AJNR

Postoperative Evaluation for Disseminated Medulloblastoma Involving the Spine: Contrast-enhanced MR Findings, CSF Cytologic Analysis, Timing of Disease Occurrence, and Patient Outcomes

Steven P. Meyers, Sarah L. Wildenhain, Ja-Kwei Chang, Eric C. Bourekas, Paul F. Beattie, David N. Korones, Denise Davis, Ian F. Pollack and Robert A. Zimmerman

Postoperative Evaluation for Disseminated Medulloblastoma Involving the Spine: Contrast-enhanced MR Findings, CSF Cytologic Analysis, Timing of Disease Occurrence, and Patient Outcomes

Steven P. Meyers, Sarah L. Wildenhain, Ja-Kwei Chang, Eric C. Bourekas, Paul F. Beattie, David N. Korones, Denise Davis, Ian F. Pollack, and Robert A. Zimmerman

BACKGROUND AND PURPOSE: Postoperative MR imaging is routinely performed for staging of medulloblastoma because of frequent tumor dissemination along CSF pathways. The goals of this study were to: 1) determine the timing of disease occurrence and contrast-enhanced MR imaging features of disseminated medulloblastoma involving the spine and their relationship to patient outcomes; and 2) compare the diagnostic accuracy of MR imaging findings with CSF cytologic analysis.

METHODS: Medical records, pathologic reports, and unenhanced and contrast-enhanced postoperative MR images of the spine and head from 112 patients who had resection of medulloblastoma were retrospectively reviewed. MR images of the spine were evaluated for abnormal contrast enhancement in the meninges and vertebral bone marrow. MR images of the head were evaluated for recurrent or residual intracranial tumor. Imaging data were correlated with available CSF cytologic results and patient outcomes.

RESULTS: Twelve patients (11%) had tumor within the spinal leptomeninges depicted on MR images at the time of diagnosis. Twenty-five patients (22%) had disseminated disease in the spine (leptomeninges, n = 22; vertebral marrow, n = 1; or both locations, n = 2) on MR images 2 months to 5.5 years (mean, 2 years) after initial surgery and earlier negative imaging examinations. Eleven other patients (10%) had recurrent intracranial medulloblastoma without spinal involvement seen with MR imaging. Spinal MR imaging had a sensitivity of 83% in the detection of disseminated tumor, whereas contemporaneous CSF cytologic analysis had a sensitivity of 60%. The sensitivity of CSF cytologic analysis increased to 78% with acquisition of multiple subsequent samples, although diagnosis would have been delayed by more than 6 months compared with diagnosis by spinal MR imaging in six patients. Spinal MR imaging was found to have greater overall diagnostic accuracy than CSF cytologic analysis in the early detection of disseminated tumor (*P* = .03). Spinal MR imaging confirmed disseminated tumor when contemporaneous CSF cytologic findings were negative in 13 patients, whereas the opposite situation occurred in only two patients. False-positive results for spinal MR imaging and CSF cytologic analysis occurred when these examinations were obtained earlier than 2 weeks after surgery. The 5-year survival probability for patients with spinal tumor was 0.24 ± 0.08 versus 0.68 ± 0.05 for the entire study group.

CONCLUSION: Spinal MR imaging was found to have greater diagnostic accuracy than CSF cytologic analysis in the early detection of disseminated medulloblastoma. CSF cytologic analysis infrequently confirmed disseminated tumor when spinal MR imaging results were negative. Delaying spinal MR imaging and CSF cytologic analysis by more than 2 weeks after surgery can reduce false-positive results for both methods. The presence of disseminated medulloblastoma in the spine seen with MR imaging is associated with a poor prognosis.

Medulloblastomas are primitive neuroectodermal tumors that occur in the posterior cranial fossa and represent approximately 25% of all intracranial neoplasms in infants and children (1–5). These neoplasms can also occur among adults (3, 6–8). These tumors frequently disseminate along the CSF pathways (1–3, 9, 10), and occasionally metastasize to bone and other sites outside of the CNS. The presence of disseminated medulloblastoma is associated with a poor prognosis (11–14).

Prior to the widespread availability of contrast-enhanced MR imaging, myelography, postmyelographic CT, and CSF cytologic analysis were routinely used for staging of medulloblastoma after initial diagnosis (15–18). Contrast-enhanced MR imaging of the spine has been reported to be more sensitive than myelography in detecting leptomeningeal spread of tumor, and is now routinely used for postoperative staging (19, 20).

The objectives of this study were to: 1) characterize the timing of disease occurrence and the contrast-enhanced MR imaging features of disseminated medulloblastoma involving the spine and their relationship to patient outcomes, and 2) compare the diagnostic accuracy of MR imaging findings with those of CSF cytologic analysis.

Methods

Patient Group

We reviewed the tumor registry files and surgery and pathology reports from five university medical centers and found records of 179 patients who had resection of medulloblastomas from 1988 through 1997. One hundred twelve of these patients had postoperative contrast-enhanced MR examinations of the spine and head at the five medical centers, and were entered into this study. The study cohort consisted of 75 male and 37 female patients. At the time of initial tumor resection, the patients ranged in age from 1 to 71 years (mean, 9.4 yr; median, 8.7 yr). Twenty-three patients were younger than 3 years; 10 patients were older than 18 years. After surgery, all patients received at least either radiation or chemotherapy. Twenty-three patients younger than 3 years at the time of diagnosis received chemotherapy as the initial postoperative treatment. Twenty of these patients subsequently received radiation treatment after the age of 3 years. Postoperative treatment for the other 89 patients included craniospinal radiation and chemotherapy (n = 81), or craniospinal radiation alone (n = 9). Radiation therapy consisted of 52–56 Gy to the posterior cranial fossa and 25–45 Gy to the other intracranial regions and spine. Chemotherapy varied depending on whether the patients were from institutions associated with the Pediatric Oncology Group (n = 37) or Childrens Cancer Group (n = 79).

MR Imaging

MR imaging was performed at 1.5 T. A total of 350 postoperative contrast-enhanced MR studies of the spine and 944 contrast-enhanced MR studies of the head were performed and reviewed for this patient group. Multisection spin-echo pulse sequences were used in all MR studies of the spine and included short-TR/short-TE (400–800/9–20/1–2 [TR/TE/excitations]), long-TR/short-TE (2000–3200/ 15–30/1–2), and long-TR/long-TE (2000–3200/70–100/1–2) sequences. Short-TR/short-TE and long-TR/short-TE images of the spine were obtained in the sagittal plane, and long-TR/long-TE images of the spine were obtained in the sagittal and axial planes. Short-TR/short-TE (400–700/9–20/1–2) images of the head were obtained in the sagittal and axial planes.

MR imaging was performed after IV administration of gadopentetate dimeglumine or gadoteridol (0.1 mmol/kg) by use of short-TR/short-TE sequences (400–900/11–20/1–2). MR images were acquired in the sagittal and axial planes for all patients, and in the coronal plane for 35 patients. Frequency-selective fat-saturation pulses were used for examinations in 41 patients. MR images of the spine were 3- to 5-mm thick, with interimage gaps of 0.3 to 1.0 mm. The acquisition matrix ranged from 256 × 192 to 256 × 512. Short-TR/short-TE images of the head were obtained in the axial plane.

The unenhanced and contrast-enhanced short-TR images of the spine were evaluated for enhancement in the pial-subarachnoidal space. Enhancement was evaluated with regard to location and configuration (nodular, linear, or both). The vertebral marrow in the fields of view was evaluated with regard to abnormal enhancement or abnormal signal alteration or both on the short- and long-TR images. MR images of the head were evaluated for lesions or abnormal enhancement in the brain parenchyma, ventricles, leptomeninges, and dura. All MR images were independently reviewed by one neuroradiologist, with subsequent correlation to the final reports of the examinations from each institution.

CSF Cytologic Analysis

Results from CSF histopathologic examinations were available for 105 patients. A total of 336 CSF samples were obtained after surgery. Two hundred three of the CSF samples were obtained within 2 weeks (mean = 4.4 days, median = 5.0 days) of the MR examinations of the spine, and these results were used for comparisons of diagnostic accuracy of MR versus contemporaneous CSF cytologic analysis for the detection of disseminated tumor.

Statistical Methods

The dates of patient deaths were correlated with the initial surgical dates and dates of initial positive MR imaging findings of the spine and head. The intervals between the dates of last contact for patients without and with disseminated disease or locally recurrent tumor and initial surgery were also determined. Progression-free survival (PFS), ie, time to disease occurrence, and 5-year survival probabilities were calculated using PRISM software (GraphPad Software Inc., San Diego CA). Distributions of PFS and 5-year survival probabilities were estimated using the Kaplan-Meier method (21). In this case control study design, determinations of sensitivity, specificity, and positive and negative predictive values were performed for spinal MR imaging and CSF cytologic analysis by use of the cross-tabulation method, with an independent reference standard for disseminated disease. Criteria for this reference stan-

FIG 1. MR images of 26-year-old man with disseminated medulloblastoma, obtained 6 years after surgery and 3 years after biopsy-proven metastatic skeletal disease.

A, Sagittal (600/9 [TR/TE]) MR image with fat suppression shows thin linear contrast enhancement along the pial surface of the spinal cord (*arrows*). Multiple enhancing skeletal metastases are also present in multiple vertebral bodies. CSF cytologic analysis obtained within 13 days of MR imaging was positive for tumor cells.

B, Sagittal (600/9) MR images with fat suppression, obtained 2 months after *A,* shows progression of disseminated disease, with enhancing tumor surrounding the spinal cord and filling the thecal sac (*arrows*). Four of four CSF samples obtained within 8 days of this MR examination were negative for tumor cells. The patient died 6 months later.

FIG 2. MR image of a 16-year-old boy, obtained 3 years after surgery and 4 years prior to death.

Sagittal (600/20) MR image with fat suppression shows two nodular contrast-enhancing lesions (*arrows*) within the distal thecal sac. Contemporaneous CSF cytologic analysis was positive.

dard were met when at least two of the following were present: positive findings from surgery, biopsy, or autopsy; evidence of disseminated intracranial tumor on MR images; or progressive clinical deterioration, leading to death. This reference standard was available for confirmation of disease in 40 patients. Comparisons of the overall diagnostic accuracy for detection of disseminated tumor between spinal MR imaging and CSF cytologic analysis were made by calculating receiver operating characteristic (ROC) curves for each of the three tests. The areas under the three ROC curves, 1) spinal MR results, 2) results of CSF samples contemporaneous with the spinal MR examinations for the detection of disseminated tumor, and 3) for accumulated results of all CSF samples in the eventual detection of disseminated tumor after surgery, were compared between tests, and two-tailed z-score transformations were used to calculate P values.

Results

MR Imaging

Thirty-seven (33%) of the 112 patients had MR evidence of disseminated medulloblastoma involving the spine. Twelve patients (11%) had contrast-enhancing tumor within the spinal leptomeninges on MR images near the time of diagnosis. Twenty-five (22%) other patients had disseminated spinal disease (leptomeninges, n = 22; vertebral marrow, n = 1; or both locations, n = 2) seen with subsequent MR imaging 2 months to 5.5 years (mean, 2 years) after initial surgery and earlier negative MR imaging examinations. Of the total of 37 patients with MR imaging evidence of disseminated spinal tumor, 25 had simultaneous MR imaging findings of disseminated intracranial tumor, six had dissem-

inated intracranial tumor seen with MR imaging prior to spinal involvement, three had the opposite pattern, and three had no MR imaging evidence of disseminated intracranial disease. Eleven additional patients had residual (n = 1) or recurrent (n = 10) intracranial medulloblastoma (leptomeninges, n = 3; fourth ventricle, n = 2; lateral ventricle, n = 1; middle cerebellar peduncle, n = 1; cerebellum, n = 3) seen with MR imaging, without evidence of spinal involvement.

The leptomeninges were the first site of disseminated tumor in the spine for 35 patients and secondary location in one patient who first had skeletal metastases. One patient had disseminated tumor in the vertebral marrow, shown by MR imaging, and not within the CNS. The initial leptomeningeal enhancement patterns were predominantly linear along the pial margins of the spinal cord (n = 17), linear and nodular (n = 10) along the spinal cord, or nodular subarachnoid lesions (n = 9) (Figs 1–3). Progression of disease was observed as amorphous filling of the thecal sac with contrast-enhancing tumor (Figs 1, 3, 4).

Pial-subarachnoidal enhancement representing subarachnoid tumor was a highly specific (97%) finding for disseminated tumor. False-positive findings for leptomeningeal metastases were encountered in two patients who underwent MR imaging of the spine 3 days after initial surgical resection of a medulloblastoma. These two patients had transient irregular zones of intrathecal material with low-intermediate signal on the short-TR images,
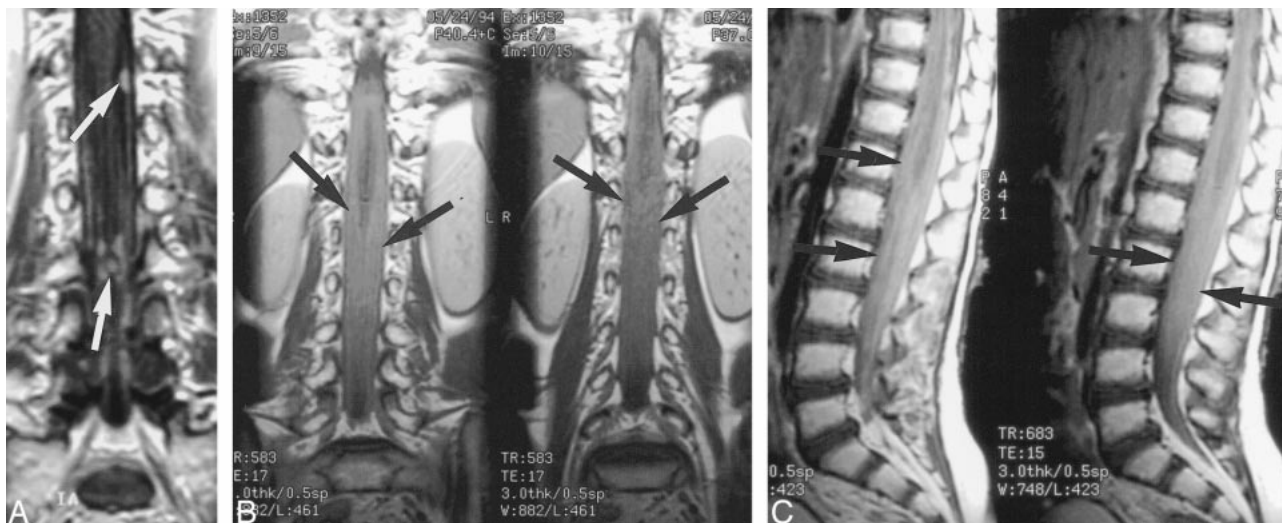
FIG 3. MR images of a 7-year-old girl, obtained 3 years after surgery.

A, Coronal (533/17) MR image shows multiple, small, contrast-enhancing lesions within the thecal sac (*arrows*). Contemporaneous CSF cytologic analysis was positive for tumor cells.

B and *C,* Coronal (583/17) MR images (*B*) and sagittal (683/15) MR images (*C*), obtained 2.5 months after *A,* shows progression of disseminated disease, with amorphous moderately enhancing tumor filling the thecal sac. The patient died 1 month later.
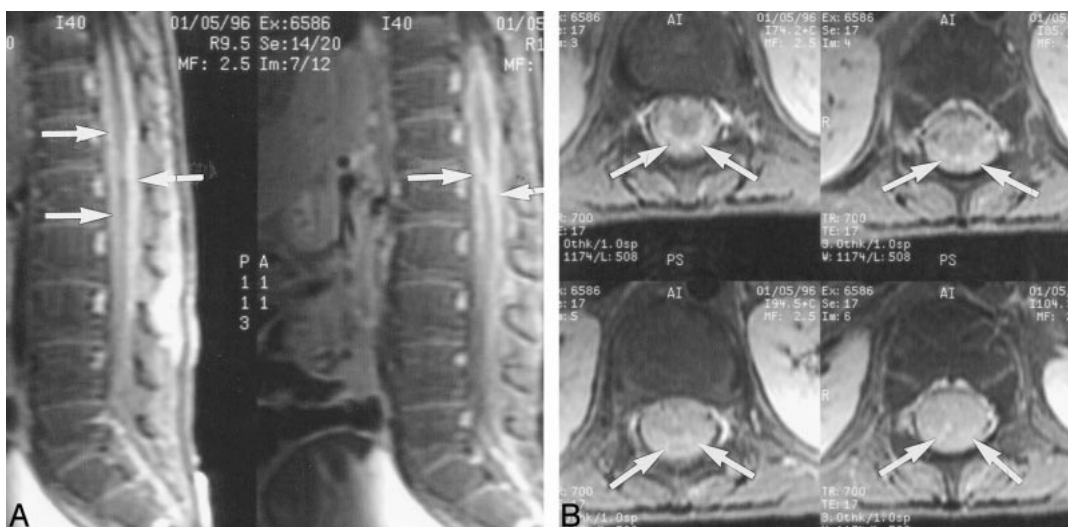

FIG 4. MR images of a 4-year-old boy, obtained 6 months after surgery (There were negative earlier imaging examinations).

A, Sagittal (600/15) fat-suppressed MR images shows thick, linear, enhancing tumor along the spinal cord and cauda equina (*arrows*). Contemporaneous CSF cytologic analysis was positive for tumor cells.

B, Axial (700/17) fat-suppressed MR images show amorphous prominently enhancing tumor filling the thecal sac. Contemporaneous CSF cytologic analysis was positive for tumor cells. The patient died 2 months later.

which enhanced to a moderate degree. This subarachnoid enhancement likely represented chemical irritation/inflammation from subarachnoid hemorrhage secondary to the recent cranial surgery, and resolved on subsequent MR examinations obtained 2 weeks (Fig 5) and 8 weeks afterward.

Skeletal Lesions

Three patients had multiple skeletal metastases in the spine and pelvis. One patient had concurrent leptomeningeal tumor and skeletal metastases at the time of diagnosis. The other two patients had skeletal lesions as the initial site of metastatic disease, which were observed 1.5 and 3 years after surgery. One of these two patients died without evidence of disseminated tumor in the CNS. The other patient eventually had MR imaging evidence of leptomeningeal tumor 3 years after the skeletal lesions were first seen (Fig 1). For the three patients with skeletal metastases, MR imaging showed markedly heterogeneous marrow signal alteration in multiple vertebrae on the short- and long-TR images. Abnormal marrow enhancement was also seen in a heterogeneous pattern within the involved vertebrae (Fig 1).
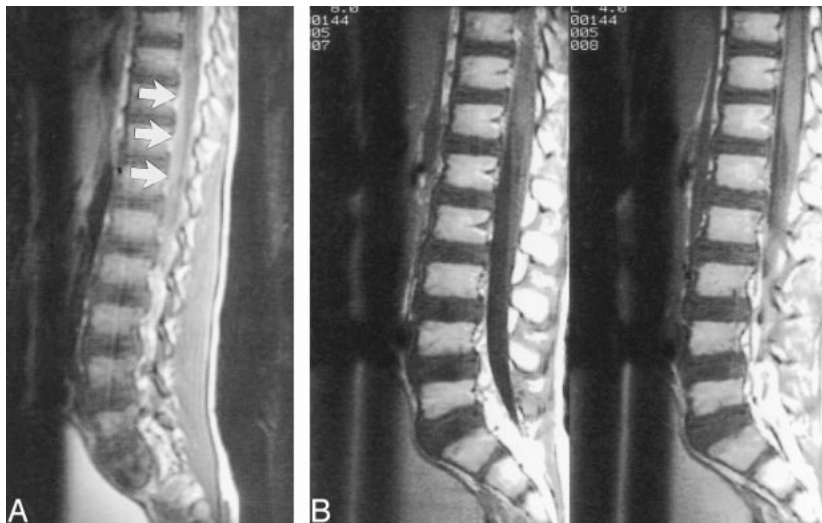
FIG 5. MR images of a 7-year-old boy, obtained 3 days (*A*) and 17 days (*B*) after surgery.
A, Sagittal (500/11) MR image shows linear enhancement along the spinal cord (*arrows*).
B, Sagittal (500/11) MR images show resolution of the intrathecal enhancement, which represented subarachnoidal hemorrhage related to surgery. This patient has been disease-free 5 years after these images were obtained.

CSF Cytology

Results from CSF cytologic examinations were available for 105 patients, including 36 patients with disseminated tumor in the spine seen with MR imaging. Thirty-four patients had at least one CSF sample positive for tumor cells. A total of 61 positive CSF samples was found for this group.

Only 23 of the 36 patients with spinal tumor seen with MR imaging had positive CSF cytologic results at the time when disseminated tumor was first seen in the spine by MR imaging. Six of the other 13 patients with negative CSF cytologic results eventually had positive CSF results 6 months to 3.5 years after disseminated tumor was first seen in the spine with MR imaging.

Five other patients had single positive CSF samples and negative spinal MR results. Three of these positive CSF samples were obtained in the early postoperative period (within 2 weeks after surgery). Subsequent CSF samples were negative for tumor cells, and all three of these patients have had no clinical or MR evidence of disease 2 to 5 years (mean, 3.5 years) after surgery. Two patients with negative spinal MR results had single positive CSF samples 7 months after surgery. Both patients had MR imaging evidence of intracranial leptomeningeal tumor. After chemotherapy and bone marrow transplantation, one of these patients has had negative CSF cytologic and MR results for 8 years. The other patient died 2 months later. Nine other patients with MR imaging evidence of intracranial tumor without spinal involvement had negative CSF cytologic results.

Comparison of MR Imaging with CSF Cytologic Analysis

The measurement properties of MR imaging and CSF evaluation are shown in the Table. An independent reference was available as a reference standard to confirm disseminated disease in 40 patients (33 patients with MR evidence of spinal tumor, 24

Diagnostic accuracy of spinal MR imaging, CSF samples obtained contemporaneously with spinal MR imaging for the detection of disseminated tumor, and all CSF cytologic examinations for detecting disseminated medulloblastoma

	Sens	Spec	PPV	NPV	ROC Area	SE
MR	.83	.97	.94	.90	.897	.038
CSF (samples contemporaneous with MR)	.60	.95	.89	.79	.777	.052
CSF (all samples)	.78	.95	.91	.87	.864	.043

Note.—sens = sensitivity, spec = specificity, PPV = positive predictive value, NPV = negative predicative value, ROC = receiver operating characteristic curve, and SE = standard error.

patients with positive CSF samples contemporaneous with spinal MR imaging, and the accumulated positive CSF results of 31 patients). Criteria for this reference standard were met when at least two of the following were present: positive findings from surgery, biopsy, or autopsy, which occurred in 11, five, and four patients, respectively; positive MR findings of intracranial disseminated tumor (n = 39 patients); and/or progressive clinical deterioration leading to death (n = 34 patients).

The sensitivity of MR imaging for the detection of disseminated tumor was 83% compared with 60% for individual contemporaneous CSF samples, and 78% for multiple CSF samples over time. Spinal MR imaging had greater diagnostic accuracy (*P* = .03) than contemporaneous CSF samples in the detection of disseminated tumor. The diagnostic accuracy of CSF cytologic analysis was improved when multiple samples over time were obtained (*P* = .10), although the difference was not significant at the *P* < .05 level. No significant difference (*P* = 0.39) was found between MR imaging and the accumulated results of all CSF samples.

Patient Outcomes

The 5-year progression-free survival probability for the study group was 0.55 + 0.05 (Fig 6). The
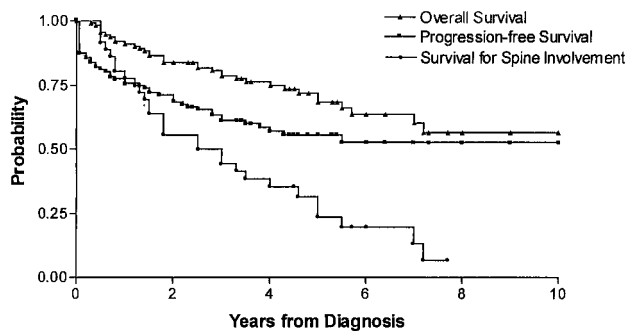
FIG 6. Kaplan-Meier estimates of PFS, overall-survival distributions for the complete study group and patients with spinal tumor.

5-year survival probability for patients with spinal tumor was 0.24 + 0.08 versus 0.68 + 0.05 for the entire study group. No significant difference ($P <$ .05) was found in the 5-year survival probabilities between patients who had spinal tumor at the time of diagnosis versus later in the postoperative period. Sixty-four patients (57%) had no clinical or MR evidence of disseminated or intracranial medulloblastoma in a mean follow-up time of 60 months after initial surgery.

Twenty-nine (81%) of the 36 patients with leptomeningeal tumor seen with spinal MR imaging died 1 month to 5 years (mean, 15 months; median, 10 months) after this enhancement pattern was initially detected. This group also included the two patients with disease in both the leptomeninges and bone marrow. The single patient with skeletal metastases without tumor in the CNS died 1.5 years after surgery. Six of the 11 other patients with MR imaging findings of recurrent intracranial medulloblastoma without MR evidence of spinal involvement died 5 months to 10 years (mean, 4 years) after surgery.

Twenty-six of the 34 patients with at least one CSF sample positive for tumor died. Only one of five patients with positive CSF cytologic and negative spinal MR results died. This single patient also had evidence of intracranial leptomeningeal tumor on MR images 1 month prior to the positive CSF sample.

Discussion

Medulloblastomas are malignant primitive neuroectodermal tumors involving the cerebellum, and are the most common type of neoplasm to disseminate along the CSF pathways (22). Aggressive treatment of these tumors has resulted in improved survival for these patients (11, 12, 15, 23–30). The current treatment of medulloblastoma includes gross total tumor resection followed by radiation therapy to the posterior cranial fossa (>50 Gy) (11, 12, 23–25). Lower-dose radiotherapy (25–45 Gy) is also given to the rest of the head and spine in children older than 3 years to treat for macro- or microscopic tumor disseminated along CSF path-

ways (11, 12, 23–26). In children younger than 3 years, radiation therapy is usually delayed until after initial postoperative chemotherapy in order to reduce radiation treatment–related neurotoxicity affecting young developing brain tissue (26). Adjuvant chemotherapy, as well as high-dose chemotherapy with bone marrow transplantation rescue, have also been shown to improve survival in some patients (11, 12, 15, 27, 28). Potential limitations of the current study include the fact that slightly different chemotherapy regimens were used at the different institutions, and that there was a potential selection bias of those patients who had postoperative MR examinations at only the five medical centers. Despite these concerns, the 5-year progression-free survival rate and 5-year overall survival rate for this patient group were comparable to the reported data in the literature (12–14, 23–25).

Staging of disease is important for assigning treatment options and assessing prognosis. The presence of micro- and/or macroscopic tumor in the leptomeninges at the time of or subsequent to diagnosis has been reported to be associated with a poor prognosis (18, 19, 21–23). Pial-subarachnoidal enhancement representing leptomeningeal tumor has been reported to be the most frequent pattern of tumor relapse in patients with medulloblastoma (10). Consistent use of the same imaging technique is essential for accurate and reproducible staging and follow-up evaluation of patients undergoing treatment for medulloblastoma (31). Myelography has been used in the past for detecting intradural tumor (15, 16, 18, 19). Contrast-enhanced MR imaging, however, has been shown to be more sensitive in detecting intradural extramedullary tumor than postmyelographic CT examinations (19, 20). Heinz et al (20) reported that contrast-enhanced MR imaging was superior to postmyelographic CT examinations in the detection of leptomeningeal tumor along the pial margins of the spinal cord. In addition, intradural lesions were more convincingly shown by MR imaging than by postmyelographic CT (20).

Postoperative surveillance using neuroimaging of the head and spine for disseminated and locally recurrent medulloblastoma is now routinely performed, and has been shown to detect a majority of recurrences before the onset of symptoms (32). CSF cytologic analysis is also routinely used in the postoperative evaluation for disseminated tumor. Early diagnosis of disseminated tumor is important for initiation of prompt treatment that may prevent neurologic deterioration, produce symptomatic improvement, and improve or prolong survival (28, 33).

Postoperative contrast-enhanced MR imaging of the complete spine is often performed 2 weeks after surgery to assess for disseminated tumor in the leptomeninges. This interval after surgery is chosen to avoid false-positive findings for subarachnoid tumor related to irritation from occult subarachnoid blood (34), as was observed for two patients in the

current study who underwent MR imaging of the spine 3 days after surgery. When feasible and clinically appropriate, preoperative contrast-enhanced spinal MR imaging could potentially avoid this problem in patients with known lesions in the cerebellum or fourth ventricle or both. Other potential pitfalls of contrast-enhanced spinal MR imaging include infectious meningitis (35) or possible enhancement of radicular and pial veins, and inflamed nerve roots that could give false-positive results (36, 37), although these problems were not encountered in the current study.

Surgery for medulloblastoma has been reported to result frequently in the shedding of tumor cells into the CSF (38). The presence of tumor cells seen in early postoperative CSF samples, however, does not always indicate that the cells are capable of establishing distal implants (38). False-positive CSF cytologic results can be seen in samples obtained soon after surgery, as was seen with three patients in this study. Criteria for establishing metastatic stage of medulloblastoma by use of CSF cytologic analysis and spinal MR imaging have been reported (28). For patients with negative initial postoperative spinal MR imaging results, Packer et al (28) considered CSF cytologic analysis to be appropriate for metastatic designation only if positive samples were obtained 21 days after surgery. False-positive CSF cytologic analysis can also occur from contamination with cartilaginous cells related to lumbar puncture, as well as the presence of reactive leptomeningeal cells resulting from chemotherapy, trauma, hemorrhage, infarction, or inflammation (39). Using CSF samples and MR imaging spinal data obtained more than 2 weeks after surgery would therefore reduce the incidence of false-positive samples for both methods.

CSF cytologic analysis has been reported to have limited sensitivity in detecting neoplastic infiltration (40–44). For primary neoplasms of the CNS with histologically confirmed meningeal involvement, the percentage of positive CSF cytologic results has been reported to range from 12% to 37% (42–44). The percentage of positive CSF cytologic results was notably higher for medulloblastoma, ranging from 43% to 62% (42, 44). The higher percentage of positive CSF cytologic results for medulloblastoma compared with other CNS neoplasms may result from the location of the primary lesions near the pial surface and tumor composition of loosely bound malignant cells that can readily exfoliate once they invade the meninges (43).

Fouladi et al (45) reported that results from CSF cytologic analysis or spinal MR imaging alone missed the diagnosis of disseminated medulloblastoma in the initial postoperative evaluation in 14% and 18%, respectively. Data used in this study were from CSF samples and spinal MR scans obtained 2 to 3 weeks after surgery (46). Limitations of this study include the absence of an independent reference standard to confirm disseminated disease, lack of data from subsequent CSF cytologic analyses, and no outcome measurements (46). It is unclear how many of these patients with positive CSF cytologic results 2 to 3 weeks after surgery and negative results on initial postoperative spinal MR images had subsequent positive CSF cytologic results obtained more than 21 days after surgery, meeting the criteria of Packer et al (28) for metastasis staging. In our study, two of the three false-positive CSF samples were acquired 13 and 14 days after surgery, and near the time when CSF samples were obtained in the study by Fouladi et al (45). Miralbell et al (46) reported that negative CSF cytologic results for medulloblastoma do not always exclude advanced stages of tumor dissemination. Eight of 11 patients with gross cerebral or cerebellar subarachnoidal tumor invasion had negative CSF cytologic results (46).

CSF cytologic analysis for tumor detection can be improved by acquiring multiple samples (33, 41, 47). In two studies of patients with meningeal metastases from non-CNS primary tumors, positive CSF cytologic results were found in 45% (47) and 54% (33) after one spinal tap, and 79% and 91% after multiple taps, respectively. Similar results were found in the current study with a primary CNS neoplasm. A delay in diagnosis of spinal tumor, however, would have occurred if CSF cytologic analysis were performed without MR imaging in 13 of 36 cases.

Olsen et al (47) reported that malignant cells are seen in CSF only when there is gross or microscopic tumor disseminated in the meninges, and rarely when the tumor is localized to the brain parenchyma. Similar results were found in the current study, in which nine of the 11 patients with MR imaging findings of residual or recurrent intracranial medulloblastoma without spinal involvement seen with MR imaging had negative CSF cytologic results. Taking these results into account would decrease the overall sensitivity of all CSF samples for detecting intracranial tumor and disseminated disease to 65%.

Wootton-Gorges et al (48) reported that spinal surveillance imaging may not be useful in patients with medulloblastoma or ependymoma who did not have evidence of disseminated tumor at diagnosis. This conclusion was based on the fact that none of the 17 patients with recurrent medulloblastoma (n = 6) or ependymoma (n = 11) in their study had imaging evidence of disseminated disease located only in the spine (48). All 17 patients had imaging evidence of recurrent tumor located either in the head (n = 13), or in both the head and spine (n = 4) (48). In the current report, six of the 43 patients with disseminated tumor, however, had evidence of disease seen only with spinal MR imaging (n = 3) or with spinal MR imaging prior to positive intracranial MR imaging findings (n = 3). In such situations, spinal MR imaging was useful for confirmation of disseminated tumor when there was no MR evidence of intracranial disease. The discrepancy of findings between the two studies is likely

related to the small sample size of the former report (48). It is also noteworthy that of the remaining 37 patients with MR imaging evidence of disseminated tumor, 25 had simultaneous findings of intracranial and spinal tumor, six had intracranial tumor prior to spinal involvement, and six only had intracranial involvement. Contrast-enhanced MR imaging of the head and spine can, therefore, provide complementary information in confirming the presence of disseminated tumor.

Disseminated medulloblastoma involving the vertebral marrow was uncommon, occurring in only 2.7% of all patients. Tarbell et al (49) reported that the addition of chemotherapy to surgery and craniospinal irradiation greatly reduced the incidence of extraneural metastases. Prior to the routine use of chemotherapy for medulloblastoma, 5% to 15% percent of patients treated with only surgery and radiation had extraneural or systemic metastases that most often involved bone marrow (49).

In conclusion, disseminated medulloblastoma was found to involve the spine in 33% of patients followed with MR imaging after surgery. Spinal tumor was predominantly located in the leptomeninges (35/37 patients) and infrequently in the vertebral marrow (3/37 patients). Spinal MR imaging had greater diagnostic accuracy than did CSF cytologic analysis in the early detection of disseminated tumor. The sensitivity of CSF cytologic analysis increased with acquisition of multiple subsequent samples, although diagnosis would have been delayed by more than 6 months compared with spinal MR imaging in six patients. Spinal MR imaging confirmed disseminated tumor when contemporaneous CSF samples were negative for tumor cells in 13 patients, whereas the opposite occurred in only two patients. Using postoperative data from MR imaging and CSF sampling obtained more 2 weeks after surgery can reduce the false-positive results from both methods. MR imaging of the head and spine can provide comprehensive evaluation of the CNS for disseminated disease. The presence of disseminated disease seen with MR imaging is currently associated with a poor prognosis.

Acknowledgments

References

1. Rorke LB. **The cerebellar medulloblastoma and its relationship to primitive neuroectodermal tumors.** *J Neuropathol Exp Neurol* 1983;42:1–15
2. Becker LE, Hinton D. **Primitive neuroectodermal tumors of the CNS.** *Hum Pathol* 1983;14:538–550
3. Russell DS, Rubinstein LJ. **Medulloblastomas.** In: *Pathology of Tumors of the Nervous System,* 5th ed. Baltimore, MD: Williams and Wilkins;1989;251–279
4. Arseni C, Ciurea AV. **Statistical survey of 276 cases of medulloblastoma (1935–1978).** *Acta Neurochir* 1981;57:159–166
5. Pollack IF. **Brain tumors in children.** *N Engl J Med* 1994;331:1500–1507
6. Koci TM, Chiang F, Mehringer CM, et al. **Adult cerebellar medulloblastoma: imaging features with emphasis on MR imaging findings.** *AJNR Am J Neuroradiol* 1993;14:929–939
7. Bourgouin PM, Tampieri D, Grahovac SZ, Léger C, Carpio RD, Melançon D. **CT and MR imaging findings in adults with cerebellar medulloblastoma: comparison with findings in children.** *AJR Am J Roentgenol* 1992;159:609–612
8. Meyers SP, Kemp SS, Tarr RW. **MR features of medulloblastomas.** *AJR Am J Roentgenol* 1992;158:859–865
9. Kochi M, Mihara Y, Takada A, et al. **MRI of subarachnoid dissemination of medulloblastoma.** *Neuroradiology* 1991;33:264–268
10. Meyers SP, Wildenhain S, Chess MA, Tarr RW. **Postoperative evaluation for intracranial recurrence of medulloblastoma: MR imaging findings with gadopentetate dimeglumine.** *AJNR Am J Neuroradiol* 1994;15:1425–1434
11. Tait DM, Thornton-Jones H, Bloom HJG, Lemerle J, Morris-Jones P. **Adjuvant chemotherapy for medulloblastoma: the first multicentre control trial of the international society for pediatric oncology (SIOP 1).** *Eur J Cancer* 1990;26:464–469
12. Evans AE, Jenkin RDT, Sposto R, et al. **The treatment of medulloblastoma.** *J Neurosurg* 1990;72:572–582
13. Albright AL, Wisoff JH, Zeltzer PM, et al. **Effects of medulloblastomas resections on outcome in children: a report from the children's cancer group.** *Neurosurgery* 1996;38:265–271
14. Zeltzer PM, Boyett JM, Finlay JL, et al. **Metastasis stage, adjuvant treatment, and residual tumor are prognostic factors for medulloblastoma in children: conclusions from the children's cancer group 921 randomized phase III study.** *J Clin Oncol* 1999;17:832–845
15. Deutsch M. **Medulloblastoma: staging and treatment outcome.** *Int J Radiation Oncology Biol Phys* 1988;14:1103–1107
16. Deutsch M, Scotti LN, Hardman DR, Reigel DH, Scarff TB. **Myelography in patients with medulloblastoma.** *Radiology* 1975;117:467–468
17. George RE, Laurent JP, McCluggage CW, Cheek WR. **Spinal metastasis in primitive neuroectodermal tumors (medulloblastoma) of the posterior fossa: evaluation with CT myelography and correlation with patient age and tumor differentiation.** *Pediat Neurosci* 1986;12:157–160
18. Packer RJ, Siegel KR, Sutton LN, Litman P, Bruce DA, Schut L. **Leptomeningeal dissemination of primary CNS tumors of childhood.** *Ann Neurol* 1985;18:217–221
19. Kramer E, Rafto S, Packer R, Zimmerman R. **Comparison of myelography with CT follow-up versus gadolinium MRI for subarachnoid metastatic disease in children.** *Neurology* 1991;41:46–50
20. Heinz R, Wiener D, Friedman, Tien R. **Detection of cerebrospinal fluid metastasis: CT myelography or MR?** *AJNR Am J Neuroradiol* 1995;16:1147–1151
21. Kaplan EL, Meier P. **Nonparametric estimation from incomplete observations.** *J Am Stat Assoc* 1958;53:457–481
22. Lee YY, Tien RD, Bruner JM, DePena CA, Van Tassel P. **Loculated intracranial leptomeningeal metastases: CT and MR characteristics.** *AJNR Am J Neuroradiol* 1989;10:1171–1179
23. Mazza C, Pasqualin A, Da Pian R, Donati E. **Treatment of medulloblastoma in children: long-term results following surgery, radiotherapy and chemotherapy.** *Acta Neurochir* 1981;57:163–175
24. Hughes EN, Shillito J, Sallan SE, Loeffler JS, Cassady JR, Tarbell NJ. **Medulloblastoma at the Joint Center for Radiation Therapy between 1968 and 1984: the influence of radiation dose on the patterns of failure and survival.** *Cancer* 1988;61:1992–1998
25. Levin VA, Rodriguez LA, Edwards MSB, et al. **Treatment of medulloblastoma with procarbazine, hydroxyurea, and reduced radiation doses to the whole brain and spine.** *J Neurosurg* 1988;68:383–387
26. Duffner PK, Horowitz ME, Krischer JP, et al. **Postoperative chemotherapy and delayed radiation in children less than three years of age with malignant brain tumors.** *N Engl J Med* 1993;328:1725–1731
27. Packer RJ, Sutton LN, Goldwein JW, et al. **Improved survival with the use of adjuvant chemotherapy in the treatment of medulloblastoma.** *J Neurosurg* 1991;74:433–440
28. Packer RJ, Sutton LN, Elterman R, et al. **Outcome for children with medulloblastoma treated with radiation and cisplatin, CCNU, and vincristine chemotherapy.** *J Neurosurg* 1994;81:690–698
29. Mahoney DH, Strother D, Camitta B, et al. **High-dose melphalan and cyclophosphamide with autologous bone marrow rescue**

for recurrent/progressive malignant brain tumors in children: a pilot pediatric oncology group study. *J Clin Oncol* 1996;14: 382–388

30. Dunkel IJ, Findlay JL. **High dose chemotherapy with autologous stem cell rescue for patients with medulloblastoma.** *J Neuro-Oncology* 1996;29:69–74

31. Mosijczuk AD, Nigro MA, Thomas PRM, et al. **Preradiation chemotherapy in advanced medulloblastoma. A pediatric oncology group pilot study.** *Cancer* 1993;72:2755–2762

32. Shaw DWW, Geyer JR, Berger MS, Milstein J, Lindsley KL. **Asymptomatic recurrence detection with surveillance scanning in children with medulloblastoma** *J Clin Oncol* 1997;15:1811–1813

33. Wasserstrom WR, Glass JP, and Posner JB. **Diagnosis and treatment of leptomeningeal metastases from solid tumors: experience with 90 patients.** *Cancer* 1982;49:759–772

34. Wiener MD, Boyko OB, Friedman HS, Hockenberger B, Oakes WJ. **False-positive spinal MR imaging findings for subarachnoid spread of primary CNS tumor in postoperative pediatric patients.** *AJNR Am J of Neuroradiol* 1990;11:1100–1103

35. Fouladi M, Heideman R, Langston JW, Kun LE, Thompson SJ, Gajjar A. **Infectious meningitis mimicking recurrent medulloblastoma on magnetic resonance imaging.** *J Neurosurg* 1999; 91:499–502

36. Lane JI, Koeller KK, Atkinson JLD. **Contrast-enhanced radicular veins on MR of the lumbar spine in an asymptomatic study group.** *AJNR Am J Neuroradiol* 1995;16:269–273

37. Jinkins JR. **MR of enhancing nerve roots in the unoperated lumbosacral spine.** *AJNR Am J Neuroradiol* 1993;14:193–202

38. Balhuizen JC, Bots GT, Schaberg A, Bosman FT. **Value of cerebrospinal fluid cytology for the diagnosis of malignancies of the CNS.** *J Neurosurg* 1978;48:747–753

39. Takeda M, King DE, Choi HY, Gomi K, Lang WR. **Diagnostic pitfalls in cerebrospinal fluid cytology.** *Acta Cytol* 1981;25:245–250

40. Glass JP, Melamed M, Chernik MD, Posner JB. **Malignant cells in the cerebrospinal fluid (CSF): the meaning of a positive CSF cytology.** *Neurology* 1979;29:1369–1375

41. Fukui MB, Meltzer CC, Kanal E, Smirniotopoulos JG. **MR imaging of the meninges. Part ll. neoplastic disease.** *Radiology* 1996;201:605–612

42. Gondos B, King EB. **Cerebrospinal fluid cytology: diagnostic accuracy and comparison of different techniques.** *Acta Cytol* 1976;20:542–547

43. Kline TS. **Cytological examination of the cerebrospinal fluid.** *Cancer* 1962;15:591–597

44. Naylor B. **The cytologic diagnosis of cerebrospinal fluid.** *Acta Cytol* 1964;8:141–148

45. Fouladi M, Gajjar A, Boyett JM, et al. **Comparison of CSF cytology and spinal magnetic resonance imaging in the detection of leptomeningeal disease in pediatric medulloblatoma or primitive neuroectodermal tumor.** *J Clin Oncol* 1999;17:3234–3237

46. Miralbell R, Bieri S, Huguenin P, et al. **Prognostic value of cerebrospinal fluid cytology in pediatric medulloblastoma.** *Ann Oncol* 1999;10:239–241

47. Olson ME, Chernik NL, Posner JB. **Infiltration of the leptomeninges by systemic cancer.** *Arch Neurol* 1974;30:122–137

48. Wootton-Gorges SL, Foreman NK, Albano EA, et al. **Pattern or recurrence in children with midline posterior fossa malignant neoplasms.** *Pediatr Radiol* 2000;30:90–93

49. Tarbell NJ, Loeffler JS, Silver B, et al. **The change in patterns of relapse in medulloblastoma.** *Cancer* 1991;68:1600–1604