original reports

Nonmetastatic Medulloblastoma of Early Childhood: Results From the Prospective Clinical Trial HIT-2000 and An Extended Validation Cohort

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abstract

PURPOSE The HIT-2000-BIS4 trial aimed to avoid highly detrimental craniospinal irradiation (CSI) in children < 4 years of age with nonmetastatic medulloblastoma by systemic chemotherapy, intraventricular methotrexate, and risk-adapted local radiotherapy.

PATIENTS AND METHODS From 2001-2011, 87 patients received systemic chemotherapy and intraventricular methotrexate. Until 2006, CSI was reserved for nonresponse or progression. After 2006, local radiotherapy was introduced for nonresponders or patients with classic medulloblastoma (CMB) or large-cell/anaplastic medulloblastoma (LCA). DNA methylation profiles of infantile sonic hedgehog-activated medulloblastoma (SHH-INF) were subdivided into iSHH-I and iSHH-II subtypes in the HIT-2000-BIS4 cohort and a validation cohort (n = 71) from the HIT group and Russia.

RESULTS Five years after diagnosis, patients with desmoplastic medulloblastoma (DMB) or medulloblastoma with extensive nodularity (MBEN; n = 42) had 93% progression-free survival (5y-PFS), 100% overall survival (5y-OS), and 93% CSI-free (5y-CSI-free) survival. Patients with CMB/LCA (n = 45) had 37% 5y-PFS, 62% 5y-OS, and 39% 5y-CSI-free survival. Local radiotherapy did not improve survival in patients with CMB/LCA. All DMB/MBEN assessed by DNA methylation profiling belonged to the SHH-INF subgroup. Group 3 patients (5y-PFS, 36%; n = 14) relapsed more frequently than the SHH-INF group (5y-PFS, 93%; n = 28) or group 4 patients (5y-PFS, 83%; n = 6; $P < .001$). SHH-INF split into iSHH-I and iSHH-II subtypes in HIT-2000-BIS4 and the validation cohort, without prognostic impact (5y-PFS: iSHH-I, 73%, *v* iSHH-II, 83%; $P = .25$; n = 99). Intelligence quotient (IQ) was significantly lower in patients after CSI (mean IQ, 90 [no radiotherapy], *v* 74 [CSI]; $P = .012$).

CONCLUSION Systemic chemotherapy and intraventricular methotrexate led to favorable survival in both iSHH subtypes of SHH-activated DMB/MBEN with acceptable neurotoxicity. Survival in patients with non-wingless (WNT)/non-SHH disease with CMB/LCA was not improved by local radiotherapy. Patients with group 4 disease had more favorable survival rates than those with group 3 medulloblastoma.

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ASSOCIATED CONTENT

Data Supplement

Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

Brain tumors are the leading cause of cancer-related death among children in the developing world,[1] and medulloblastoma is one of the most frequent high-grade pediatric brain tumors.[2] Survivors of childhood medulloblastoma frequently suffer from significant long-term sequelae, such as physical impairment, reduced neurocognitive functioning, psychological disability, and poor social outcomes.[3-6] Many late effects show a strong association with radiotherapy given to the entire CNS (craniospinal irradiation [CSI]).[7] Therefore, treatment protocols for childhood medulloblastoma aim at avoiding CSI by combination chemotherapy with or without autologous stem cell

support,[8-12] intraventricular chemotherapy,[8,9] or combination with local radiotherapy.[13]

The current WHO classification divides medulloblastoma into at least 4 molecular entities: medulloblastoma with wingless (WNT) activation, medulloblastoma with sonic hegehog (SHH) activation and TP53 mutation, medulloblastoma with SHH activation/TP53 wild type, and non-WNT/non-SHH medulloblastoma,[14] the latter being further subdivided into molecularly defined subtypes group 3 and group 4.[15] Because of the strong correlation of desmoplastic medulloblastoma (DMB) or medulloblastoma with extensive nodularity (MBEN) with SHH activation,[16-18] the 2016 edition of the WHO classification introduced SHH activation as a requirement for the diagnosis of DMB or MBEN.

The molecular definition of medulloblastoma has strong clinical implications in early-childhood medulloblastoma. Unlike (non-WNT/non-SHH) medulloblastoma with classic medulloblastoma (CMB) or large-cell/anaplastic (LCA) histology, SHH-activated DMB and MBEN of early childhood have a favorable prognosis when treated with radiation-sparing approaches.[8,19] However, survival rates were excellent only for patients with SHH-activated DMB/MBEN if treatment included either intraventricular methotrexate (MTX)[8,9] or high-dose chemotherapy (HDCT).[20,21] Omission of both led to high rates of relapses.[12,22] Additional subtyping using DNA methylation profiling revealed that early-childhood SHH medulloblastoma splits into 2 subtypes (iSHH-I and iSHH-II) with strong prognostic relevance.[12,22] This was suggested before by a large retrospective study,[23] which split early-childhood SHH-activated medulloblastoma into 2 subtypes (SHH-β and SHH-γ), with SHH-β having cytogenetic and clinical features similar to iSHH-I and SHH-γ similar to iSHH-II, and worse prognosis in iSHH-I/SHH-β.

In the HIT-2000 trial, patients < 4 years of age with nonmetastatic medulloblastoma received systemic chemotherapy with intraventricular MTX (HIT-SKK chemotherapy) with the aim to avoid CSI. Beginning January 1, 2006, patients with nonmetastatic CMB/LCA received additional focal radiotherapy. This article describes outcomes of trial patients and analyzes the prognostic relevance of methylation profiling–based subdivision of SHH medulloblastoma and the newly identified iSHH subtypes using the trial cohort and an extended series of patients with nonmetastatic medulloblastoma treated with HIT-SKK chemotherapy.

PATIENTS AND METHODS

Eligibility Criteria of the HIT-2000 Trial and Stratification Into HIT-2000-BIS4

Patients were eligible for the multiarm trial HIT-2000 (ClinicalTrials.gov identifier: NCT00303810) based on the following criteria: age < 21 years with a histologic diagnosis of medulloblastoma, ependymoma or CNS–peripheral neuroectodermal tumor according to the WHO classification valid at the time of inclusion and initial neurosurgical resection between January 1, 2001, and December 31, 2011. A total of 87 patients were eligible and stratified into the treatment scheme HIT-2000-BIS4 (patients with nonmetastatic disease < 4 years of age at surgery). Outcomes of 45 patients treated from 2001 to 2006 were reported previously.[9] The HIT-2000 trial was approved by the central ethics committee in Wuerzburg, Germany. Written informed consent, including consent for molecular analysis, was obtained from the legal representatives of all participants before inclusion.

Staging Procedures in HIT-2000

Tumors from all patients underwent central neuropathologic review according to the WHO classification valid at surgery. Central review of contrast-enhanced presurgical and postsurgical cerebral magnetic resonance imaging (MRI), spinal MRI, and cytospin examination of CSF was available for 72 patients (83%). Subtotal resection was defined as a residual tumor ≥ 1.5 cm^2 on an early postoperative MRI.

Post Hoc Workup of Tumor Tissue

Histopathology was reevaluated for all tumors according to the 2007 WHO classification. One was initially classified as DMB and described accordingly in 2011[9] but was reclassified as CMB after a rereview in 2014. For patients with available tumor material, tumors were classified according to DNA methylation profile using the Heidelberg Brain Tumor Classifier Version 11b4.[24,25] Patients with nonmedulloblastoma histology on rereview or classified as nonmedulloblastoma on DNA methylation profiling were excluded (n = 4; Fig 1). Targeted next-generation sequencing was performed for selected cancer genes,[26] where sufficient tumor DNA could be collected. Methylation profiles of infantile-type SHH-activated medulloblastoma (SHH-INF) were further subclassified by *t*-distributed stochastic neighbor embedding (*t*-SNE) to differentiate between iSHH-I and iSHH-II (Data Supplement, online only).

Treatment in HIT-2000-BIS4

Patients treated until 2006 received 3 cycles of HIT-SKK chemotherapy with intraventricular MTX, followed by 2 cycles of modified HIT-SKK chemotherapy (mSKK).[9] Starting in 2006, patients with CMB or LCA, or patients with DMB/MBEN in incomplete remission received 54 Gy of focal radiotherapy to the tumor bed with a 2-cm safety margin after 3 cycles of HIT-SKK chemotherapy (Fig 1; Data Supplement). Quantification of the cumulative dose of intraventricular MTX was previously defined.[27]

Neuropsychological Assessment

Cognitive function was assessed 5 years after diagnosis using the Würzburger Psychologische Kurzdiagnostik (WUEP-KD) short battery.[28] The Developmental Test of

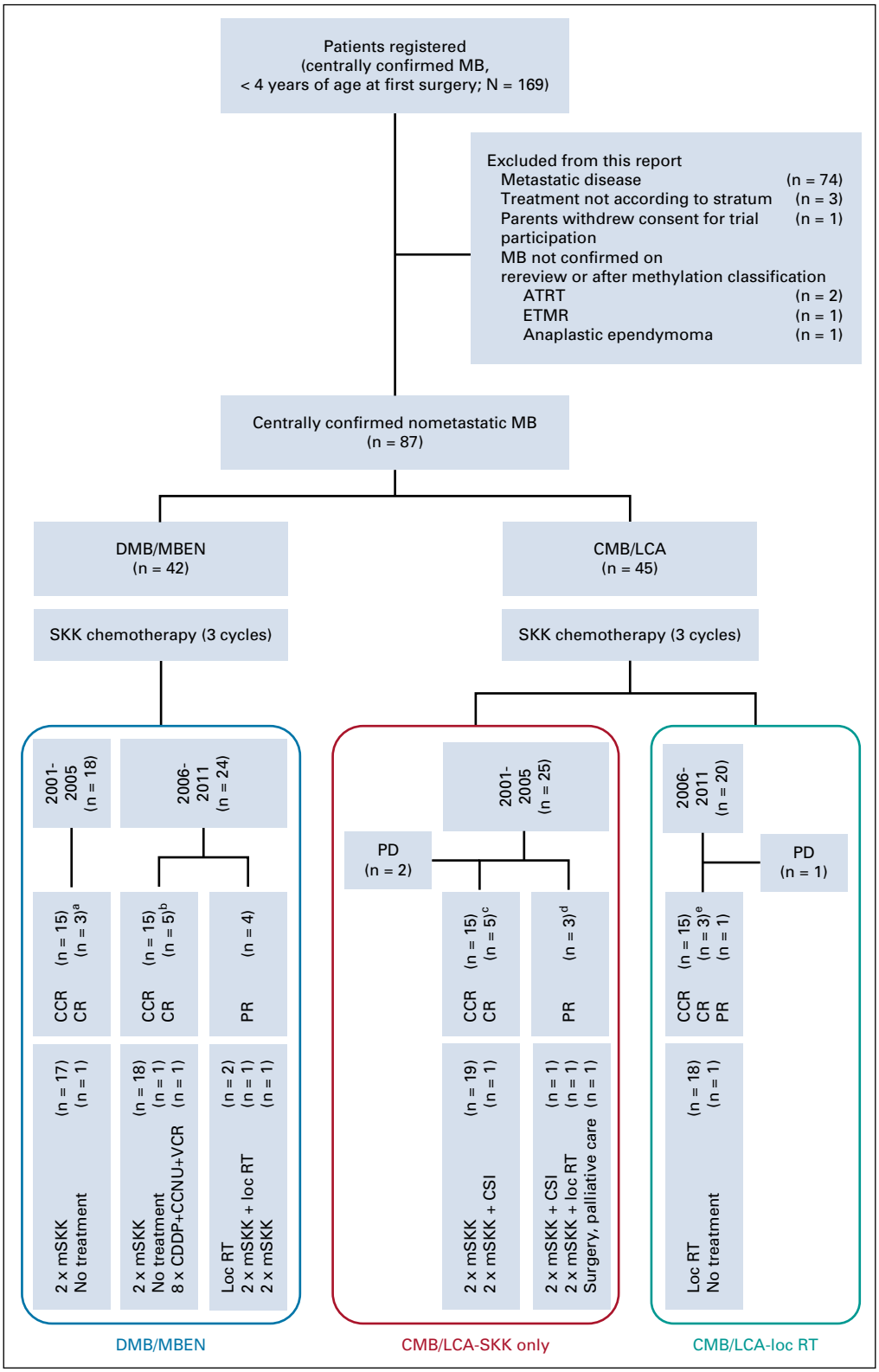


FIG 1. Consort diagram. Patients with desmoplastic medulloblastoma (DMB)/MB with extensive nodularity (MBEN; blue box) are analyzed as one cohort irrespective of date of recruitment. Patients with classic MB (CMB)/large-cell/anaplastic MB (LCA) treated with either chemotherapy alone (red box) or with local radiotherapy after systemic chemotherapy with intraventricular methotrexate (HIT-SKK chemotherapy; teal box). The boxes in the lower section describe response to three cycles of HIT-SKK chemotherapy and further therapy after three cycles. ([a]) One patient in complete response (CR) had no metastase, residual tumor (MOR) > 1.5 cm^2, and two patients in CR had MOR < 1.5 cm^2 on early postoperative magnetic resonance imaging (MRI). ([b]) Four patients in CR had MOR > 1.5 cm^2, and one patient in CR had MOR < 1.5 cm^2 on early postoperative MRI. ([c]) Two patients in CR had MOR > 1.5 cm^2, and three patients in CR had MOR < 1.5 cm^2 on early postoperative MRI. ([d]) Two patients in CR had MOR > 1.5 cm^2, and one patient in CR had MOR < 1.5 cm^2 on early postoperative MRI. ([e]) All three patients in CR had MOR < 1.5 cm^2 on early postoperative imaging. ATRT, atypical teratoid rhaboid tumor; CCR, countinued complete remission; CDDP, cisplatin; CNNU, chlorethyl-cyclohexyl-ntroso-urea; ETMR, embryonal tumor with multilayered rosettes; loc RT, local radiotherapy; mSKK, modified HIT-SKK chemotherapy; PD, progressive disease; PR, partial response; VCR, vincristine.

Visual-Motor Integration (VMI), Raven's Coloured Progressive Matrices (CPM), Kaufman Assessment Battery for Children (KABC) number recall subtest (KABC-NR), and Riddels subtest (KABC-Riddels) were used to describe cognitive function. Overall intelligence quotient (IQ) was defined as the mean value of VMI, CPM, and KABC-NR.[8]

Validation Cohort of Patients With Nonmetastatic SHH-INF

The validation cohort for SHH subtyping consisted of 71 additional patients treated between 1993 and 2018 with nonmetastatic medulloblastoma, classified as SHH-INF by DNA methylation profiling using the Heidelberg brain tumor classifier and treatment according to the HIT-SKK protocols. Patients were treated within HIT study group centers or in the Burdenko Neurosurgical Institute in Moscow, Russia (Burdenko cohort). HIT registries were approved by the ethics committee in Wuerzburg (ClinicalTrials.gov identifier: NCT02238899) and Hamburg (ClinicalTrials.gov identifier: NCT02417324), Germany. The data collection from the Burdenko cohort was approved by the ethics committees of the Burdenko Neurosurgical Institute in Moscow and Heidelberg. Written informed consent was

TABLE 1. Patient Characteristics

	HIT-2000			Validation	
Characteristic	**DMB/MBEN**	**CMB/LCA-SKK Only**	**CMB/LCA-loc RT**	**HIT**	**Burdenko Cohort**
Histology					
MBEN	14	0	0	8	20
DMB	28	0	0	13	28
CMB	0	22	19	2	0
LCA	0	3	1	0	0
Age, years					
Median	1.7	3.0	2.7	1.7	2.0
Range	0.3-3.8	1.8-4.0	1.3-3.8	0.5-3.1	0.5-3.0
Sex					
Female	14	8	7	12	24
Male	28	17	13	11	24
Staging					
GTR	33	20	19	21	48
STR ($\geq$ 1.5 cm^2)	9	5	1	2	0
Methylation profiling result					
WNT	0	1	0	0	0
iSHH-I	15	0	0	14	27
iSHH-II	13	0	0	9	21
SHH, adult	0	1	0	0	0
MB G3	0	6	8	0	0
MB G4	0	3	3	0	0
NA	14	14	9	0	0
Follow-up in patients alive at last follow-up, years					
Median	10.1	13.8	8.0	5.7	3.9
Range	5.5-17.4	10.2-15.7	1.5-12.4	0.7-21.8	1.2-15.0
Total	42	25	20	23	48

NOTE. Data are No. unless otherwise indicated. HIT-2000-BIS4: 87 patients with nonmetastatic medulloblastoma were included in the HIT-2000-BIS4 trial, which stratified patients into those with DMB/MBEN histology, patients with CMB/LCA histology treated with HIT-SKK chemotherapy alone (CMB/LCA-SKK only), or CMB/LCA histology treated with HIT-SKK chemotherapy followed by local radiotherapy (CMB-loc RT). Validation: characteristics of 64 independent patients with nonmetastatic medulloblastoma belonging to the SHH-INF methylation subgroup according to the brain tumor classifier from either the HIT group or the Burdenko Institute who were used as a validation cohort for SHH-INF subtyping.

Abbreviations: CMB, classic medulloblastoma; DMB, desmoplastic medulloblastoma; G3, group 3; G4, group 4; GTR, gross total resection; HIT-SKK, systemic chemotherapy with intraventricular methotrexate; LCA, large-cell/anaplastic medulloblastoma; loc RT, local radiotherapy; MB, medulloblastoma; MBEN, medulloblastoma with extensive nodularity; NA, not available; SHH, sonic hedgehog; SHH-INF, infantile sonic hedgehog-activated medulloblastoma; STR, subtotal resection; WNT, wingless.

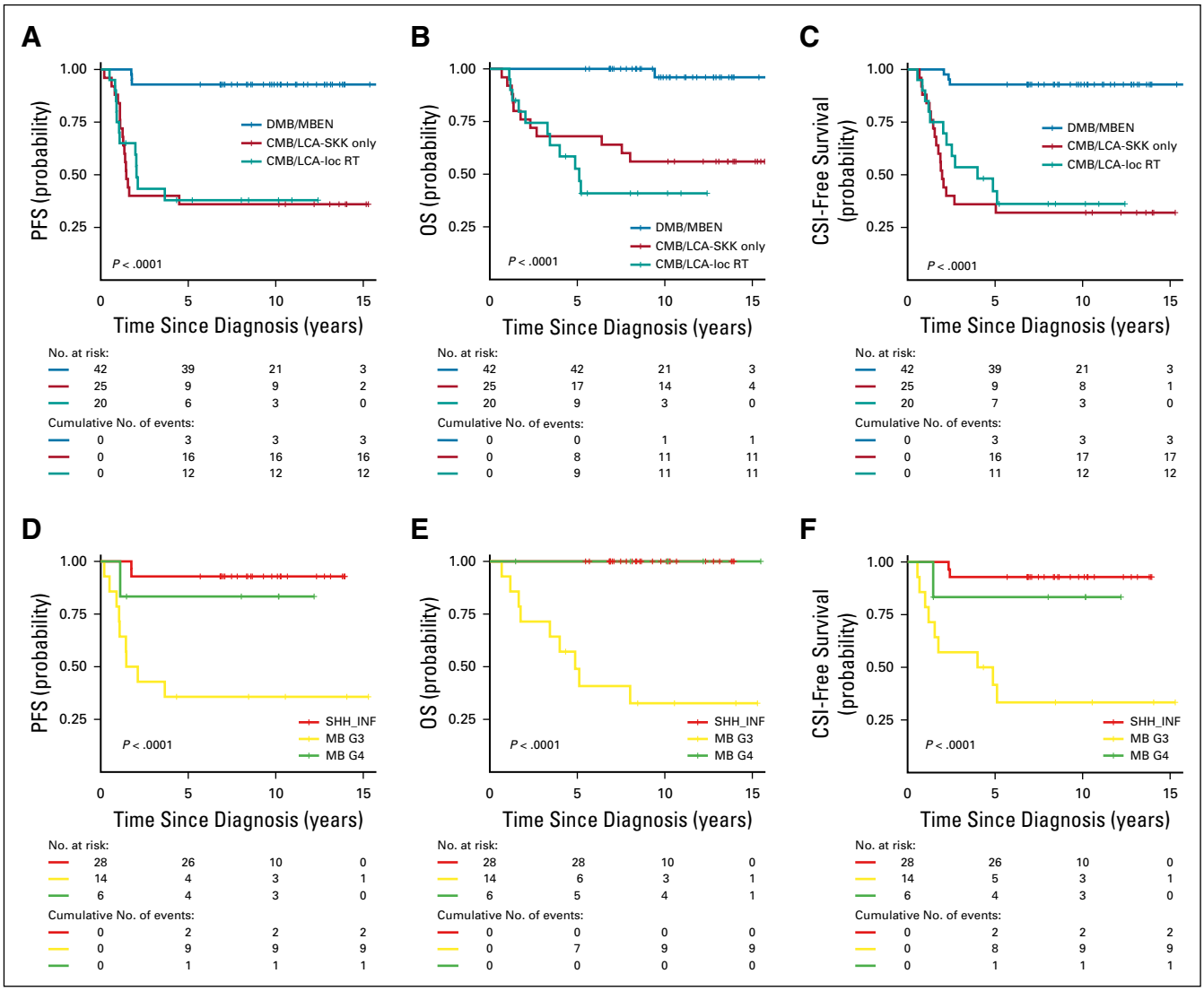


FIG 2. (A) Progression-free survival (PFS), (B) overall survival (OS), and (C) craniospinal irradiation (CSI)–free survival for 87 patients with nonmetastatic medulloblastoma (MB) included in the HIT-2000-BIS4 trial. Forty-two patients with desmoplastic MB (DMB)/MB with extensive nodularity (MBEN) histology had excellent survival (blue line) compared with 45 patients with classic MB (CMB)/large-cell/anaplastic MB (LCA) histology treated with systemic chemotherapy with intraventricular methotrexate (HIT-SKK chemotherapy; red line, n = 25), or HIT-SKK-chemotherapy followed by local radiotherapy (loc-RT; teal line, n = 20). (D) PFS, (E) OS (or PFS after [D]), and (F) CSI-free survival for 48 patients with methylation profiling available according to brain tumor classifier result: infantile sonic hedgehog-activated MB (SHH-INF; red line), group 3 (G3; yellow line), and group 4 (G4; green line). Data for 1 patient with wingless-activated MB and 1 patient with adult/child-type SHH MB are not shown.

obtained from the legal representatives of all participants before inclusion.

Statistics

Progression-free survival (PFS) was defined as the time from the first tumor surgery to progression, relapse, or death. Overall survival (OS) was defined as the time from the first tumor surgery to death from any cause. CSI-free survival was defined as time from the first tumor surgery to craniospinal radiotherapy or death from any cause. All three were censored at last follow-up for patients without an event. Survival rates were estimated using the Kaplan-Meier method. Survival data were compared using the log-rank test, categorical variables were compared using Fisher's exact test, and steady variables were compared using the Welch test. For comparison of neuropsychological test results with the normal population, results were compared using a 1-sample *t* test against a mean value of 100 for IQ scores. All statistical tests were 2-sided. In the HIT-2000 protocol, no statistical endpoint was set for the HIT-2000-BIS4 stratum; therefore, all *P* values are to be considered explorative. The local significance level was set at .05. No adjustment for multiple testing was performed. Analysis and data visualization were performed using

TABLE 2. Pattern of Relapse in Patients With CMB/LCA

Site of Relapse	CMB/LCA-SKK Only (No.)	CMB/LCA-loc RT (No.)
Local only	11	0
Distant only	3	11
Combined	2	1[a]
No relapse	9	8
Total	25	20

NOTE. Of 16 relapses occurring after systemic chemotherapy with intraventricular methotrexate (HIT-SKK chemotherapy) only, 5 had distant metastasis, whereas after addition of local radiotherapy, no patient had a local component.

Abbreviations: CMB, classic medulloblastoma; LCA, large-cell/anaplastic medulloblastoma; loc RT, local radiotherapy.

[a]One patient with combined relapse was stratified to receive loc RT but experienced relapse during SKK chemotherapy before local radiotherapy.

R 3.5.2, with the survival, survminer, ggplot2, conumee, and complexheatmaps packages.

RESULTS

Patient Characteristics

Detailed patient characteristics are provided in Table 1 and Figure 1. Because the therapy algorithm for patients with DMB/MBEN did not substantially change in 2006, all 42 patients with DMB/MBEN are described as one cohort. Median follow-up was 10.6 years (range, 1.5-17.4 years) for the 64 patients alive at the last follow-up. PFS was 64% (95% CI, 55% to 75%) 5 and 10 years after diagnosis for the entire cohort (n = 87); OS was 80% (95% CI, 72% to 89%) and 72% (95% CI, 63% to 83%); and CSI-free survival was 65% (95% CI, 56% to 76%) and 63% (95% CI, 53% to 74%), respectively.

Favorable Outcomes in Patients With Nonmetastatic DMB/MBEN

Forty-two patients with DMB/MBEN initiated therapy according to the protocol. Figure 1 describes therapy details. Three patients had disease progression, on average, 1.7 years (range, 1.72-1.75) after diagnosis and received relapse treatment including CSI, which led to long-term remissions in all patients. Five-year PFS (5y-PFS) was 93% (95% CI, 85% to 100%), 5-year OS (5y-OS) was 100%, and 5-year CSI-free (5y-CSI-free) survival was 91% (95% CI, 85% to 100%; Fig 2).

Second malignancies occurred in 2 patients during follow-up: 1 glioblastoma in a patient who required CSI after relapse and 1 osteosarcoma of the femur in a patient in first complete response. Information on cancer predisposition syndromes was unavailable for both patients. Histologic subtype (DMB *v* MBEN), presence of residual tumor, or cumulative dose of intraventricular MTX did not influence survival in this cohort (Data Supplement).

Local Radiotherapy Does Not Improve Survival in Patients With Nonmetastatic CMB/LCA Medulloblastoma and Induces a Shift From Local to Metastatic Relapses

Twenty-five of 45 patients with CMB/LCA were included before 2006 (CMB/LCA-SKK only; Fig 1) and were stratified to receive mSKK after 3 cycles of HIT-SKK chemotherapy; 20 patients treated after 2006 were stratified to receive local radiotherapy after HIT-SKK chemotherapy (CMB/LCA–local radiotherapy; see Fig 1 for details).

Patients with CMB/LCA showed an 5y-PFS of 37% (95% CI, 25% to 55%), with no difference between patients scheduled to receive mSKK or local radiotherapy ($P = .823$). Five-year OS was 62% (95% CI, 49% to 78%) for the entire group, with no difference between both groups ($P = .336$; Fig 2). Presence of postoperative tumor or cumulative dose of intraventricular MTX did not influence survival (Data Supplement).

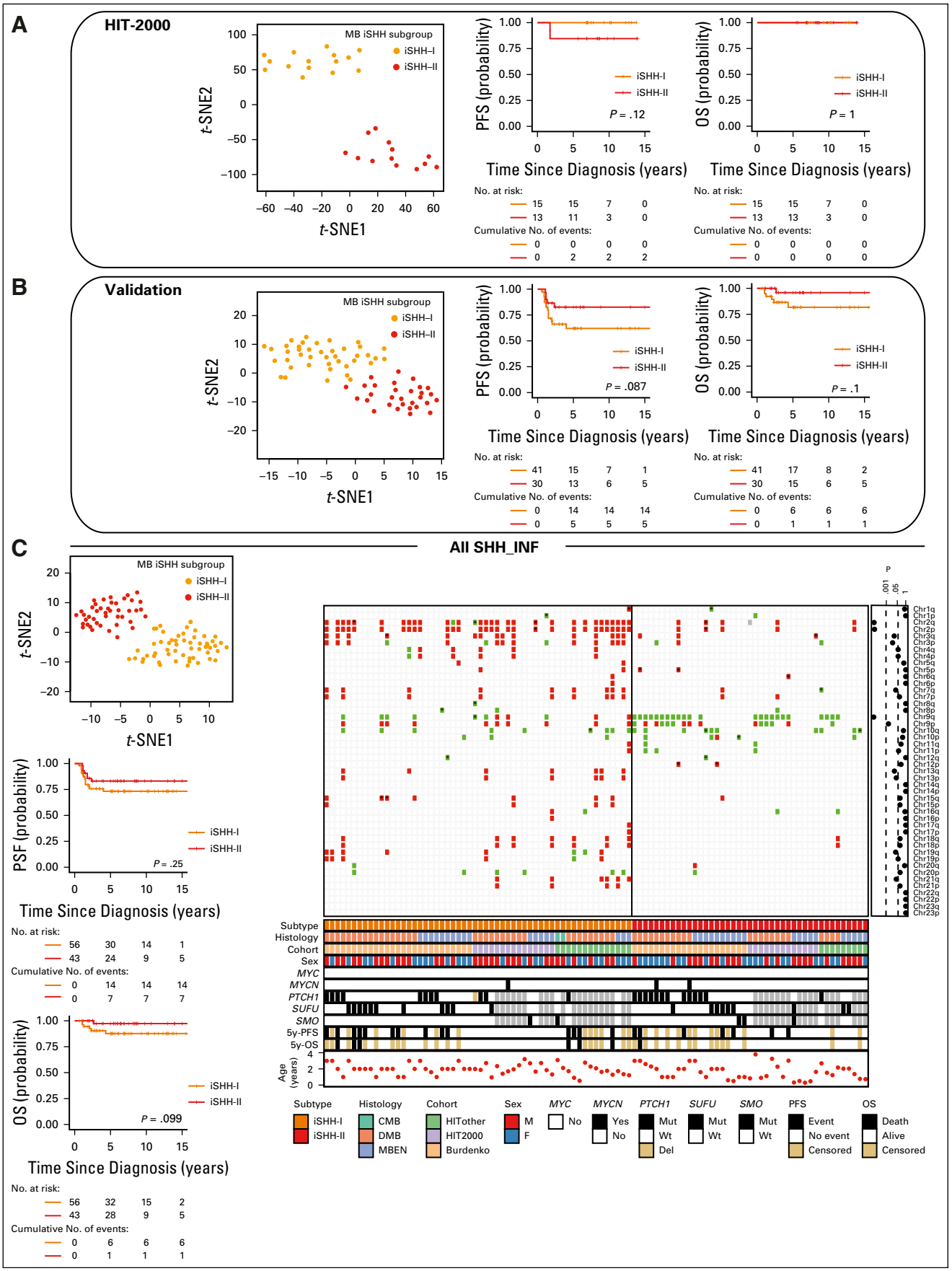
Local radiotherapy induced a shift toward distant relapses with high rates of local tumor control (Table 2). Nine of 11 patients relapsing after local radiotherapy received CSI during relapse treatment, sparing the primary radiotherapy field in many. CSI-free survival was not different between patients treated with or without local radiotherapy ($P = .500$; Fig 2), whereas there was a trend toward shorter postrelapse survival in patients treated with local radiotherapy ($P = .13$; Data Supplement). One second malignancy (acute myeloid leukemia) was reported in a patient that had multiple relapses treated with systemic chemotherapy, including HDCT, CSI, and focal reirradiation.

Excellent Survival in SHH-INF and Group 4 Medulloblastoma

DNA methylation profiling was available for 50 of 87 HIT-2000-BIS4 patients (Table 1). All 28 patients with DMB/MBEN belonged to the SHH-INF methylation subgroup, whereas no SHH-INF profiling results were found among the 22 patients with CMB/LCA. Two patients with group 3 medulloblastoma had an *MYC* amplification, and 1 patient had a gain of 8q including *MYC*. Survival was high in SHH-INF and group 4 medulloblastoma (5y-PFS SHH-INF, 93%; 95% CI, 84% to 100% *v* group 3, 36%; 95% CI, 18% to 72% *v* group 4, 83%; 95% CI, 58% to 100%; $P < .001$; 5y OS SHH-INF, 100% *v* group 3, 49%; 95% CI, 28% to 85% *v* group 4, 100%; $P < .001$; Fig 2). One patient each belonged to the WNT and the adult-type SHH subgroup (Data Supplement).

Methylation Profiling Splits the SHH-INF Subgroup Into 2 Subtypes

t-SNE-based clustering of the 28 SHH-INF profiles from the HIT-2000-BIS4 trial allowed a split into 2 subtypes. Chromosomal aberrations resembled those found by Robinson et al[12] with chromosome 2 gains found predominantly in 1 group ($P = .015$), designated iSHH-I accordingly (n = 15), whereas chromosome 9q losses/



PTCH1 deletions were enriched in the second group (P = .114), designated iSHH-II (n = 13). The only patient with *MYCN* amplification belonged to the iSHH-I subtype. DMB and MBEN histology were equally distributed between iSHH-I and iSHH-II (P = 1.000). Favorable survival rates without survival differences between both subtypes were detected (5y-PFS iSHH-I, 100% *v* iSHH-II, 84.6%; 95% CI, 67% to 100%; P = .121; 5y-OS, 100% in both groups; P = 1.000; Fig 3).

In the validation cohort, the 2 subtypes (iSHH-I, n = 41; iSHH-II, n = 30) were reproduced. The subtypes harbored the same chromosomal aberrations found in the HIT-2000-BIS4 cohort. *PTCH1, SUFU,* and *SMO* mutations were found about equally distributed among both subtypes (Fig 3). *TP53* mutations were absent in all but 1 patient, who harbored a *TP53* variant of uncertain significance, together with a PTCH1 deletion. Again, no survival differences between patients with iSHH-I and iSHH-II were detected (5y-PFS iSHH-I, 62%; 95% CI, 48% to 81% *v* iSHH-II, 83%; 95% CI, 90% to 98%; P = .087; 5y-OS iSHH-I, 82%; 95% CI, 69% to 97% *v* iSHH-II, 96%; 95% CI, 88% to 100%; P = .100; Fig 3). Even after combining the two cohorts (n = 99), neither SHH-INF subtyping (5y-PFS iSHH-I, 73%; 95% CI, 62% to 84% *v* iSHH-II, 83%; 95% CI, 73% to 95%; P = .25; 5y-OS iSHH-I, 88%; 95% CI, 79% to 98% *v* iSHH-II 97%; 95% CI, 92% to 100%; P = .099), nor additional potential molecular or clinical risk factors were prognostic (Data Supplement). Only a trend toward inferior survival in iSHH-I remained.

Neuropsychological Outcome 5 Years After Treatment Correlates With Use of Radiotherapy

Neuropsychological test results 5 years after diagnosis were available for 43 trial participants (Fig 4). Patients who did not receive radiotherapy had scores below normal (median values: CPM, 96, P = .025; VMI, 85, P < .001; KABC-NR, 90, P = .008; KABC-Riddels, 91, P = .014), but were significantly better than those who received CSI during their treatment course (Fig 4). Of patients who did not receive radiotherapy, only 9 of 27 patients had overall IQs lower than 1 standard deviation below average, whereas 5 of 5 patients treated with local radiotherapy and 7 of 13 patients who required CSI fell into this group (P = .010).

DISCUSSION

Balancing the survival benefit of highly effective CSI against its significant detrimental neurocognitive long-term effects remains a dilemma in the treatment of young children with medulloblastoma. Using our strategy that combines systemic chemotherapy with intraventricular MTX, we obtained favorable survival rates, especially in the cohort of SHH-activated early-childhood DMB/MBEN. Importantly, our results suggest that the recently obtained poor outcomes of patients treated with systemic chemotherapy alone[12,13] can be improved by the addition of intraventricular MTX. In contrast to findings by Robinson et al[12] and Cavalli et al,[23] survival rates in our series were high in both recently described subtypes of early-childhood SHH medulloblastoma. This suggests that the higher risk of relapse in the less favorable iSHH-I/SHH-β subtype can be abrogated by the addition of intraventricular MTX to systemic chemotherapy, improving PFS rates from 20%-30%[12,22] to 100% in this trial and 73% in the combined trial/validation cohort. Treatment of SHH-activated early-childhood DMB/MBEN with more intensive chemotherapy including HDCT also led to favorable PFS when examining the low-risk infant medulloblastoma cohort as a whole,[20,21] indicating that this might be an alternative to intraventricular MTX. Still, biologically informed data on children treated with HDCT are scarce so far. However, either intraventricular chemotherapy or HDCT alongside systemic chemotherapy seems to be necessary in radiation-sparing strategies for SHH-INF medulloblastoma.[29] More research is required to compare both strategies.

Despite previously reported excellent outcomes for patients with SHH-INF treated with chemotherapy alone, the 83% 5y-PFS in iSHH-II and 73% 5y-PFS in iSHH-I in our large, combined cohort of patients with SHH-INF argue against treatment de-escalation in this cohort, especially because neurocognitive outcomes in our series were acceptable and seem to be within the range of patients treated with surgery only[30] within Head-Start II[31] or P99703.[20,32] Patients with iSHH-I especially might not represent a true low-risk cohort, and evaluation of additional intensification of therapy may be justified in future trials.

Survival remains disappointing in patients with early-childhood CMB/LCA. Only 37% of patients were alive

FIG 3. Clinical characteristics of 99 patients with nonmetastatic infantile sonic hedgehog-activated (SHH-INF) medulloblastoma (MB) treated with systemic chemotherapy with intraventricular methotrexate (HIT-SKK chemotherapy). (A) *t*-distributed stochastic neighbor embedding (*t*-SNE) clustering for 28 HIT-2000-BIS4 patients only, revealing 2 clusters within the SHH-INF subgroup and associated progression-free survival (PFS) and overall survival (OS), showing no survival difference between these subtypes. (B) *t*-SNE clustering for 71 validation cohort patients revealing 2 stable subgroups for the iSHH subtyping and associated PFS and OS, showing no significant survival difference between the 2 subtypes, with a trend toward lower survival in iSHH-I. (C) *t*-SNE clustering, PFS, and OS for all 99 patients with SHH-INF combined and associated copy number variations and clinical characteristics. Gains are depicted in red, losses in green. Gain of chromosome 2 was predominantly found in iSHH-I, whereas losses on chromosome 9q were enriched in iSHH-II. *P* values on the right indicate (unadjusted) *P* values of Fisher's exact test searching for the difference in gains and/or losses on the corresponding chromosomal arm between iSHH-I versus iSHH-II. (*) Indicates incomplete gains/losses (including small deletions). 5y-OS, 5-year-OS; 5y-PFS, 5-year PFS; CMB, classic MB; del, deletion; DMB, desmoplastic MB; MBEN, MB with extensive nodularity; mut, mutated; wt, wild type.

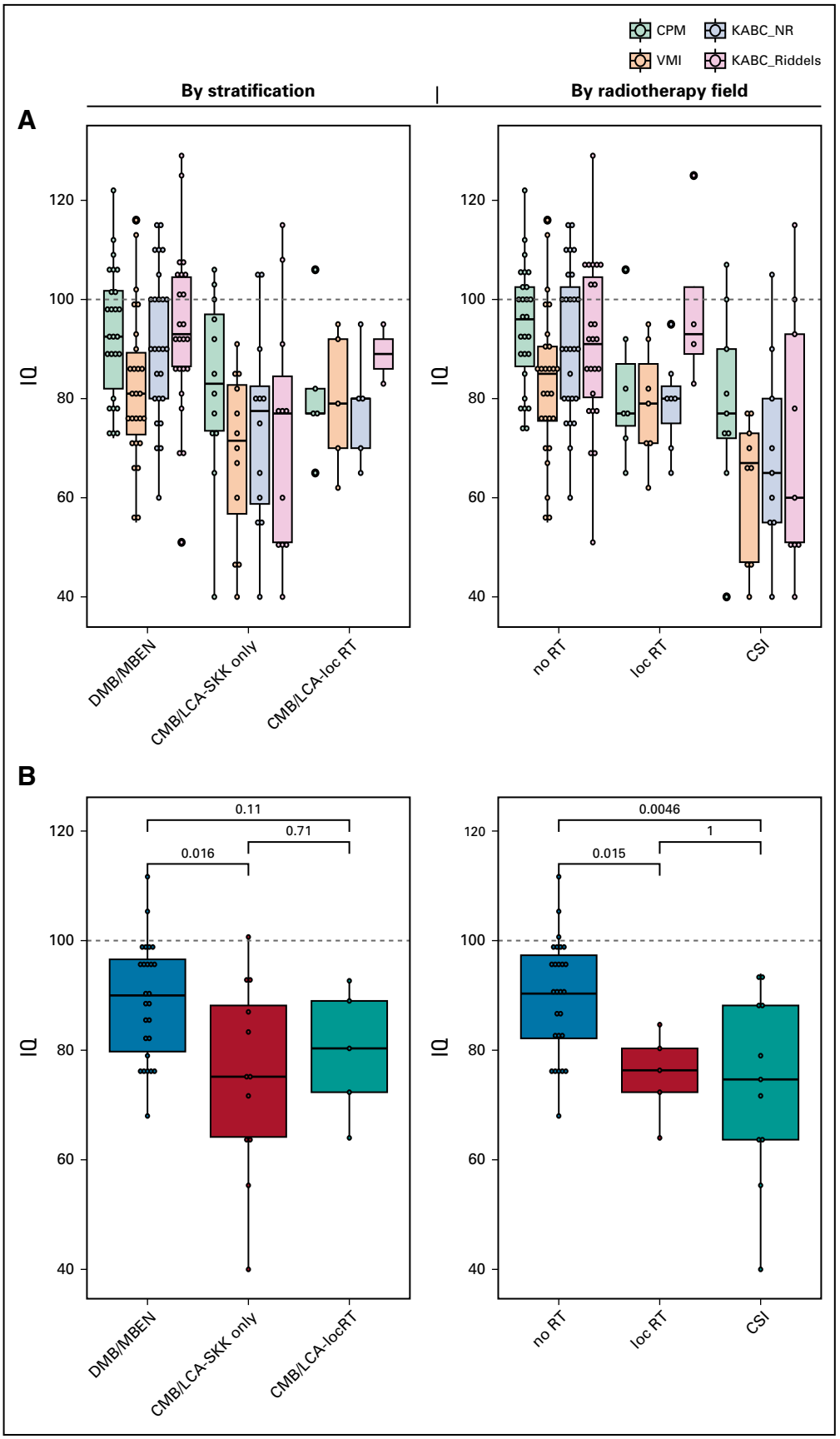


FIG 4. Results of neuropsychological assessment 5 years after diagnosis in 43 surviving patients according to stratification (left panel) and radiotherapy field (right panel). Two patients received both local radiotherapy (loc RT) and salvage craniospinal irradiation (CSI) before testing and are displayed with the CSI group in the right panel. (A) Detailed results of 4 subtests. (B) Sum score of 3 subtests: Raven's Coloured Progressive Matrices (CPM), Developmental Test of Visual-Motor Integration (VMI), and the number recall subtest of the Kaufman Assessment Battery for Children (KABC-NR). Numbers indicate *P* values for intergroup comparisons using the *t* test. CMB, classic medulloblastoma; CSI, craniospinal radiotherapy; DMB, desmoplastic medulloblastoma; IQ, intelligence quotient; KABC-Riddels, the Riddels subtest of the KABC; LCA, large-cell/anaplastic medulloblastoma; MBEN, medulloblastoma with extensive nodularity; loc RT, local radiotherapy; no RT, no radiotherapy.

without relapse 5 years after surgery. Although poor survival has been reported for non-SHH CMB/LCA in almost every series of patients treated with CSI-sparing approaches,[10,12,13,19,20] again, use of intraventricular MTX might be associated with slightly higher PFS compared with conventional chemotherapy alone.[12,13] Using intensified approaches including HDCT, slightly higher PFS rates have been reported,[10,20] although survival without CSI still remained unsatisfactory. The observation of predominantly local relapses in nonmetastatic patients treated with radiation-sparing approaches had encouraged the use of local radiotherapy in primary therapy. Still, its use did not improve survival in any published series.[12,13] Interestingly, almost all patients with CMB/LCA had distant or combined relapses after local radiotherapy.[12,13] One might speculate that local radiotherapy reduced disease burden of the primary tumor and subclinical metastasis in the posterior fossa, leading to a survival advantage of distant subclinical metastasis over local residues.

Neurocognitive outcomes were poor in survivors of CMB/LCA, which was closely related to use of radiotherapy. While this association has repeatedly been documented[20,32] and is independent of the underlying disease,[33] the role of intraventricular or systemic chemotherapy is less clear. Neurocognitive outcomes of patients with brain tumors treated with HDCT but without radiotherapy are comparable to outcomes observed here.[32] Even patients treated with surgery alone show relevant declines in neurocognitive functioning.[30] The effect of intrathecal administration of MTX is controversial in patients with leukemia as well.[33,34] However, concerns remain for the combination of intraventricular MTX with radiotherapy. Despite slightly improved survival in children treated with intraventricular MTX compared with chemotherapy alone, the concerns about neurotoxicity discourage its use in children deemed eligible for salvage radiotherapy in case of early relapse. Treatment approaches using more intensive systemic chemotherapy seem reasonable if radiation-sparing therapy is indicated. Although parents seem to be willing to accept adverse effects if they help to improve survival, especially in high-risk disease,[35,36] in children < 3 years of age, the survival advantage of primary CSI-containing strategies needs to be carefully balanced against neurocognitive sequelae. This must also be taken into account in patients with group 4 medulloblastoma, who displayed favorable PFS in this series. Unlike group 3 patients, most children with group 4 medulloblastoma are > 3 years of age at diagnosis, but PFS was equally poor in both groups in previous CSI-sparing series.[12,20] Because of their age, most patients with group 4 medulloblastoma will also be eligible for upfront CSI-containing strategies. Therefore, additional research on the role of CSI-sparing treatment strategies for early-childhood non-SHH medulloblastoma needs to account for the differences between both subgroups.

The rarity of early-childhood medulloblastoma and the strong influence of the molecular risk profile put a considerable burden on research and optimization of outcomes in this devastating disease. Despite international collaboration and a long recruitment period, we were only able to collect data on 99 patients with nonmetastatic SHH-activated early-childhood medulloblastoma treated according to this protocol. Patients in the validation cohort received treatment under routine conditions with varying standards, which might have contributed to their lower survival. The interpretation of additional rare risk factors (eg, *MYCN* amplification) requires larger cohorts. However, the exclusion of patients with potentially confounding risk factors like metastatic disease or older age, as well as the inclusion of patients receiving homogenous, radiation-sparing therapy selected on biologic criteria, resulted in a well-defined population for comparisons between iSHH-I and iSHH-II. The limitation of patient numbers also applies for patients with (non-WNT/non-SHH) CMB/LCA. Therefore, a historically controlled design was chosen to test the addition of local radiotherapy. Because data suggest no effects, or even adverse effects, of local radiotherapy, additional development of this approach does not seem justified. Future trials should collect high-quality tumor material for biologically based stratification, granting less observer-dependent, more reproducible results and for use in prospective research. International collaboration is required to improve both survival and quality of survival in these highly vulnerable patients.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Nonmetastatic Medulloblastoma of Early Childhood: Results From the Prospective Clinical Trial HIT-2000 and an Extended Validation Cohort

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