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Evaluation of Prognostic Factors and Role of Participation in a Randomized Trial or a Prospective Registry in Pediatric and Adolescent Nonmetastatic Medulloblastoma — A Report From the HIT 2000 Trial

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This study was based on the HIT (HIT = German acronym for brain tumor) registry data. The authors do not own these data and hence are not permitted to share them in the original form (only in aggregate form, eg, publications). At the time of request data were provided by the HIT-MED study center in Hamburg, Germany.

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Abstract

Purpose: We aimed to compare treatment results in and outside of a randomized trial and to confirm factors influencing outcome in a large retrospective cohort of nonmetastatic medulloblastoma treated in Austria, Switzerland and Germany.

Methods and Materials: Patients with nonmetastatic medulloblastoma (n = 382) aged 4 to 21 years and primary neurosurgical resection between 2001 and 2011 were assessed. Between 2001 and 2006, 176 of these patients (46.1%) were included in the randomized HIT SIOP PNET 4 trial. From 2001 to 2011 an additional 206 patients were registered to the HIT 2000 study center and underwent the identical central review program. Three different radiation therapy protocols were applied. Genetically defined tumor entity (former molecular subgroup) was available for 157 patients.

Results: Median follow-up time was 7.3 (range, 0.09-13.86) years. There was no difference between HIT SIOP PNET 4 trial patients and observational patients outside the randomized trial, with 7 years progression-free survival rates (PFS) of 79.5% ± 3.1% versus 78.7% ± 3.1% ($P = .62$). On univariate analysis, the time interval between surgery and irradiation ($\leq$ 48 days vs $\geq$ 49 days) showed a strong trend to affect PFS (80.4% ± 2.2% vs 64.6% ± 9.1%; $P = .052$). Furthermore, histologically and genetically defined tumor entities and the extent of postoperative residual tumor influenced PFS. On multivariate analyses, a genetically defined tumor entity wingless-related integration site-activated vs non-wingless-related integration site/non-SHH, group 3 hazard ratio, 5.49; $P = .014$) and time interval between surgery and irradiation (hazard ratio, 2.2; $P = .018$) were confirmed as independent risk factors.

Conclusions: Using a centralized review program and risk-stratified therapy for all patients registered to the study center, outcome was identical for patients with nonmetastatic medulloblastoma treated on and off the randomized HIT SIOP PNET 4 trial. The prognostic values of prolonged time to RT and genetically defined tumor entity were confirmed.

Introduction

The HIT (German acronym for brain tumor) treatment network is a joint working group for childhood brain tumors of the German Society for Pediatric Oncology and Hematology (GPOH). It is a unique collaborative project of German-speaking countries (Germany, Austria and Switzerland) to offer central review and treatment recommendations in dedicated central review institutions. The aims are to perform research projects and clinical trials but also to improve treatment and outcome for all patients even outside randomized trials.

One important research project was the HIT 2000 trial, which among others included patients with nonmetastatic medulloblastoma (MB) aged 4 to 21 years (HIT AB4 stratum). Parts of this stratum were the German cohort of the HIT SIOP PNET 4 trial (ClinicalTrials.gov identifier: NCT01351870). Patients not eligible for the HIT SIOP PNET 4 trial could be registered as observational patients and receive centrally reviewed and risk-stratified treatment.

Protocols combined surgery, craniospinal irradiation (CSI) with a boost to the posterior fossa or the tumor site, and chemotherapy.[1,2] Various factors influencing outcome in patients with MB have been identified, for example, histology or residual tumor. Others are still a matter of debate, for example, time from surgery to radiation therapy (RT).[3,4-9] Moreover, definition of histologically and genetically defined MB entities (former molecular subgroups) in the 2016 World Health Organization (WHO) classification of central nervous system tumors changed our view on MB.[10-13]

The primary purpose of this study was to compare outcomes of patients with nonmetastatic MB treated with upfront RT during the HIT 2000 protocol era included in the randomized HIT SIOP PNET 4 trial with patients not included in the trial. We sought to achieve an equivalent outcome for patients treated outside the trial by using a centralized review program for the nontrial observational patients. Furthermore, we intended to confirm prognostic factors, for example, the time from surgery to RT, in a large retrospective cohort.

Methods and Materials

Patient selection

Between 2001 and 2011, 419 patients were registered to the HIT 2000 trial. According to inclusion criteria as specified in Figure 1, 382 patients were selected. The cohort does not match with the standard risk group as used today, because patients with high-risk features (residual disease > 1.5 cm^2, large cell anaplastic) were also included.[14] The cohort was divided into 2 treatment eras, the HIT SIOP PNET 4 era (2001-2006) and the era beyond the trial (2007-2011) and according to participation in the trial as shown in the consort diagram (Fig 1). Central review of pre- and postoperative magnetic resonance imaging (MRI), spinal MRI, and cerebrospinal fluid cytology was offered for all patients either upfront or retrospectively and was completely available for 91.1% of

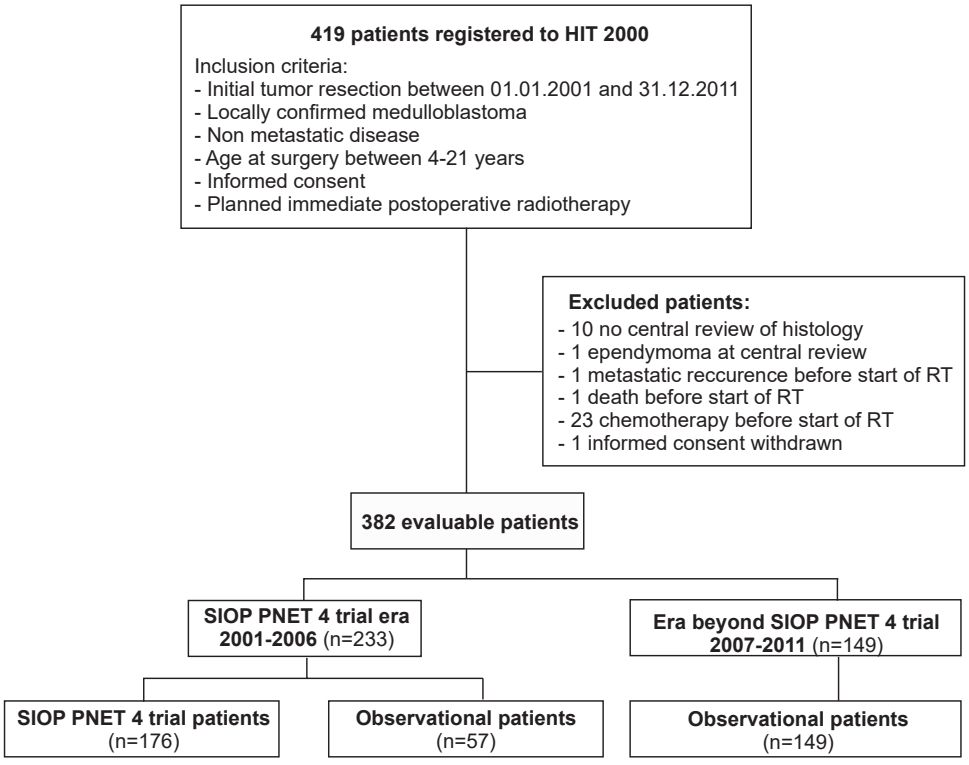

Figure 1 Consort diagram of the present study.

Table 1 Clinical characteristics of the entire cohort itemized by study/observational patients and treatment era

	HIT SIOP PNET 4 era All patients (n = 233)	HIT SIOP PNET 4 era Trial only (n = 176)	HIT SIOP PNET 4 era Non-trial (n = 57)	After HIT SIOP PNET 4 (n = 149)
Median follow-up time of survivors (years)	9.3 (0.2-13.9)	9.4 (0.2-13.9)	9.1 (0.3-12.8)	4.7 (0.1-8.0)
Male	141	110	31	98
Female	92	66	26	51
Median age at surgery (years) (range)	9.3 (4.0-20.8)	9.4 (4.0-20.8)	8.7 (4.2-19.5)	9.7 (4.1-20.9)
Residual tumor				
<1.5 cm^2	193	150	43	137
≥ 1.5 cm^2	22	20	2	10
Not documented	18	6	12	2
Histologically defined entity				
D/N	31	23	8	21
Classic	193	150	43	115
LC/A	9	3	6	13
Genetically defined entity				
WNT-activated	26	23	3	12
SHH-activated (TP53-wt and mutant)	11	10	1	12
non-WNT/non-SHH, group 3	11	10	1	13
non-WNT/ non-SHH, group 4	50	48	2	22
Not evaluable/not done	135	85	50	90
RT				
STRT23.4 Gy	99	85	14	119
HFRT36.0 Gy	84	83	1	0
STRT35.2 Gy	43	7	36	13
Other	7	1	6	1
Not documented	0	0	0	16
Time to RT (days) (range)	33 (11-89)	33 (15-80)	32 (11-89)	32 (16-63)
Duration RT (days) (range)	46 (30-158)	45 (30-79)	46 (37-158)	43 (21-90)
Tumor progressions	51	38	13	29
Deaths	44	32	12	25

Abbreviations: D/N = desmoplastic medulloblastoma; HFRT = hyperfractionated RT; LC/A = large cell/anaplastic medulloblastoma; RT = radiation therapy; STRT23.4 = standard fractionated reduced dose craniospinal RT; STRT35.2 = standard fractionated high dose craniospinal RT; WNT = wingless-related integration site.

patients. Central review of histopathology according to the 2007 WHO classification was available for all patients and was reclassified for patients diagnosed before 2007.[15]

The HIT 2000 trial was approved by the ethics committee Wuerzburg. All patients or their legal representatives signed informed consent before registration to the HIT 2000 trial.

Adjuvant treatment

All patients received postoperative RT according to 1 of these protocols:

Hyperfractionated RT (HFRT)

Total craniospinal dose 36 Gy, followed by a boost to the whole posterior fossa to 60 Gy and further boost to 68 Gy to the tumor bed in 2-daily, 10-weekly fractions of 1.0 Gy (34 days with RT, RT duration without interruptions 46-48 days).

Standard fractionated reduced dose craniospinal RT (STRT23.4)

Total craniospinal dose 23.4 Gy followed by a boost to the posterior fossa to 54.0 Gy in 1-daily, 5-weekly fractions of 1.8 Gy (30 fractions, RT duration without interruptions 40-42 days).

Standard fractionated high dose craniospinal RT (STRT35.2)

Total craniospinal dose of 35.2 Gy in 1-daily, 5-weekly fractions of 1.6 Gy followed by a boost to the posterior fossa to 55.2 Gy in 1-daily, 5-weekly fractions of 2.0 Gy (in total 32 fractions; RT duration without interruption 44-46 days).

Table 2 Assessment of potential risk factors for PFS according to the Kaplan-Meier method and log rank test

	n	7-year PFS (%)	7-year OS (%)	PFS *P*
All patients	382	80.3 ± 3.1%	80.2 ± 2.3	
Age at diagnosis				
<5 y	23	77.3 ± 8.9	76.2 ± 9.3	.460
5-9 y	190	82.1 ± 2.8	82.7 ± 3.0	
10-14 y	102	75.9 ± 4.6	79.8 ± 4.6	
>14 y	67	75.1 ± 5.6	74.1 ± 6.4	
Sex				
Male	239	77.7 ± 2.8	80.1 ± 2.9	.190
Female	143	81.3 ± 3.4	80.4 ± 3.7	
HIT SIOP PNET 4 trial participation				
HIT SIOP PNET 4 trial patient	176	79.5 ± 3.1	81.0 ± 3.0	.620
Observational patient	206	78.7 ± 3.1	79.2 ± 3.4	
Treatment era				
During HIT-SIOP PNET 4 trial era	233	79.5 ± 2.7	81.9 ± 2.6	.710
After HIT-SIOP PNET 4 trial era	149	79.4 ± 3.5	79.2 ± 4.0	
Treatment era (only STRT23.4)				
During HIT-SIOP PNET 4 trial era	99	76.7 ± 4.4	81.2 ± 4.1	.858
After HIT-SIOP PNET 4 trial era	119	79.9 ± 3.8	79.4 ± 4.5	
RT protocol				
HFRT36 Gy (1)	84	82.6 ± 4.2	82.1 ± 4.3	.797
STRT35.2 Gy (2)	56	79.6 ± 5.5	82.5 ± 5.4	(1) vs (2): .702
STRT23.4 Gy (3)	218	77.8 ± 3.0	79.2 ± 3.2	(1) vs (3): .641
				(2) vs (3): .998
RT protocol (only classic/D/N, residual tumor ≤1.5 cm^2, and time from surgery to RT <49 d)				
STRT35.2 Gy	30	82.4 ± 7.2	85.3 ± 6.8	.952
STRT23.4 Gy	171	81.3 ± 3.0	81.2 ± 3.4	
RT protocol (only LC/A)				
STRT35.2 Gy	13	84.6 ± 10.0	83.1 ± 11.0	.288
STRT23.4 Gy	5	53.3 ± 24.8	53.3 ± 24.8	
Time from surgery to RT start				
<49 d	342	80.4 ± 2.2	80.5 ± 2.4	.052
≥49 d	32	64.6 ± 9.1	73.6 ± 8.8	
Duration of RT only STRT 23.4 Gy				
≤49 d	206	78.6 ± 3.0	79.4 ± 3.3	.261
>49 d	12	64.3 ± 14.6	74.1 ± 12.9	
Residual tumor				
≤1.5 cm^2	330	80.5 ± 2.3	80.8 ± 2.4	.045
>1.5 cm^2	32	63.7 ± 8.8	70.6 ± 9.2	
Histologically defined entity				
Classic (1)	308	81.8 ± 2.3	82.6 ± 2.4	.090
D/N (2)	52	66.7 ± 7.0	70.3 ± 7.2	(1) vs (2): .042
LC/A (3)	22	70.8 ± 10.3	69.5 ± 10.6	(1) vs (3): .263
				(2) vs (3): .830
Genetically defined entity				
WNT-activated (1)	38	93.2 ± 4.7	91.5 ± 5.8	.092
SHH-activated (TP53-wt and mutant) (2)	23	73.4 ± 11.1	76.9 ± 11.1	(1) vs (2) .083
non-WNT/non-SHH, group 3 (3)	24	70.8 ± 9.3	67.8 ± 10.4	(1) vs (3): .011
non-WNT/non-SHH, group 4 (4)	72	81.5 ± 4.7	81.6 ± 5.1	(1) vs (4): .161

Abbreviations: D/N = desmoplastic medulloblastoma; HFRT = hyperfractionated RT; LC/A = large cell/anaplastic medulloblastoma; OS = overall survival; PFS = progression-free survival; RT = radiation therapy; STRT23.4 = standard fractionated reduced dose craniospinal RT; STRT35.2 = standard fractionated high dose craniospinal RT; WNT = wingless-related integration site.

HIT SIOP PNET 4 trial patients were randomized to receive STRT23.4 or HFRT.[1] If inclusion criteria of the HIT SIOP PNET 4 trial were not fulfilled, patients were included in an observational study and received RT according to individual considerations (STRT35.2 or STRT23.4). In the post-HIT SIOP PNET 4 era, STRT35.2 was recommended for patients with large cell/anaplastic histology and STRT23.4 for all other patients.

Vincristine during RT and 8 blocks of adjuvant chemotherapy (cisplatin, lomustine, vincristine) were administered as previously described.[1,16]

Genetically defined MB entities

Assignment to MB entities was based on DNA-methylation profiling or a minimal methylation classifier and were published previously for subcohorts.[4,17-19] Additionally, wingless-related integration site (WNT)-activation was documented by the demonstration of nuclear accumulation of β-catenin protein and activating *CTNNB1* mutation also in the absence of further profiling.[4] In contrast to the WHO classification, all SHH-activated tumors were grouped together (SHH-activated TP53-wildtype and mutant) because data on TP53 mutation were not available.[12,13]

Statistics

Median follow-up time was calculated according to the method of Schemper and Smith.[20] For progression-free survival (PFS), events were defined as radiographic or cytologic evidence of progression or relapse, or death of any cause. For overall survival (OS) death by any cause was taken into account. Survival times were calculated from the date of surgery onwards. Time to RT was defined as interval from first tumor surgery to first day of RT. The Kaplan–Meier method was used to estimate OS and PFS rates. Survival estimates were compared with the log rank test. For Cox regression analysis, all factors associated with $P < .1$ on univariate analysis were forwarded to a multivariable analysis without variable selection. Two separate multivariate Cox regression models were generated, depending on availability of molecular data. Associations between variables were examined using χ^2 tests. All statistical tests were considered explorative. Because of the explorative design and multiple testing we did not define a P value for significance in the univariate analyses. Results with P value $< .05$ in the multivariate models were defined as significant. All analyses were performed using the Statistical Package for Social Sciences, version 24 (SPSS Inc, Chicago, IL).

Results

Patients' characteristics

Characteristics of the 382 eligible patients treated in 63 institutions are provided in Figure 1 and Table 1. One hundred seventy-six patients (46.1%) participated in the international HIT SIOP PNET 4 trial.[1,21] All patients underwent initial surgery. A second surgery before RT was performed in 17/382 (4.5%) patients. Median age was 9.4 years (range, 4.0-20.9 years).

Median follow-up time in the present study was 7.3 (range, 0.09-13.86) years for all patients and 9.4 (range, 0.22-13.86) years for the HIT SIOP PNET 4 patients. Eighty patients (20.9%) showed disease progression or relapse, and 69 patients died (18.1%). PFS rates at 3, 5, and 7 years was 83.9% ± 1.9%, 80.3% ± 2.1%, and 79.0% ± 2.2%. The corresponding OS rates were 91.4% ± 1.5%, 86.5% ± 1.8%, and 80.2% ± 2.3%.

Effect of participation in the randomized HIT SIOP PNET 4 trial

There was no difference between HIT SIOP PNET 4 trial patients and observational patients outside the randomized trial (7 years PFS 79.5% ± 3.1% vs 78.7% ± 3.1%; $P = .62$; Table 2; Fig 2A,B). To evaluate potential biases due to different treatment eras or RT protocols, we compared patients treated during versus after the HIT SIOP PNET 4 trial recruitment era and found no differences in PFS, either for the whole cohort (79.5% ± 2.7% vs 79.4% ± 3.5%; $P = .710$) or for the subgroup of patients treated with STRT23.4 Gy (76.7% ± 4.4% vs 79.9% ± 3.8%; $P = .858$).

Analyses of prognostic factors in MB

Results of univariate comparisons of multiple potential prognostic factors are presented in Table 2. Subsequent multivariate analyses were done including all factors with $P < .1$ in the univariate analyses (histologically/genetically defined entity, residual tumor, time from surgery to RT start) and in 2 separate cohorts based on the availability of genetic annotation data (Table 3). These factors were identified as of interest:

Time from surgery to RT start

Time to RT was known in 374 patients (97.9%). The median time to RT was 32 days (range, 11-89 days). The protocol defined start of RT within 29 days postsurgery, which was achieved in 120/374 patients (32.1%). Thirty-two patients (8.6%) started RT 49 days after surgery or later. Time to RT ≥ 49 days showed a trend for worse PFS in univariate testing (64.6% ± 9.1%

Table 3 Multivariate analysis of risk factors for PFS: Two multivariable regression analyses were done, 1 for all patients but not considering genetically defined MB entity (cohort 2) and 1 considering only patients with genetical annotation (cohort 1)

	Cohort 1 (n = 147)				Cohort 2 (355)			
	Factors included: Histology, residual tumor, time from surgery to RT start, genetically defined entity				Factors included: Histology, residual tumor, time from surgery to RT start			
Category	n	Hazard ratio	95% CI	*P*	n	Hazard ratio	95% CI	*P*
Histologically defined entity								
Classic	117	Ref.			286	Ref.		
D/N	24	1.00	0.25-4.02	.996	48	**2.01**	**1.12-3.60**	**.019**
LC/A	6	0.96	0.12-7.57	.971	21	1.95	0.83-4.58	.125
Residual tumor								
≤1.5 cm^2	137	Ref.			325	Ref.		
>1.5 cm^2	10	2.69	0.90-8.08	.078	30	1.89	0.97-3.69	.061
Time from surgery to RT start								
<49 d	132	Ref.			323	Ref.		
≥49	15	**3.460**	**1.31-9.11**	**.012**	32	**2.208**	**1.15-4.26**	**.018**
Genetically defined entity								
WNT-activated	35	Ref.			Data not available			
SHH-activated (TP53-wt and mutant)	21	4.76	0.73-31.20	.104				
non-WNT/non-SHH, group 3	23	**5.49**	**1.42-21.24**	**.014**				
non-WNT/non-SHH, group 4	68	2.213	0.61-8.01	.226				

Abbreviations: CI = confidence interval; D/N = desmoplastic medulloblastoma; LC/A = large cell/anaplastic medulloblastoma; MB = medulloblastoma; PFS = progression-free survival; RT = radiation therapy; WNT = wingless-related integration site.
Significant differences are printed in bold.

vs 80.4% ± 2.2%; $P = .052$, Fig 2C). However, it was an independent risk factor on PFS in both cohorts of the multivariate analysis (hazard ratio [HR], 2.01; $P = .012$/HR, 3.46; $P = .018$).

Duration of RT

The duration of RT ranged between 21 and 158 days (median, 44 days). The proportion of patients with duration of RT > 49 days varied between the different treatment protocols and was 5.5% (STRT23.4), 19.6% (STRT35.2), and 40.5% (HFRT) (χ^2 $P < .01$). Duration of RT (≤ 49 days vs > 49 days) had no effect on PFS for the whole cohort (78.9% ± 2.4% vs 78.8% ± 5.5%; $P = .931$). A trend for inferior PFS for RT duration > 49 days was seen when analysis was restricted to patients with STRT23.4 7-year PFS (64.3% vs 78.6%; $P = .261$). However, protracted RT was only given in 12 patients.

Residual tumor ≥1.5cm²

Central review of the postoperative MR imaging was available in 364 cases (95.3%). Complete tumor resection or residual tumor <1.5 cm^2 was achieved in 330 of 362 patients (91.2%). In 20 patients, the extent of resection could not be assessed. Postoperative residual tumor influenced PFS in the univariate analysis (80.5% ± 2.3% vs 63.7% ± 8.8%; $P = .045$), but the extent of resection was not maintained as an independent risk factor on multivariate analysis ($P = .061$/$P = .078$).

Histologically defined tumor entity

Central histologic review revealed classic MB (classic) in 308 (80.6%), desmoplastic MB (D/N) in 52 (13.6%), and large cell/anaplastic MB (LC/A) in 22 cases (5.8%). Univariate group comparisons of the histologically defined entities showed different PFS between classic and D/N (81.8% ± 2.3% vs 66.7% ± 7.0%; $P = .042$). Classic histology versus D/N remained an influencing factor on PFS in cohort 2 (n = 355) of the multivariate analyses but lost its effect after adjustment for additional genetical annotation (cohort 1, n = 147).

We additionally evaluated the effect of RT strategy in LC/A. With todayés risk stratification, LC/As are considered high-risk and usually not eligible for an STRT23.4 strategy. Among the 22 patients with LC/A, the 5 patients treated with reduced dose CSI 23.4 Gy had a trend for poorer PFS than those treated with STRT35.2 (53.3% ± 24.8% vs 84.6% ± 10.0%; $P = .288$). Interestingly, there were 2 patients with WNT-activated MB among patients with LC/A MB (1 STRT23.4, 1 HFRT). Both were free of an event after more than 10 years of follow-up.

Genetically defined tumor entity

Results of subsequent molecular/epigenetic analyses were available for 157 patients (41.1%). Non- WNT/non-SHH MBs, found in 56.4% (with subgroups: group 4, 45.9%; group 3, 15.3%), were most frequent, followed by WNT-activated (24.2%) and SHH-activated tumors

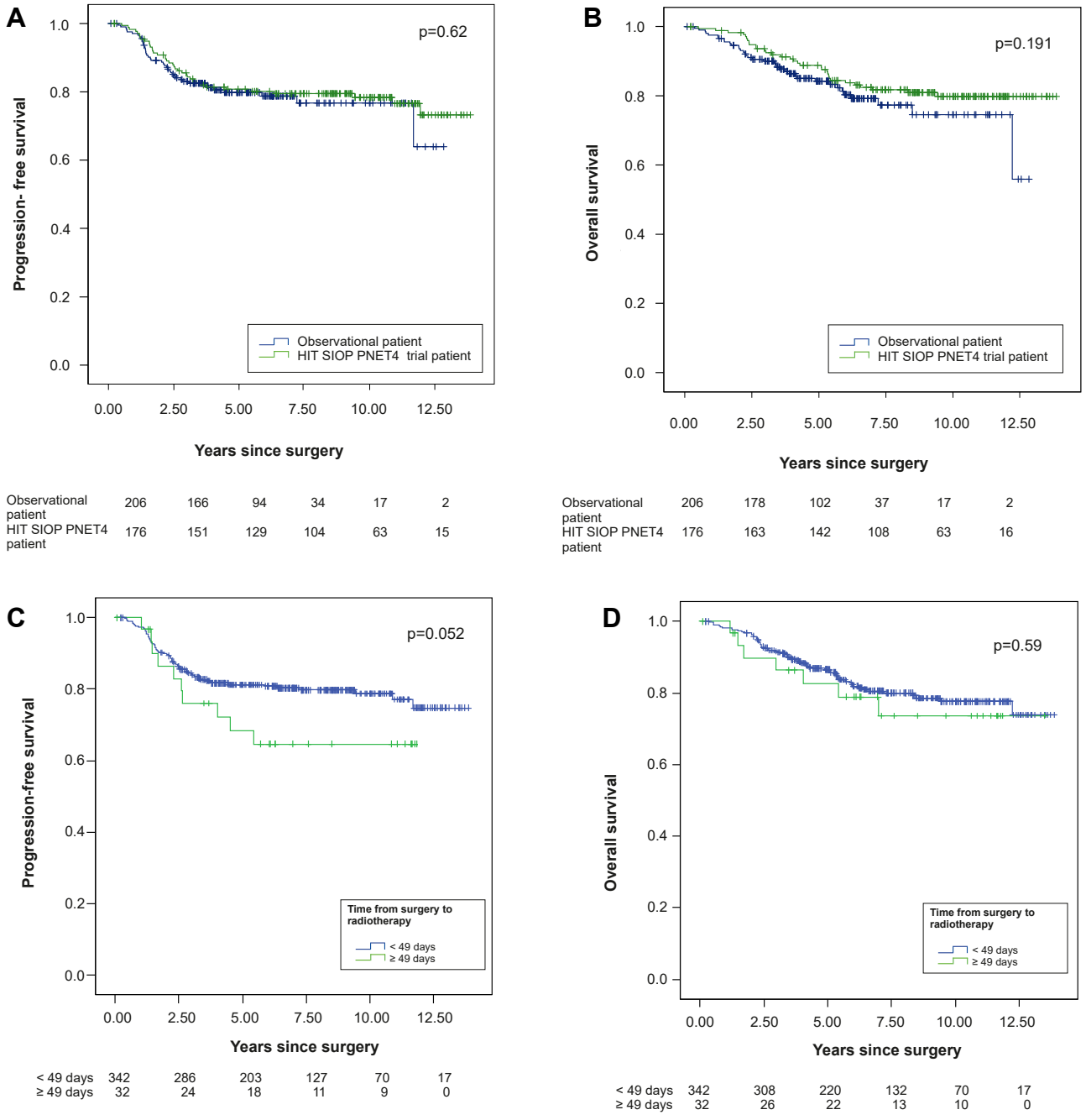

Figure 2 Kaplan-Meier plots of progression free survival (PFS) and overall survival (OS): (A) PFS and (B) OS of patients treated within (trial patients) versus outside (observational patients) the HIT-SIOP PNET 4 trial. (C) PFS and (D) OS according to time from surgery to start of radiation therapy (RT) $<$ 49 days versus $\geq$ 49 days. (E) PFS and (F) OS according to genetically defined entity (all SHH-activated tumors were grouped together [SHH-activated TP53-wildtype and mutant] because data on TP53 mutation were not available).

(14.6%). Univariate comparisons of the different molecular/epigenetic subgroups revealed differences in PFS between WNT-activated and non-WNT/non-SHH, group 3 (93.2% $\pm$ 4.7% vs 70.8% $\pm$ 9.3%; $P = .011$; Fig 2E,F) This difference was also maintained in the multivariate analysis (HR, 5.49; $P = .014$).

We additionally evaluated the subgroup of WNT-activated MBs (n = 38; 25 STRT23.4, 3 STRT35.2, 8 HFRT, 2 RT regimen not documented). The only 2 relapses occurred among patients who did not fulfill inclusion criteria for the current SIOP PNET 5 MB Low Risk trial (WNT; age $<$ 16; no residual

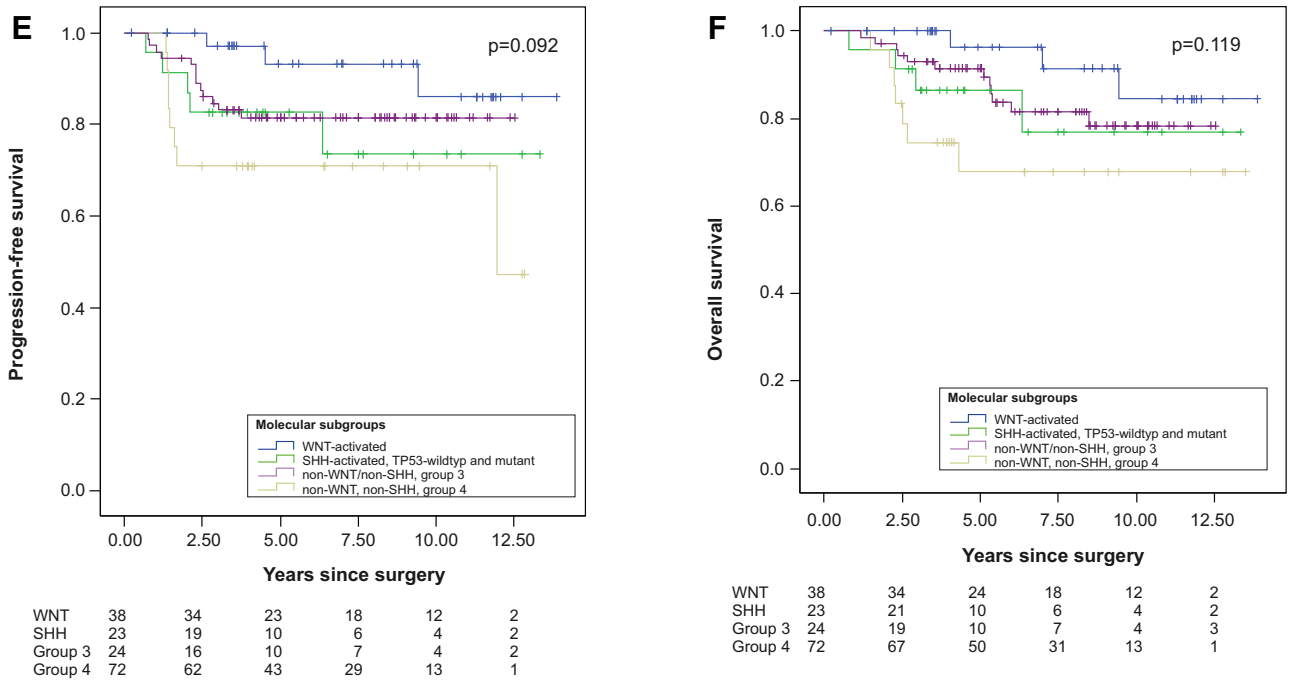

Figure 2 *(Continued).*

tumor > 1.5 cm^2; RT start ≤ 40 days after surgery). One patient was 16 years old, had residual tumor > 1.5 cm^2 and started RT at day 57 after surgery. The second patient started RT at day 54 after surgery. None of the 18 patients who would have fulfilled inclusion criteria of the low risk arm showed progressive disease, but 2 patients developed secondary malignancies (1 melanoma and 1 glioblastoma) 8.2 and 8.6 years after diagnosis, respectively. Patients, who were potentially suitable for the low risk arm had a 7 years PFS and OS of 100% as compared with 80.5 ± 4.8 ($P = .174$) and 78.1 ± 5.6 ($P = .216$) for patients, who fulfilled the criteria of the standard risk arm (n = 77, non-WNT/non-SHH [group ¾] or SHH-activated tumors [no data on *TP53* mutational status], no residual tumor > 1.5 cm^2; RT start ≤40 days after surgery).

Discussion

In the present analysis we assessed patient characteristics, treatment, outcome, and possible risk factors of a large cohort of nonmetastatic MB in children and adolescents. Approximately half of the patients were enrolled into the European HIT SIOP PNET 4 trial. Outcome was reported previously, however, with a shorter follow-up.[1] Results matched those of previous prospective randomized studies. In 2009, von Hoff et al published the long-term outcome of patients treated in the multicenter trial HIT'91. The 10-year event-free survival (EFS) and OS rates of all 114 M0-patients were 65 ± 5 and 73% ± 4%, respectively. The 45 patients with M0 and maintenance chemotherapy had a 10-year EFS and OS of 83 ± 6 and 91% ± 4%, respectively.[22]

Effect of treatment under protocol conditions

Our primary purpose was to evaluate the effect of "on-protocol" treatment. There is a widespread belief that inclusion in clinical trials offers the best treatment and outcome. A "trial effect" on outcome has not been generally proven so far. In pediatric studies, however, positive effects were apparently seen.[23] Centrally reviewed staging played an important role. In the Children's Oncology Group (COG) A9961 study of Packer et al, central neuroradiographic review revealed that 30 of 409 reviewed patients had evidence of residual or metastatic disease. In retrospect, the latter were inappropriately assigned to the study with disseminated disease. This cohort had a significantly worse EFS than the fully assessable patients ($P < .005$).[16] In our cohort, HIT SIOP PNET 4 trial participants and observational patients, as well as patients in the HIT SIOP PNET 4 era and patients in the era after closure of the HIT SIOP PNET 4 trial, had identical regulations for staging and central review and were treated according to central disease stratification. No difference in PFS and OS were found between the on and off protocol cohorts. To evaluate potential biases due to different treatment eras and treatment protocols we performed further subgroup analyses and also found no differences. Using a

centralized review program for prospective trials produced equivalent outcome for patients within and outside a randomized trial. However, we had no control group of patients without a central review program. Therefore, we cannot quantify the benefit compared with patients without central review. In contrast to the COG A9961 trial, all patients who were ineligible were identified before start of treatment and allocated to the corresponding treatment protocols of the HIT 2000 trial.[16]

Effect of time factors

The detrimental effect of delayed RT is continuously a matter of debate. Kann et al demonstrated worse outcome when RT started more than 90 day after surgery.[6] Other retrospective analysis with different cut-offs between 21 and 42 days failed to prove an effect.[7,24,25] In the national database analysis of Chin et al, delaying RT more than 35 days but not more than 90 days was not associated with inferior outcome. But the time scale of 35 to 90 days was not further subdivided or continuously evaluated.[8] By contrast, the HIT SIOP PNET 4 patients, in whom RT started with a delay of 49 days or more, had a 5-year EFS of 67% compared with 81% when RT started within 48 days ($P = .04$).[1] In our study, a 7-year PFS of 64.6% was seen in patients starting RT after 49 days versus 80.4% ($P = .052$ in univariate analysis). These findings were confirmed by multivariate Cox regression analyses in all models, including the presence of molecular subgrouping data ($P = .012$, $P = .018$). An effect of time interval to RT was also proven as a continuous category in the HIT SIOP PNET 4 trial. Timely initiation of RT is therefore important for patient outcome and a prolonged time-to-RT should be avoided.

In the SIOP-UKCCSG-PNET 3, in which a STRT35.2 RT schedule was used, there was a better EFS for patients completing RT within 50 days compared with those taking more than 50 days (3-year EFS of 78.5% vs 53.7%; $P = .0092$).[9] A negative effect of protracted RT on PFS or local control was also demonstrated in other retrospective analyses.[7,25] In the HIT SIOP PNET 4 trial, an effect of duration of RT on EFS could not be demonstrated.[1] In our analysis, no difference in PFS between both groups was seen for the whole cohort ($P = .931$). Because of the different number of days with RT between the 3 schedules and the resulting different RT durations (STRT23.4, 40-42 days; STRT35.2, 44-46 days; HFRT, 46-48 days), a second analysis was done with STRT23.4-patients only. A trend for inferior PFS for RT duration $>$ 49 days (7-year PFS 64.3% vs 78.6%; $P = .261$) was seen in this cohort. The statistical observation is, however, of limited value, because a protracted RT was given in only 12 patients.

Effect of residual tumor

In univariate analysis we could confirm the findings of HIT SIOP PNET 4 and Children's Cancer Group (CCG) 921 trials for residual disease above 1.5 cm^2.[1,5] They had a 7-year PFS of 63.7% compared with 80.5% achieved in patients with minor or no residual disease ($P = .045$). On multivariate analysis, some of this effect was attributed to confounding factors ($P = .061$). However, when interpreting these findings together with published data, the assumption of a negative effect of postoperative residual tumor in patients with nonmetastatic MB can be supported.

Histologically defined tumor entity

On univariate analysis, the presence of D/N had a prognostic negative effect on outcome for patients in whom no data for genetic annotation to MB entities were available. Because most D/N relate to SHH-activated MB, this might be explained by the presence of SHH/TP53-mutant MBs with worse prognosis in these cases.[26] Significantly worse outcome of LC/A MB was seen in the COG A9961 study (OS 75% vs 89%) and in a subcohort of patients of The International Society of Pediatric Oncology - United Kingdom Children's Cancer Study Group - PNET 3 (SIOP-UKCCSG-PNET 3) trial.[9,16,27] In a larger cohort of patients, including infants, in the preceding HIT'91 trial, LC/A MB was a significant negative prognostic factor.[28] In the HIT SIOP PNET 4 trial patients with LC/A were excluded after 2003. Therefore, only 16 patients with LC/A MB were analyzed and showed a nonsignificant inferior outcome compared with patients with non-LC/A MB (7-year EFS 64.0% vs 80%; $P = .21$).[1] Patients of our cohort treated with conventional fractionated full dose CSI (STRT35.2 Gy) achieved a 7-year PFS of 84.6% and 7-year OS of 83.1%, respectively, suggesting a higher craniospinal dose for patients with LC/A. Only 2 patients with WNT-MB had an LC/A (no relapse occurred).

Genetically defined tumor entity

The annotation to genetically defined MB entities confirmed the prognostic importance of the genetic MB classification according to WHO 2016, with best outcome for WNT-activated tumors and worst prognosis of non-WNT/non-SHH group 3.[29-31] Because of the small number of patients, no conclusions can be made as to whether the trend for worse PFS of non-WNT/non-SHH group 3 compared with group 4 confirms the different outcomes of these groups as described by Schwalbe et al or if an equal outcome can be expected like in the HIT SIOP PNET 4 cohort.[31,32] Worst prognosis of all groups could also be expected in the SHH-activated TP53 mutant

MB, but this group could not be identified because of lacking TP53-mutational analysis.[26] The 7-year PFS and OS of WNT patients were 93.2% and 91.5%, respectively, in our cohort, and confirm the subgroup analyses of the HIT SIOP PNET 4 trial.[4,32] This result matches also with other patient cohorts even in metastatic disease.[29,31,33,34] The potential for reduction of treatment intensity, including a reduced dose of 18 Gy CSI, in this cohort is presently under evaluation. (eg, SIOP PNET 5 trial). However, reduction of CSI dose has to be done with caution. The results of the COG ACNS0331 showed worse PFS after 18 Gy CSI but without biologically defined risk stratification.[35]

Conclusions

The results of this study reflect treatment and outcome of patients with nonmetastatic MB > 4 years in 63 participating centers of German-speaking countries during the HIT 2000 era between 2000 and 2011. OS and PFS rates were high even outside a randomized clinical (HIT SIOP PNET 4) trial but with identical quality control procedures. We interpret this as a result of consequent management standards, including central review of imaging and pathology as well as central individualized treatment recommendations. Nevertheless, inclusion into prospective clinical trials is strongly encouraged to achieve further refinement of biological stratification and disease management with the aim of improving outcome. Time to RT was an important predictor of survival, suggesting a timely initiation of RT.

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