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Long-term outcome and clinical prognostic factors in children with medulloblastoma treated in the prospective randomised multicentre trial HIT'91

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ABSTRACT

Purpose: To analyse long-term outcome and clinical prognostic factors in medulloblastoma.
Methods: We analysed 280 patients with medulloblastoma (3–18 years) included from 1991 to 1997 in the randomised multicentre trial HIT'91 comparing pre-('sandwich') and postradiation ('maintenance') chemotherapy (median follow-up of survivors for 10 years).
Results: In 187 patients with complete staging, overall survival (OS) was higher after maintenance compared to sandwich treatment for M0 (10-year OS 91% and 62%, $p = 0.001$) and M1 patients (10-year OS 70% and 34%, $p = 0.020$). In M2/3 disease, 10-year OS was 42% and 45%. Incomplete staging, metastases, younger age and sandwich chemotherapy were independent adverse risk factors. Twelve percent of all relapses (13 of 107) occurred after more than five years, and 12 patients had secondary neoplasms.
Conclusions: After maintenance therapy, long-term survival was excellent in fully assessable patients with localised medulloblastoma, and favourable for M1 patients. Patients should be followed longer for late relapses and secondary tumours.

1. Introduction

Medulloblastoma, a primitive neuroectodermal tumour (PNET) of the cerebellum, is the most common malignant brain tumour in children. It contributes to 20% of all central nervous system tumours in children[1] and has the tendency to metastasise by leptomeningeal spread. The advent of chemotherapy to radiotherapy as well as advanced radiotherapy techniques and mechanisms for quality control has significantly improved the outcome rates since the 1980s.[2–4] Current

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treatment protocols stratify patients according to their clinical risk factors, and patients with low-risk disease achieve three to five-year survival rates of 80% and higher.[5,6] Immediate radiotherapy after surgery has become the mainstay of treatment for low-risk patients, and maintenance chemotherapy after radiotherapy is widely used. Outcome of high-risk patients is worse, although intensified chemotherapy regimens have been used in combination with radiotherapy.[6–9] The optimal treatment strategy in high-risk patients is not yet defined. In the prospective, randomised, multicentre trial HIT'91 for children and adolescents from 3 to 18 years, the effect of postoperative neoadjuvant multiagent chemotherapy followed by radiotherapy was compared to immediate radiotherapy followed by adjuvant maintenance chemotherapy. The study showed a benefit of the maintenance strategy for all randomised children except patients with M2/3 stages.[10]

Whilst the relevance of intracranial (M2) and spinal (M3) leptomeningeal spread for classification as high-risk disease is unequivocal, there is still some uncertainty about treatment of microscopic dissemination into the cerebrospinal fluid (CSF) (M1), and about the role of postoperative residual tumour.[8,11,12] The acute toxicity profiles of maintenance chemotherapy have been well described,[13] but little is known about the long-term effects of chemotherapy, and about the impact of therapeutic dose reductions due to toxicity. Furthermore, little is known about the rates of late relapses and secondary tumours, as the median follow-up rarely exceeds five years in most reports.[14]

Here, we present the long-term results on survival rates, clinical risk factors, toxicities, late events and secondary tumours of patients treated within the HIT'91 trial.

2. Methods

2.1. Patients and diagnostic procedures

Between August 1991 and December 1997, 280 patients 3–18 years of age with newly diagnosed medulloblastoma as well as children with other histologies were treated according to the HIT'91 trial as described.[10,15,16] Treatment was performed at 68 participating hospitals in Germany and Austria (all members of the German Society for Paediatric Haematology and Oncology, GPOH). Recommended staging included pre- and postoperative cranial magnetic resonance imaging (MRI) or computed tomography (CT), spinal MRI and evaluation of CSF cytology. Central histopathological review and postoperative imaging not later than 48 (–72) hours after surgery were recommended, as well as CSF-sampling 14 d postoperatively in case of previous positive cytology. Available CT/MRI scans and CSF cytospin samples were centrally reassessed. Detailed standards for radiotherapy were given and documentation was centrally controlled.[17] The extent of resection was classified by postoperative imaging, and the size of the postoperative residual tumour was assessed. An early analysis including the intent-to-treat results of 158 patients has been published previously.[10]

Complete diagnostic evaluations as recommended by the study were not performed for all patients. Therefore in the current analysis, patients were classified according to the completeness of staging and to their clinical risk factors: Of 280 patients, complete staging for metastases was done in 213 (76%) patients. In 41 patients (15%), no spinal MRI was performed, and 26 patients without solid intracranial or spinal metastases had no evaluation of CSF cytology. Of 33 patients with positive M1 stage, CSF-sampling was done preoperatively in three, intraoperatively (before the onset of tumour surgery) in four, within 13 days after surgery in six, and after more than 13 days postoperatively in 15 patients. Date of sampling was not documented in five patients.

Central histopathological review was done in 232 of 280 patients (83%). Since lack of histopathological review represents a possible bias for the analysis of risk groups, patients were only assigned to the group with complete staging if histopathology was centrally reviewed. Overall, 187 patients (67%) were classified as having complete staging.

2.2. Treatment

After informed consent was obtained from all patients and/or legal representatives, patients were randomly assigned to receive either immediate radiotherapy followed by 'maintenance' chemotherapy, or immediate preradiation 'sandwich' chemotherapy starting within 14 days after surgery, as previously described.[10,15,16] If the randomisation was declined by the local physicians or parents, an elective decision for one treatment arm was possible.

Briefly, the craniospinal axis was irradiated with a dose of 35.2 Gray (Gy) given in 22 fractions (1.6 Gy fractionated dose) over a period of 4.5–5 weeks followed by a boost to the posterior fossa to 55.2 Gy in two weeks (2.0 Gy fractionated dose). Whenever feasible metastatic deposits in the spine and supratentorial region were boosted up to a total dose of 50 Gy.

Chemotherapy of patients in the maintenance arm corresponded to the 'Packer protocol'.[18] Vincristine was given weekly concomitantly with radiotherapy. Maintenance chemotherapy was started six weeks after completion of radiotherapy and consisted of eight cycles with CCNU, vincristine and cisplatin. Dose modifications were recommended in case of symptomatic leukopaenia and thrombocytopaenia for CCNU, neuropathy for vincristine and nephrotoxicity or ototoxicity for cisplatin. If there was a hearing loss of less than 20 dB within the 1000–3000 Hz range, or of more than 40 dB in the 4000–8000 Hz range, cisplatin was replaced by carboplatin. In case of hearing loss of more than 20 dB in the 1000–3000 Hz range, platin derivatives were omitted.

Sandwich chemotherapy consisted of two courses, each containing four cycles of chemotherapy (ifosfamide, etoposide; high-dose methotrexate; cisplatin, cytarabine). In case of measurable disease at the onset of therapy, partial or complete response was required for the start of the second chemotherapy course. Otherwise (in case of stable or progressive disease) immediate radiotherapy was started, followed by maintenance chemotherapy. Maintenance chemotherapy was also administered in any case of residual tumour after radiotherapy.

2.3. Statistical analyses

Data were collected at the HIT'91 study centre at the Children's University Hospital of Wuerzburg. Data of patients

from Austria were collected at the Children's University Hospital of Graz, and data from patients of the former East-German countries were collected at the Children's University Hospital of Magdeburg. Radiotherapy data were collected at the Department of Radiation Oncology, University of Tuebingen.

Primary end-point was overall survival (OS), measured from primary surgery to death of any cause or last evaluation, whichever came first. Secondary end-point was event-free survival (EFS), measured from primary surgery to first documented progressive disease, to death of any cause, to diagnosis of second malignancy or to last evaluation, whichever came first.

For univariable analyses, therapy was considered 'as treated', and Kaplan–Meier estimates and log-rank test were used for OS and EFS rates (±standard errors). For multivariable analyses, Cox regression models with forward and backward stepwise selection (inclusion criterion: p-value of the score test $\leqslant 0.05$, exclusion criterion: p-value of the likelihood ratio test $\geqslant 0.10$) were used to analyse the possible impact of the following variables: age (continuous), metastatic disease (M stage, categorical), therapy arm as randomised (intention to treat, categorical), therapy arm as received (as treated, categorical), residual tumour (categorical), sex (categorical), completeness of staging (categorical) central histopathological review (categorical). For Cox regression, p-values of likelihood ratio test are given unless otherwise noted.

The generalised Fisher's exact test was used to analyse the association between two categorical variables. The Wilcoxon– and the Kruskal–Wallis tests were used to compare continuous variables between independent groups.

All p-values were considered as explorative, no significance level was fixed.

Analyses were performed with SPSS software, version 15.0. Figures were done with *R*, version 2.7.0.

3. Results

At the time of analysis, 179 of 280 patients (64%) were alive at last follow-up with a median follow-up of survivors of 10 years. Ten-year OS and EFS rates for all patients were 63% (±3%), and 57% (±3%), respectively.

Seventy of 280 patients were not randomised and received therapy as to the decision of the treating physician (maintenance chemotherapy, 18; sandwich chemotherapy, 52).

3.1. *Long-term survival according to stage and assessability*

Overall, 187 patients (67%) had complete staging assessments and central histopathological review. Patient characteristics are shown in Table 1. Rates for OS and EFS according to metastasis stage and assessability are shown in Table 2. OS and EFS were different for staging (OS: $p = 0.002$, Fig. 1; EFS: $p = 0.002$, Fig. 2). OS of 93 patients with incomplete staging (10-year OS 63 ± 5%) was worse than OS of M0 patients (10-year OS 73 ± 4%, $p = 0.077$), and better than OS of M1 (10-year OS 53 ± 9%, $p = 0.400$) and M2/3 patients (10-year OS 43 ± 8%, $p = 0.029$) (Fig. 1).

Forty-five of 114 fully assessable patients with M0 disease were treated with immediate radiotherapy and maintenance chemotherapy. These patients had a better EFS and OS compared to 69 patients treated with sandwich chemotherapy (10-year OS 91 ± 4% and 62 ± 6%, $p = 0.001$; Fig. 3). Residual tumour of any size was detected by postsurgical MRI in 32 of 114 M0 patients, and was not associated with an impaired outcome for EFS and OS. Ten-year OS rate of these patients was 75% (±8%), compared to 73% (±5%) for 82 patients without residual tumour ($p = 0.679$). Size of the residual tumour was below 1.5 cm^2 in 25 of 32 patients (1 unknown size). One of six patients with a residual tumour of at least 1.5 cm^2 had a relapse.

M1 disease without macroscopic metastases (M2/3) was diagnosed in 33 fully assessable patients. Ten-year EFS and OS of 17 patients with M1 treated in the maintenance arm was better compared to 16 children treated in the sandwich arm (10-year OS 70 ± 12% and 34 ± 12%, $p = 0.020$; Fig. 4).

In contrast, the sequence of therapy had no influence on OS of 40 fully assessable patients with M2/3 metastases (sandwich arm, 19 patients: 10-year OS 45 ± 12%, maintenance arm, 21 patients: 10-year OS 42 ± 11%, $p = 0.990$; Fig. 5).

3.2. *Multivariable analysis of clinical risk factors*

Stepwise selection identified incomplete staging and metastases ($p = 0.001$), age at primary surgery ($p = 0.005$) and therapy (as treated) ($p = 0.006$) as independent risk factors for OS. Hazard ratios as compared to M0 stage increase from 1.54 for patients with incomplete staging to 2.11 for M1 stage, and to 3.06 for M2/3 stage (Table 3). Higher age at primary surgery had a positive impact on survival (HR, 0.93). Furthermore, sandwich chemotherapy (as treated) was associated with less favourable outcome compared to immediate radiotherapy followed by maintenance chemotherapy (HR, 1.76) (Table 3).

3.3. *Dose modifications of maintenance chemotherapy in M0 and M1 patients*

Maintenance chemotherapy was administered to 62 fully assessable patients with M0 or M1 disease. Six of 62 patients received less than four cycles: one because of progressive disease after the second cycle of chemotherapy, and five due to parent's decision. Two of them had a relapse 0.6 and 5.4 years after primary surgery, respectively, and four patients were alive without evidence of disease 5.9–12.4 years after primary surgery. These patients were excluded from the following analysis. Fifty-six patients received four or more cycles of chemotherapy. Chemotherapy was discontinued due to toxicity in 6 of 56 patients (four cycles, one; six cycles, three; seven cycles, two). Of those 50 patients who were given eight cycles of chemotherapy as intended by the protocol, 20 received the full dose of chemotherapy in the last cycle. Overall, dose reductions of chemotherapeutic agents due to toxicity were done in 40 of 56 patients (71%). Reasons for dose reductions were neurotoxicity (21 patients; grades 3, 4; grades 4, 1), ototoxicity (20 patients; grades 3, 2; grade 4, none; see dose reduction scheme in Section 2), vomiting or cachexia (12 patients; grade 3: 3; grade 4: 1), and myelosuppression (15 patients). In 19 of 40 patients, more than one toxic side-effect

Table 1 – Patient characteristics and assessability.

	Complete staging $n = 187$	Incomplete staging $n = 93$
Median age (years)	7.6	7.3
Gender		
Female	66 (35%)	35 (38%)
Male	121 (65%)	58 (62%)
Therapy – as treated		
Sandwich	83 (44%)	44 (47%)
Maintenance	104 (56%)	49 (53%)
Residual tumour	54 (29%)	27 (29%)
Metastases		
M0	114 (61%)	18/18[a] (19%/19%[a])
M0/1 (no CSF cyt.)		26/3[a] (28%/3%[a])
M1	33 (18%)	2/2[a] (2%/2%[a])
M2/3	40 (21%)	6/6[a] (6%/6%[a])
No spinal MRI		41/19[a] (44%/20%[a])

Patient characteristics according to completeness of staging. Abbreviations: CSF cyt., cerebrospinal fluid cytology; MRI, magnetic resonance imaging.
a Number of patients without central histopathological review.

Table 2 – Univariable Kaplan–Meier analyses of prognostic factors in 280 patients.

	n	10-y EFS (±SE)	p	10-y OS (±SE)	p
M0	114	65% (±5)		73% (±4)	
Therapy			0.004		0.001
Maintenance	45	83% (±6)		91% (±4)	
Sandwich	69	53% (±6)		62% (±6)	
Residual tumour			0.746		0.679
R0	82	65% (±6)		73% (±5)	
R+	32	63% (±9)		75% (±8)	
M1	33	54% (±9)		53% (±9)	
Therapy			0.023		0.020
Maintenance	17	71% (±11)		70% (±12)	
Sandwich	16	36% (±12)		34% (±12)	
M2/3	40	36% (±8)		43% (±8)	
Therapy			0.812		0.990
Maintenance	21	32% (±11)		42% (±11)	
Sandwich	19	40% (±12)		45% (±12)	
Incomplete staging	93	57% (±5)		63% (±5)	
Therapy			0.355		0.392
Maintenance	44	62% (±8)		66% (±7)	
Sandwich	49	54% (±7)		60% (±7)	

Influence of therapy (as treated) according to metastasis stage and assessability. Abbreviations: n, number; p, p-value of the log-rank test; SE, standard error; EFS, event-free survival; OS, overall survival; R0, no residual tumour; R+, residual tumour: any residual tumour visible on postsurgical MRI/CT regardless of size.

was relevant for dose reduction. Table 4 depicts the amount of dose reductions due to toxicity. OS of patients with and without dose reductions due to toxicity was not different: Ten-year OS rates were 80% (±11%) for 16 patients without any dose reduction, and 88% (±5%) for 40 patients with dose reduction ($p = 0.585$, Fig. 6).

3.4. *Patterns of relapse and secondary tumours*

At the time of analysis, relapse or progression was reported in 107 patients (range, 0.1–12.2 years after primary surgery; median, 1.6 years). Thirteen of 107 relapses (12%) were diagnosed more than five years after primary surgery. Time to first relapse was longer with lower initial disease stage. Median time to relapse or progression was 2.0 years, 1.6 years and 1.1 years after M0 disease, M1 disease and M2/3 disease, respectively (Kruskal-Wallis test: $p = 0.028$). Median time to relapse or progression was also longer with increasing age at initial surgery: 1.4 years for patients aged $\leqslant$7.5 years, and 2.0 years for patients with age >7.5 years at diagnosis, respectively (Wilcoxon test: $p = 0.019$).

Site of relapse (local, distant, combined local and distant) was not different according to initial staging (M0, M1, M2/3, generalised Fisher's exact test: $p = 0.429$) and therapy

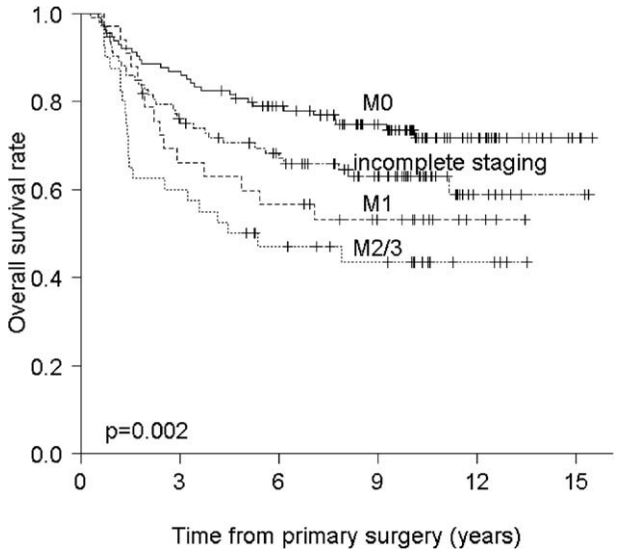

Fig. 1 – Overall survival of patients according to assessability and metastasis stage.

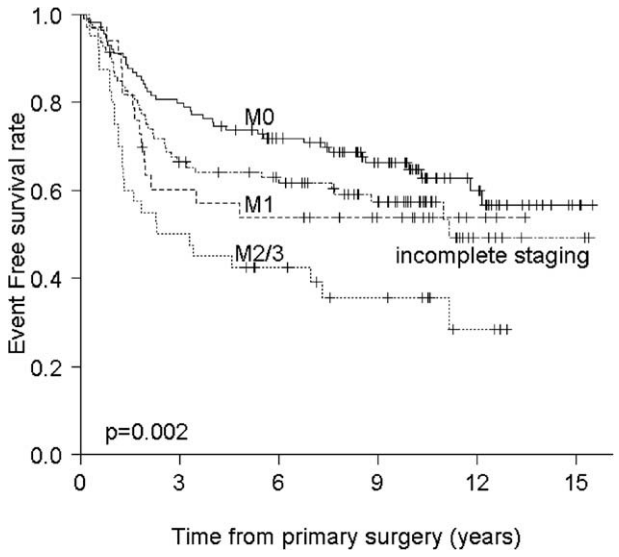

Fig. 2 – Event-free survival of patients according to assessability and metastasis stage.

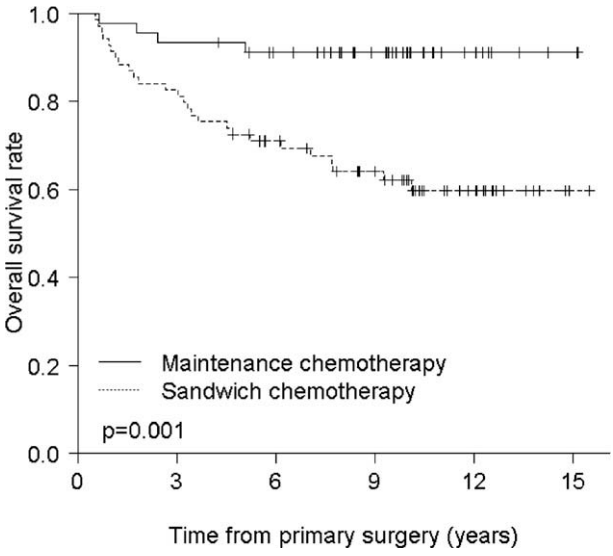

Fig. 3 – Overall survival of patients with complete staging and M0 disease according to therapy (as treated).

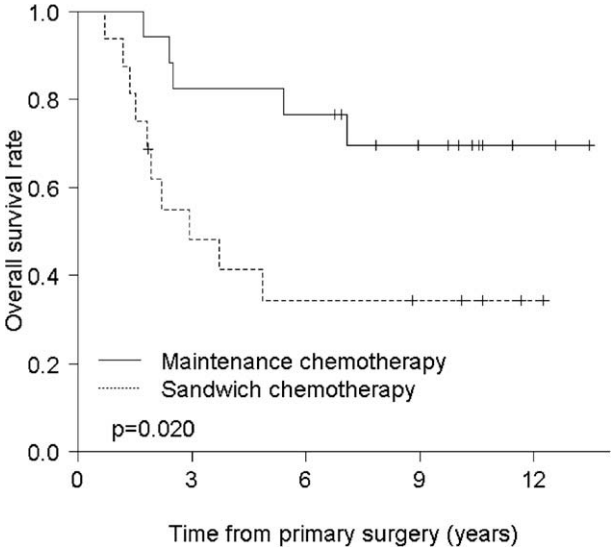

Fig. 4 – Overall survival of patients with complete staging and M1 disease according to therapy (as treated).

(sandwich versus maintenance; generalised Fisher's exact test: $p = 0.773$). Site of relapse was distant in 51 (54%) of 94 relapses occurring within the first five years after primary surgery, combined in 29 (31%) and local in 14 (15%). Site of relapse tended to be more often local in 13 patients relapsing after more than five years (distant, 4 (31%); combined, 4 (31%); local, 5 (38%), Fisher's exact test: $p = 0.096$).

Twelve of 280 patients developed secondary tumours 4.3 to 11.8 years after primary surgery (median, eight years), and eight of these patients were treated in the 'sandwich arm'. Histologies were high-grade glioma (three patients), meningioma (two patients), thyroid carcinoma (two patients), pontine glioma, sarcoma of the skull, malignant melanoma, intestinal adenocarcinoma and osteoma of the jaw. The latter two secondary tumours represent most likely clinical manifestations of an underlying syndromal disease as Turcot syndrome (intestinal adenocarcinoma) and Gardner syndrome. At the time of analysis, four patients had died from their secondary tumour.

4. Discussion

The present study is one of the first reports on a large series of homogeneously treated medulloblastoma patients with long follow-up time. It describes the impact of treatment, clinical risk factors, patient assessability, and chemotherapy dose-modifications on long-term tumour control, and underlines the importance of a sustained follow-up to detect late events and secondary tumours.

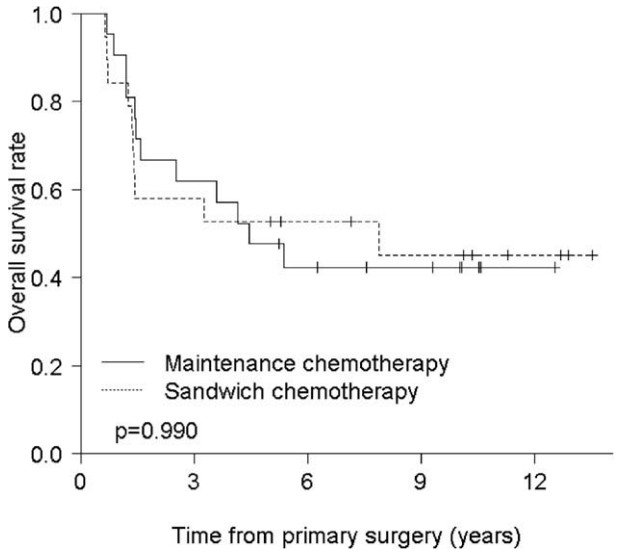

Fig. 5 – Overall survival of patients with complete staging and M2/3 disease according to therapy (as treated).

In our multicentre series, fully assessable patients (with central histopathological review and complete staging) with M0 disease had excellent long-term survival rates (10-year OS, 91%) when treated with immediate postoperative radiotherapy followed by maintenance chemotherapy. In contrast, survival rates of fully assessable M0 patients treated with preradiation chemotherapy were lower (10-year OS, 62%). Since the present study is the only large series comparing sandwich and maintenance chemotherapy regimens containing identical radiotherapy protocols in both treatment groups, the impairment of survival may be best explained by the different sequence of therapy elements. Immediate postoperative radiotherapy is likely to be crucial for optimal disease control in localised disease. This fits to the favourable results of other groups albeit reported with a shorter follow-up so far,[5,13] as well as to the inferior results achieved with preradiation chemotherapy for standard risk medulloblastoma.[19] By contrast, the PNET-3 study reported higher survival rates after preradiation chemotherapy and conventional radiotherapy as compared to conventional radiotherapy alone.[12] Interestingly, an SFOP study using hyperfractionated radiotherapy alone with strict quality control also showed promising results in localised medulloblastoma,[20] which indicates that high quality of radiotherapy is possibly an important contributing factor for the therapeutic outcome. In HIT‘91, radiotherapy protocol violations were detected only in 5% of cases.[17]

As already shown in the previous report on the HIT‘91 study,[10] the presence and size of a postoperative residual tumour again was not a relevant risk factor within the M0 group at longer follow-up. Likewise, in the PNET-3 study, residual tumour had no negative impact on the outcome of M0/1 patients.[12] Comparisons to other studies are difficult, as patients with large residual tumours are treated as high-risk patients in most series. However, our results are in contrast to the CCG-921 study for high-risk patients including M0 patients with either T3b/4 disease and/or residual tumour larger than 1.5 cm^2, where a significant negative impact of postoperative residual tumour was observed in M0 patients.[8] Smaller

Table 3 – Multivariable Cox regression analysis of prognostic factors for overall survival in 280 patients.

	n	HR	95% CI	*p*
Staging				0.001
M0[a]	114			
M1	33	2.11	1.13–3.94	
M2/3	40	3.06	1.76–5.33	
Incomplete staging	93	1.54	0.94–2.52	
Age (in years, continuous)	280	0.93	0.88–0.98	0.005
Therapy (as treated)				0.006
Maintenance[a]	127			
Sandwich	153	1.76	1.17–2.67	

Abbreviations: *n*, number of patients; HR, hazard ratio; 95% CI, 95% confidence interval; *p*, *p*-value of the likelihood ratio test.
a Reference group for comparison.

Table 4 – Absolute numbers of 56 patients with M0 or M1 disease and maintenance chemotherapy, who received the respective number of chemotherapy cycles without dose reduction.

Number of cycles	1	2	3	4	5	6	7	8
Vincristine	52	51	48	45	43	41	36	33
CCNU	53	53	53	51	46	43	36	36
Cisplatin	54	51	52	49	41	38	35	31
All medicaments	49	45	43	38	29	25	20	20[a]

a Four patients had only single, temporary dose reductions and received full dose of chemotherapy at the last cycle.

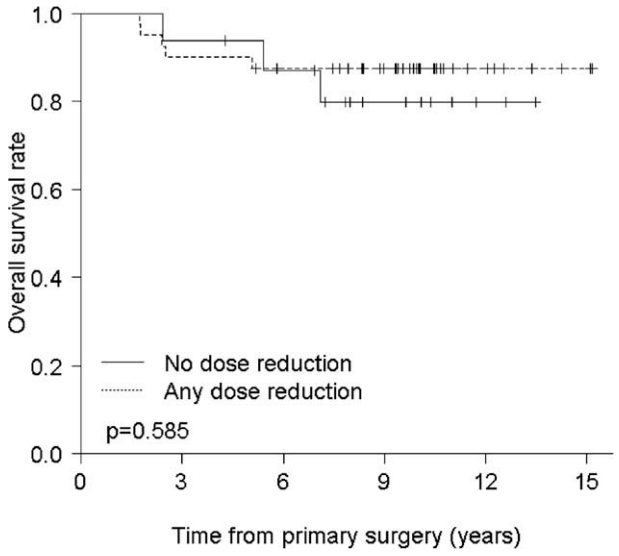

Fig. 6 – Overall survival of patients with complete staging, M0 or M1 disease and maintenance chemotherapy according to chemotherapy dose reductions.

studies failed to show a negative influence of residual tumour within high-risk patients.[6,21,22] As in our study only 6 of 32 patients with M0 and residual tumour had a residual tumour larger than 1.5 cm^2, there is not enough evidence for a definite conclusion. The impact of the extent of resection also depends on the applied treatment regimen, and therefore, its role may become more relevant with less intensive therapy regimens in future.

Our study confirms the negative impact of M1 metastases on survival. Several studies have found an intermediate risk for M1 metastases, with outcome rates lower than in M0 but superior to M2/3 dissemination.[3,7,8,23–25] This is in accordance with our observations showing that the presence of tumour cells in the CSF in an otherwise localised disease was associated with a hazard ratio of 2.1 for death compared to M0 disease, whilst the hazard ratio for death was 3.1 with M2/3 dissemination. As in M0 stage, patients with M1 disease had a significantly better outcome when treated with immediate radiotherapy and subsequent maintenance chemotherapy as compared to preradiation chemotherapy followed by radiotherapy (10-year OS, 70% and 34%, respectively). Although speculative, early craniospinal irradiation might be more efficient in controlling microscopic tumour dissemination than postoperative systemic chemotherapy. Our results obtained in the maintenance arm compare favourably to studies using pre- and postradiation chemotherapy with different regimens.[7,8] However, the evidence of the present study is limited by the rarity of M1 disease and by the lack of adherence to strictly defined diagnostic criteria for M1 stage: It is not known whether the cut-off of 14 days postoperatively as used in most studies is optimal. Given the high impact on treatment stratification, the diagnostic criteria for M1 stage, including CSF-sampling and relevance of sparse tumour cells, should be further specified in the future.

Chemotherapy as used in this study is often associated with relevant toxicity, and chemotherapy modifications are often necessary. In our series, dose reductions due to toxicity were required in 40 of 56 M0 and M1 patients who were treated with maintenance chemotherapy. Similar rates of dose reductions were described by Packer et al. who established this regimen.[13,18,21] Interestingly, there was no negative influence of toxicity-related dose reductions on survival in our series, and to our knowledge this effect has not been analysed by others so far. It remains open, whether differences in pharmacologic metabolism in patients requiring chemotherapy dose reductions can explain our observation. However, our data suggest permissive protocol guidelines for toxicity-related reduction of this type of maintenance chemotherapy in low-risk patients. Future studies may evaluate the safety of less toxic treatment regimens in low-risk patients with a favourable biological risk profile, as candidates have been identified in retrospective series.[6,26]

For patients with gross leptomeningeal disease dissemination (M2/3) the long-term analysis showed no benefit of either one of the treatment strategies. This is in line with the results of the POG 9031 study, which compared the use of chemotherapy before or after radiotherapy for patients with high-risk disease.[27] Comparable results were also obtained by other groups,[7,9] and more recent studies have achieved higher survival rates: In the St. Jude medulloblastoma-96 trial, patients with high-risk disease were treated with high-dose chemotherapy after radiotherapy. Whilst only 9 of 42 included patients with metastatic disease had M1 disease, the five-year EFS was as high as 66%.[6]

Given the median follow-up of 10 years of the surviving patients, our study suggests that there is a relevant risk for late events: Twelve percent of all relapses diagnosed so far occurred more than five years after surgery. As the median follow-up of published medulloblastoma studies rarely exceeds 5–7 years, there are only limited data on the frequency of late relapses in the literature.[28,29] Our data suggest that late relapses occur even after intensive multimodal treatment. We also observed a substantial rate of secondary neoplasms, and the frequency of 12 secondary neoplasms within 280 initially treated patients compares to the cumulative incidence of 4% at 10 years described by others.[30,31] Longer follow-up may be warranted to estimate the real incidence of secondary malignancies.

5. Conclusion

Long-term outcome was excellent for patients with localised disease and maintenance chemotherapy after immediate radiotherapy. Likewise, patients with M1 disease profited from immediate radiotherapy. Toxicity-related reduction of maintenance chemotherapy did not result in inferior survival rates in low-risk patients. Patients who were not fully assessable by staging and histological review had inferior survival rates. Late relapses as well as secondary neoplasms compromised long-term outcome, and patients need to be followed longer for detection of late events.

Conflict of interest statement

None declared.

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