

Cerebrospinal fluid M staging for medulloblastoma: Reappraisal of Chang's M staging based on the CSF flow

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Tumor seeding is a strong negative prognostic factor for patients with medulloblastoma. Because Chang's M staging is based primarily on CT and myelographic findings and might be contradictory to the direction of normal cerebrospinal fluid (CSF) flow, seeding patterns and appropriate staging of medulloblastoma need to be revisited in patients diagnosed in the MRI era. We retrospectively reviewed the clinical and radiological data of 86 patients with a diagnosis of medulloblastoma who were treated in the MRI era. The presence of seeding in each subarachnoid space compartment and the patterns of seeding were analyzed in correlation with patient survival data. Thirty-four patients had gross seeding on perioperative MRI. Thirty-two patients had seeding in the spinal compartment. Sixteen and 12 patients had seeding in the infratentorial and supratentorial compartments, respectively. There was an apparent hierarchy of seeding (ie, from seeding in the spinal compartment up to the supratentorial compartment). Patients with seeding in the spinal compartment had longer progression-free survival ($P = .038$) and a tendency toward better overall survival ($P = .053$) compared with patients with seeding in intracranial compartments. We modified Chang's M staging based on the CSF flow and termed this approach "CSF M staging." CSF M staging for medulloblastoma, in which intracranial seeding occupies a higher rank than

spinal seeding, was a better predictor of patient prognosis. This modified staging method may be applied to metastatic staging of brain tumors located in the fourth ventricle.

Keywords: cerebrospinal fluid, medulloblastoma, prognosis, seeding, staging.

Medulloblastoma, a lethal brain tumor of childhood, is highly malignant in nature, and dissemination via the cerebrospinal fluid (CSF) pathway is common.¹ Surprisingly, the introduction of craniospinal irradiation and chemotherapy has enhanced the survival of patients with medulloblastoma, up to 70%.^{2,3} However, more than one-third of the patients still die of the disease. Moreover, the treatment policy for this tumor is changing, reducing craniospinal irradiation to prevent long-term neurological sequelae following high-dose irradiation in survivors.^{4,5} Therefore, a sophisticated risk evaluation procedure for individual patients based on precise prognostication is warranted to balance the needs for higher survival rates and fewer treatment-related toxicities.⁶

Several clinical factors have been associated with the prognosis of patients with medulloblastoma. Young age (<3 years), a large residual tumor, dissemination of a tumor at presentation, involvement of the brainstem, and anaplastic histology have been correlated with a poor prognosis, although the prognostic importance of some of the factors has been debated.^{6,7}

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Tumor dissemination at presentation is found in about 30% of patients with newly diagnosed medulloblastoma and, according to several studies, is one of the worst prognostic factors for this disease.^{8,9}

In 1969, Chang et al.¹ published a seminal article on the classification of the clinical stages of medulloblastoma. The classification, termed Chang's staging, consists of local tumor extension stages (T stages) and tumor dissemination stages (M stages), which is reminiscent of the TNM staging used for solid tumors in other organs.^{1,10} Although the utility of T staging has been refuted, Chang's M staging has been adopted widely in the field of neuro-oncology.^{7,8,11} Chang's M staging is a simple and practical scheme that is highly relevant for the prognosis of patients.

However, Chang's M staging has several shortcomings. First, it is based primarily on CT and myelographic findings. Currently, MRI is the main diagnostic and staging modality for patients with medulloblastoma. CT and myelography were used to determine M staging of some patients in many studies that included patients treated over several decades.^{11–13} Therefore, the seeding patterns and appropriate staging of medulloblastoma need to be revisited in patients diagnosed in the MRI era. Second, in Chang's scheme, seeding in the spinal subarachnoid space (SAS) ranked higher (M3 stage) than seeding in the intracranial SAS, including the supratentorial compartment (M2 stage). This might be somewhat contradictory to the normal CSF flow from the fourth ventricular outlet to the spinal SAS and on to the intracranial SAS.¹⁴ If tumor cells dislodge from the primary mass in the fourth ventricle, the majority of them will descend along the CSF flow to the spinal SAS and then ascend to the intracranial SAS. In Chang's M staging, this physiological conjecture is reversed. The staging of a disease needs to be reasonable in both conceptual and prognostic dimensions. Therefore, the hierarchy of M staging needs to be critically reviewed based on patient survival data.

In this study, we evaluated the preoperative M staging of 86 patients with medulloblastoma, all of whom received a diagnosis and were treated in the MRI era. The long-term treatment outcome was analyzed in correlation with M staging. We propose that modification of Chang's staging would enhance the prognostic value of preoperative M staging in patients with medulloblastoma.

Patients and Methods

Data Sources

The institutional review boards of Seoul National University Hospital and Seoul National University College of Medicine approved the study protocol. We accessed data in the medical records of Seoul National University Children's Hospital, Seoul National University Hospital, and Seoul National University Bundang Hospital. Information on patient characteristics, such as age and sex, and disease characteristics,

including tumor size, location, and pathology, were collected from the electronic medical records. Detailed information on treatment was supplemented with operation records, chemotherapy sheets, and radiotherapy sheets from each department concerned, which were not fully available electronically. Treatment outcome was confirmed from the medical records of each medical facility, and death certificate information was obtained from the National Statistical Office and the Ministry of Public Administration and Security.

Patient Selection and Database Construction

Patients diagnosed with medulloblastoma and treated at Seoul National University Children's Hospital, Seoul National University Hospital, or Seoul National University Bundang Hospital from January 1997 to February 2008 were eligible for this study. We included only patients for whom perioperative brain and spinal contrast-enhanced MRIs were available for review. A minimum clinical follow-up period of 24 months from the time of surgery was required, with the exception of patients who died before 24 months. Ninety-seven patients were diagnosed with medulloblastoma and treated from January 1997 to February 2008. Ten patients were excluded because their perioperative contrast-enhanced MRI results were unavailable for review. One patient was excluded because he was lost to follow-up immediately after surgery, without further appropriate treatment. Therefore, 86 patients were included in the study population.

We developed a structured data extraction form, and data were input via double entry. Brain and spinal MRIs were reviewed independently by a neuroradiologist (I.-O.K.) and 2 other authors, and disagreements were resolved by discussion of the case. To prevent overestimation of spinal seeding, we did not regard thin linear enhancement along the spinal cord as dissemination. Only linear enhancement with nodular components was considered as meaningful. Seeding patterns were analyzed as follows: gross compartments of the SAS (spinal, infratentorial, and supratentorial), specific locations, and shape (nodular or diffuse leptomeningeal). Because the staging of all patients was based on the MRI instead of the CT and myelography, Chang's M staging was defined by the MRI results supplemented by lumbar CSF cytology data. Death certificate data were merged with the electronic medical record data using the patient identification number as a unique identifier. After a manual check of inconsistent cells, the database was locked for the analysis.

Statistical Analysis

We presented the characteristics of participants with a seeding pattern of the tumor and calculated manually the conditional probability of metastasis among the CSF compartments to generate the hypothesis of hierarchy in tumor spread. Although some authors contended that Chang's classification was not in agreement with

CSF physiology, all of us agreed to start from a clean slate, without any assumption of misclassification by the old staging method. The results of the calculations were interpreted based on the simple premise that findings from the advanced stage of disease tend to arise after those from the early stage of disease, which will be especially true for conditions such as tumor metastasis. This tendency will lead to the relative rarity of the presence of advanced-stage findings in the absence of early-stage findings. In other words, the probability of observing advanced-stage findings in the condition of early stage disease will be smaller than the probability of observing early-stage findings in the condition of advanced stage disease.

We then used the log-rank test to compare the survival of patients with M2 and M3 stage disease, as assessed using Chang's classification and the new classification. The Cox proportional hazards model was used to analyze the usefulness of the M staging system to predict the prognosis of patients, adjusting for possible confounding factors with a P value $< .1$ in the univariate analysis. In addition to such well-known prognostic factors as young age (< 3 years), a large residual tumor, and anaplastic histology, we planned to control for potential confounding factors by adjusting for sex and year of treatment. Progression of disease was defined as documentation of new enhancing lesions or growth of previous residual lesions ($> 25\%$ in two-dimensional analyses) on follow-up brain and/or spinal MRI. All participants were followed from the date of surgery until the date of death or until March 18, 2010, whichever came first.

The relationship between dichotomous variables was assessed by the χ^2 test. For comparison of continuous variables between groups, we used the Student t -test and analysis of variance (ANOVA). The P values were two-sided, with significance set at $P < .05$. The SPSS 17.0 software (SPSS Inc.) was used in the statistical analyses.

Results

Demographic Characteristics and Clinical Profile

The median age at diagnosis was 7 years (range, 8 months to 36 years). Of the 86 patients, 13 (15%) were under the age of 3 years and 4 patients (5%) were over the age of 18 years at diagnosis. Fifty-nine patients (69%) were male, and 27 patients (31%) were female.

All patients had preoperative contrast-enhanced brain MRI. The tumor was located in the midline—the fourth ventricle and vermis—in 75 patients (87%). Eleven patients (13%) had a tumor with a lateral location (in the cerebellar hemisphere in 9 patients and in the cerebellopontine angle in 2 patients). All patients had contrast-enhanced whole-spine MRI, either preoperatively (54 patients, 63%) or postoperatively (32 patients, 37%). Postoperative spinal MRI was obtained within 2 weeks (2–13 days) in 14 patients and delayed

over 2 weeks (14–21 days) in 18 patients. Although ventricular CSF cytology was obtained from the majority of patients before or at the time of surgery, lumbar CSF cytology was obtained postoperatively in 33 patients (38%). Thirty-five patients (41%) exhibited seeding of the tumor in perioperative neuroimaging studies and/or lumbar CSF cytology. There was no significant difference in the rate of positive spinal MRI according to the time of spinal MRI (preoperative, within 2 weeks, and after 2 weeks; $P = .189$, ANOVA).

Treatment and Follow-up

All patients received maximal decompressive surgery. The extent of resection was evaluated using a postoperative brain MRI, which was acquired in all patients within 48 h of operation. Gross total resection with no residual mass in the primary site was confirmed in 63 patients (73%). Ten patients (12%) had a large residual tumor ($> 1.5 \text{ cm}^2$), which is a known poor prognostic factor.¹⁵ Pathological examination revealed a classic medulloblastoma in 61 patients (71%), a desmoplastic variant in 11 patients (13%), and an anaplastic variant in 14 patients (16%).

Radiation therapy (RT) was administered to all patients over 3 years of age, with radiation deferred until the age of 3 years for younger patients. RT consisted of craniospinal irradiation, a booster to the primary site, and a booster to localized spinal metastases, if indicated. The median radiation doses were as follows: 23.4 Gy to the whole brain (range, 12.6–54.0 Gy), 23.4 Gy to the whole spinal cord (range, 0–36.5 Gy), and 28.8 Gy to the posterior fossa (range, 0–30.6 Gy) as a booster. One patient could not receive the scheduled spinal irradiation because of disease progression during RT. Boosters to localized spinal metastases were administered to 22 patients at a median dose of 10.8 Gy (range, 6.0–22.5 Gy). A booster to localized supratentorial seeding was delivered to only 1 patient (10 Gy). Chemotherapy was administered to 83 patients (97%). Two patients could not receive chemotherapy because of a poor medical condition resulting from disease progression or surgical complications. One patient refused chemotherapy after RT. The Children's Cancer Group (CCG) 9931 and 9921 protocols were applied to patients assessed before 2001 (19 patients).^{16,17} The eight-drugs-in-one-day regimen was applied to patients assessed between 2001 and 2004 (36 patients).¹⁸ The Korean Society for Pediatric Neurooncology (KSPNO) protocol for medulloblastoma was applied to patients assessed from 2005 (21 patients); this protocol consists of risk-adapted craniospinal RT followed by chemotherapy with CDDP (*cis*-diamminedichloroplatinum), cyclophosphamide, etoposide, and vincristine. Four patients received chemotherapy based on carboplatin, vincristine, and etoposide. Two patients received a regimen that consisted of CDDP, CCNU (chloroethylcyclo-hexylnitrosourea), and vincristine. One patient received chemotherapy based on methotrexate, vincristine, etoposide, and cyclophosphamide.



Fig. 1. Medulloblastoma seeding in the SAS. (A) Leptomenigeal seeding in the spinal SAS. Nodular enhancement was found along the surface of the spinal cord and at the end of the thecal sac (arrows). (B) Diffuse leptomenigeal seeding in the infratentorial SAS compartment. Nodular and linear enhancement was observed along the tentorial surface of the cerebellum (arrowheads). (C) Extensive leptomenigeal seeding in the supratentorial SAS compartment. Thick leptomenigeal enhancement was observed in the bilateral sylvian fissures (white arrows) and in the interhemispheric fissure (black arrow). Thick enhancement was also found in the quadrigeminal cistern and in the sulci of the superior cerebellar vermis (arrowheads).

Table 1. Seeding of medulloblastoma assessed by perioperative brain and spinal MRI and/or lumbar CSF cytology

Subarachnoid space compartment	No. of patients	Specific seeding pattern	No. of patients
Supratentorial compartment	12	Seeding in the suprasellar area	7
		Diffuse leptomenigeal seeding	6
		Discrete nodular seeding	3
Infratentorial compartment	16	Seeding in the prepontine/interpeduncular cisterns	10
		Seeding on the cerebellar surface	11
Spinal compartment	32	Diffuse leptomenigeal seeding (cervico-thoracic area)	25
		Diffuse leptomenigeal seeding (lumbo-sacral area)	24
		Single drop seeding	4
Positive lumbar CSF cytology	7	With gross seeding on MRI	6
		Without gross seeding on MRI	1

The mean follow-up period was 50 months (range, 5–169 months). The 49 patients (57%) who survived to the last follow-up are currently being followed up in the outpatient clinic.

M Staging

Tumor seeding was found in the perioperative brain and/or spinal MRI in 34 patients (40%). Seven patients had positive findings for lumbar CSF cytology. Thirty-two patients (37%) had seeding in the spinal compartment. Sixteen patients (19%) had seeding in the infratentorial compartment. Twelve patients (14%) had seeding in the supratentorial compartment (Fig. 1).

The specific location and shape of seeding are summarized in Table 1.

Six of the 7 patients with positive findings for lumbar CSF cytology also had gross seeding in the spinal compartment; only 1 patient had positive lumbar CSF cytology results without gross seeding on MRI. Among the 16 patients with seeding in the infratentorial compartment, 15 patients also had seeding in the spinal compartment. Among the 12 patients with seeding in the supratentorial compartment, 10 patients had seeding in the infratentorial compartment and 11 patients had seeding in the spinal compartment (Fig. 2). There was only one case each of isolated seeding in the supratentorial and infratentorial compartments. This pattern of seeding indicates that there is a hierarchy of seeding in

Positive lumbar CSF cytology	Spinal compartment	Infratentorial compartment	Supratentorial compartment
1	1	1	1
	2	2	2
	3	3	3
	4	4	4
	5	5	5
	6	6	6
	7	7	7
	8	8	8
	9	9	9
	10	10	10
2	11	11	
	12	12	
	13	13	
	14	14	
	15	15	
3	16		11
4	17		
5	18		
6	19		
	20		
	21		
	22		
	23		
	24		
	25		
	26		
	27		
	28		
	29		
	30		
	31		
	32	16	
			12
7			

Fig. 2. Patterns of seeding in medulloblastoma. Red represents the presence of seeding in the corresponding compartment of SAS. Green represents the absence of seeding in the corresponding compartment. White represents a lack of evaluation for the compartment (ie, no lumbar tapping was undertaken). Each horizontal row corresponds to one patient. Numbers were consecutively attributed to patients who were positive for seeding in each compartment.

the SAS compartments, from the spinal compartment up to the supratentorial compartment. Nonetheless, according to Chang's M staging, in which seeding in the spinal compartment takes a higher rank than intracranial SAS, in our study population 51 patients (59%) corresponded to the M0 stage (no seeding), 1 patient (1%) corresponded to the M1 stage (positive CSF cytology), 2 patients (2%) corresponded to the M2 stage (intracranial seeding), and 32 patients (37%) corresponded to the M3 stage (spinal seeding). Table 2 shows patient characteristics and treatment according to seeding patterns.

Survival and Relevant Prognostic Factors

For the 86 patients, the actuarial progression-free survival (PFS) rates were 61% in the second year and 51% in the fifth year. The median PFS was 74 months. The actuarial overall survival (OS) rates were 76% in the second year and 57% in the fifth year. The median OS

was 72 months (95% confidence interval [CI] = 42–102 months). There were significant differences in both PFS and OS between patients without seeding (M0 stage) and patients with seeding (M1–3 stages; Fig. 3; $P < .001$ and $P < .001$, respectively; log-rank test).

A multivariate analysis using the Cox proportional hazards model revealed that age < 3 years at diagnosis ($P = .003$, relative risk [RR] = 3.284, 95% CI = 1.485–7.262), anaplastic histology ($P = .003$, RR = 3.409, 95% CI = 1.527–7.614), and seeding ($P < .001$, RR = 4.034, 95% CI = 2.094–7.770) were significantly correlated with shorter PFS (Table 3). However, only tumor seeding ($P = .001$, RR = 3.227, 95% CI = 1.641–6.348) was significantly correlated with shorter OS in multivariate analyses (Table 4). Therefore, in our patient cohort, tumor seeding was the most important prognostic variable for survival.

Seeding Patterns and Other Prognostic Factors

In 34 patients with documented seeding on MRI, seeding in the intracranial compartments was significantly related to anaplastic histology compared with seeding in the spinal compartment only ($P = .020$; χ^2 test). Six of 18 patients with seeding in the intracranial compartments showed anaplastic histology, whereas none of the patients with seeding in the spinal compartment had only anaplastic histology. Sex, age < 3 years at diagnosis, lateral tumor location, and large residual tumor ($> 1.5 \text{ cm}^2$) were not significantly related to seeding patterns.

Survival According to Seeding Patterns

According to Chang's M staging, 32 patients corresponded to the M3 stage and only 3 patients corresponded to the M1 or M2 stages. Therefore, the PFS and OS of patients with M3 stage were inherently close to the survival of all patients with seeding (35 patients). Although the M0 and M3 stages were clearly differentiated in survival curves, there was virtually no discriminative power among M1–3 stages because of the small number of patients in the M1 and M2 stages in Chang's scheme.

On the basis of the apparent hierarchy in seeding patterns in SAS compartments, we divided the 34 patients who exhibited gross seeding on MRI into 3 groups: patients with seeding exclusively in the spinal compartment (SP group, 16 patients), patients with seeding in the infratentorial compartment but not in the supratentorial compartment (IT group, 6 patients), and patients with seeding in the supratentorial compartment (ST group, 12 patients). An IC group represented patients with seeding in the intracranial compartment and was the sum of the IT and ST groups (18 patients).

The median PFS was longer for the SP group (18 months; 95% CI = 0–54 months) than for the IT group (8 months; 95% CI = 0–20 months), ST group (7 months; 95% CI = 0–15 months), or IC group

Table 2. Patient characteristics and treatments according to seeding pattern

M stage	No seeding (CSF M ₀)	Positive CSF cytology (CSF M ₁)	Spinal seeding only (CSF M ₂)	Intracranial seeding (CSF M ₃)
Number	51	1	16	18
M: F	33:18	1:0	12:4	13:5
Age at diagnosis (year)	9.1 ± 6.9	18.0	6.6 ± 4.6	5.8 ± 3.6
Age <3 y at diagnosis	6 (12%)	0	3 (19%)	4 (22%)
Lateral tumor location	9 (18%)	0	0 (0%)	2 (11%)
Anaplastic histology	8 (16%)	0	0 (0%)	6 (33%)
Large residual tumor (>1.5 cm ²)	4 (8%)	1	1 (6%)	4 (22%)
Radiation dose to supratentorial area (Gy)	25.8 ± 6.0 (n = 45)	36	29.6 ± 5.0 (n = 16)	30.4 ± 6.2 (n = 17)
Radiation dose to infratentorial area (Gy)	53.7 ± 1.5 (n = 46)	54	52.7 ± 3.1 (n = 16)	49.6 ± 8.3 (n = 17)
Radiation dose to spinal cord (Gy)	24.7 ± 3.6 (n = 44)	36	27.2 ± 4.9 (n = 15)	27.9 ± 9.5 (n = 15)
Booster to spinal seeding (Gy)	9.1 ± 2.7 (n = 5) ^a	Not applied	12.3 ± 5.7 (n = 10)	11.5 ± 4.7 (n = 7)
Chemotherapy regimen	9931/9921 (n = 7); 8 in 1 (n = 23); KSPNO (n = 14); Carboplatin-VCR-VP16 (n = 2); CCNU-CDDP-VP16 (n = 1); Others (n = 3); None (n = 1)	CCNU-CDDP-VP16 (1)	9931/9921 (n = 6); 8 in 1 (n = 6); KSPNO (n = 3); Carboplatin-VCR-VP16 (n = 1)	9931/9921 (n = 6); 8 in 1 (n = 6); KSPNO (n = 4); None (n = 2)

^aThese patients received booster radiation to presumed spinal seeding in the past, but retrospective reviews of spinal MRIs concluded that it was vascular enhancement rather than spinal seeding.

(8 months; 95% CI = 2–14 months). The median OS was longer for the SP group (69 months; 95% CI = 9–129 months) than for the IT group (12 months; 95% CI = 0–31 months), ST group (25 months; 95% CI = 23–27 months), or IC group (25 months; 95% CI = 23–27 months). There was no difference in survival between the IT group and the ST group. Compared with the IC group, the SP group had PFS that was significantly longer ($P = .038$, log-rank test) and OS that was longer but did not quite reach significance ($P = .053$, log-rank test; Fig. 4).

On the basis of these data, we modified Chang's M staging by basing it on the CSF flow and termed this approach "CSF M staging" for medulloblastoma (Table 5). In CSF M staging, the CSF M₀ stage represents no evidence of seeding; the CSF M₁ stage corresponds to positive lumbar CSF cytology without gross seeding in MRI; the CSF M₂ stage corresponds to gross seeding in the spinal SAS; the CSF M₃ stage represents gross seeding in the intracranial SAS, including both the supratentorial and infratentorial compartments; and the CSF M₄ stage is reserved for the rare patients with extraneural metastasis at presentation. Figure 5 shows the plots of the PFS and OS according to the proposed CSF M staging in our patient cohort.

Discussion

Staging of cancer is of paramount importance. Patient stratification, selection of treatment, and patient counseling all depend heavily on the stage of the cancer. Moreover, staging of cancer is a unified language used by oncologists in the design of clinical studies and interpretation of data.¹⁹ In the brain, where extirpation of the whole organ is impossible and virtually no lymphatic system is found, traditional T and N staging is of no, or limited, clinical value. In contrast, tumor seeding along the CSF pathway is a poor prognostic factor for many malignant brain tumors, including medulloblastoma. Tumor seeding at presentation was the strongest predictor of poor outcome in medulloblastoma, in this and other studies.^{8,9}

Chang's M staging has been used for decades. The 2 basic concepts underlying the staging are the division of microscopic (M₁ stage) and macroscopic (M₂/M₃ stages) seeding and the division of SAS compartments into spinal (M₃ stage) and intracranial (M₂ stage) compartments. Chang's M staging, which is basically dependent on CT and myelographic findings, inevitably exhibits some discrepancy with the detailed visualizations provided by MRI.¹⁸ This discrepancy has been relieved, however, as many clinicians use a virtually

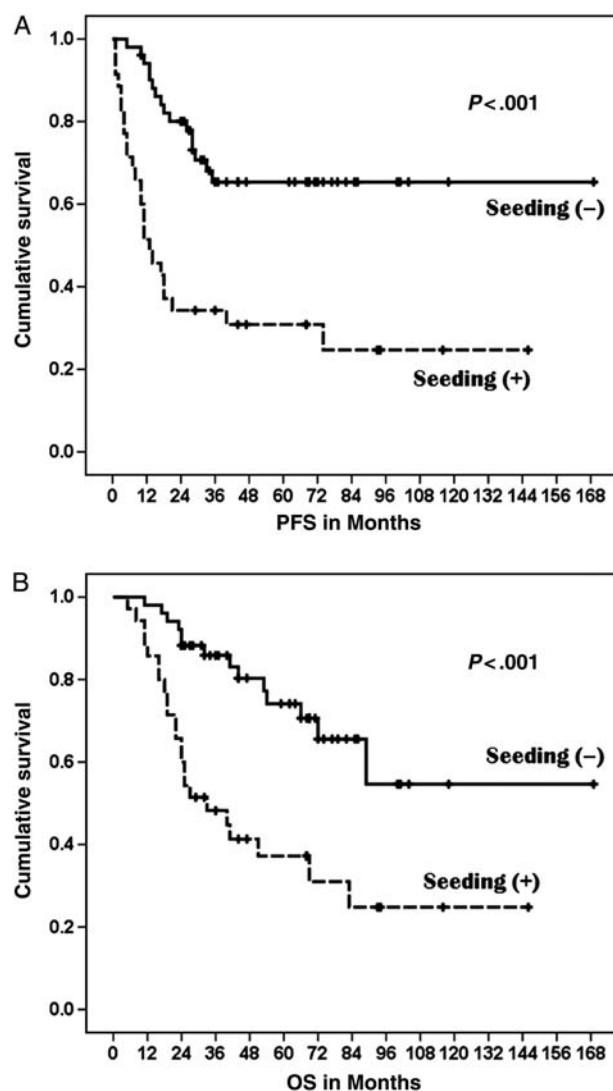


Fig. 3. Kaplan-Meier survival plots for PFS and OS according to the status of seeding at presentation. There were significant differences in PFS and OS between patients without seeding (M0 stage) and patients with seeding (M1–3 stages; $P < .001$ and $P < .001$, log-rank test).

Table 3. Relative risks for shorter PFS estimated with a Cox proportional hazards model

Clinical factor	Univariate analysis			Multivariate analysis		
	<i>P</i> value	RR	95% CI	<i>P</i> value	RR	95% CI
Sex (male) ^a	.990	0.996	0.516–1.923	.299	0.697	0.353–1.377
Age <3 years at diagnosis	.010	2.674	1.267–5.642	.003	3.284	1.485–7.262
Year of treatment	.194	0.938	0.851–1.033	NA	NA	NA
Lateral tumor location	.415	0.651	0.232–1.828	NA	NA	NA
Anaplastic histology	.057	2.062	0.978–4.346	.003	3.409	1.527–7.614
Seeding at presentation	<.001	3.531	1.879–6.634	<.001	4.034	2.094–7.770
Large residual tumor (>1.5 cm ²)	.958	1.028	0.366–2.891	NA	NA	NA

RR, relative risk; CI, confidence interval.

^aSex was included in the multivariate analysis model as a basic variable.

unaltered staging system after substituting MRI for the older imaging modalities. In fact, many studies with a long inclusion period used both CT and MRI data for

M staging.^{12,13} However, the proportion of patients in each M stage determined purely by MRI remains obscure. In this study, which was conducted in the

Table 4. Relative risks for shorter OS estimated with a Cox proportional hazards model

Clinical factor	Univariate analysis			Multivariate analysis		
	P value	RR	95% CI	P value	RR	95% CI
Sex (male)	.356	1.409	0.681–2.917	.639	1.195	0.568–2.516
Age <3 y	.605	1.260	0.525–3.024	.502	1.355	0.558–3.292
Year of treatment	.756	0.982	0.876–1.101	NA	NA	NA
Lateral tumor location	.551	0.729	0.258–2.061	NA	NA	NA
Anaplastic histology	.126	1.928	0.832–4.466	NA	NA	NA
Seeding at presentation	<.001	3.292	1.689–6.417	.001	3.227	1.641–6.348
Large residual tumor (>1.5 cm ²)	.609	1.280	0.497–3.294	NA	NA	NA

RR, relative risk; CI, confidence interval.

^aSex and age <3 years were included in the multivariate analysis model as basic variables.

MRI era, patients with M1 and M2 stages composed surprisingly small proportions (1% and 2%, respectively). The small proportion of patients with the M1 stage can be attributed partly to the small number of patients who received a lumbar tap; the invasive lumbar tapping procedure was omitted when discrete seeding was found on MRI. It could also be the result of enhanced resolution of spinal MRI in the detection of leptomeningeal seeding in patients who might have been considered to have M1 stage disease in the absence of spinal MRI. However, the small proportion of patients with the M2 stage cannot be explained by the enhanced sensitivity of MRI, as it affects both the brain and spinal MRI.

Although the prognostic value of the M1 stage has been questioned and remains controversial, little doubt exists regarding the prognostic validity of the M2 and M3 stages.^{7,8,11} Glioma disseminates mainly through white matter tracts, whereas medulloblastoma usually disseminates through the SAS via the CSF flow. A ventriculostomy is required frequently in patients with medulloblastoma to control intracranial pressure. Ventricular CSF can be obtained during the procedure. However, cytological examination of ventricular CSF correlates with a high false-negative rate and is of little value for M staging because it lies upstream of the tumor in the CSF pathway.²⁰ Under normal conditions, CSF flows from the ventricles to the spinal SAS, and then on to the supratentorial SAS via the infratentorial SAS.¹⁴ A fraction of the CSF flows directly from the fourth ventricular outlet to the intracranial SAS, but this represents a minor contribution compared with the main flow of the CSF.^{21,22} Therefore, the spinal SAS can be largely considered as being upstream of the intracranial SAS in the CSF pathway.

In our study, the majority of patients with seeding in the supratentorial SAS also had seeding in the infratentorial and spinal SAS. Isolated seeding in downstream compartments (ie, supratentorial SAS or infratentorial SAS) without seeding in the spinal SAS was rare. This finding suggests that there is a hierarchy in the pattern of medulloblastoma seeding: it tends to dislodge from the primary tumor, first to the spinal SAS, and then up to the intracranial SAS via the directional flow of the CSF. Although the intracranial SAS is apparently closer

to the primary tumor in the fourth ventricle compared with the spinal SAS, it is more distantly located; thus, it is more difficult for tumor cells to reach and to grow in this location. However, it should be considered that the CSF flow may be perturbed in patients with a large mass in the fourth ventricle and that stagnation of CSF in the spinal SAS, rather than actual CSF flow, may be a greater contributor to the frequent seeding observed in spinal SAS.

Whether the presence of farther-reaching tumor seeding suggests a more malignant tumor nature represents an additional problem inherent to staging. Although much has been learned regarding tumor metastasis, there is little information on the cellular and molecular events related to medulloblastoma seeding along the CSF pathway. Medulloblastoma with anaplastic histology has a poor prognosis according to our study and others.^{23,24} It is also correlated with seeding at presentation.²⁵ In our data, intracranial seeding was significantly related to anaplastic histology and also indicated concomitant seeding in spinal SAS in the majority of patients. Therefore, the extent of seeding in medulloblastoma may reflect the aggressiveness of the tumor's biological nature as well as therapeutic considerations. If seeding is confined to a small area or to one compartment, a booster radiation dose can be readily applied whereas if diffuse seeding is found throughout the whole neuraxis, both the sequelae of the tumor and treatment-associated toxicity become overwhelming. In this study, the shorter PFS and OS observed in patients with the CSF M3 stage compared with that observed in patients with the CSF M2 stage reflected the increased disease burden in patients.

There are some limitations in this study. First, the data collection and analyses were retrospectively performed and treatment was not uniform, especially with regard to radiation dose and chemotherapy regimen. To estimate the influence of varied treatment regimens on prognosis, we added the year of treatment as a variable to survival analyses because treatment regimens changed over time. The year of treatment was not a significant factor that affected PFS and OS, but this cannot completely eliminate the bias of different treatments administered. Further validation

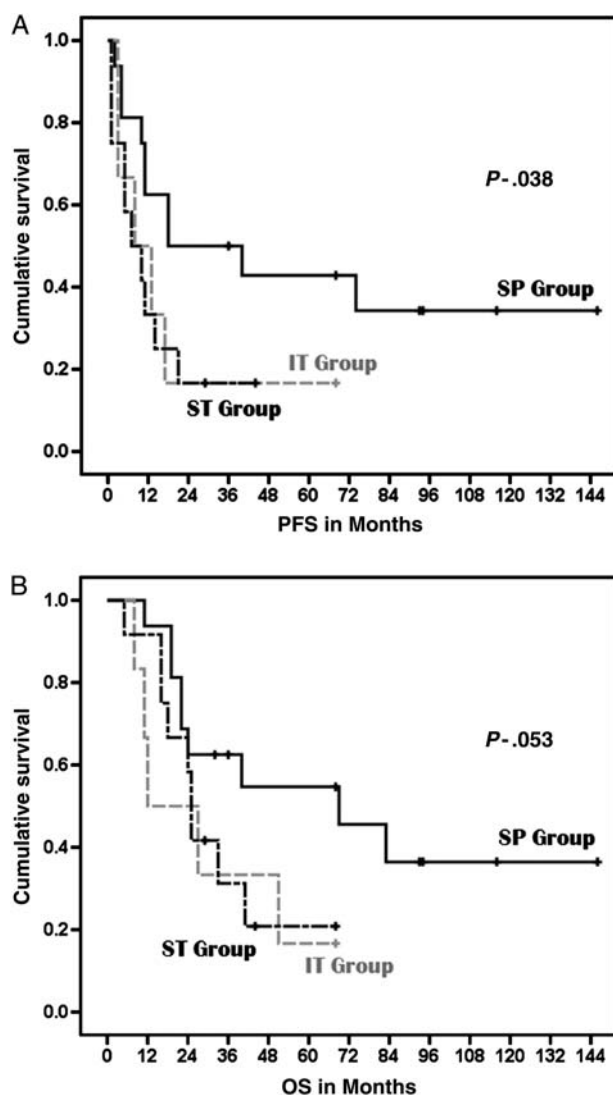


Fig. 4. Kaplan-Meier survival plots according to the seeding patterns. SP group: patients with seeding only in the spinal compartment ($n = 16$); IT group: patients with seeding in the infratentorial compartment but not in the supratentorial compartment ($n = 6$); ST group: patients with seeding in the supratentorial compartment ($n = 12$); IC group: patients with seeding in the intracranial compartment (ST group + IT group; $n = 18$). There was no difference in survival between the IT and ST groups. Compared with the IC group, the SP group had PFS (A) that was significantly longer ($P = .038$, log-rank test) and OS (B) that was longer but did not quite reach significance ($P = .053$, log-rank test).

Table 5. Proposed CSF M staging for medulloblastoma

CSF M stage	Description
CSF M 0	No subarachnoid or hematogenous metastasis
CSF M 1	Microscopic tumor cells found in CSF
CSF M 2	Seeding only in spinal subarachnoid space
CSF M 3	Seeding in intracranial subarachnoid space, lateral and third ventricles
CSF M 4	Extraneuraxial metastasis

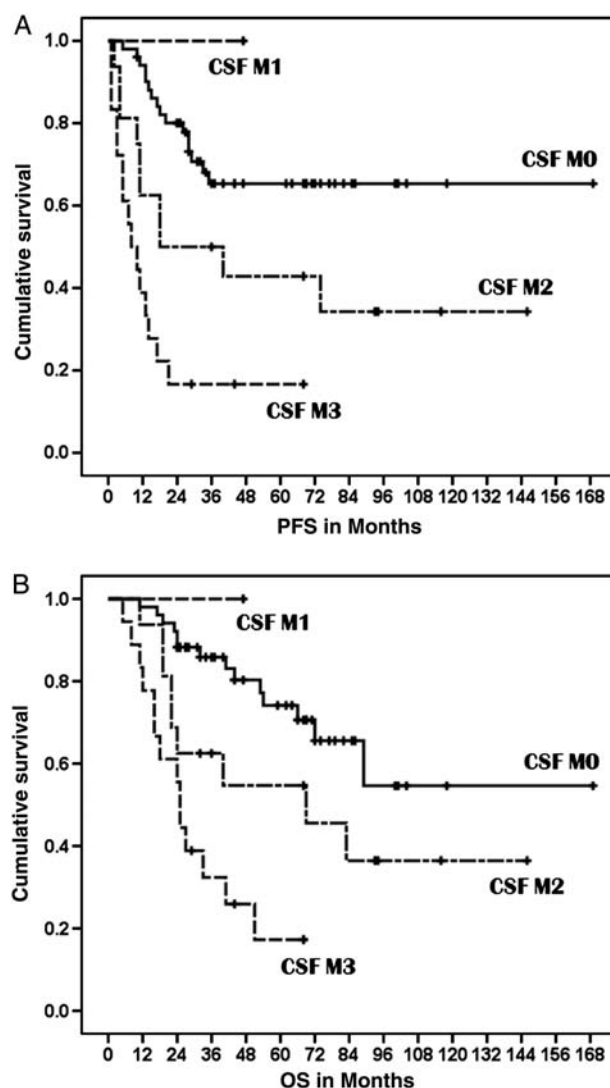


Fig. 5. Kaplan-Meier survival plots for PFS (A) and OS (B) according to the CSF M staging, which was modified from Chang's M staging based on the CSF flow.

of the hypothesis in consistently treated patients is required in future prospective trials. Second, we applied a booster radiation to spinal disseminations in selected patients, but a booster to brain seeding was applied to only 1 patient, partly because spinal seeding was considered more grave than intracranial seeding according to Chang's original scheme in the past. This preferential augmentation of therapy for spinal seeding may enhance the survival of the patients with spinal seeding only. Last, interpretation of spinal MRI is a challenging task in medulloblastoma patients. It is often difficult to distinguish vascular enhancement from spinal seeding. In this study, we tried to reduce the false-positive rate by setting the diagnostic threshold high for spinal seeding, but application of high-tesla MRI and avoidance of post-operative spinal MRI may be helpful in the accurate stratification of patients.

In this study, we proposed “CSF M staging” for medulloblastoma. We included only patients diagnosed and treated in the MRI era, and we applied a standard staging workup for the patients. The proposed staging is conceptually more relevant for the tumor seeding mechanism via the CSF flow. Our survival data also showed that seeding at distant (and multiple) compartments is riskier than seeding at proximal compartments in the CSF flow, just as tumor seeding itself negatively influences the outcome of patients with medulloblastoma, so does the extent of tumor seeding. This CSF M staging could be further applied to other intraventricular brain tumors, such as ependymoma, which readily seed along the CSF pathway. However, this approach might not be suitable for recurrent medulloblastoma and ependymoma because the CSF flow may be perturbed after surgery, especially when CSF diversion procedures such as a third ventriculostomy and ventriculoperitoneal shunt are performed.

Conclusions

We propose a new staging approach, CSF M staging, for medulloblastoma, in which intracranial seeding occupies a higher rank than spinal seeding. This modified staging correlates better with the seeding mechanism along the CSF pathway and with the updated patient survival data; therefore, it may be applied to the metastatic staging of brain tumors in the fourth ventricle.

Conflict of interest statement. None declared.

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