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Evaluation of age-dependent treatment strategies for children and young adults with pineoblastoma: analysis of pooled European Society for Paediatric Oncology (SIOP-E) and US Head Start data

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Abstract

Background. Pineoblastoma is a rare pineal region brain tumor. Treatment strategies have reflected those for other malignant embryonal brain tumors.

Patients and Methods. Original prospective treatment and outcome data from international trial groups were pooled. Cox regression models were developed considering treatment elements as time-dependent covariates.

Results. Data on 135 patients with pineoblastoma aged 0.01–20.7 (median 4.9) years were analyzed. Median observation time was 7.3 years. Favorable prognostic factors were age ≥4 years (hazard ratio [HR] for progression-free survival [PFS] 0.270, $P < .001$) and administration of radiotherapy (HR for PFS 0.282, $P < .001$).

Metastatic disease (HR for PFS 2.015, $P = .006$), but not postoperative residual tumor, was associated with unfavorable prognosis. In 57 patients <4 years old, 5-year PFS/overall survival (OS) were 11 ± 4%/12 ± 4%. Two patients survived after chemotherapy only, while 3 of 16 treated with craniospinal irradiation (CSI) with boost, and 3 of 5 treated with high-dose chemotherapy (HDCT) and local radiotherapy survived. In 78 patients aged ≥4 years, PFS/OS were 72 ± 7%/73 ± 7% for patients without metastases, and 50 ± 10%/55 ± 10% with metastases. Seventy-three patients received radiotherapy (48 conventionally fractionated CSI, median dose 35.0 [18.0–45.0] Gy, 19 hyperfractionated CSI, 6 local radiotherapy), with ($n = 68$) or without ($n = 6$) chemotherapy. The treatment sequence had no impact; application of HDCT had weak impact on survival in older patients.

Conclusion. Survival is poor in young children treated without radiotherapy. In these patients, combination of HDCT and local radiotherapy may warrant further evaluation in the absence of more specific or targeted treatments. CSI combined with chemotherapy is effective for older non-metastatic patients.

Key words

high-dose chemotherapy | pediatric | pineoblastoma | radiotherapy | treatment

Importance of the study

There are only limited data on effectiveness of treatment for pineoblastoma of infancy or childhood. Therefore, detailed original clinical data from 11 international brain tumor groups were combined for this analysis. Clinical risk factors were assessed and effects of treatment elements were analyzed using time-dependent Cox regression, thereby minimizing the inherent bias of retrospective treatment evaluations. In the absence of a clinical trial for this rare entity, this analysis gives a more comprehensive overview over the applied treatment modalities and their effectivity than previous reports, which are based either on small cohorts or on data extracted from published reports. These results are very valuable for clinical decision making as well as for the development of specific guidelines and prospective clinical trials for infants and children with pineoblastoma.

Pineoblastoma is a rare malignant embryonal tumor of the pineal region, which predominantly occurs in children and young adults.[1] The incidence of pineoblastoma is approximately 6 cases in 1 000 000 patient-years.[2–4] While the terms pineal "central nervous system primitive neuroectodermal tumor" (CNS-PNET) and "pineoblastoma" have previously been used synonymously by some authors,[5] it has become evident, that pineoblastoma is a molecularly unique entity, different from other CNS embryonal tumors.[6,7] Somatic as well as germline DICER1 mutations[8] and retinoblastoma 1 (RB1) mutations[9,10] have been described in pineoblastoma.

Treatment for pineoblastoma has been established based on experiences from studies that have been designed for medulloblastoma and/or CNS-PNET. Most published case series comprise very small numbers of original patient data,[2,3,11–15] limiting the clinical evidence and ability to compare data. Treatment regimens strongly depend on the age of the patient. As for other embryonal tumors of the CNS, maximal safe surgical resection followed by craniospinal irradiation (CSI) and chemotherapy are used as standard therapy for older children with progression-free survival (PFS) rates of 60%–70% for non-metastatic patients.[2,13,14,16–19] The prognosis of young patients with pineoblastoma treated with "infant type chemotherapy" without radiotherapy is very poor.[3,11,19–21] Regimens with high dose chemotherapy (HDCT; ie, high dose myeloablative and autologous hematopoietic stem cell support) have been used with or without application of focal irradiation or CSI.[21–23] The extent of resection and the presence of metastatic disease have been proposed as risk factors of survival, and therapy stratification based on these risk factors has been suggested.

The aim of this study was to determine clinical risk stratification parameters and to evaluate the impact of different treatment elements in each clinical risk group. Harmonized datasets were gathered by an international collaborative group of clinical researchers and were pooled for analysis. Datasets included detailed information on timing of treatment elements for individual patients to allow fitting more appropriate Cox regression models with time-dependent covariates. Patients from both previously published and unpublished series were included.

Patients and Methods

Patient Identification and Data Assembly

Patients were eligible for this analysis if they were younger than 21 years, if their tumor was diagnosed by institutional

or central pathology review as pineoblastoma or pineal CNS-PNET, if the primary diagnosis was between 1987 and 2011, if they were registered to one of the participating trial group's scientific programs, and if informed consent given by either the patient or the legal representative allowed de-identified data transfer. Patients with known trilateral retinoblastoma were excluded. Treatment according to a clinical trial protocol was not a prerequisite. The participating study group members cooperatively prepared a common database, which contained information on key diagnostic staging results, therapy, treatment sequence (postoperative chemotherapy, HDCT, radiotherapy, and chemotherapy after radiotherapy), as well as outcome (relapse, location of relapse, and survival). Data of previously published patients were included.[2,3,17,21] Data were merged and analyzed centrally. All clinical trials contributing data to this analysis were approved by the responsible ethics committees and performed according to the Declaration of Helsinki. Supplementary Table S1 gives an overview of the treatment protocols included in this analysis.

Clinical Questions and Statistical Analysis

The primary objective of this analysis was to identify treatment-related factors that influence survival in pineoblastoma patients. To quantify the effect of treatment elements, we first identified the most relevant clinical risk factors. Subsequently, we adjusted treatment-related effects in subgroups defined by the selected risk factors. Specifically, questions of interest were the impact of (a) dose-intense induction therapy/HDCT in younger patients, (b) the therapy sequence (chemotherapy first versus radiotherapy first) in older patients, (c) HDCT in older patients, (d) incomplete tumor resection in non-metastatic patients, and (e) different radiotherapy regimens.

Regarding question (a), applied chemotherapy regimens in patients <4 years old were categorized by the intent to use HDCT. Induction chemotherapy with the intent to use HDCT was applied within "Head Start" protocols,[21,24] HIT2000 (young, metastatic patients),[3] Milan chemotherapy protocol,[23] and French PNET-HR[25,26] protocols. Conventional chemotherapy regimens (without the intent to use HDCT) were applied within HIT-SKK'87,[27] HIT-SKK'92,[28] HIT 2000 (older patients, or young not metastatic),[3] BBSFOP,[29] PNET III,[30] the UKCCSG/SIOP CNS9204 trial,[31] and the French VP Carbo/RT protocol. Evaluation of individually administered drugs and doses was not planned due to expected statistical futility, and respective data of this factor were not acquired.

The most relevant clinical risk factors were identified by a multivariable Cox regression analysis with variable selection independently for PFS and overall survival (OS). Potential covariates analyzed were gender, age, clinical stage, and therapy elements. To account for different treatment intentions with differing application time of treatment after diagnosis, therapy elements (postoperative chemotherapy, HDCT, radiotherapy, and post-radiotherapy chemotherapy) were included as time-dependent variables. Patients were excluded from the analysis if information on start of radiotherapy or start of HDCT was missing. Age was included as a categorical parameter because the proportional hazard assumption was violated in some analyses when used as a continuous parameter. Four years of age at diagnosis was chosen as the cutoff because it was the best-discriminating breakpoint for survival, after serial calculations of different possible age values. To evaluate if risk or treatment factors were relevant only in a subgroup of patients, selected interaction terms were included for age*staging, age*HDCT, age*radiotherapy, and staging*HDCT. Staging was included in 2 formats: M0R0/M0R+/M+ and M0/M+. Akaike's information criterion[32] was used to identify the optimal model.

Risk factors identified in this model were used to define clinical subgroups for further evaluation of treatment effects (age <4 y and age ≥4 y) and to adjust the effects of therapy elements within these subgroups. Hazard ratios (HRs) were adjusted for gender, radiotherapy, and staging (M0 vs M+) for PFS and radiotherapy and staging (M0 vs M+) for OS in both age groups.

Univariable PFS and OS rates were estimated using the Kaplan–Meier method and are reported as estimate ± standard error. The log-rank test was used for univariable intergroup OS/PFS comparisons. Results of multivariable Cox regression analyses are reported as HRs and 95% CI. PFS was defined from day of first operation or biopsy to date of first progression, relapse, or death. Survival data were censored at the day of last evaluation. Associations between categorical variables were investigated by Fisher's exact test. All analyses were performed using R version 3.1.0[33] with packages survival 2.37–7[34] and forestplot.[35]

Inferential statistics are intended to be exploratory (hypotheses generating), not confirmatory, and are interpreted accordingly. The comparison-wise type I error rate was controlled instead of the experiment-wise error rate. The local significance level was set to .05. No adjustment for multiple testing was performed.

Results

Patients' Characteristics

Data on 135 patients with a histopathologically confirmed pineoblastoma were available from 11 national or trial groups (Austria 4; Czech Republic 1; France 24; Germany 32; Hungary 1; Italy 14; the Netherlands 20; Portugal 3; UK 14; USA ["Head Start"] 21; Switzerland 1). Final diagnosis has been made by one of the trial group's central histopathology review institutions in 97 cases (72%) and by institutional report without central review in 38 patients. The median age at diagnosis was 4.9 years (range 0.01 to 20.7). Table 1 gives an overview of patients' basic characteristics.

Antineoplastic treatment was initiated in 132 patients and differed between younger and older patients (Fig. 1 A and B). Relapse or progression occurred in 76 of the patients who received treatment, and in all 3 patients without treatment. Seventy-four patients died. The median observation time for the 60 patients alive at last follow-up was 7.9 years (range 0.3–19.1 y). Five-year OS was 43 ± 4%; 5-year PFS was 41 ± 4%.

Relapses occurred early, especially in young patients (median time to progression 0.53 y for 50 patients aged <4 y at diagnosis with an event). Relapses in older patients occurred later and sporadically were observed more than 5 years after diagnosis (median time to progression 1.6 y

Table 1 Patients' characteristics of 135 patients with pineoblastoma. Initial staging was incomplete in 3 patients because of inability to confirm/exclude metastasis in 1 patient and missing postoperative imaging in 2 patients (both M0).

Sex	Male	64
	Female	71
Age	<4	57
	≥4	78
Histology review	Yes	97
	No	38
Staging	M0R0	28
	M0R+	60
	M+	44
	NA	3
Year of diagnosis	1987–1992	10
	1993–1998	39
	1999–2004	49
	2005–2012	37
Study group	Austria	4
	Czech Republic	1
	France	24
	Germany	32
	USA – "Head Start"	21
	Hungary	1
	Italy	14
	The Netherlands	20
	Portugal	3
	Switzerland	1
	UK	14

M0R0 = no evidence of metastasis at diagnosis, no evidence of postoperative residual tumor; M0R+: no evidence of metastasis at diagnosis with postoperative residual tumor; M+: metastasis at diagnosis; NA = not available.

for 29 patients ≥4 y old at diagnosis with an event, 2 cases with late relapses more than 5 y after diagnosis).

Clinical Risk Factor Analysis

Data on 127 patients were included in the multivariable Cox regression models for PFS and OS. Two patients with missing information on the start of radiotherapy, 2 patients with missing information on start of HDCT, 1 patient who died on the day of surgery, and 3 patients with incomplete information on staging were excluded. For both PFS and OS, age ≥4 years at diagnosis (HR 0.270 for PFS and 0.230 for OS, both $P < .001$), use of radiotherapy (HR 0.282 for PFS, $P < .001$ and 0.419 for OS, $P = .006$), and metastatic disease (HR 2.015 for PFS, $P = .006$ and 1.613 for OS, $P = .056$; Fig. 2A) were identified as independent prognostic markers. The variable selection process dropped the staging variable containing information on postoperative residual tumor from the final Cox regression model.

Because of the strong influence of age on both clinical management and outcome, hereafter results are separately presented for the 2 age groups (<4 y at diagnosis and ≥4 y at diagnosis; Fig. 3).

Patients <4 Years Old at Diagnosis

Five-year PFS and OS for patients <4 years old at diagnosis were 11 ± 4% and 12 ± 4%, respectively (Fig. 3). Presence of metastasis had no significant impact on survival in univariable comparisons (5-y PFS 15 ± 6% for M0 versus 6 ± 6% for M+, $P = .494$; 5-y OS 13 ± 6% for M0 versus 12 ± 8% for M+, $P = .633$).

Chemotherapy

Fifty-three of 57 patients <4 years old at diagnosis were primarily treated with chemotherapy ($n = 1$ CSI; $n = 3$ no treatment initiated). The type/protocol of chemotherapy was further specified in 47/53 patients (88%). Twenty-five received more dose-intense induction chemotherapy with the intention to apply HDCT: 3 on Head Start I, 8 on Head Start II, 4 on Head Start III, 3 on HIT2000, 2 on Milan chemotherapy, 1 on AIEOP High Risk Infant Protocol, and 4 on the French PNET-HR 2002/PNET HR/PNET HR-5 trials.Twenty-two received conventional, mostly "baby-type" chemotherapy regimens: 1 on HIT-SKK'87, 4 on HIT-SKK'92, 6 on HIT2000, 4 on BBSFOP, 2 on PNET III, 2 on UKSSCG/SIOP CNS9204 protocol, and 3 on the French VP Carbo/RT protocol. Out of the 53 patients treated with chemotherapy, 13 in complete remission (CR) and 10 in partial remission (PR) after postoperative chemotherapy were considered as responders (objective response 43%). Five patients had stable disease (SD) and 24 patients had disease progression (PD) during induction chemotherapy. Response rates were higher after dose-intense induction chemotherapy for HDCT (13/25) than after conventional chemotherapy (7/22; $P = .271$). Thirteen of 25 patients received HDCT after induction chemotherapy as a component of therapy before relapse (11 PR/CR, 2 SD after postoperative induction chemotherapy). Five further patients received HDCT, 2 after BBSFOP chemotherapy and 3 after induction chemotherapy that was not specified.Three patients received HDCT after relapse.

Radiotherapy

Radiotherapy was used in 11/57 patients <4 years old at diagnosis during first-line therapy: 6 received CSI (M0R0: 1, M0R+: 1; M+: 4), 2 with a "reduced" conventionally fractionated CSI dose of 23.4/24.0 Gy, 1 a hyperfractionated radiotherapy (HFRT) CSI with 31.2 Gy, and 2 with a conventionally fractionated CSI dose of 35.0 Gy (1 not documented). Another 5 received local radiotherapy (M0R0: 1; M0R+: 5). Median dose to the tumor bed was 54.0 Gy (range 45.0–59.4 Gy) in the 10 patients with data available (1 not documented).

A further 11 patients received "salvage" radiotherapy after relapse or progression, all with conventional fractionation: 6 received a "reduced" dose CSI (18.0–25.0 Gy), 3 conventional dose CSI (35.0–37.8 Gy), and 1 local radiotherapy. In one patient who received CSI, dose was not documented. Median dose to tumor bed was 54.6 Gy (range 35.0–59.4 Gy) in 10 patients with radiotherapy at relapse and data available (1 not documented).

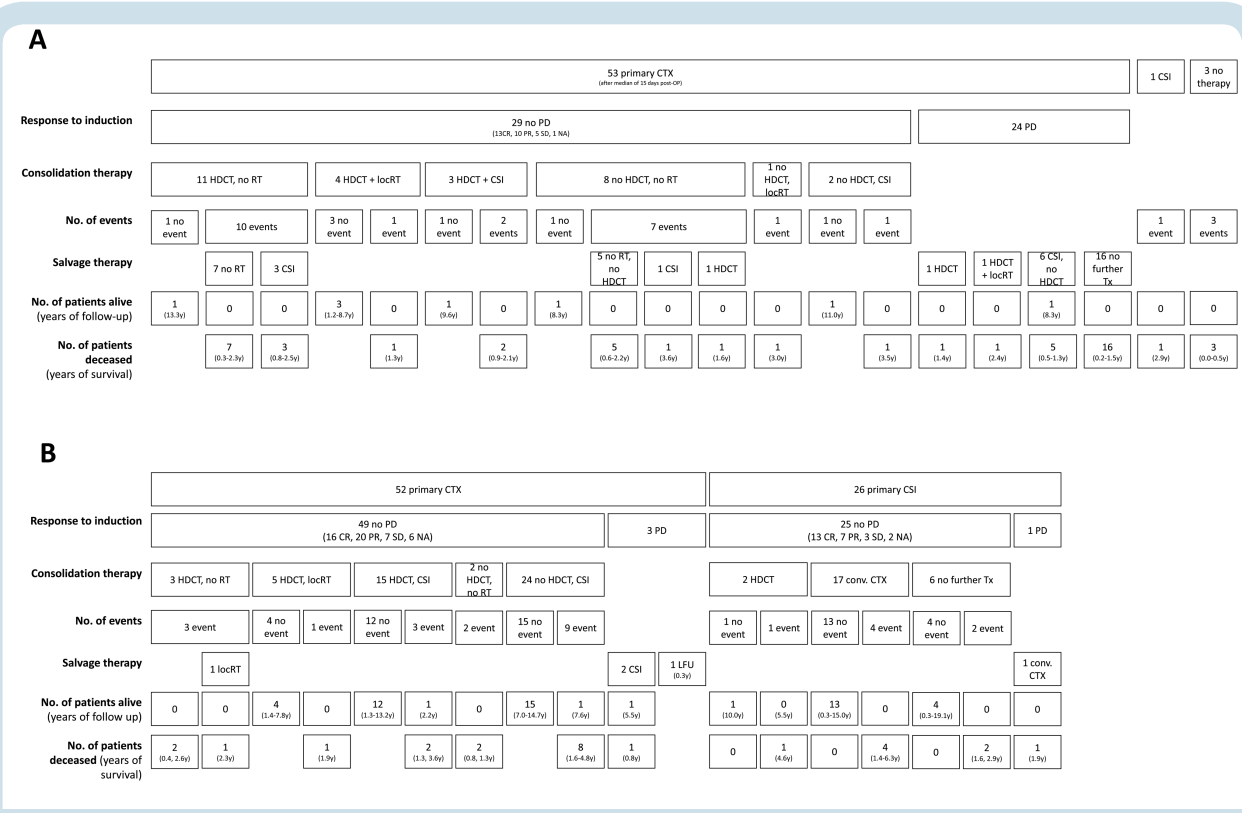


Fig. 1 Therapy courses for (A) 57 patients <4 years old at diagnosis and (B) 78 patients ≥4 years old at diagnosis. CR: complete remission; CTX: chemotherapy; locRT: local radiotherapy; LFU: lost to follow-up; NA: not available; PD: progressive disease, Tx: therapy; PR: partial remission; SD: stable disease; RT: radiotherapy; y: years

Effects of treatment elements on survival

Of the 8 patients alive at last follow-up, 6 had received radiotherapy: 2 CSI and 3 local radiotherapy during first-line therapy, 1 CSI after relapse. All 3 survivors after local radiotherapy had received HDCT (all M0). Adjusted HRs for use of radiotherapy were 0.431 (95% CI: 0.159–1.170, $P = .099$) for PFS and 0.605 (95% CI: 0.283–1.290, $P = .193$) for OS. Adjusted HRs for use of dose-intensified induction chemotherapy aiming at HDCT were 0.784 (95% CI: 0.413–1.489, $P = .457$) for PFS and 0.989 (95% CI: 0.523–1.868, $P = .972$) for OS (Fig. 2B), and therefore comparable to those of use of HDCT: 0.827 (95% CI: 0.412–1.662, $P = .594$) for PFS and 1.066 (95% CI: 0.563–2.022, $P = .843$) for OS.

Patients ≥4 Years Old at Diagnosis

Five-year PFS and OS for patients ≥4 years old at diagnosis were 63 ± 6% and 66 ± 6% (Fig. 3). In univariable comparisons, survival was inferior in patients with metastatic disease (5-y PFS 72 ± 7% for M0 versus 50 ± 10% for M+, $P = .015$; 5-y OS 73 ± 7% for M0 versus 55 ± 10% for M+, $P = .062$).

Chemotherapy, therapy sequence, and HDCT

Of the 78 patients aged ≥4 years at diagnosis, 52 received chemotherapy and 26 CSI (one with simultaneous carboplatin) as first treatment element. After postoperative chemotherapy, 16 were in CR, 20 had PR, 7 had SD, and 3 PD (6 NA; objective response rate 78%). Twenty-six of 27 patients with metastatic disease were initially treated with chemotherapy, while 26/50 patients with localized disease started with chemotherapy, 24 started with radiotherapy; 24 patients received HDCT during first-line therapy (12 M0, 12 M+; $P = .112$).

Radiotherapy

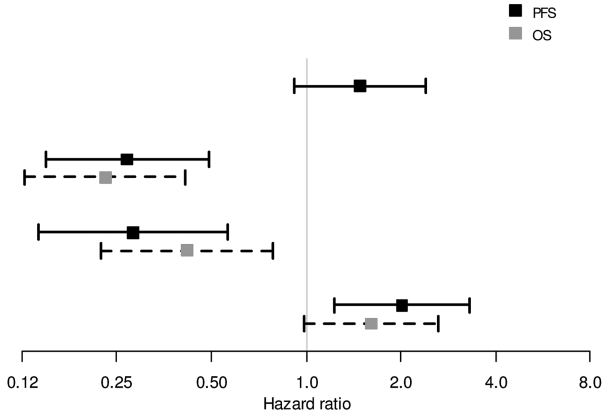
Of the 78 patients aged ≥4 years at diagnosis, 46 received conventionally fractionated CSI, 19 hyperfractionated CSI (14 hyperfractionated, 5 hyperfractionated accelerated [HART]), and 5 local radiotherapy during first-line therapy. The median dose of conventional CSI was 35.0 Gy (range 18.0–45.0 Gy) followed by a boost to a median cumulative dose of 55.0 Gy (range 54.0–60.8 Gy). Four patients received a "reduced dose" CSI with dose <30 Gy (one 18.0 Gy, two 23.4 Gy, and one 24.6 Gy). The median dose of hyperfractionated CSI was 36.0 Gy (range 31.2–47.0 Gy) with boost doses of median 67.2 Gy (range 50.0–72.0 Gy). All 5 patients who received local radiotherapy received a total dose of 54 Gy, all conventionally fractionated, 5 with photons, 1 with protons.

Two additional patients received conventionally fractionated craniospinal radiotherapy after relapse (one 23.4 Gy CSI/59.4 Gy boost to tumor region, one 35.0 Gy CSI/45.0 Gy to tumor region), and one received local radiotherapy after relapse (54.0 Gy to tumor region).

A

All patients

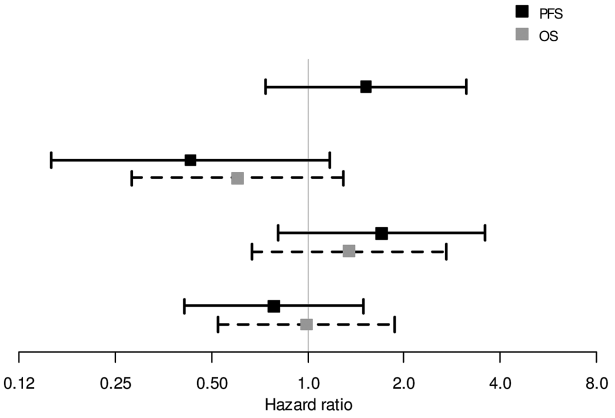
Variable	HR (95% CI)	p
Gender	1.482 (0.918 - 2.394)	0.108
male vs. female	NA (NA - NA)	NA
Age	0.27 (0.149 - 0.491)	<0.001
>=4 years vs. < 4 years	0.23 (0.128 - 0.414)	<0.001
Radiotherapy	0.282 (0.141 - 0.565)	<0.001
after vs. before	0.419 (0.224 - 0.783)	0.006
Staging	2.015 (1.224 - 3.317)	0.006
M+ vs. M0	1.613 (0.987 - 2.635)	0.056



B

Patients < 4 years at diagnosis

Variable	HR (95% CI)	p
Gender	1.52 (0.742 - 3.112)	0.252
male vs. female	NA (NA - NA)	NA
Radiotherapy	0.431 (0.159 - 1.17)	0.099
after vs. before	0.605 (0.283 - 1.29)	0.193
Staging	1.701 (0.806 - 3.59)	0.163
M+ vs. M0	1.342 (0.667 - 2.7)	0.409
Chemotherapy	0.784 (0.413 - 1.489)	0.457
aiming at HDCT vs. conv	0.989 (0.523 - 1.868)	0.972



C

Patients ≥ 4 years at diagnosis

Variable	HR (95% CI)	p
Gender	0.866 (0.406 - 1.849)	0.71
male vs. female	NA (NA - NA)	NA
Radiotherapy	0.136 (0.039 - 0.475)	0.002
after vs. before	0.128 (0.034 - 0.483)	0.002
Staging	1.725 (0.761 - 3.909)	0.192
M+ vs. M0	1.586 (0.668 - 3.768)	0.296
HDCT	0.705 (0.287 - 1.728)	0.444
after vs. before	0.678 (0.256 - 1.801)	0.436

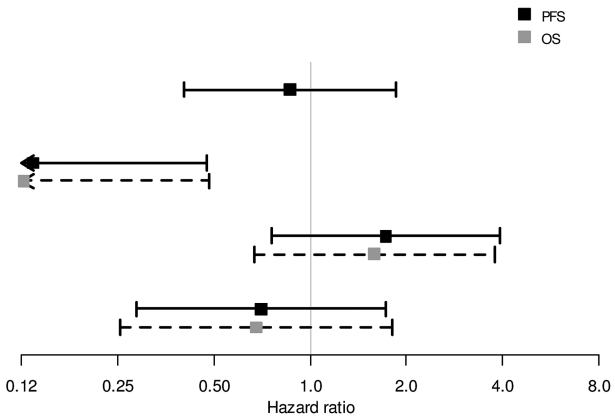


Fig. 2 Forest plot of Cox proportional hazard models of the entire group (A) or age-defined subgroups (B, C) for both PFS (black boxes/first line) and OS (gray boxes/second, dashed line). Therapy elements were modeled as time-varying covariates. (A) Selected model by variable selection algorithm in 130 patients with complete data for staging, start of HDCT and start of radiotherapy. Gender was only selected in the model for PFS, but not in the model for OS. HDCT or postoperative, pre-RT chemotherapy were not selected as influencing factor for PFS and OS models by the variable selection algorithm. (B) Cox proportional hazard models in patients <4 years old at diagnosis who started therapy with chemotherapy and with complete data on chemotherapy strategy, staging, starting dates of HDCT and radiotherapy. The model contains most important risk factors as defined in (A) plus type of chemotherapy (intensified, aiming at HDCT versus conventional). (C) Cox proportional hazard model in patients ≥4 years old at diagnosis with available data on staging and starting dates of HDCT and radiotherapy. The model contains most important risk factors identified in (A) plus HDCT. In each age group (<4 years and ≥4 years), the model is being presented with the best model fit (lowest Akaike information criterion) of the models described within the text.

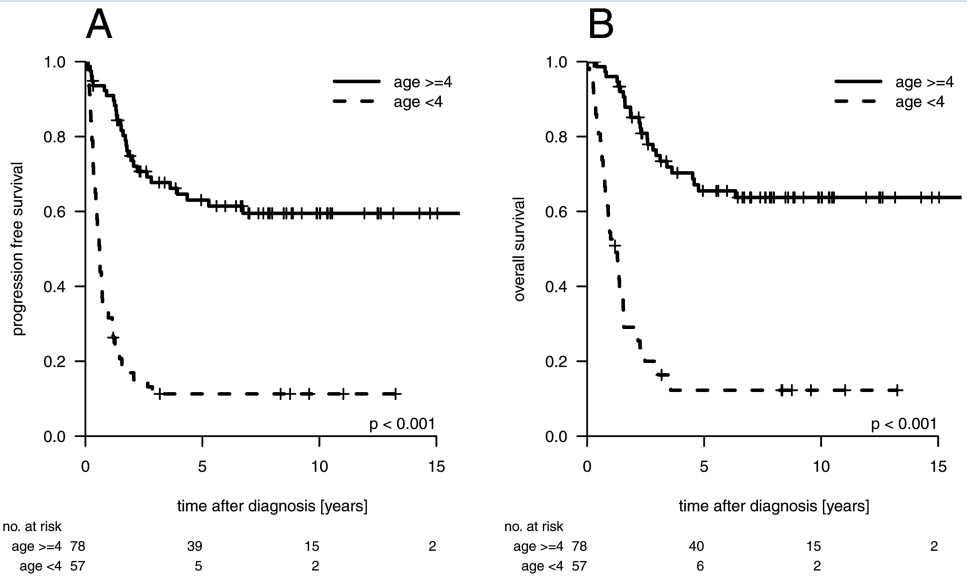


Fig. 3 PFS (A) and OS (B) according to age. Univariate 5-year PFS/OS estimates were 10 ± 4%/12 ± 4% for patients <4 years old at diagnosis versus 63 ± 6% / 66 ± 6% in patients ≥4 at diagnosis.

Effects of treatment elements on survival.

The use of radiotherapy remained the strongest risk factor for both PFS and OS. Adjusted HRs were 0.136 (95% CI: 0.039–0.475, $P = .002$) for PFS and 0.128 (95% CI: 0.034–0.483, $P = .002$) for OS in the model presented in Fig. 2C. There was no difference in survival according to the type of radiotherapy used: adjusted HRs for use of HFRT/HART versus conventional CSI were 1.857 (95% CI: 0.736–4.688; $P = .190$) for PFS and 1.710 (95% CI: 0.647–4.515; $P = .278$) for OS. Adjusted HRs for use of local radiotherapy versus conventional CSI were 1.572 (95% CI: 0.188–13.142; $P = .676$) for PFS and 2.664 (95% CI: 0.570–12.453; $P = .213$) for OS (Supplementary Fig. S1). Because only 4 patients received "reduced dose" CSI with <30 Gy, meaningful statistical analysis on dose could not be done. However, 3 of these 4 patients were alive with a follow-up of 3.2 to 13.2 years after diagnosis. All long-term survivors had received radiotherapy. Both PFS and OS did not differ between patients who received radiotherapy or chemotherapy first; adjusted HRs for treatment start with chemotherapy were 0.834 (95% CI: 0.302–2.353; $P = .74$) for PFS and 0.831 (95% CI: 0.290–2.380; $P = .731$) for OS. Inclusion of an interaction variable first therapy element*staging did not improve the model fit. Use of HDCT had limited impact: adjusted HRs were 0.705 (95% CI: 0.287–1.728; $P = .444$) for PFS and 0.678 (95% CI: 0.256–1.801; $P = .436$) for OS (Fig. 2C). When an interaction-term for staging*HDCT was included into the Cox regression model, the effect of HDCT was strongest in patients with metastatic disease: adjusted HRs for use of HDCT in metastatic patients were 0.372 (95% CI: 0.064–2.168; $P = .272$) for PFS and 0.633 (95% CI: 0.089–4.511; $P = .648$) for OS, but the model fit was inferior compared with the model without interaction.

Postoperative Residual Tumor

The variable coding for postoperative residual tumor was not selected in the Cox proportional hazards model for the entire group. Therefore, we aimed at further characterizing the impact of a postoperative tumor residual in non-metastatic patients. PFS and OS did not differ between patients with or without postoperative residual tumor, either in univariable analysis (Supplementary Fig. S2) or in a multivariable Cox regression model adjusting for age and radiotherapy. Adjusted HRs were 1.058 (95% CI: 0.535–2.094; $P = .871$) for PFS and 1.084 (95% CI: 0.546–2.154; $P = .817$) for OS.

Pattern of Relapse

Information on location of relapse or progression was available for 64/79 relapses/progressions—38 patients with relapse/progression had non-metastatic disease at diagnosis. Relapse/progression of radiotherapy naïve patients with non-metastatic disease at diagnosis was localized only for 12, combined localized and metastatic for 7, and metastatic only for 6 patients. Frequency of distant relapse was higher after local (local progression/relapse 1, combined 0, distant 2) and CSI with local boost (local progression/relapse 2, combined 2, distant 6), suggesting a dose effect of the local boost to the tumor region.

Discussion

To gain insight into the effectiveness of currently applied conventional treatment regimens in a rare disease like pineoblastoma, a sufficient quantity of high quality clinical

data is required. This analysis is based on a broad international collaboration, which allowed the pooled analysis of original data of 135 pediatric or adolescent patients with pineoblastoma from 11 study groups. We confirm the prominent impact of age at diagnosis and application of radiotherapy upon the outcome of patients with pineoblastoma. Young patients have a poor outcome, especially if they do not receive radiotherapy during their initial therapy. The survival of older patients, who routinely can receive radiotherapy, exceeded 60% five years after diagnosis in this series, which is in line with previously published series.[2,13,14,19,36]

We aimed at identifying the relevant clinical risk factors, providing an overview of applied treatment regimens, and describing the impact of different treatment elements and their timing on the PFS and OS of the patients. We have evaluated the role of treatment elements as time-dependent variables to account for the different therapeutic strategies with a great variation in timing of treatment elements as radiotherapy and HDCT. Consideration of timing of therapy elements is highly important for valid assumptions on treatment effects, especially in series where events must be expected while the patient is on therapy.

In the analyzed series, treatment choice differed mainly by age. Because application of craniospinal radiotherapy has severe long-term side effects in young patients, the decision whether to use upfront radiotherapy strongly depends on the patient's age, which again influences the choice of chemotherapy and general treatment decisions.

Age of the patient was the most dominant risk factor in our analysis and had a strong impact on the outcome, independent of the therapy given. This is in line with previous observations that young children have poor prognosis,[3,11,19–21,24,37] while for older patients, survival rates between 57% and 92% were reported.[2,13,14,16,17,19,23,38,39] One could argue that this is because of the selected treatment strategies, aiming to delay or avoid irradiation. However, time to progression was shorter for younger than for older patients, and response rates to induction chemotherapy were higher for older patients, which indicates that disease biology might differ with patient's age. Because of the major differences in clinical risk and treatment choices, we stratified the analysis of treatment elements by age.

In children <4 years of age at diagnosis, conventional chemotherapy without radiotherapy was not sufficient to induce sustained remissions in pineoblastoma. This supports previous observations of the POG-8633,[20] CCG-921,[15] and HIT-SKK[3,40] trials, which demonstrated poor survival in these patients. Even after intensification of chemotherapy with or without consolidating HDCT, most survivors required radiotherapy. Almost all patients ≥4 years old received radiotherapy, while neither the sequence of postoperative adjuvant therapy (radiotherapy first versus chemotherapy first) nor the use of HDCT as consolidating chemotherapy was associated with a relevant survival advantage in our series.

Consistent with the literature,[15,16,22,23,38,39,41] use of radiotherapy was the most dominant therapeutic risk factor in this analysis, with most patients having received CSI with boost to the primary tumor region. There was no influence of hyperfractionation of CSI on outcome in older patients. Indeed, HRs for HFRT/HART versus conventional radiotherapy were >1, indicating that it is not likely that HFRT/HART is associated with higher effectiveness than conventional irradiation. Most of the older patients treated with conventionally fractionated irradiation received a CSI dose of approximately 35 Gy. Only 4 of 68 patients treated with CSI as part of initial therapy received dose-reduced CSI <30 Gy. While meaningful statistics are not possible with these case numbers, it is of interest that 3 of 4 such patients survived with no evidence of disease at last follow-up.

A small group of younger patients with localized disease survived after local radiotherapy together with HDCT. Because of the lower neurotoxicity of local radiotherapy compared with CSI, this might be an interesting approach for young patients. However, confirmation of these findings in a larger prospective series is required.

Salvage radiotherapy was used only in a subset of young patients after relapse and had limited effect on the outcome: only 1 of 11 patients treated with salvage radiotherapy survived after relapse or progression.

Still, pineoblastoma seems to be responsive to chemotherapy, even though it is not sufficient to induce long-term remissions without additional radiotherapy.[15,20,40] We found a high rate of response to chemotherapy in this series, and response seemed to be improved after more dose-intense chemotherapy. Older patients who received chemotherapy before irradiation did not demonstrate improved outcomes compared with patients with initial irradiation followed by chemotherapy. As only 6 patients did not receive chemotherapy, an analysis of the necessity of combined treatment is not possible.

The influence of HDCT on outcome was weak, and most pronounced in the group of older, metastatic patients. To evaluate if HDCT may be beneficial in patients with poor prognosis, namely young patients and older patients with metastatic disease, prospective evaluation is needed.

Unlike other series,[19] we found that extent of tumor resection in non-metastatic patients was not a risk factor for PFS and OS. This is of clinical relevance for the patients, because it suggests that in difficult intraoperative situations, where further tumor resection is associated with a relatively high risk of postoperative morbidity, excessive surgery should not be pursued. Nevertheless, these data have been achieved retrospectively and therefore cannot exclude a prognostic relevance of postoperative tumor burden. Our data should not limit the surgical intention to perform a maximal safe tumor resection.

Several limitations of this analysis have to be acknowledged. First, central pathological review in all patients would have been ideally performed. As the time period required to collect this size of sample spanned more than 25 years, heterogeneity in diagnostic standards would be anticipated. Due to practical limitations, retrieval of tumor material was not deemed possible, which precluded diagnostic reevaluation as well as further molecular analyses. We repeated key statistical analyses in the patients, in whom a central reviewer had confirmed the diagnosis. We did not find contradictions to the results presented here (see Supplementary results). Furthermore, the results derive from a retrospective analysis of clinical data, and data had to be simplified because of the heterogeneity of treatment regimens. With limited ability to assess

individual drug modifications in a heterogeneous retrospective cohort, drug-specific evaluations were deemed to be not meaningful, and therefore only treatment sequence and intensity of chemotherapy were considered in this analysis. Trial specifications and drugs used are listed in Supplementary Table S1.

Despite these shortcomings, this work has clear strengths. The analyzed sample was large and derived from several established multi-institutional trial groups. The quality of data was high, with very few missing data and well-documented courses of therapy elements, which enabled us to model treatment elements as time-dependent covariates in the Cox regression analyses. This is important because modeling of treatment elements as time-fixed (constant) covariates leads to an inappropriate overestimation of treatment effects, caused by allocation of patients with early event/death into the group of patients who did not receive the respective treatment element. Therefore, estimation of effects of treatment elements as time-varying covariates leads to a better estimation of the true effect of the element.[42]

Intensified efforts to study this disease is highly required. High quality biological material should be collected during resection whenever this is safe for the patient, and patients should be offered to participate in clinical and biological research projects. Further research is highly needed to improve our understanding of the frequency and role of germline mutations (eg, retinoblastoma 1 and DICER1) for the etiology of pineoblastoma and develop innovative treatment options. Due to the rarity of pineoblastoma, only global collaboration for prospective clinical and biological studies is likely to provide the progress necessary to elucidate our understanding of the disease and to improve the outcome for high-risk pineoblastoma patients.

Supplementary material

Supplementary material is available online at *Neuro-Oncology* (http://neuro-oncology.oxfordjournals.org/).

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