

## Health status, health-related quality of life, and socioeconomic outcome in childhood brain tumor survivors: a German cohort study

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### Abstract

**Background.** With rising numbers of childhood cancer survivors, somatic and socioeconomic outcome as well as health-related quality of life (QoL) gain increasing relevance. Based on the first nationwide German Survey on Life Situation, State of Health, and Quality of Life of Childhood Cancer Survivors, the VIVE survey, we report the outcome of survivors of childhood brain tumors localized in the posterior fossa.

**Methods.** Two hundred seventy participants with a median follow-up period of 21.9 years completed a questionnaire on socioeconomic and somatic late effects as well as a standardized QoL questionnaire (European Organisation for Research and Treatment of Cancer QLQ-C30). Comparisons were performed between World Health Organization (WHO) grades I–II, WHO grades III–IV brain tumor survivors (BTS), and the general population adjusting for potential confounders.

**Results.** The socioeconomic and QoL results of WHO grades I–II BTS were largely comparable to the general population, while grades III–IV BTS were at higher risk for significantly worse outcomes. Of WHO grades III–IV BTS, 36.8% were still living with their parents or in assisted living facilities compared with 16.1% of grades I–II BTS and 7.8% of the age-adjusted general population. Of grades III–IV BTS, 60.8% achieved at least an intermediate school degree in comparison to 80.5% of grades I–II BTS and 75.6% of the general population. Grades III–IV BTS developed up to 2 times more somatic late effects than survivors of grades I–II tumors.

**Conclusion.** Derived from a large and homogeneous cohort, these results stress the importance of an appropriate follow-up period focusing not only on physical aspects but encompassing the entire living situation to allow patient-tailored support.

### Key Points

1. WHO grades I–II BTS are comparable to the general population regarding socioeconomic status and QoL.
2. WHO grades III–IV BTS report worse outcome than grades I–II BTS with significantly more somatic late effects.

## Importance of the Study

Other studies concerning socioeconomic and somatic late effects after treatment for childhood cancer have shown that BTS tend to a poor outcome relating to educational and social attainment in comparison to other childhood cancer survivors. This study not only assesses socioeconomic and somatic late effects in a

German BTS cohort but also links these results to health-related QoL, thus allowing a more holistic evaluation of the quality of survival. This might help to provide better patient-tailored care and psychosocial support in individual patients and will contribute to more risk-stratified follow-up concepts.

Brain tumors are the second most common childhood cancer, accounting for 23% of all new childhood cancer cases per year in Germany.<sup>1</sup> Primary brain tumors are classified by the World Health Organization (WHO) as benign, low-grade (grades I–II) and malignant, aggressive high-grade (grades III–IV).

With up to 50% of all brain tumors, the posterior fossa is a predilection site for highly aggressive neoplasms such as medulloblastomas and other primitive embryonal tumors. In addition, low-grade neoplasms such as astrocytomas may be localized in the posterior fossa.<sup>2</sup> Depending on size, degree of infiltration, and the extent of surgery, sequelae of tumors localized in the same region of the brain may be comparable. Yet complementary local and systemic radiochemotherapy adds to the overall therapeutic burden with potentially significant influence on long-term outcome. While the role of the cerebellum in motor function and coordination is well known, it is also key for neurocognitive functions such as executive function, speech, verbal intelligence, and social and emotional behavior.<sup>3,4</sup> Tumors or lesions in this region may therefore have a devastating impact on patients' everyday life.

Since the 1970s, childhood cancer patients in Germany have been treated in consecutive consensus treatment protocols, including phase III trials, facilitating standardized risk classification and stratification with a continuous improvement of outcome over time. Consequently, the 5-year overall survival (OS) in childhood cancer patients has reached up to 85% nowadays, with a 5-year OS for brain tumor patients of 77%.<sup>1,5</sup> Due to increasing numbers of former childhood cancer patients reaching adulthood, long-term side effects and quality of life (QoL) have moved into the focus of clinical research. Overall, former brain tumor patients have the highest risk for adverse events in comparison to other childhood cancer survivors during both short- and long-term follow-up.<sup>6–11</sup>

QoL is a highly subjective concept including a variety of factors such as physical health, psychological well-being, social functionality, and level of independence. While many studies analyzed somatic long-term effects and health-related QoL in former childhood cancer patients, little is known about the association of QoL with somatic and socioeconomic variables such as educational and occupational status, relationship status, independent living situation, and disability. The aim of this study was to identify somatic and socioeconomic outcomes that are linked to QoL in former patients with grades I–II versus grades III–IV brain tumors of the posterior fossa.

This study represents a subgroup analysis of the first Basic Survey on Life Situation, State of Health, and Quality of Life of Childhood Cancer Survivors in Germany, the VIVE survey. The VIVE survey examines long-term effects,

socioeconomic outcomes such as education and occupational attainment, as well as living situation and QoL in childhood cancer survivors. Due to the exceptionally long follow-up, former patients are now part of the middle-aged population. Therefore, socioeconomic aspects become relevant and are here compared for the first time with the census data of the entire German population.

## Patients and Methods

Inclusion criteria for the VIVE study were: primary International Classification of Childhood Cancer 3 (ICCC-3) diagnosis at an age <15 years, as up to the reporting date, the German Childhood Cancer Registry (GCCR) only registered patients up to this age; residency in Germany at the time of diagnosis; follow-up >5 years and age at survey between 25 and 45 years. Written consent for contact through the GCCR was also required.<sup>12</sup> Upon receipt of the VIVE study outline, patients willing to participate signed another consent form also allowing the GCCR to transfer pseudonymized information such as allocation to treatment protocols to the VIVE coordinators.

Among other standardized questionnaires, the VIVE survey included the European Organisation for Research and Treatment of Cancer–Quality of Life Core Questionnaire (EORTC QLQ-C30) to assess disease-specific QoL complemented by questionnaires assessing somatic late effects and socioeconomic status. The EORTC QLQ-C30 consists of 9 multi-item scales (5 functioning, 3 symptoms, 1 global QoL) assessed by up to 5 questions and 6 single scales. While the functioning scales reflect everyday functionality, such as physical, role, emotional, cognitive, and social functioning, the symptom scales address adverse medical effects. The questions are answered using a 4-point Likert scale<sup>13</sup> for the scales and single items and a 7-point scale for global QoL. Answers are transferred to scores from 0 to 100 according to the EORTC QLQ-C30 scoring manual.<sup>14</sup> Higher scores on the functional scales and on the global health status scale indicate better functioning and quality of life, whereas higher scores on the symptom scales represent more pronounced symptoms.<sup>13</sup>

An EORTC comparison group ( $n = 743$ ) was drawn from a population-based, representative sample of the German population ( $n = 2028$ ) who had signed a broad consent form allowing for their data to be used in various studies; the raw data were kindly provided by the investigators.<sup>15</sup> Socioeconomic norm data were extracted from the German census of 2014–2015. The participants for both control groups were randomly selected.<sup>15,16</sup> For socioeconomic status, we evaluated the educational level, occupational

achievement, and living situation. In Germany, 9 years of schooling are compulsory starting at an average age of 5.5 years. After elementary school, pupils follow 3 different schooling tracks depending on academic ability: high school (*Gymnasium*), intermediate school (*Realschule*), and compulsory school (*Hauptschule*). With an age at diagnosis ranging from 0.17 to 14.92 years, the vast majority of the cohort had not completed school before being diagnosed with cancer. The cutoff for further analysis concerning somatic late effects was set at an incidence >10% in the cohort of brain tumor survivors (BTS) except for epilepsy as a typical disorder associated with brain tumors, thus yielding the following relevant symptoms: hearing impairment, impaired sight, sensitivity disorders, paralysis, scoliosis, growth restriction, hypothyroidism, and dyspnea.

## Statistical Analysis

Characteristics of the study participants are described by median values with ranges or numbers with percentages as appropriate.

Three groups of outcome variables were analyzed: (i) 15 QoL domains based on the EORTC QLQ-C30, (ii) 9 variables indicating the presence of somatic late effects (yes–no), as well as the accumulation of somatic late effects, (iii) socioeconomic outcomes: living situation, educational level, and occupational achievement.

The QoL data showed strong ceiling effects and were highly skewed toward zero (symptom scales and items) or 100 (functioning scales and QoL). To deal with these specific distributions we used zero-or-one inflated beta regression<sup>17</sup> to analyze the QoL scores. Zero-or-one inflated beta regression models are a class of mixture models, each modeling 2 processes: The first process distinguishes between zeros (ones) and non-zeros (non-ones) using a logistic regression model, and the second process models the values between zero and one using beta regression. The scores of the EORTC QLQ-C30 variables were converted to proportions by dividing them by 100. The models comparing control, grades I–II, and grades III–IV regarding QoL variables were adjusted for age and sex. The *P*-values for the zero-or-one inflated beta regression models were obtained by likelihood-ratio tests on the associations between WHO grade and the QoL variables. When comparing more than 2 groups (eg, control, grades I–II, and grades III–IV) and the global *P*-value was significant, the *P*-value for each group comparison was obtained by restrictive linear hypothesis testing (ie, comparing the models under the null hypothesis [no difference between groups, 2 at a time]) with the respective full model. For the QoL variables, the group differences between norm, grades I–II, and grades III–IV are additionally shown by differences of mean values ( $\Delta$ ) and Cohen's *d* (*d*).

Logistic regression models were used to compare grades I–II and grades III–IV with regard to somatic late effects. Models were adjusted for age, sex, and follow-up time. Estimates obtained from the models are represented as odds ratios (ORs) with 95% CIs. The analysis of the accumulation of somatic late effects was done using a Poisson regression model, adjusted for age at diagnosis,

sex, and age. Furthermore, the association of the somatic late effects and socioeconomic variables with QoL was analyzed using zero-or-one inflated beta regression models, as described above. These models were adjusted for WHO grade, age at diagnosis, sex, and follow-up time.

Chi-squared tests were used to compare controls, grades I–II, and grades III–IV regarding the socioeconomic variables.

The Bonferroni correction was applied to adjust for multiple comparisons as indicated. Test results with *P*-values <0.05 were considered significant. Analyses were carried out using the R Software for Statistical Computing v3.3.2<sup>18</sup> and SPSS v24.

## Results

### Characteristics of the Study Population

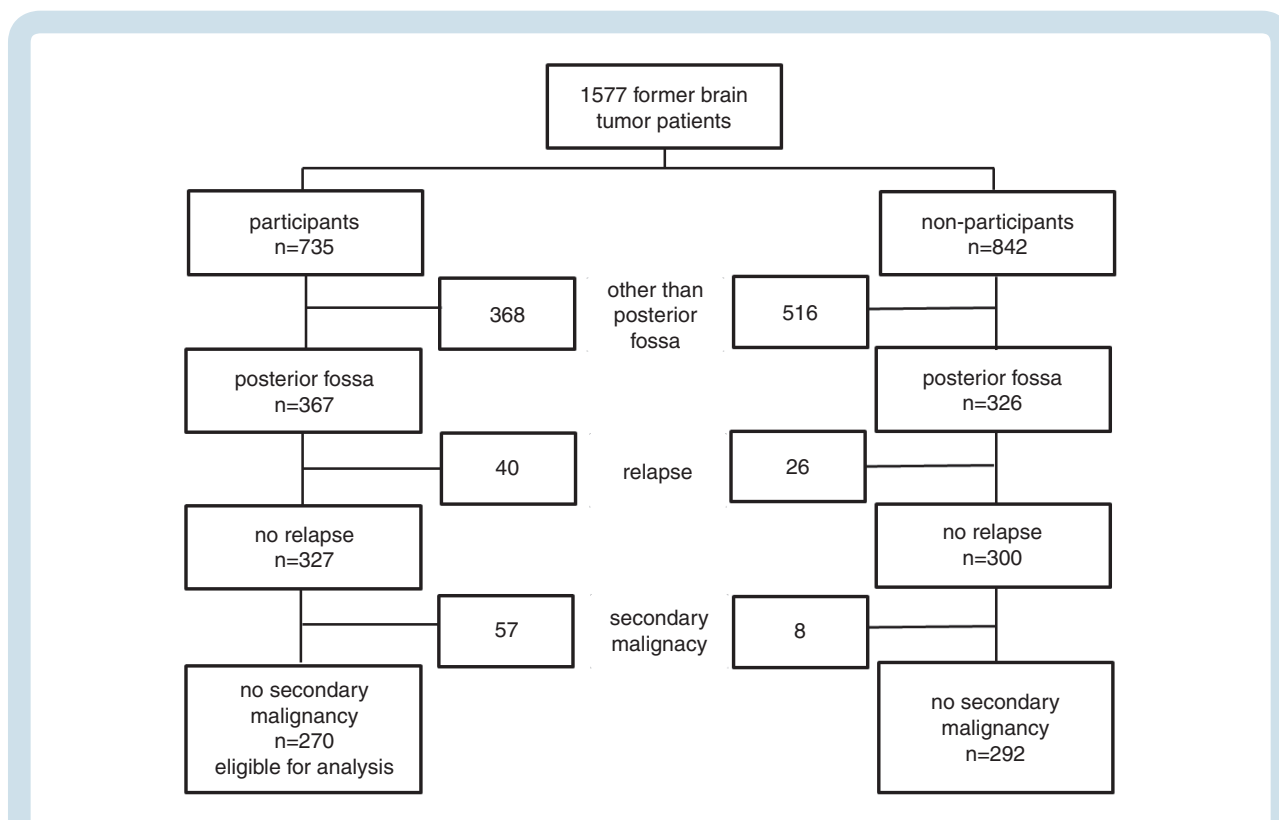
Out of 1577 former brain tumor patients contacted by the GCCR, 735 (46.6%) returned the questionnaire; of these, 367 (49.9%) had suffered from a tumor of the posterior fossa. Therefrom, 270 patients without a relapse or a secondary malignancy were eligible for analysis (Fig. 1). Participants did not differ from nonparticipants in terms of sex, age at diagnosis, and follow-up period. However, a smaller proportion of grades I–II BTS participated in the survey compared with grades III–IV BTS (*P* = 0.001; Table 1).

The final cohort consisted of 133 grades I–II and 137 grades III–IV BTS. Both groups were comparable regarding age at diagnosis and follow-up. The observed difference in sex distribution with a smaller proportion of males among grades I–II BTS than grades III–IV BTS (46.6% vs 63.5%) is due to the differences in the male-female ratios for astrocytomas (1.1) and medulloblastoma (1.9). The main diagnoses were astrocytomas in the grades I–II group (85.0%) and medulloblastomas (84.7%) in the grades III–IV group (Table 1).

### Quality of Life

In the general population, the mean values for physical, role, cognitive, and social functionality<sup>15</sup> ranged from 93 to 96 and from 76 to 80 for emotional functioning and global QoL. The symptom scales and items yielded mean values from 1 to 12 (Fig. 2).

Grades I–II BTS reported similar results to the general population for physical and social functioning as well as global QoL. Significantly lower scores, albeit with trivial effect sizes,<sup>19</sup> were seen for role ( $\Delta$  = 2.89, *d* = –0.16, *P* = 0.013), emotional ( $\Delta$  = 4.56, *d* = –0.194, *P* = 0.048), and cognitive functioning ( $\Delta$  = 8.53, *d* = –0.47, *P* < 0.001). Overall the scores of the symptom scales and items of grades I–II BTS were largely comparable to the general population. Nonetheless, grades I–II BTS reported higher scores than the general population, with small but significant effect sizes for fatigue ( $\Delta$  = –7.40, *d* = 0.35, *P* < 0.001), insomnia ( $\Delta$  = –11.04, *d* = 0.41, *P* < 0.001), appetite loss ( $\Delta$  = –6.66, *d* = 0.35, *P* = 0.023), constipation ( $\Delta$  = –3.35, *d* = 0.26, *P* = 0.042), and financial difficulties ( $\Delta$  = –3.00, *d* = 0.15, *P* = 0.009; Fig. 2).



**Fig. 1** Response rates among BTS with a posterior fossa tumor in the VIVE study.

Grades III–IV BTS, in contrast, reported significantly poorer results than the general population on all functioning and symptom scales and items, with large effect sizes for cognitive ( $\Delta = 16.24$ ,  $d = -0.82$ ,  $P < 0.001$ ) and social functioning ( $\Delta = 18.95$ ,  $d = -0.73$ ,  $P < 0.001$ ; Fig. 2). The effect sizes for physical functioning ( $\Delta = 11.52$ ,  $d = 0.77$ ,  $P < 0.001$ ), fatigue ( $\Delta = -14.04$ ,  $d = 0.64$ ,  $P < 0.001$ ), and dyspnea ( $\Delta = -6.74$ ,  $d = 0.39$ ,  $P < 0.001$ ) were medium, while the other scales and items showed only trivial or small effect sizes.

In direct comparison between the different WHO groups, grades III–IV BTS reported significantly worse results for physical ( $\Delta = 8.61$ ,  $d = 0.50$ ,  $P < 0.001$ ), role ( $\Delta = 8.08$ ,  $d = 0.35$ ,  $P = 0.005$ ), cognitive ( $\Delta = 7.71$ ,  $d = 0.33$ ,  $P = 0.001$ ), and social ( $\Delta = 14.95$ ,  $d = 0.54$ ,  $P < 0.001$ ) functioning as well as for financial difficulties ( $\Delta = -12.98$ ,  $d = 0.49$ ,  $P = 0.001$ ) than grades I–II BTS with a medium effect size for social functioning and small effect sizes for the other domains (Supplementary Tables 1, 2).

### Educational and Occupational Attainment

In the 2014 census data, 43.1% of the general population graduated from *Gymnasium*, 32.5% from *Realschule*, and 20.3% from *Hauptschule*, while 3.8% did not obtain any school diploma and 5.1% were unemployed.

The educational achievement of grades I–II BTS was comparable to the general population, with 48.9% graduating from high school (OR 1.35, 95% CI: 0.94–1.94,  $P = 0.344$ ; Fig. 3A), 29.3% from intermediate school (OR 0.91, 95% CI: 0.61–1.34,  $P = 1.000$ ) and 15%

from compulsory school (OR 0.73, 95% CI: 0.44–1.19,  $P = 0.743$ ). 3% did not receive a diploma (OR 0.81, 95% CI: 0.25–2.27,  $P = 1.000$ ). Furthermore, grades I–II BTS reported a similarly low unemployment rate (6.2%; OR 1.30, 95% CI: 0.51–3.09;  $P = 1.000$ ) as the general population (Fig. 3A).

In contrast, with 26.3% a significantly lower proportion of grades III–IV BTS graduated from high school (OR 0.49, 95% CI: 0.33–0.73;  $P = 0.001$ ) compared with the general population. There were no significant differences seen between grades III–IV BTS and the general population for intermediate school (35%, OR 1.18, 95% CI: 0.82–1.71,  $P = 1.000$ ) and compulsory school (25%, OR 1.41, 95% CI: 0.94–2.11,  $P = 0.318$ ). However, significantly more grades III–IV BTS failed to receive a school diploma (9.5%, OR 2.73, 95% CI: 1.46–4.99,  $P = 0.002$ ) and were more often unemployed (13.1%, OR 2.82, 95% CI: 1.53–5.10,  $P < 0.001$ ) than the general population.

In direct WHO subgroup comparison, grades III–IV BTS were significantly less likely to graduate from high school than grades I–II BTS (OR 0.36, 95% CI: 0.21–0.63,  $P < 0.001$ ), while there were no significant differences for the other school forms (Fig. 3A). Furthermore, with 22.9% versus 4.6%, significantly more grades III–IV BTS than grades I–II BTS (OR 5.88, 95% CI: 2.03–18.26,  $P = 0.001$ ) exercised elementary occupations, including those working in sheltered workshops.

For documentation of career progression from school across vocational training to subsequent occupation, the entire BTS cohort was subjected to analyses and compared with the general population. Of the latter, 23.3% held an

**Table 1** Characteristics of participants and nonparticipants as well as of the final cohort

	Nonparticipants (n = 292)		Participants (n = 270)		P	Final Cohort				P
						Grades I–II (n = 133)		Grades III–IV (n = 137)		
	n	%	n	%		n	%	n	%	
<b>Sex</b>					0.443					0.007
Male	171	58.6	149	55.2		62	46.6	87	63.5	
Female	121	41.4	121	44.8		71	53.4	50	36.5	
<b>Age group at diagnosis</b>										
0–4.9	48	16.4	48	17.8		30	22.6	18	13.1	
5–9.9	106	36.3	99	36.7		41	30.8	58	42.3	
10–14.9	138	47.3	123	45.6		62	46.6	61	44.5	
<b>Median age at diagnosis (range)</b>	9.54 (.08–14.75)		9.38 (0.17–14.92)		0.655	9.08 (0.42–14.92)		9.42 (0.17–14.75)		0.514
<b>Age group at survey</b>										
25–29.9	136	46.6	113	41.9		48	36.1	65	47.4	
30–34.9	98	33.6	98	36.3		52	39.1	46	33.6	
35–39.9	35	12.0	37	13.7		21	15.8	16	11.7	
40–45.9	23	7.9	21	7.8		11	8.3	10	7.3	
46–49.9	—	—	1	0.4		1	0.8	0	0.0	
<b>Median age at survey (range)</b>	30.50 (25.58–45.83)		30.67 (25.50–46.67)		0.404	31.75 (25.50–46.67)		30.17 (25.58–45.83)		0.096
<b>Median interval since diagnosis (range)</b>	22.00 (11.33–34.17)		21.92 (11.92–34.08)		0.674	23.42 (11.92–34.08)		21.50 (12.33–34.00)		0.068
Year of birth	1968–1988		1967–1988			1967–1988		1968–1988		
Year of diagnosis	1980–2002		1980–2002			1980–2002		1980–2001		
<b>ICCC-3</b>					0.013					<0.001
Astrocytoma	157	53.8	114	42.2		113	85.0	1	0.7	
Ependymoma	23	7.9	17	6.3		9	6.8	8	5.8	
Medulloblastoma	85	29.1	116	43.0		0	0.0	116	84.7	
Intracranial germ cell tumor	7	2.4	12	4.4		1	0.8	11	8.0	
Glioma	5	1.7	2	0.7		1	0.8	1	0.7	
Specific brain tumor	4	1.4	2	0.7		2	1.5	0	0.0	
Unspecific brain tumor	11	3.8	7	2.6		7	5.3	0	0.0	
<b>WHO classification</b>					0.001					
I–II	174	63.5	133	49.3						
III–IV	100	36.5	137	50.7						

academic degree and 58.7% completed vocational training. Of the 37.4% BTS that graduated from high school, 17.9%,  $P = 0.054$ , achieved a college or university degree, but only 10.1% proceeded to an academic profession. With 64.2% the majority of the BTS cohort completed vocational training and 37.9% eventually worked as clerks or services and sales workers, 11% as craftsmen.

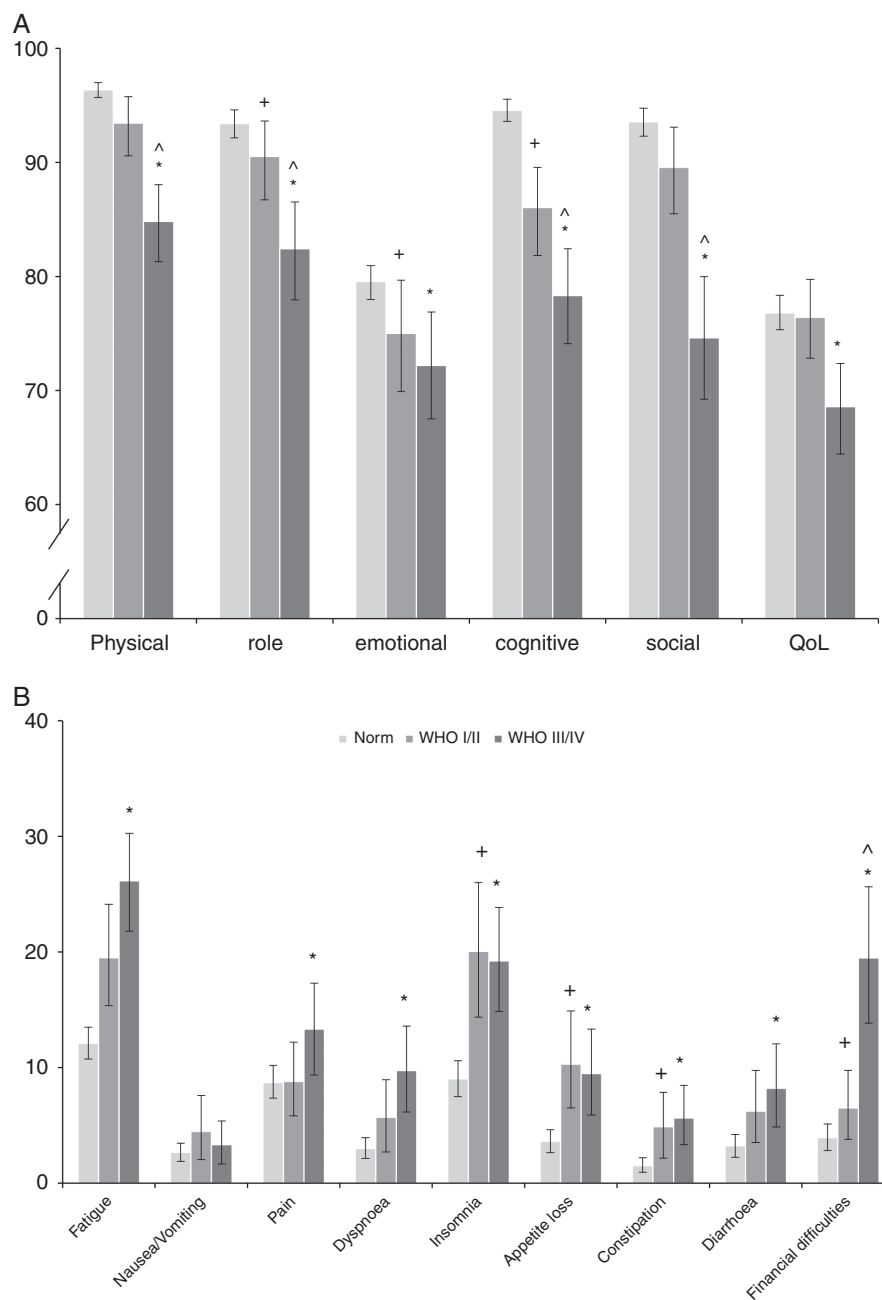
### Living Situation

Of the general population, 32.1% lived alone, while 60.1% were living with a partner and 7.8% still resided with their parents.

Compared with the general population, grades I–II BTS were less likely to live alone (20.8%, OR 0.55, 95% CI: 0.35–0.86,  $P = 0.018$ ) and conversely more likely to still reside with their parents or in assisted living (16.1%, OR 2.27, 95% CI: 1.38–3.71,  $P = 0.001$ ). There was no significant difference for living with a partner between grades I–II BTS (56.9%, OR 0.88, 95% CI: 0.61–1.26,  $P = 1.000$ ) and the general population.

In contrast, grades III–IV BTS were significantly less likely to live with a partner (25.6%, OR 0.23, 95% CI: 0.15–0.34,  $P < 0.001$ ) than the general population, whereas the percentage of grades III–IV BTS that lived alone (34.6%, OR 1.12, 95% CI: 0.77–1.62,  $P = 1.000$ ) did not





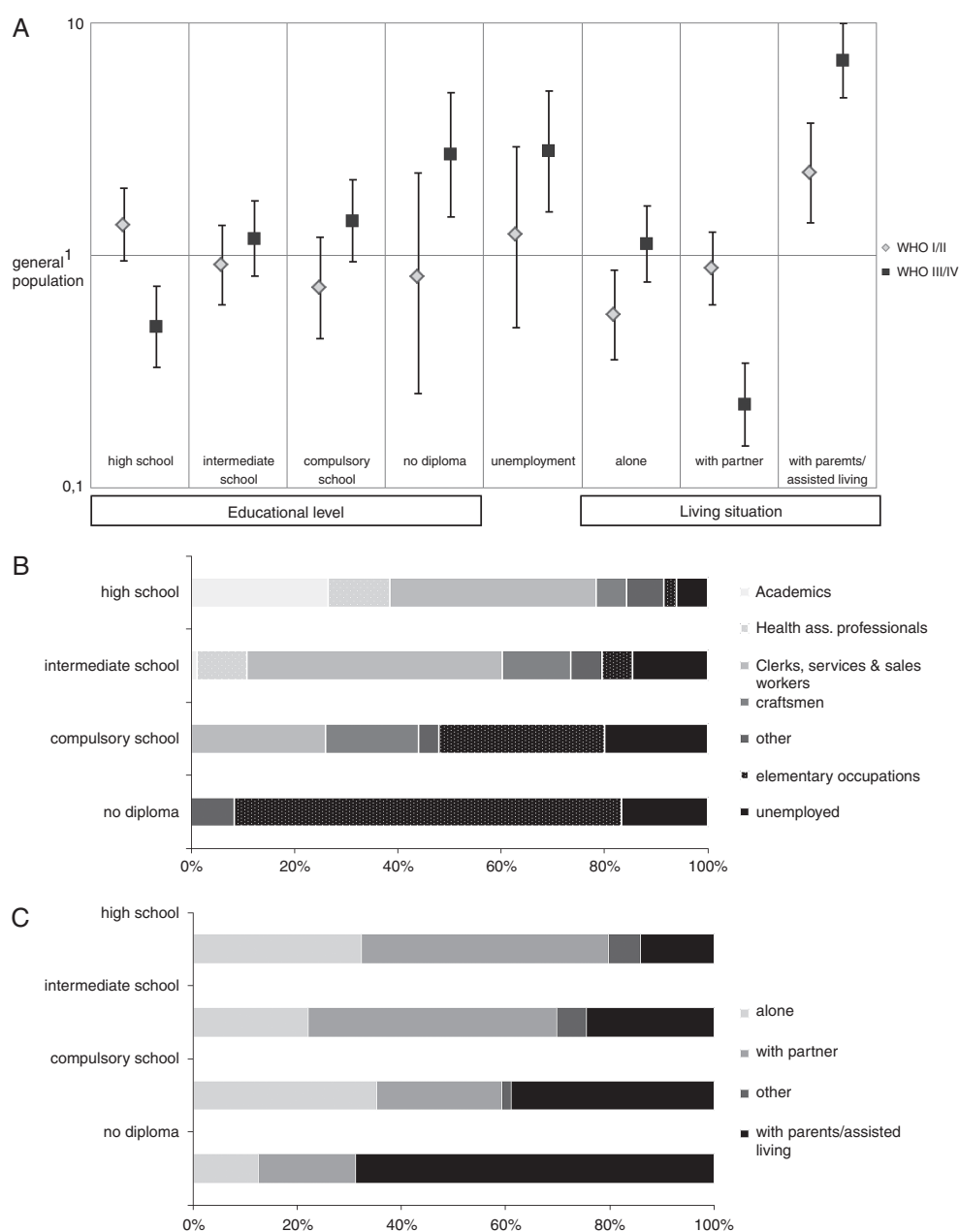
**Fig. 2** EORTC scales; mean scores with 95% CI. + $P < 0.05$  grades I–II vs general population; \* $P < 0.05$  grades III–IV vs general population; ^ $P < 0.05$  grades I–II vs grades III–IV;  $P$ -values obtained from zero-or-one inflated beta regression models adjusted for age and sex;  $P$ -values are Bonferroni corrected for multiple testing across the number of items. (A) Functioning scales and QoL. Note: interruption of the  $y$ -axis to support clarity of the figure. (B) Symptom scales and items.

differ significantly (Fig. 3A). A large proportion of grades III–IV BTS were still living with their parents or in assisted living facilities (36.8%, OR 6.88, 95% CI: 4.74–9.96,  $P < 0.001$ ).

Comparing the WHO subgroups directly, grades III–IV BTS were significantly less likely to live independently (OR 0.36, 95% CI: 0.19–0.66,  $P = 0.004$ ) than grades I–II BTS.

### Impact of Socioeconomic Outcome on QoL

One of the relevant aspects in cancer survivorship is the influence of socioeconomic outcome on QoL. BTS with posterior fossa tumors living at home or in assisted facilities assessed their everyday functioning and QoL as lower; however, the difference was only



**Fig. 3** (A) OR for grades I–II and grades III–IV BTS in comparison to the general population for educational achievement, unemployment, and living situation. (B) Occupational attainment in relation to educational achievement. (C) Living situation in relation to educational achievement.

significant for cognitive functioning ( $P = 0.042$ ; Table 2). The differences in global QoL, physical, role, emotional, and social functioning did not reach statistical significance, indicating the importance of family support for self-perceived well-being (Supplementary Table 3). In keeping with this notion, the participants still living with their parents were more likely to have a lower educational level (Fig. 3C). Higher educational achievement, in contrast, was associated with significantly better physical ( $P < 0.001$ ) and role ( $P = 0.003$ ) functioning (Table 2) as well as fewer financial difficulties ( $P = 0.003$ ; Supplementary Table 4).

### Somatic Late Effects

Cancer-induced somatic late effects considerably impact on daily life. As such information is naturally not available for the general population, in the following, grades I–II BTS are directly compared with grades III–IV BTS.

Grades III–IV BTS developed 1.93 times more somatic late effects than grades I–II BTS (95% CI: 1.62–2.34,  $P < 0.001$ ; Supplementary Table 5). Grades III–IV BTS were significantly more likely to suffer from hearing impairment, scoliosis, and endocrinopathies than grades I–II BTS, with the highest risks for the latter (growth restriction OR 15.89, 95% CI: 7.56–36.91,

**Table 2** EORTC functioning scales and QoL

	Physical			Role			Emotional			Cognitive			Social			QoL		
	Δ	d	P	Δ	d	P	Δ	d	P	Δ	D	P	Δ	d	P	Δ	d	P
<b>Education</b>			<0.001			<0.001			0.254			0.020			0.011			0.033
High vs intermediate	6.36	0.434	<0.001	1.60	0.077	<0.001	4.14	0.164		5.785	0.278	0.404	6.58	0.259	0.002	4.14	0.197	0.034
High vs compulsory	9.47	0.629	<0.001	8.59	0.357	<0.001	6.79	0.241		11.97	0.517	<0.001	10.26	0.377	<0.001	9.60	0.441	<0.001
High vs no diploma	29.88	1.081	<0.001	33.41	1.16	<0.001	10.36	0.404		21.40	1.116	0.056	41.02	1.227	0.006	24.59	1.282	0.005
Intermediate vs compulsory	3.11	0.198	<0.001	6.99	0.317	<0.001	2.65	0.095		6.19	0.256	0.002	3.68	0.125	<0.001	5.46	0.226	0.008
Intermediate vs no diploma	23.52	0.84	<0.001	31.81	1.173	<0.001	6.22	0.245		15.63	0.765	<0.001	34.44	0.98	<0.001	20.45	0.933	<0.001
Compulsory vs no diploma	20.41	0.723	<0.001	24.82	0.835	<0.001	3.56	0.125		9.43	0.413	<0.001	30.77	0.842	<0.001	14.99	0.661	<0.001
<b>Living situation</b>			0.023			0.574			0.045			0.007			0.438			0.259
Alone vs parents	7.77	0.384	0.028	6.15	0.237		3.35	0.13		-0.95	-0.043	0.392	9.68	0.301		4.90	0.217	
Alone vs partner	-3.77	-0.267	0.548	-2.33	-0.11		-1.64	-0.065		-5.41	-0.241	0.029	-5.43	-0.212		-4.06	-0.194	
Alone vs other	-3.23	-0.255	0.915	-6.44	-0.515		21.44	0.747		6.69	0.248	0.274	-5.68	-0.228		3.72	0.188	
Parents vs partner	-11.55	-0.586	0.001	-8.48	-0.327		-4.99	-0.187		-4.46	-0.207	<0.0005	-15.11	-0.502		-8.95	-0.381	
Parents vs other	-11.01	-0.589	0.509	-12.59	-0.589		18.10	0.604		7.64	0.291	0.110	-15.36	-0.521		-1.17	-0.052	
Partner vs other	0.54	0.046	0.710	-4.11	-0.224		23.09	0.785		12.10	0.454	0.663	-0.26	-0.011		7.78	0.371	

\*Δ = difference, d = Cohen's d, P-values obtained from zero-or-one inflated beta regression models adjusted for age and sex. P-values are Bonferroni corrected for multiple testing across the number of items.



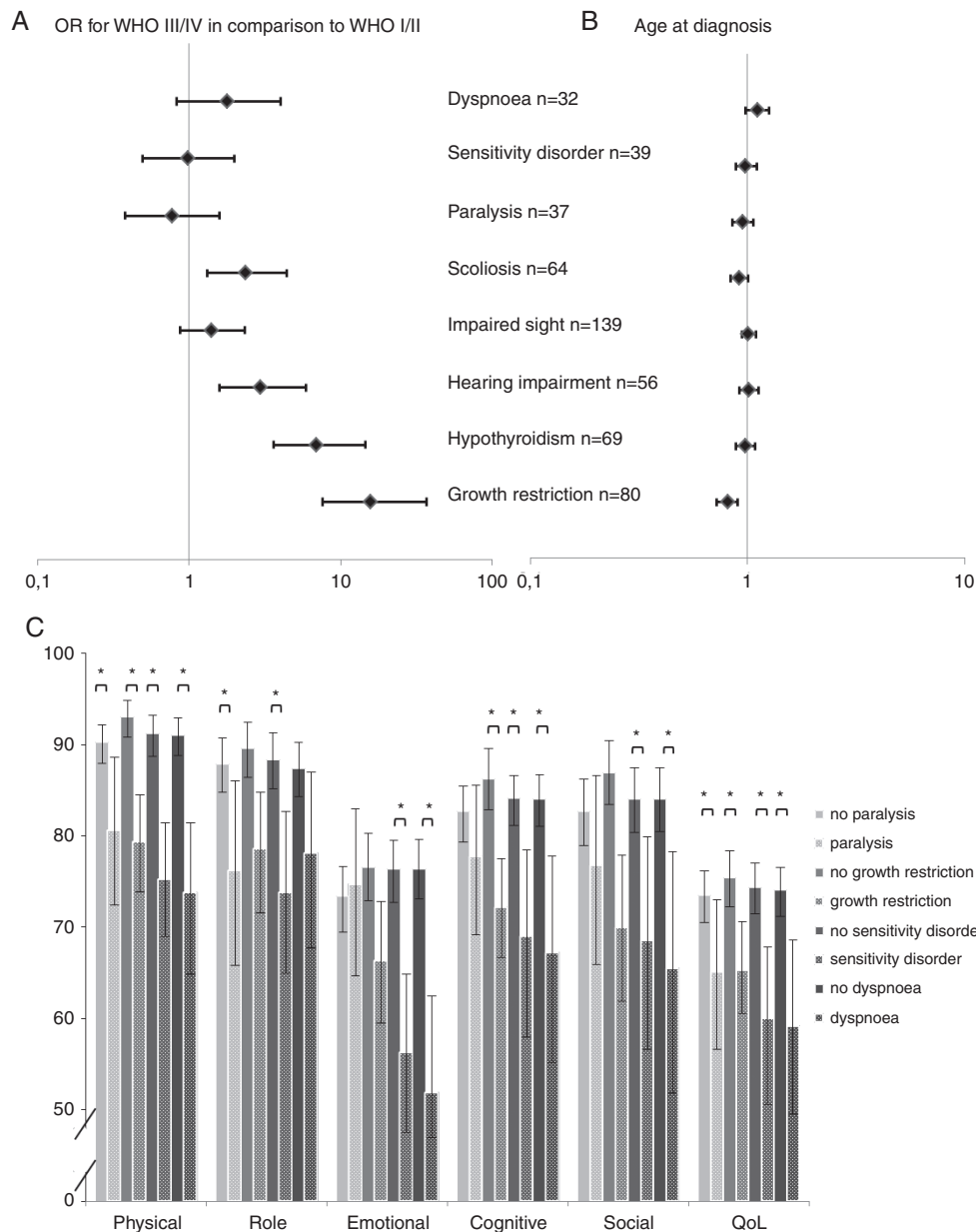
$P < 0.001$ ; hypothyroidism OR 7.01, 95% CI: 3.59–14.52,  $P < 0.001$ ; Fig. 4A). Grades I–II and III–IV BTS were equally as often affected by paralysis, impaired sight, sensitivity disorders such as paresthesia and numbness, as well as dyspnea.

For analysis of the influence of these physical impairments on QoL, the entire BTS cohort was again submitted to evaluation. Sensitivity disorders and dyspnea had the strongest association with EORTC QLQ-C30 domains (Fig. 4C). The most substantial differences with large effect sizes were seen for global QoL ( $\Delta = 14.39$ ,  $d = 0.62$ ,  $P < 0.001$ ;

$\Delta = 14.91$ ,  $d = 0.63$ ,  $P < 0.035$ , respectively) and fatigue ( $\Delta = -25.71$ ,  $d = -1.03$ ,  $P < 0.001$ ;  $\Delta = -26.90$ ,  $d = -0.98$ ,  $P < 0.001$ , respectively). This also applied to the symptom scales and items (Supplementary Tables 6, 7).

Younger patients at diagnosis had a higher risk to develop a growth restriction (OR 0.81, 95% CI: 0.72–0.90,  $P = 0.002$ ; Fig. 4B, Supplementary Table 8). Overall, the frequency of participants suffering from epilepsy was rather low (4.4%).

We also found that BTS who reported a sensitivity disorder were significantly less likely to graduate from high school (OR



**Fig. 4** (A) OR for grades III–IV BTS in comparison to grades I–II for somatic late effects; ORs obtained from logistic regression models adjusted for sex and age at diagnosis. (B) Age dependency (OR) of development of somatic late effects; ORs obtained from logistic regression models adjusted for sex and WHO grade. (C) Impact of selected somatic late effects on the EORTC functioning scales. \* $P < 0.05$ ,  $P$ -values obtained from zero-or-one inflated beta regression models adjusted for WHO grade, sex, age at diagnosis and follow-up time,  $P$ -values are Bonferroni corrected for multiple testing across the number of items. Note: interruption of the  $y$ -axis to support clarity of the figure.

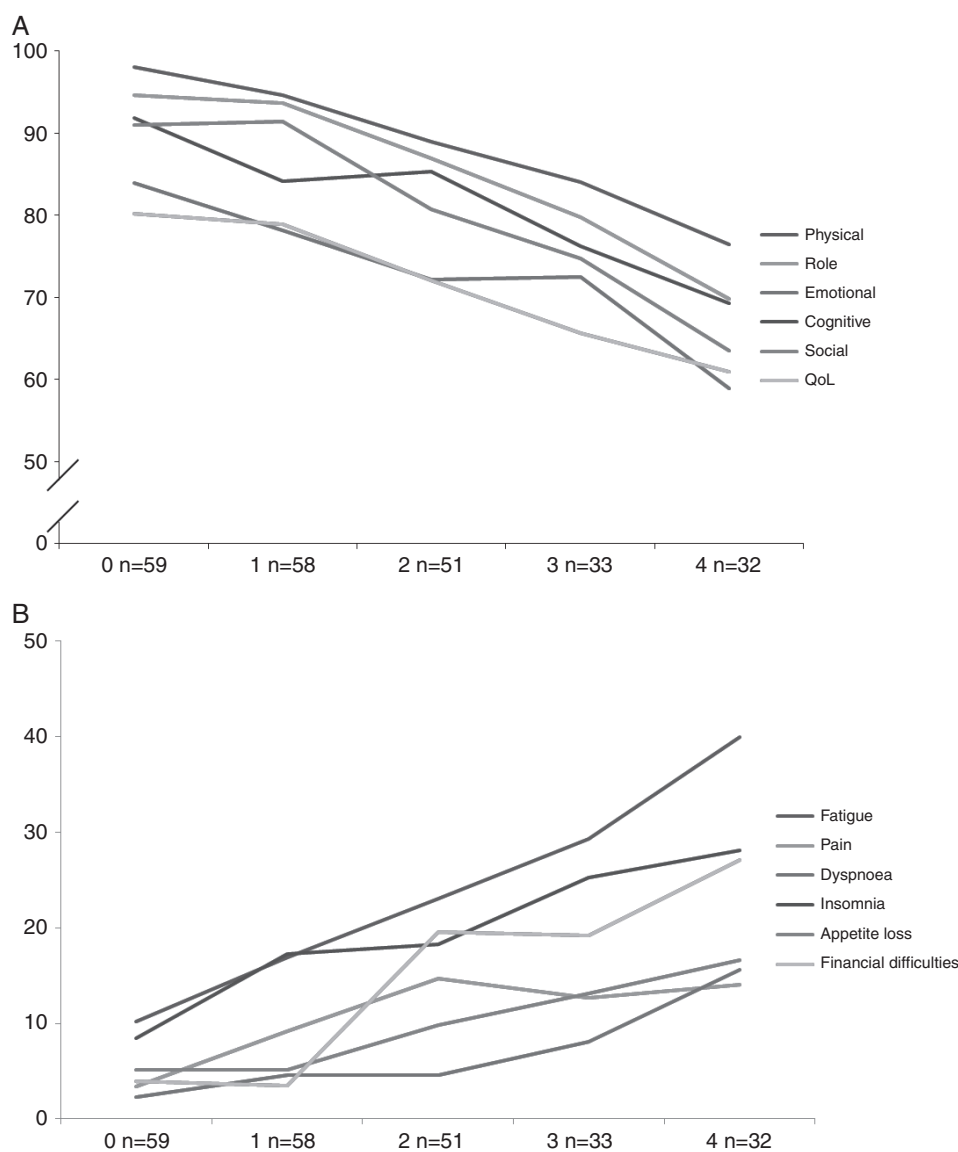
0.23, 95% CI: 0.09–0.59,  $P = 0.016$ ). No impact on educational achievement was observed for the other somatic late effects.

Reporting at least one long-term late effect were 65.4% of grades I–II BTS and 87.6% of grades III–IV BTS. Of the entire BTS cohort, only 7.4% reported more than 4 somatic late effects. An analysis of all BTS participants together demonstrated that the more somatic late effects are experienced per patient, the more functionality aspects are reported as negatively affected (Fig. 5A). This was also true for the symptom scales and items (Fig. 5B). Constipation, diarrhea, and nausea-vomiting, as typical acute medical side effects, did not show a high variability (data not shown).

### Impact of Treatment Intensity

Discrepancies in overall outcome reported between grades I–II and grades III–IV BTS may be attributed to differences

in aggressiveness of disease as well as treatment burden. To evaluate the latter notion, we analyzed outcome in 2 smaller VIVE subsets for whom intention-to-treat details could be procured. Protocols specifying treatment guidelines became available as of the 1990s. Eighty percent of 22 grades I–II BTS underwent surgery alone, while 15% received additional radiotherapy with 54 Gy to the tumor bed and 5% of patients underwent complementary chemotherapy. In contrast 88.4% of grades III–IV BTS ( $n = 69$ ) procured for analysis during the same time received all 3 treatment modalities: surgery, chemotherapy, and cranio-spinal radiotherapy with 25–35 Gy and a boost to the tumor bed adding up to 45–55 Gy. Of note, differences in outcome between these grades I–II versus grades III–IV-subsets, although limited by lower follow-up period and median age at survey, in essence reflect the results of the entire VIVE BTS grades I–II and III–IV-cohorts and underscore



**Fig. 5** (A) EORTC functioning scales in dependency of the number of somatic late effects. (B) EORTC symptom scales and items in dependency of the number of somatic late effects (nausea/vomiting, diarrhea, and constipation omitted).

the relevance of radiotherapy as one of the major determinants for poorer somatic and socioeconomic status and self-perceived QoL (Supplementary Tables 9–12).

## Discussion

Ever since overall prognosis in children and adolescents with cancer has significantly improved, assessment of long-term outcome has reached beyond documentation of survival and late somatic side effects, progressively encompassing a more holistic concept of health and well-being.

So far the studies directly comparing grades I–II and grades III–IV BTS consistently reported poorer but not always significant QoL in grades III–IV BTS<sup>10,20,21</sup> despite certain methodological differences in study design, such as various QoL questionnaires and duration of follow-up. With an exceptionally long follow-up period, our analysis supports these findings. In relation to the general population, we found mostly comparable results for grades I–II BTS and significantly worse outcome for grades III–IV BTS on the EORTC QLQ-C30.

One of the reasons that might account for these marked differences between the grades I–II and grades III–IV BTS is the disparity in therapy burden. Due to the invasive and faster growth of grades III–IV, brain tumor surgery might easily be more destructive than with grades I–II tumor. The pre- and perioperative complications such as hydrocephalus or neurological deficits, which were not addressed in this survey, might also contribute to poorer outcome in grades III–IV BTS as other studies have shown.<sup>22–24</sup> Also, the radiotherapy strategies and doses differ completely, with a rather restrictive indication in only a few of the grades I–II BTS as opposed to the majority of grades III–IV BTS irradiated including the entire cranium and spine. This general difference in treatment intensity is also reflected in our VIVE cohort. Craniospinal radiotherapy in particular has been shown to be an important predictor of intellectual decline,<sup>23–26</sup> also in patients with other oncologic diseases—for example, leukemia.<sup>6</sup> Consistently we observed the most substantial difference with a large effect size for cognitive functioning in the EORTC QLQ-C30, which was also reflected by the educational attainment of the 2 subgroups.

While comparability of educational achievement in studies from different countries is somewhat hampered by the differing schooling systems, a clear trend with poorer educational achievement for BTS in comparison to the general population and other childhood cancer survivors has been reported. In a French cohort, 40.6%<sup>6</sup> of BTS were reported to have no or only minor schooling, while in a Swiss cohort 16.4%<sup>8</sup> had completed only compulsory school, which is comparable to our results (20.4%). The subgroup comparison in our analysis allows a more differentiated assessment. While grades I–II BTS did not differ from the general population regarding educational achievement, grades III–IV BTS were significantly more likely to have no diploma (9.5% vs 3.8%). Furthermore, the disparity between the 2 WHO subgroups remained substantial for graduation from high school (grades I–II BTS 48.9%, grades III–IV

BTS 26.3%). This was also reflected by the higher percentage of grades I–II BTS achieving a college/university degree (24.8%) in comparison to grades III–IV BTS (11.7%). Generally speaking a higher school diploma was associated with better functioning, even though results were only significant for physical and role functioning. The subjective financial difficulties were significantly more pronounced in those with a lower educational degree. The choice of occupation and consequently income is tightly associated with educational achievement, such that the differences between the 2 subgroups described above naturally extend to the occupational attainment. Thus, grades III–IV BTS were more likely both to perform only elementary occupations, including work in sheltered workshops, than the grades I–II BTS (22.9% vs 4.6%) and to be unemployed (13.1% vs 6.2%). It is noteworthy that even though the overall unemployment rate of 9.8% in our BTS cohort was significantly higher in comparison to the general population (5.1%), it is still considerably lower than in a Canadian study with 25%,<sup>27</sup> and a French study with 28%.<sup>6</sup> These disparities might reflect differences in the labor market of different countries such as unemployment rates in adolescents and young adults during the survey period as well as in the respective supportive systems.

The results on educational attainment presented here complement the numerous studies that have shown that medulloblastoma (grades III–IV) BTS score significantly lower than control groups on different intelligence measuring scales,<sup>20,22,28</sup> with age at diagnosis being an important predictor for cognitive outcome.<sup>22,27–29</sup> Even though the majority of the grades III–IV BTS (36.8%) were still living with their parents or in assisted living, this is still substantially less than reported for medulloblastoma survivors in a Canadian (85%)<sup>27</sup> and in an American study (~80%),<sup>22</sup> though both cohorts were rather small ( $n = 16–20$ ) and participants were comparatively young (median age 21.9 y). Besides cognitive and physical functioning, the WHO subgroup comparison also showed an important difference concerning role and social functioning, while emotional functionality and QoL were rated similarly in both groups. With a substantial proportion of the entire BTS cohort still living with their parents, the worse outcome in social and role functioning might be an expression of their concerns about the future or mirror their social isolation while currently content with their situation.

Besides the EORTC QLQ-C30 symptom scales and items, the VIVE survey assessed somatic late effects with 78.4% of BTS reporting at least one chronic medical condition, which is in line with the findings of Armstrong et al (82%).<sup>30</sup> In our analysis it is the accumulation of different somatic late effects that has a substantial negative impact with large effect sizes on the domains of physical, cognitive, social functionality, and QoL. As shown by Huang et al, the somatic late effects or the symptoms arising therefrom are weighing in more on QoL than socioeconomic outcome.<sup>31</sup>

Overall grades I–II BTS show a better outcome than grades III–IV BTS concerning the EORTC QLQ-C30, the socioeconomic variables, and the somatic late effects. However, when affected by an adverse event (either socioeconomic or somatic) the impact on the EORTC QLQ-C30 is often more pronounced in grades I–II BTS than in grades III–IV BTS. This might be partially explained by

a less marked “response shift” in the grades I–II group. Response shift is a phenomenon that has been described as a change in one’s self-perception due to an adaptation to cancer-related limitations followed by an adjustment of one’s expectations<sup>32</sup> also described for childhood cancer survivors.<sup>9</sup> Such changes are also enhanced by social support and social comparisons.<sup>32</sup> Particularly the underlying mechanisms might be influenced by the social environment, which is highly determined by living situation and workplace. As grades III–IV BTS are more often living and working in sheltered environments, they experience higher levels of social support and their social comparisons are more limited to people with similar impairments.

Despite the cross-sectional design of the study, we were able to follow the progress from school to occupational attainment. The continuous decline in proportion from 37.4% of participants achieving a high school degree to 17.9% completing higher secondary education and eventually 10.1% being academics might indicate a certain “growing into deficit.”<sup>27</sup> The slight but significant decline in self-reported cognitive functioning with increasing follow-up time supports these findings.

### Strengths and Limitations

A certain participation bias cannot be completely ruled out, even though participants and nonparticipants did not differ regarding sociodemographic characteristics. The overrepresentation of grades III–IV BTS in the total BTS cohort, which might lead to an overestimation of the prevalence of unfavorable outcomes, was addressed by adjusting for WHO grade. The long follow-up of our cohort is certainly a strong asset but as BTS are reported to age prematurely characterized by increased neurocognitive impairments<sup>27</sup> and frailty<sup>33</sup> and the median age of participants was 30.7 years, the challenges that might still lie ahead of our cohort are not completely mirrored in this survey. This underlines the paramount importance of a long-term follow-up.

### Conclusions and Outlook

While it is apparent that BTS struggle with long-term sequelae affecting everyday life and QoL, it is noteworthy that a remarkable proportion manage to live an independent life. To consolidate these results, which might to a great extent be the merit of family support, both subgroups need lifelong follow-up and support to assist them with arising adverse events. Especially when parents may no longer be available as primary caregivers due to health issues or old age, comprehensive support systems are needed for those groups at risk, mediating the transition from family- to community-based care. Related to long-term care in general and in view of less detailed clinical information after a surveillance beyond 30 years, WHO grading might be a reasonable estimator for follow-up intensity and frequency, keeping in mind the exceptions related to the reduced response shift. To facilitate the transition from school to working life, intensified psychosocial and career counseling seem to be recommendable in view of our data.

### Supplementary Material

Supplementary data are available at *Neuro-Oncology* online.

### Keywords

childhood brain tumor | long-term late effects | long-term survivors | posterior fossa | quality of life

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