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Treatment of high risk medulloblastomas in children above the age of 3 years: A SFOP study☆

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ABSTRACT

Aim: Improvement of EFS of children older than 3 years with high risk medulloblastoma.
Methods: Between 1993 and 1999, 115 patients (3–18 years, mean 8 years) with high risk medulloblastoma were included. After surgery treatment consisted of chemotherapy ('8in1' and etoposide/carboplatin) before and after craniospinal radiotherapy.
Results: Patients were staged using Chang-criteria (PF residue only, M1 and M2/M3) by local investigator as well as by central review panel (82.4% concordance). Chemotherapy was well tolerated without major delays in radiotherapy. With a mean follow up of 81 months (9–119), 5-year EFS was 49.8% and OS 60.1%. In detail according to subgroups EFS was 68.8% for PF residue only, 58.8% for M1 disease and 43.1% for M2/M3.
Conclusion: M1 patients are legitimate high risk patients. Survival rates are still very low for high risk medulloblastoma patients and future trials should therefore focus on more intensive (chemotherapy/radiotherapy) treatment.

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1. Introduction

Medulloblastoma is by definition a primitive neuro-ectodermal tumour (PNET) arising in the cerebellum or fourth ventricle. Of all malignant brain tumours in childhood it has the highest incidence (20%) with a tendency for leptomeningeal spread. The mean age at diagnosis is 6 years.

Patients may be classified having standard or high risk medulloblastoma. The high-risk factors have been defined in several studies: metastatic disease at brain (Chang stage M2) or spinal level (M3)[1] at diagnosis is the most important negative predictive factor. More debated are the presence of tumour cells in the cerebrospinal fluid (M1) and incomplete surgery.[1,2] Age below 3 years is also correlated with lower outcome but this is partly related to the fact that some therapy-modalities are not possible at this age.[3]

The actual standard treatment for high risk medulloblastomas – at least for metastatic disease – comprises the use of craniospinal radiotherapy (35–36 Gy with a boost up to 55–56 Gy to the posterior fossa and boosts to the metastatic lesions) and chemotherapy after surgery.

Pre-radiotherapy chemotherapy – so-called sandwich chemotherapy – has theoretical advantages of high vascularity of the tumour bed and disruption of the blood-brain-barrier after surgery with a possible higher delivery of chemotherapy drugs, of treatment of microscopic metastases and of reduction of tumour burden before radiotherapy. Moreover haematological tolerance of chemotherapy may be better since skull and spine are not irradiated yet at time of chemotherapy administration.

The primary aim of this prospective study was to increase event free survival (EFS) in children older than 3 years with a high-risk medulloblastoma. EFS at the time of writing of the protocol was about 50%.[4,5] Secondary aims were (1) evaluation of tumour-response to postoperative pre-irradiation chemotherapy; (2) quality control of radiotherapy and (3) set up of a prospective follow up study of neurological, sensorial, psychomotor, endocrine and orthopaedic long term effects.

The benefit of adjuvant chemotherapy for medulloblastoma has been proven in earlier reports.[6,7] Our treatment protocol was designed using the sandwich chemotherapy principle. The chemotherapy '8 drugs in 1 day' and the association etoposide-carboplatin were chosen because of the responses obtained in former studies.[8,9] The particularity of radiotherapy in this protocol was a dose reduction of 36 to 30 Gy on the brain in case of no supratentorial metastases with the intention to diminish neurocognitive sequelae and a dose reduction of craniospinal irradiation to 25 Gy in case of complete remission at start of radiotherapy when residual disease without metastases at diagnosis.

Maintenance chemotherapy after radiotherapy was included using the same drugs.

2. Patients and methods

2.1. Patient selection

Patients between 3 and 18 years old having a high-risk medulloblastoma could be registered after surgery. Inclusion criteria were: no prior chemo- or radiotherapy, no prior treatment for another malignancy, authorisation of legal guardian and no contra-indication for postoperative chemotherapy. Patients were considered high-risk when presence of a measurable residual tumour and/or supratentorial or spinal metastases and/or invasion of cerebrospinal fluid. Patients were classified as R1 when having residual disease only, as M1 when having positive CSF (whatever the status of the residual disease) and as M2/M3 in the case of metastatic disease.[1,10]

After preoperative imaging (MRI in preference) surgery was performed. Cerebrospinal derivation was to the discretion of the local neurosurgeon.

An early CT- or MRI-scan within 48 h after surgery was performed to evaluate the presence of a residual tumour. Further requirements were cytological examination of the CSF by spinal tap (between the 7th and 15th postoperative day), spinal MRI and brain MRI.

2.2. Treatment protocol

2.2.1. Chemotherapy

Adjuvant chemotherapy was started as soon as possible from the 7th postoperative day and consisted of two courses of '8in1' , followed by two courses of etoposide 100 mg/m^2/d and carboplatin 160 mg/m^2/d days 1 to 5. Maintenance chemotherapy started 30 days after irradiation and consisted of two courses of '8in1' alternated with two courses of etoposide 150 mg/m^2/d and carboplatin 200 mg/m^2/d on days 1, 2 and 3. Courses were planned with an interval of 2 weeks after '8in1' and 3 weeks after etoposide/carboplatin.

When chemotherapy could not start before the 30th postoperative day, only one '8in1' course was to be given. A dose reduction of 1/3 had to be applied to the second postoperative etoposide-carboplatin course when this was delayed beyond 28 days after the start of the first course.

Before each chemotherapy course neutrophils were to be $>500 \times 10^6$/L and platelets $>75{,}000 \times 10^6$/L and increasing. Delays in chemotherapy had to be avoided to ensure start of radiotherapy before day 90. Transfusions were given to maintain a platelet count above $50{,}000 \times 10^6$/L throughout the whole treatment because of the risk of CNS bleeding.

2.2.2. Radiotherapy

Irradiation was to be started no later than day 90(±15) after surgery. Patients were treated in prone position for all radiation fields. Immobilisation devices were mandatory and varied among different centres. Radiotherapy was administered in daily fractions of 1.8 Gy, 5 days per week and all fields were irradiated each day. For better thyroid-protection the mobile cranial-spinal junction was set at C6–C7 or C7–Th1. When two fields were required to cover the spinal canal and thecal sac a mobile junction was used and set whenever possible under the spinal cord.

All doses were specified at the posterior margin of the vertebral bodies according to ICRU 50. The total dose on the posterior fossa (PF) was 54 Gy. The dose delivered to the supratentorial compartment was 30.6 Gy and 36 Gy in the case of supratentorial metastases or positive CSF at the end of postoperative chemotherapy. A boost up to 54 Gy was given to solitary supratentorial lesions. Dose to the spinal axis was 36 Gy. Spinal metastases were treated with boosts of 10–14 Gy

below L2 and of 4 Gy when above L2. Craniospinal dose-reduction to 25.2 Gy was given in case of postoperative isolated residual tumour with complete response to postoperative chemotherapy.

For cranial and cervical irradiation, two lateral opposed fields of photons of energy 4–12 MV or cobalt were used and safety margins were specified in order to include all brain parenchyma and meninges with particular attention to the cribriform plate and the temporal lobe. Safety margin below the orbital roof and the upper part of the orbital block was 5 mm and 10 mm between the posterior part of the orbital block and the lowest part of the temporal fossa. The anterior border for the spine was at 5 mm anterior to the vertebra, posterior or superior borders were at discretion of the local radiation oncologist.

Irradiation of the whole posterior fossa was performed with two opposed lateral fields using high energy sources (RX of 25 or 10 MV were recommended). One or two lateral fields of cobalt, RX or electrons were used for the spinal axis. Inferior borders were at S2–S3 or 1 cm underneath the thecal sac visualised on MRI. Width of the fields was at least 6 cm for electrons and 5 cm for photons.

2.3. Histology control

Four neuropathologists of the SFOP have examined the initial histological slides to confirm the diagnosis of medulloblastoma. At the time of central review the subtype of large cell/anaplastic medulloblastoma was not identified separately.[11]

2.4. Radiological control

Four radiologists of the Cerebral Tumour committee of the SFOP have reviewed the pre- and postoperative imaging examinations for the presence of high risk criteria. Patient data files were classified as confirmed (when unequivocal imaging), unconfirmed or doubtful high risk diagnosis or as incomplete data.

Pre-radiotherapy imaging examinations were centrally reviewed for evaluation of response to sandwich chemotherapy. Because classical criteria of partial remission (> or <50%) are difficult to use for leptomeningeal spread lesions, data were classified: as complete remission (CR), as partial remission (PR) when radiological response of lesions was observed in combination with a negative CSF cytology, as stable disease in the case of (a) positive CSF at diagnosis (M1) which remained positive or (b) stable radiological imaging (without progression in CSF cytology) and as progression when progression on imaging or when a negative CSF cytology became positive.

2.5. Radiotherapy control

A retrospective quality control of radiotherapy was performed by eight radiation oncologists of the SFOP. Definition of minor and major deviations was according to radiotherapy targeting guidelines as established in a SFOP study.[12] Records of treatment-planning , simulator films of all fields, port films and dosimetry were reviewed and analysed for deviations without knowledge of patient outcome. Data of quality control were subsequently compared to the pattern of relapse.

2.6. Evaluation after treatment

Post-treatment follow up consisted of clinical examination and brain and spinal MRI in decreasing frequency till 5 years after end of treatment.

Toxicity surveillance included yearly audiometry using the Brock grading system[13] and yearly glomerular clearance. Endocrine follow up was clinical (standing/sitting height), radiological (bone age) and biochemical (growth and thyroid hormones) 2 and 5 years after irradiation or on clinical grounds. In case of clinical (progressing) puberty, serum levels of LH, FSH and estradiol for girls / testosterone for boys were measured. In the occurrence of deficiency, substitution was to be started. Early puberty could be treated with an inhibitory therapy to diminish the risk of a reduced final height.

To evaluate neurocognitive sequelae data were collected on Lansky score during and after treatment, on language and memory skills, on schooling and IQ, on fine motor skills and on need of supportive care (orthophony, physiotherapy and psychological support). Prospectively acquired data of self and parental assessment of health status were analysed by using a validated French version of the Health Utilities Index (HUI) but with variable delays.[14]

2.7. Statistical methods

The main criterion was EFS at 18 months. The study was designed as such that with an estimated 18-months EFS of 50%, inclusion of 100 patients was needed to obtain a 95% confidence interval of ±10%. The following were considered as events: progression (when patient never reached CR) and relapse (for patients in CR) as well as death. Taking in account a recruitment of 20 patients a year, it was estimated that the goal of 100 patients had to be achieved in a period of 5 years.

The Fleming multi-step procedure based on the level of progressions observed during pre-irradiation chemotherapy was implied to be able to stop the study precociously in case of an unacceptable level of progressions. Progression was defined by classical criteria for measurable lesions[10] and by any increase in the number of meningeal lesions. A level of progression inferior to 10% was considered as acceptable, a level above 20% as unacceptable. The risk of accepting the protocol in error thereby set at 8% and the risk of rejecting it in error at 10%. An analysis was made every 20 patients.

Overall survival (OS) and event free survival were estimated by the Kaplan–Meier method and compared by the log-rank test. Survival rates are expressed together with the 1.96 times the standard error.

The review panel studies (pathology, radiology and radiotherapy) were performed after inclusion so results are presented as with intention to treat.

3. Results

3.1. Study population

Between January 1993 and June 1999, 115 patients with an institutional diagnosis of high risk medulloblastoma were eligible for inclusion. Age at diagnosis of the 115 included

patients – 84 boys and 31 girls – varied from 3 to 18 years with a median age of 8 years.

At diagnosis only 17 patients (15.6%) had a normal neurological examination; in 75.4% of patients clinical signs of intracranial hypertension were observed.

3.2. *Pre-operative imaging*

Pre-operative MRI was performed in 105 patients, eight others only underwent CT scan and for two patients pre-operative imaging files were not available.

One hundred and eight tumours were located in the fourth ventricle and/or vermis (including 20 with involvement of a cerebellar hemisphere), six tumours were located in a cerebellar hemisphere only and one tumour in the pontocerebellar angle. Radiographic signs of hydrocephalus were present in 72.8% of cases (83/114).

3.3. *Surgery*

Pre-operative shunting of cerebrospinal fluid was performed in 60% (69) of patients.

Tumour resection was considered as complete in 40.4% (46), as near total tumour resection in 42.1% (48) and as partial in 17.5% (20) of patients. In 28.6% (32) of patients there was no infiltration of the tumour observed by the neurosurgeon, in the other cases tumour infiltration was mostly towards the floor of the fourth ventricle and the cerebral peduncles.

3.4. *Histology*

As reported by the local pathologists 96 patients (84.2%) were diagnosed with classic medulloblastoma and 16 with desmoplastic medulloblastoma. Medullomyoblastoma and PNET were reported in two cases.

3.5. *Postoperative evaluation*

All patients had early postoperative imaging with CT-scan or MRI. Spinal MRI was performed in all patients. A spinal tap was performed in 111 patients with a median postoperative delay of 12 days (range: 1–42). Patients were classified using the Chang criteria by the local investigator, Table 1, column 1.

3.6. *Chemotherapy*

Sandwich chemotherapy could be started in 115 patients with a median postoperative delay of 14 days (3–44). In total 93 patients (80.9%) received the pre-radiotherapy chemotherapy completely. Non administration of a course was mainly due to observe the delay of radiotherapy required by the protocol.

Toxicity was mainly haematological: grade 3 and 4 anaemia and thrombocytopenia. A total of 88 patients necessitated at least one red blood cell transfusion and 102 at least one platelet transfusion during the sandwich chemotherapy period. Grade 3 and 4 infectious episodes occurred in 14 and two patients respectively. There was no toxic death.

Dose reductions were applied in 39 courses mainly because of toxicity. Thirty-four of these reductions took place during the last chemotherapy course.

Table 1 – Review of initial staging

	Local (n = 115) % (n)	Review (n = 92) % (n)
R0M0		**5.4** (5)
R1	**23.5** (27)	**17.4** (16)
M1	**21.7** (25)	**18.5** (17)
M2/M3 (any PF and/or M1)	**54.8** (63)	**57.6** (53)
Uncertain		**1.1** (1)
File insufficient		(23)

Percentages of risk groups at diagnosis as by local investigator and by review panel (bold). Absolute numbers ( ) are more difficult to compare because of the large share of files not available for review.

3.7. *Pre-radiotherapy evaluation*

Response to 'sandwich' chemotherapy was assessed by brain and spinal MRI and by cytological examination of the CSF through spinal tap. MR images were again centrally reviewed. The results of pre-radiotherapy evaluation reported by the local investigators are shown in Table 2, column 1.

3.8. *Radiotherapy*

Because of progression before the required date of irradiation, one patient did not receive radiotherapy as decided by the local investigator.

The median delay between surgery and irradiation was 98 days (67–210). Thirty-one patients started radiotherapy after day 105. No statistically significant difference in OS nor in EFS, could be observed between the patients starting radiotherapy before or after day 98 nor for patients commencing before or after day 105.

The median duration of radiotherapy was 44 days (34–66) with interruptions of radiotherapy for 13 patients and no interruption for 93 patients (no data for eight patients).

The median doses were: 54 Gy (50–58) on the posterior fossa, 30 Gy (25–40) on the brain and 36 Gy (25–39) craniospinal. Of the 17 patients who received a craniospinal dose of 25 Gy, seven did so because of the permitted dose reduction for R1 patients in CR before the start of radiotherapy, two

Table 2 – Radiological response to pre-radiotherapy chemotherapy

	Local (n = 114) % (n)	Central (n = 68) % (n)
CR	**33.3** (38)	**36.8** (25)
PR	**38.6** (44)	**27.9** (19)
Stable disease	**15.8** (18)	**10.3** (7)
Progressive disease	**8.8** (10)	**14.7** (10)
Non evaluable	**3.5** (4)	**10.3** (7)
Not done	(1)	(47)

Percentages of responses to sandwich-chemotherapy as by local investigator and by review panel (bold). Absolute numbers () are more difficult to compare because of the large share of files not available for review.

because of a second surgery with complete resection, three by error, one because of parental refusal and four without a specified reason. In contrast four R1-patients in CR before the start of radiotherapy were treated with a dose of 30 Gy on the brain and 36 Gy (3 pts) or 30 Gy (1pt) on the spine.

Radiotherapy-toxicity was mainly haematological (assessed in 104 patients): 22 patients required red blood cell transfusions, five of whom needed multiple transfusions. Platelet transfusions were given in 31 patients with nine patients having received more than four transfusions. Infectious problems were rare: 13 patients had a febrile episode, nine patients needed antibiotherapy and four Varicella zoster infections were reported.

3.9. *Maintenance chemotherapy*

Sixteen patients did not receive maintenance chemotherapy for different reasons: as according to the protocol, (R1-patients in CR before radiotherapy, 4), because of progressive disease (2), because of investigator's decision (4), because of toxicity (3), for a non-specified reason (2) and because of parental refusal (1).

Maintenance chemotherapy was started in 99 patients with a median delay of 32 days (6–114) after the end of radiotherapy, for nine patients this was more than 50 days. Seven patients started with maintenance chemotherapy even if not required by the protocol (R1-patients in CR before irradiation).

The complete schedule of four courses was administrated in 76 patients, 23 patients received less than four courses (three courses: seven ; two courses: nine and one course: seven).

Haematological toxicity of maintenance chemotherapy has lead to platelet transfusions in 94 patients with a median of four transfusions and to red blood cell transfusions in 84 patients with a median of two transfusions. Grade 3 infections were reported in nine patients and grade 4 in one patient. No toxic death was reported.

3.10. *End of treatment evaluation*

The evaluation at the end of treatment was performed two months after the last chemotherapy course. A total of 105 files have been transmitted to the principal investigator but a complete evaluation with clinical examination, CSF cytology by lumbar tap and brain and spinal MRI was available for 76 patients. Brain MRI was performed in 105 patients, spinal MRI in 91 and lumbar puncture in 81. Seven evaluations were not done because of death prior to the end of treatment and three other evaluation files were not transmitted.

3.11. *Relapses and progressions*

During and after treatment four persistent progressions and 57 relapses were observed. About one quarter (13) of the relapses occurred during sandwich–chemotherapy. The delay for the other relapses ranged from 6 to 88 months after surgery. For classification of relapses according risk criteria see Table 3 (column 1). In nine cases, the relapse was confined to the posterior fossa; 16 patients showed a combined local and distant relapse in the CNS and in 32 cases there was only distant relapse.

3.12. *Stopping rule*

The stopping rule was evaluated every 20 patients, and the upper boundary has never been crossed. Analysis of 100 patients showed that 12 progressions or relapses were observed whereas the upper limit was set at 15 progressions.

3.13. *Survival*

The median follow-up at last update of data was 81 months (range 9–119 months).

Based on the results of all initially enrolled 115 patients , the 18 month-event free survival is 65.9% ± 8.7% compatible with the primary endpoint of the trial. EFS is 54.4% ± 9.1% at 3 years follow up, and 49.8% ± 9.2% at 5 years. OS at 3 year is 68.4% ± 8.5% and 60.1% ± 9% at 5 years follow up. The survival curves are depicted in Fig. 1. Of the 64 survivors at the last update, 54 of them were in first CR, eight were in second CR and two were in progression.

The event-free curves of these 115 patients according to their risk group at diagnosis are shown in Fig. 2a. EFS at 5 years is 56.3% ± 19.9% for R1, 56.0 ± 19.5% for M1 and 44.2% ± 12.3% for M2/M3.

3.14. *Sequelae*

Data on side effects were available for 66 patients (see Table 4).

3.14.1. *Evaluation of health status*

The Health Utility Index (HUI) questionnaire was filled out for 41 (64.1%) of the survivors at last update. In 37 cases (90.3%)

Table 3 – Relapses

	Patient stage at diagnosis according to		Localisation of relapse
	Local investigator (n = 115)	Central review (n = 91)	
R1	12/27	6/16	4/6 PF
M1	10/25	6/17	2 CSF, 2 PF, 2 combined.
M2/M3	35/63	30/53	PF : 7/12 resid + 3/18 resid −
R0/M0		5/5	3 PF

'resid +' = residual tumour at diagnosis; 'resid −' = no residual tumour at diagnosis.

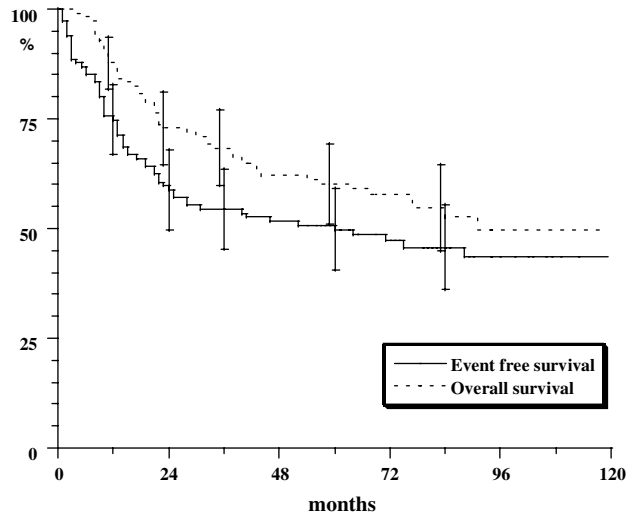

Fig. 1 – Event free survival and overall survival.

by the patients, three times (7.3%) by the parents and one time (2.4%) by both. Median delay of evaluation after surgery was 7 years (4–11 years), with a median age at evaluation of 16 years (9–28 years). The levels for each attribute are shown in Table 5. Cognition and emotion were most frequently affected, 63.4% and 53.7% respectively, followed by pain, vision, speech and ambulation. Overall, the levels on all eight attributes could be calculated for 38 patients, 34 (89.5%) showed at least one altered attribute of the HUI-3 scale. Most frequently the impairment is of level 2 on a scale of 1 (normal) to 6 (severely altered) except for cognition and speech (score of at least 3 in 48.8% and 25.7% respectively). Impairment of only one attribute was observed in 13.2%, of two in 23.7%, of three in 21% and of at least four attributes in 31.6% of patients. General health status was evaluated in the 41 patients. It was good in 26 (63.4%), relatively good in 14 (34.2%) and bad in one (2.4%).

3.15. *Reviews*

3.15.1. *Histology*

Of the 110 centrally reviewed files, 109 cases were confirmed medulloblastomas. Sixteen patients (14.5%) had a desmoplastic medulloblastoma and 93 (84.5%) had a classic medulloblastoma (including the medullomyoblastoma and PNET as reported by the local pathologists). According to our results the subtype of histology was not predictive for final outcome. One patient was withheld by the review panel with a diagnosis of ependymoma (metastatic at diagnosis). For five patients histological slides were not available for central review.

3.15.2. *Radiology*

Review was assessed at two time points: postoperatively and after sandwich chemotherapy. For comparison of classifications at the postoperative stage by local investigator and central review committee see Table 1, column 2. There was complete concordance between the two classifications in 75 cases (82.4%).The discordant cases were five cases with no high risk features, two patients being reclassified as R1-patients because of absence of metastases on central review and nine patients with metastases not reported by the local radiologist.

A second central review of radiographic films was performed, regarding those done before the start of radiotherapy. This evaluation could be completed for only 68 patients out of the 115 patients enrolled (59.1%), the other files were incomplete or not transmitted for central review. Comparison of pre-radiotherapy radiological evaluation – by local investigator and central review – are summarised in Table 2. 63.3% were classified in the same response group. Thirteen patients (21.7%) were 'underestimated' (classified by the local investigator as a lesser response than by the central review panel) and nine patients (15%) were 'overestimated' by the local investigator.

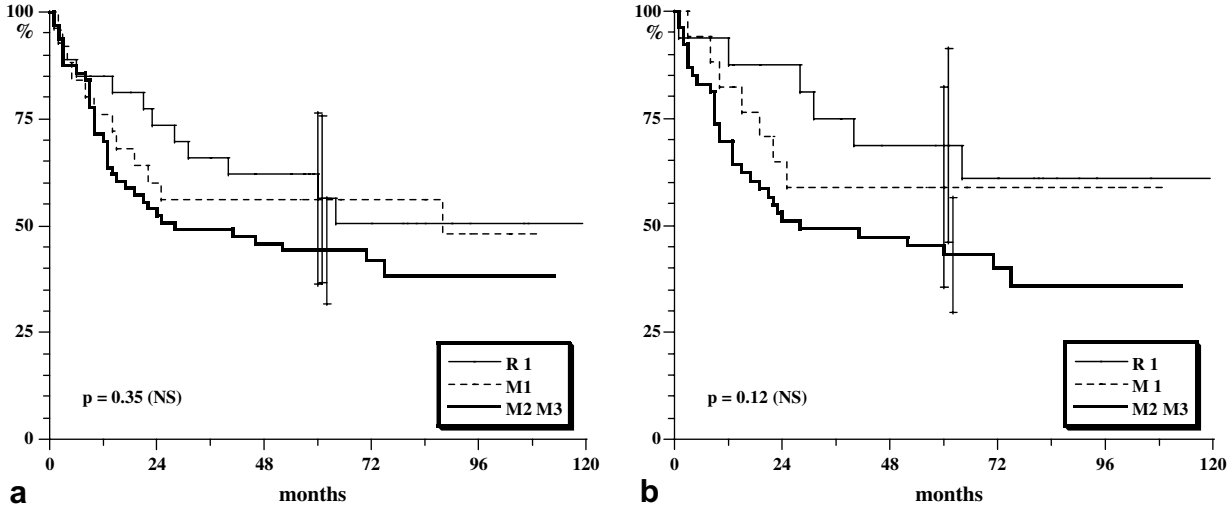

Fig. 2 – (a) Event free survival according to initial risk group staging. (b) Event free survival according to reviewed risk group staging.

Table 4 – Sequelae

	Number of pts evaluated	*n*(%)
Neurological impairment[a]		
Walking difficulties	66	30 (45.5%)
Writing difficulties	63	31 (49.2%)
Motor deficit	65	10 (15.4%)
Cranial nerve sequelae	64	12 (18.8%)
Epilepsy	65	0 (0%)
Change of laterality	62	3 (4.8%)
At least one neurological impairment	66	38 (57.6%)
Schooling[a]	62	
Behind at school before the diagnosis		2 (3.2%)
Normal school without assistance		31 (50%)
Normal school with assistance		14 (22.6%)
Special school		17 (27.4%)
Normal school but with more than 2 years behind		21 (33.9%)
Need for specialised management[a]		
Speech therapy	65	22 (33.8%)
Physiotherapy	66	26 (39.4%)
Psychological support	65	29 (44.6%)
Other support, usually occupational therapy	63	23 (36.5%)
At least one form of assistance	66	45 (68.2%)
Auditory sequelae	44	
Normal hearing		29 (65.9%)
Grade 1 toxicity		8 (18.2%)
⩾Grade 2 toxicity		7 (15.9%)
Endocrine sequelae[a]	65	
Hormone replacement therapy		47 (72.3%)
GH		39 (60.0%)
Thyroid		28 (43.1%)
Other hormone replacement		7 (10.8%)
Puberty-delaying treatment		10 (15.3%)
Alopecia	64	
No alopecia		19 (29.7%)
Limited to the posterior fossa field		24 (37.5%)
Limited to the supra-tentorial area		1 (1.6%)
Posterior fossa field and supra-tentorial area		20 (31.2%)
Intelligence quotient (IQ)	42	
Median global IQ		86
Median performance IQ		79
Median verbal IQ		92

a Not exclusive.

3.15.3. *Relapse patterns*

For patients with a central reviewed risk group, the site of relapse was re-analysed (Table 3). When looking within each risk group, four out of six R1 patients relapsed within the posterior fossa (two of them combined). When subdividing the M2/M3 group in those with and those without residual tumour at initiation of therapy, seven out of 12 with and three out of 18 without showed a posterior fossa relapse. In the M1 group, two CSF-only, two posterior fossa and two combined relapses were observed.

3.15.4. *Survival*

The survival data according to risk group at diagnosis were recalculated based on the 86 centrally reviewed – and classified as high risk – data files. EFS at 5 years is 68.8% ± 22.7% for R1-patients, 58.8% ± 23.4% for M1 patients and 43.1% ± 13.4% for M2/M3 patients. Survival curves are depicted in Fig. 2b.

3.15.5. *Radiotherapy*

A total of 104 patient files (90.4%) were available for central quality control. For 71 children (68.3%) no major deviations were observed, one major deviation in 23 patients (22.1%) and more than one in ten patients (9.6%). EFS was not significantly different for patients with no or one deviation or for patients with two or more deviations, as depicted in Fig. 3.

4. Discussion

During a 6 year and 6 month period, 115 patients with a high risk medulloblastoma were enrolled, an incidence rate of 17.7 cases/year. These data as well as the age-distribution (3–18 years) with a median of 8 years and the male predominance are consistent with data published in literature.

Since the recognition of criteria such as postoperative tumour residue and metastatic spread which influence outcome of children with medulloblastoma and because of age related sequelae, age and risk-adapted therapy has been applied by most collaborative groups.

At present standard risk patients are generally treated with maximal resection followed by chemotherapy and craniospinal radiotherapy (25 Gy and a boost upto 55–56 Gy to the posterior fossa). Several studies using different chemotherapy regimens report similar event-free survivals of about 65–75% at 5 years[15,16] and some current studies are focused on lowering the radiotherapy dose to 18 Gy.[17]

The criteria for high risk medulloblastoma are not very clear and have been debated in many studies. Chang stages M2/M3 are accepted by all groups as high risk features. By limiting inclusion to patients above the age of 3 years we did not evaluate the influence of young age on outcome. M1 disease is not clearly defined as a high risk feature throughout literature. Several studies excluded M1 patients from their high risk group.[5] Some authors found M1 to be compatible with high risk disease,[2] while others claim the opposite, as for example the German HIT'91 study, where young age and M2/3 were significant prognostic factors and M1 and/or residual disease were not.[4] In our study we found that patients with M1 disease (with/without residual mass) are real high risk patients with no significantly different outcome compared to patients with solid metastases.

The extent of surgery or the presence of residual tumour is another factor which has not been proven in all studies to be of high risk.[2,6] In the present study, patients with residual tumour were eligible, even in the absence of other high risk features (solid metastases or positive CSF). This is confirmed by our relapse data revealing that those patients with a localized residual tumour (R1 patients) have a higher incidence of localised recurrences. Posterior analysis of the size of the residual tumour using the 1.5 cm^2 cut off value as used in other studies could not reveal any significant differences may be because groups were too small to obtain reliable statistical results. Our survival data show an EFS of

Table 5 – Distribution of the HUI-3 attribute levels

Attribute (HUI3)	Total	Attribute levels, *n* (%)						Children with impairment in attribute, *n* (%)
		1	2	3	4	5	6	
Vision	41	25 (61)	16 (39)	–	–	–	–	16 (39)
Hearing	41	40 (97.6)	1 (2.4)	–	–	–	–	1 (2.4)
Speech	39	25 (64.1)	4 (10.2)	9 (23.1)	–	1 (2.6)	nd	14 (35.9)
Ambulation	40	26 (65)	12 (30)	–	1 (2.5)	1 (2.5)	–	14 (35)
Dexterity	41	33 (80.5)	4 (9.8)	–	1 (2.4)	2 (4.9)	1 (2.4)	8 (19.5)
Emotion	41	19 (46.3)	17 (41.5)	5 (12.2)	–	–	nd	22 (53.7)
Cognition	41	15 (36.6)	6 (14.6)	2 (4.9)	12 (29.2)	4 (9.8)	2 (4.9)	26 (63.4)
Pain	41	23 (56.1)	14 (34.1)	4 (9.8)	–	–	nd	18 (43.9)

nd: not defined.
For each attribute five or six levels of capacity are predefined. An attribute is impaired when it is not at level 1.

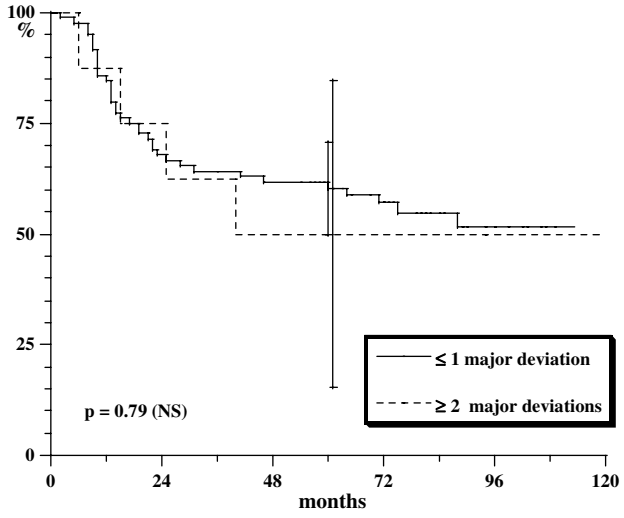

Fig. 3 – Event free survival according to quality control review of radiotherapy.

56.3% ± 19.9% at 5 years. This result is not significantly different than that of M1 patients (56.5% ± 19.5%) nor of metastatic patients (44.2% ± 12.3%). In contrast to R1 patients, patients with M1 disease have a higher proportion of metastatic failures.

The outcome of high risk patients has always been poor. Over many years research has been directed towards pre-radiotherapy chemotherapy. The present study was designed in view of the theoretical advantages of this sandwich-chemotherapy.[18] The choice of '8 drugs in 1 day' and etoposide-carboplatin was based on results of earlier studies.[8,9] Moreover '8in1' has a low risk for thrombocytopenia, permitting its use in the early postoperative phase. Carboplatin was chosen for maintenance chemotherapy to reduce the risk for hearing impairment in patients with elevated doses of cisplatinum and irradiation of the central nervous system.

Sandwich chemotherapy has been used in several studies, with or without the use of maintenance chemotherapy. The French M7 study (1985–1988) showed a 7-year PFS of 57% for children with metastatic disease using '8in1' before and after radiotherapy.[19] While central review showed a great discordance in risk grouping in the SIOP II trial (1984–1989) no benefit for 'sandwich' chemotherapy was shown (EFS: 56.3% *versus* 52.8%) but the authors speculated that the chemotherapy may have been used at sub-optimal doses.[5] In the CCG-921 study it was concluded that the sandwhich arm with '8in1' was inferior to the PCV regimen due to either delayed timing of radiotherapy or the reduced vincristine dose intensity (EFS: 45% *versus* 63%).[2] The German HIT'91 study (1991–1997) observed a high response rate in the sandwich-CT arm, but a higher rate of interruptions of subsequent radiotherapy and extended overall treatment time. This may have adversely affected the final outcome.[4]

With our study protocol we obtained an overall 5-year EFS of 49.7% and OS of 60.1%, data which seem to be consistent with, but not better than, the overall results obtained in these other studies. Results of these studies should be interpreted with caution since sub-groups of high-risk patients were often very small and thus of little statistical relevance.

For the subgroup of M2/M3 patients our study yields a 5 year EFS of 43%. This is again comparable with the 40% of the CCG-921 and the 40% of the HIT'91. The SIOP/UKCCSG PNET3 study observed a 5 years EFS of 34.7% for M2/M3 patients as published recently.[20] The subgroup of M1 patients has not been evaluated (separately) in all studies. The 5 year survival rate of 59% in this study is equal to the 57% in the HIT'91. For R1-patients 5 year survival rates are 65%, 70% and 68% (SIOPII, CCG-921 and HIT'91 respectively), again comparable to the 69% in our study.

Efficacy evaluation showed that about 64.7% of patients obtained an objective response with sandwich chemotherapy. These are similar results as obtained with pre-radiotherapy CT in an early study by Pendergrass *et al.* (57%), in the German HIT'88/'89 pilot study (67%) and the HIT'91 study (41.6% for patients with residual tumour and 56.5% for M2/M3 disease).[4,21,22] However, response to sandwich chemotherapy in our study was not predictive for final outcome.

We observed 12% progressions before start of radiotherapy comparable to the 16.1% progressions seen in HIT'91 and the 9.6% in POG-9031 study.[4,23] These progressions may be attributed to the controversial delay of radiotherapy intrinsic to the principle of sandwich chemotherapy. Timing

of radiotherapy differed considerably between the several studies testing this sandwich chemotherapy making it difficult to compare the results in terms of delay of start of radiotherapy. Radiotherapy in our study could take start with a median delay of 98 days after surgery but for 27% of patients it was started after day 105 (start according to protocol at day 90 ± 15). For patients starting before or after both delays, no statistically significant difference, neither in OS nor in EFS, could be observed. Several studies have shown the influence of total duration of radiotherapy on outcome,[24,25] but interruptions of radiotherapy were not very frequent in our study (11.4%) and median total duration of radiotherapy was 44 days (range: 34–66 days).

In most studies craniospinal radiotherapy was used at standard doses of 35–36 Gy. By analogy with the standard risk patients, in the present study a dose reduction to 25 Gy was used for R1 patients in CR at the start of irradiation and a dose reduction of 36–30 Gy to the brain in the absence of supratentorial metastases. These dose reductions have not led to more relapses as there were no significant differences observed between the survival curves of the different risk groups, but data should be seen with caution given the small number of patients.

The quality of craniospinal irradiation is very important in terms of relapse and many criteria are involved. The number of major deviations in radiotherapy is associated with an increased risk in tumour relapse.[12] The 5-year EFS in our study was not statistically different for patients with no or one major deviation or for patients with more than one, possibly due to the low number of patients (eight patients) but also because the impact of a deviation might be less when the dose is higher and thus less risk for irradiation below the critical radiotherapy dose.

Only 66% of patients received the complete maintenance chemotherapy, mainly because of haematological toxicity. This can be attributed to the previously received sandwich chemotherapy and craniospinal irradiation. It is difficult to say if omitting the maintenance chemotherapy for R1 patients in CR before irradiation is legitimate, since this was a very small subgroup (only four patients), but none of them relapsed.

Prospective evaluation of cognitive sequelae is very important in a multicentre study. A complete neurocognitive assessment of attention, temporospatial orientation, reasoning, writing and language, in addition to precise assessment of other sequelae, allows a more adapted management of these children in order to improve their integration. Impairment of higher functions is often evaluated by a delay in schooling.[26] But this is not a useful tool for comparing results of different international studies, because of the differences in educational systems. The need for special schooling appears to be more reliable. In our study, about 25% of children required special schooling, which is comparable to other series.[26–28] The HUI questionnaire is a very practical tool in multi-centre prospective studies because it is simple and reproducible and the results can be easily collected in patient cohorts.[14] Emotion and cognition were most frequently impaired, whereas speech and cognition scored a higher degree of impairment. Neurological sequelae affected mostly gait or writing.

5. Conclusion

The criteria of high risk medulloblastoma have been much debated over the years. From the data of our study, we can conclude that the M1 patient group is a legitimate high risk group, with a higher proportion of metastatic relapse in contrast to patients with residual tumour who are more prone to local failure. For the latter group treatment should therefore be focussed on second-look surgery and/or higher more focussed irradiation to the residual tumour. At present, the survival rates of children with a high risk medulloblastoma are still not very encouraging. Further research on histological sub-typing and other biological factors which may influence the outcome has to be conducted to reach better survival rates for these children.[29] Targeted treatments may play a more important role in future treatment regimens.

The results of our study indicate again the need for an improved treatment for high-risk medulloblastoma. The EFS and OS data are within the range as seen in other studies but are not satisfactory. More intensive treatments, be it with more intensive chemotherapy as for example marrow ablative chemotherapy in metastatic patients[30,31] or with other radiotherapy modalities have to be investigated. The use of hyperfractionated[32,33] or accelerated radiotherapy can be one of the tools to reach better survival. The theoretical advantages of sandwich chemotherapy have not shown to be of real benefit in our study and the risk of postponing radiotherapy, and with it the increased risk of early progression will always be a difficult issue. However this problem may be partially avoided by the use of haematological stem cell support in regimens with sequential high dose chemotherapy.

Conflict of interest statement

None declared.

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