearance of endocrinological disturbances was the somatotropic axis first in 16 participants (48%), thyreotropic axis in 12 participants (36%), and corticotropic axis or disturbance of all axes first in two (6.1%). In one participant (3.0%), a disturbance in the somatotropic and thyreotropic axis was observed first. Among the 29 participants with a dysregulated thyreotropic axis, 13 had central and 16 peripheral hypothyroidism. Reduced sitting and standing height (≥2 SD) were found in 12 (35%) and 10 (29%) of the 34 participants older than 18 years, respectively (Table S4). All these had received radiotherapy. Ten participants with reduced sitting height and seven with reduced standing height had been treated with growth hormone replacement therapy, respectively. Among the 44 participants who had received radiotherapy, 33 (75%)
had developed disturbances in hormonal regulation requiring hormone replacement therapy, whereas none of the six patients treated without radiotherapy had endocrinological deficits. In multivariable analysis, treatment including chemotherapy significantly increased risk of endocrinological deficits, \( P = .0042 \).

### 3.6 | Epilepsy

Sixteen participants (32%) were diagnosed with epilepsy and received antiepileptic medication; all had been diagnosed before this follow-up study. Seizures refractory to medication were reported in eight participants. No participants diagnosed before two years of age had developed epilepsy. We do not have information neither on seizure type nor on date of first seizure. There was a significantly higher frequency of epilepsy in CNS-PNET participants than in medulloblastoma survivors, \( P = .008 \). Epilepsy was found to significantly affect most cognitive domains (Table 3). None of the six patients treated without radiotherapy developed epilepsy.

### 3.7 | Second primary neoplasms

A total of 15 participants (30%) experienced 23 cases of second primary neoplasms. Median occurrence was 21 years from time of first surgery, and all participants had received radiotherapy. Meningioma was diagnosed in nine participants (18%), some with multiple and some in need of multiple surgical interventions. Three participants had been diagnosed with papillary thyroid carcinoma, two participants with thyroid follicular adenoma and one participant with glioblastoma. Additionally, four participants had experienced multiple basal cell carcinomas and one participant a squamous cell carcinoma at the left ear as well as a rectal adenocarcinoma. All meningiomas and the glioblastoma were located within the radiotherapy target volume. The other second primary neoplasms, except a rectal carcinoma which was located in a region receiving scattered radiation, were in the radiotherapy field. Also, based on this and a previous retrospective study, the suspicion of Gorlin syndrome was raised in one participant who is now under diagnostic work-up to test for this syndrome. Girls were found to have an increased risk of second primary neoplasms (HR = 5.9).

### 3.8 | Vision

Seven participants (14%) had grade 3-4 visual sequelae; five of these had been operated for cataract, and all five had received radiotherapy. One participant experienced grade 3 preretinal haemorrhages with diffusion into bulbus oculi resulting in decreased vision of the right eye, 6.5 years after completion of radiotherapy. One participant developed retinal detachment grade 4 (Coats disease) with loss of vision of the affected eye, 15 years after completion of chemotherapy. This participant had not been treated with radiotherapy. None of the participants had surgery that could potentially compromise vision or had other risk factors for decreased vision.

### 3.9 | Cerebrovascular and cardiovascular status

Four participants (8%) had experienced grade 3-4 cerebrovascular or cardiovascular late effects, all diagnosed and confirmed by MRI or echocardiography, respectively. One participant who had metastatic CNS-PNET at the time of diagnosis had suffered an arteria cerebri media infarction at the age of 7 years, 3 years after time of first surgery. This participant required parental assistance at the time of examination. Another participant had several transient ischaemic attacks and cerebral infarctions that occurred from when the participant was 50 years old, 33 years after time of first surgery. A third participant had developed grade 4 cardiac toxicity with aortic stenosis and mitral insufficiency at the age of 43 years, 36 years after time of first surgery. This patient had been operated with aortic valve replacement and valvuloplasty twice. A fourth participant experienced several pontine infarctions, 25 years after time of first surgery. Additionally, three participants had grade 2 cardiovascular long-term sequelae with moderate to large tricuspidal insufficiency (one participant) and mild aortic insufficiency (two participants). None of these seven participants had received cardiotoxic chemotherapy, four of them had received only radiotherapy, and all seven had received craniospinal radiotherapy.

### 4 | DISCUSSION

As survival rates for medulloblastoma and CNS-PNET continuously improve, long-term follow-up to diagnose and manage late sequelae becomes imperative. The present study stands out because of the very long median follow-up of 20 years. Also, 79% of survivors accepted study participation and a broad range of organ systems and areas of functioning were examined.

More than two thirds of participants in this study had severe cognitive impairments, including 22% with full-scale IQ scores below 70. The fact that only 10% of participants showed no evidence of cognitive impairments fits well with abundant data correlating medulloblastoma and CNS-PNET treatment to a decline in cognitive function. Somewhat contradictory to previous findings, performance IQ was significantly higher than verbal IQ for the participants. This finding is interesting, but should be interpreted with caution because non-verbal tasks in the test of intelligence used herein (WASI) are less dependent upon reaction time than in the full Wechsler battery. WASI was chosen because it covers the whole age range of participants. Recall of visual information was the most affected domain, and the only where the mean score was in the low range. Memory impairments have been reported in other studies on brain tumour survivors; however, it was a bit surprising that visual memory was more impaired than verbal. This signals the need for further studies to explore the relative importance of visual and verbal memory. The
immature brain has been shown to be more prone to cognitive impairments induced by radiation and the lower the age, the greater the damage potential. This was corroborated by findings in this study; participants who were between two and seven years of age when they received their antineoplastic treatment had the largest impairments. Deficits in decision-making and memory have been related to irradiation of frontal and temporal lobes. Armstrong and colleagues found that patients receiving a dose of more than 30 Gy to the temporal region were at increased risk of memory impairment. As the whole brain is irradiated to doses in this range in medulloblastoma and CNS-PNET patients, it was not surprising that radiotherapy significantly affected memory in patients also in our study. The fact that participants in this study who had not received radiotherapy had a lesser degree of cognitive impairments, further supported this conclusion. The relatively better cognitive outcome in the youngest age group (<2 years at time of first surgery) could also be explained by less use of radiotherapy. Importantly, as epilepsy was shown to impact most cognitive domains, the low frequency of epilepsy in this age group was also a possible explanation for this observation. It is well-known that cerebellar mutism syndrome has a potentially negative impact on cognition. Unfortunately, it was impossible to collect proper data on this syndrome from the medical records of most participants. We were therefore unable to comment on any connection between cerebellar mutism syndrome and long-term cognition.

Sensorineural hearing loss is a possible consequence of treatment with platinum-based chemotherapy such as cisplatin and carboplatin as well as radiotherapy affecting the inner ear. It was therefore a bit surprising to us that only chemotherapy and not radiotherapy significantly contributed to reduced hearing for participants in this study. We found a higher percentage of reduced hearing than what has been seen previously, probably related to the longer median follow-up of the present study. This finding underscores the importance of long follow-up for this patient group and also fits well with accepted knowledge on permanent and delayed onset hearing loss from platinum, with progressive loss occurring many years after completion of therapy.

Many brain tumour patients receiving craniospinal irradiation will with time develop hormonal deficiencies requiring replacement therapy. As expected, the somatotropic axis was the most frequently affected in this study, followed by the thyreotropic. It should be noted that nearly half of patients with a dysregulated thyreotropic axis had peripheral hypothyroidism, probably related to radiotherapy exit dose affecting the thyroid gland. Also, it was interesting to note that chemotherapy significantly contributed to endocrinological dysfunction.

Epileptic seizures are one of the most significant neurological complications of brain tumours, and they can occur at any time from diagnosis to years after completion of treatment. The neoplastic disease itself and antineoplastic treatment may both increase the risk for seizures and the observed 32% of participants with epilepsy in this study fits well with previously published data. The fact that epilepsy significantly affected the majority of cognitive domains highlights the need for special follow-up of this survivor subgroup.

The relative risk for second primary neoplasms in medulloblastoma has been calculated to be 4.6-20. Solid tumours such as glioma and meningioma inside the radiotherapy target volume and thyroid cancer and sarcomas outside have been the most commonly reported. The 30% of participants in this study experiencing second primary neoplasms was higher than what has been found in other studies, probably because of the long follow-up in this study. We cannot explain the seemingly increased risk of second neoplasms in females compared with males. The late occurrence of most second primary neoplasms showed that the risk neither reaches a plateau nor declines the first 10 years after time of first surgery.

In our study, five participants (10%) had developed cataract, well in line with previous publications. Based on the data from Chodick et al, reporting that 36% of cancer survivors who had received a lens dose of 20 Gy or more developed cataract within 5 years after end of radiotherapy, radiation was the most probable cause of cataracts observed.

The appearance of radiation-induced cerebrovascular and cardiovascular toxicity has a typical latency period of more than 10-15 years from time of first surgery. The most common late effects reported are pericarditis, coronary artery disease, diffuse myocardial fibrosis, conduction abnormalities and valvular heart disease. Only the latter was found among participants in this study and only three participants had experienced cerebrovascular and four participants cardiovascular toxicity. This was less frequent than the rate of late-occurring strokes for brain tumour survivors of 267.6 per 100 000 person-years reported by Bowers et al. The explanation for the relatively low rate of cerebrovascular and cardiovascular disease in this study is not obvious. With the long follow-up in this study, we would expect the opposite. It might be speculated that a number of medulloblastoma and CNS-PNET survivors with such toxicity had already succumbed to such disease and could therefore not be included in this study. It is also possible and even likely that, among the 21% of survivors not accepting participation in this study, there was a higher percentage of cerebrovascular and cardiovascular toxicity.

As many as 86% of participants had unmet rehabilitation needs. Knowledge on the effects of rehabilitation for paediatric brain tumour survivors is not very extensive, with the exception of cognition. It should be kept in mind that children and adolescents cured for cancer are at significant risk of unwanted late effects also following the transition into adulthood. We believe that a proper and standardised follow-up of this patient group will enable early and targeted rehabilitation, leading to a better life in terms of education, work, social contact as well as greater independence from family and society in general. Based on findings from this study, we propose that medulloblastoma and CNS-PNET survivors should be followed by a multidisciplinary team in a late effect clinic. To some extent, this follow-up can be targeted, but most if not all survivors should be offered regular follow-up consultations. It is very important that survivors not meeting at planned consultations should be approached for new appointments, simply because several of them have cognitive challenges...
including memory deficits making it hard to remember appointments. Late effect clinics must have or at least be connected to expertise in endocrinology, audiometry, ophthalmology, cardiology, dermatology, neurology, neuropsychology, physiotherapy and ergotherapy. Because of the high risk of secondary neoplasms, the threshold for radiological examinations in general and MRI head in particular should be low. This applies also and not least 10 years or more from the diagnosis of neoplastic disease.

4.1 | Strengths and limitations

The strengths of this study were the cohort design, the exceptionally long median follow-up time of 20 years and the high number of invited persons accepting study inclusion. On the other hand, this was a single institutional study and it is also likely that participants with severe late effects did not accept the invitation to participate. Thereby, it is probable that the late effect frequencies presented here are in fact underestimated. Also, the sample size was small, and the statistical findings should therefore be interpreted with caution.

5 | CONCLUSION

A large and long-standing need for follow-up and rehabilitation for paediatric medulloblastoma and CNS-PNET survivors was revealed; a need that is currently not well met. Most oncologists do not have dedicated time and most general practitioner do not have sufficient knowledge to follow these patients adequately. Based on this study, we propose that such follow-up should be done by specialised clinics with multidisciplinary rehabilitation teams for late effects. 30

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section.