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S F. Kralik

D P. O'Neill

A P. Kamer

E Rodriguez
Henry Ford Health System, enriquer@rad.hfh.edu

C Y. Ho

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Radiological diagnosis of drop metastases from paediatric brain tumours using combination of 2D and 3D MRI sequences

S.F. Kralik [a,*], D.P. O'Neill [a], A.P. Kamer [a], E. Rodriguez [b], C.Y. Ho [a]

[a] Department of Radiology and Imaging Sciences, Indiana University School of Medicine, Indianapolis, IN, USA
[b] Department of Radiology, Henry Ford Hospital-Wayne State University, Detroit, MI, USA

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AIM: To evaluate spinal magnetic resonance imaging (MRI) examinations using a combination of two-dimensional (2D) and three-dimensional (3D) MRI sequences for diagnosis of drop metastases.

MATERIALS AND METHODS: Fifty-five paediatric patients with primary brain tumours were evaluated for drop metastases at initial presentation using spinal MRI including sagittal 2D T1-weighted (W) contrast-enhanced (+C), axial 3D T1W+C volumetric interpolated breath-hold (VIBE), and sagittal 3D T2W SPACE (Sampling Perfection with Application optimised Contrasts using different flip angle Evolutions).

RESULTS: The MRI false-negative rate was 4%, and cerebrospinal fluid (CSF) false-negative rate was 16% (p=0.07). The 3D T1W+C VIBE increased the number of drop metastases detected in 42% of patients. Drop metastases were more conspicuous in 25% of patients on 3D T2W SPACE.

CONCLUSION: Spinal MRI examinations including 2D and 3D sequences demonstrate characteristics that may improve radiological diagnosis of drop metastases.

Introduction

Paediatric brain tumours may disseminate via the cerebrospinal fluid (CSF) into the spinal canal, resulting in leptomeningeal drop metastases. Accurate diagnosis of drop metastases is critical for determining prognosis and directing proper treatment regimens in paediatric brain tumours, including medulloblastoma.[1] Consequently, mischaracterising the absence or presence of drop metastases directly affects patient care, potentially resulting in either inadequate or excessive treatment of disease.

Currently, CSF cytology and spinal MRI are the tests of choice for the detection of leptomeningeal drop metastases. Unfortunately, neither of these tests have perfect diagnostic accuracy.[2–4] Current limitations of spinal MRI that may contribute to indeterminate or inaccurate detection of drop metastases include technical artefacts (e.g., CSF flow artefacts) and suboptimal spatial resolution. Improvements in spinal MRI techniques that limit CSF flow artefacts or improve detection of small tumour deposits, therefore, would be expected to improve the overall accuracy in detecting drop metastases.

3D MRI sequences have been developed that significantly decrease CSF flow artefacts, improve the contrast between

* Guarantor and correspondent: S. F. Kralik, Department of Radiology and Imaging Sciences, Indiana University School of Medicine, 714 N. Senate Ave., Indianapolis, Indiana, 46202, USA. Tel.: +1 (317) 963 7121; fax: +1 (317) 948 8383.
E-mail address: steve.kralik@gmail.com (S.F. Kralik).

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the CSF and spinal cord, and utilize thinner section thickness, all without significantly lengthening imaging time. One such three-dimensional (3D) T1-weighted (W) contrast-enhanced (+C) MRI sequence is the volumetric interpolated breath-hold (VIBE) sequence, which allows thin section imaging with reduced CSF flow artefacts.[5] Similar MRI sequences include T1W high resolution isotropic volume examination (THRIVE) or liver acquisition with volume acceleration (LAVA). Another 3D T2W sequence that demonstrates improved visualisation of small structures in the CSF within the spinal canal is the T2W Sampling Perfection with Application optimised Contrasts using different flip angle Evolutions (SPACE) sequence.[6] Similar MRI sequences include volume isotropic turbo spin echo acquisition (VISTA) or CUBE. Because leptomeningeal drop metastases occur along the surface of the spinal cord, a 3D sequence would theoretically possess an advantage in accurate detection of drop metastases; however, to the authors' knowledge, 3D sequences have not been specifically evaluated in this regard. The purpose of this research was to evaluate the performance of spinal MRI, including a combination of 2D and 3D MRI sequences, for the radiological diagnosis of drop metastases among paediatric patients with primary brain tumours on initial presentation.

Materials and methods

Following institutional review board approval, a retrospective search from 1 January 2011 to 6 January 2015 identified a total of 55 paediatric patients (defined as age $\leq$18 years) with a primary brain tumour who underwent an MRI of the entire spine with axial 3D T1W+C VIBE and sagittal 3D T2W SPACE for detection of drop metastases on initial presentation prior to any surgical intervention and who had CSF cytology obtained within 4 weeks of the spine MRI. Therefore, patients were excluded if no CSF cytology was obtained; if CSF cytology was obtained >4 weeks from the total spine MRI; if the total spine MRI was not performed at presentation; and/or if tumour histopathology was not obtained or was unavailable in the medical record with exception of tumours located in the brainstem.

Imaging was performed using 1.5 or 3 T MRI units (Siemens Avanto and Verio, Erlangen, Germany). The spinal MRI protocol consisted of a combination of 2D and 3D MRI sequences as follows: (1) sagittal 2D T1W+C turbo spin echo (TSE) with fat saturation (473–543 ms repetition time [TR], 10 ms echo time [TE], 256×384 matrix, 3 mm section thickness; 1 mm gap, average time 4 minutes 30 seconds); (2) axial 3D T1W+C VIBE (6.3–9.9 ms TR, 2.5–4.7 ms TE, 12° flip angle, 205×256 matrix, 2.5–3 mm section thickness; 0 mm gap, average time 4 minutes 15 seconds); (3) sagittal 3D T2W SPACE (1,100–1,200 ms TR, 116–121 ms TE, 150° flip angle, 320×322 matrix, 2 mm section thickness, 0 mm gap, average time 6 minutes 45 seconds) with sequences performed of the upper half of the spine then and repeated for the lower half of the spine in the order listed above for a total imaging time of approximately 30 minutes. A standard volume of 0.1 mmol/kg of gadobenate dimeglumine (Multihance, Bracco Diagnostics, Princeton, NJ, USA) was administered intravenously for post-contrast imaging.

Two fellowship trained board certified neuroradiologists (A.K., 3 years of experience and D.O., 8 years of experience) with certificate of added qualification (CAQ) in neuroradiology performed a retrospective individual blinded review of all sequences from the total spine MRI for the presence or absence of drop metastases. Drop metastasis diagnosis was based on the reviewer's experience and broadly defined as abnormal leptomeningeal enhancement or nodularity in the spinal canal. The reviewers were blinded to the brain MRI, tumour histopathology, CSF cytology, follow-up imaging, and official radiology report.

The reviewers were instructed to first evaluate only the sagittal 2D T1W+C TSE images for presence of drop metastases (yes, no, indeterminate), and subjective image quality (five-point scale: 1 = non-diagnostic, 2 = below average with artefacts affecting interpretation; 3 = average anatomical detail with minimal artefacts, 4 = above average anatomical detail without significant artefacts; 5 = excellent anatomical detail and no significant artefacts). Next, the reviewers evaluated the axial 3D T1W+C VIBE for the final diagnosis of drop metastases (yes, no, indeterminate), subjective image quality of the axial images (as above), and if the number of drop metastases detected increased with addition of axial images (yes, no). Lastly, the reviewers analysed the 3D T2W SPACE images to compare the overall conspicuity of drop metastases to the sagittal 2D T1W+C TSE and axial 3D T1W+C VIBE images (e.g., more conspicuous, similar conspicuity, less conspicuous, or not visible). For all patients in whom there was a discordant diagnosis for drop metastases, the reviewers performed a combined review and reached a consensus diagnosis for drop metastases (yes, no, indeterminate). The interobserver agreement between reviewers for the diagnosis of drop metastases was calculated by using the Kappa statistic (κ). A κ value of 0.81–1.0 indicated excellent agreement between the two reviewers, 0.61–0.80 indicated good agreement, 0.41–0.60 indicated moderate agreement, 0.21–0.40 indicated fair agreement, and 0–0.20 indicated only slight agreement.

A retrospective review of each patient's medical record was performed to determine the age of the patient at presentation, duration of time between initial spinal MRI to a follow-up spinal MRI (if present), and final tumour histopathological diagnosis per surgical specimen analysis by an experienced board-certified neuropathologist. Only those patients with brainstem tumours did not have a final histopathological diagnosis from a surgical specimen. All CSF samples were obtained through a lumbar puncture and were reviewed by an experienced board-certified cytopathologist using Diff-Quick and Papanicolau-stained SurePath slides to obtain a positive or negative CSF cytology diagnosis. The reviewers' consensus diagnosis for the presence or absence of drop metastasis was compared to the CSF cytology diagnosis to determine the false-negative MRI rate (negative MRI/ positive CSF) and false-negative CSF rate (negative CSF/positive MRI). A 95% confidence interval (CI) for the proportion of false-negatives between MRI and CSF cytology was obtained. McNemar's test was

used to compare the results of spinal MRI versus CSF cytology, and an unpaired two-tailed *t*-test was used to the subjective image quality with $p<0.05$ considered statistically significant (VassarStats: Statistical Computation Web Site, 2013, http://vassarstats.net).

Results

The mean age was 6.7 years (range 0.2–17 years). The mean follow-up duration was 8.1 months (range 4–16 months) and no patients who had an initial negative MRI developed drop metastases on the follow-up spinal MRI within 6 months from the initial spinal MRI.

Results of MRI and CSF cytology for detection of drop metastases are listed in Tables 1 and 2. A total of 14/55 patients (25%) were diagnosed with drop metastases, including 9/55 (16%) by MRI only, 2/55 (4%) by CSF cytology only, and 3/55 (5%) with both MRI and CSF cytology. Therefore, the MRI false-negative rate was 4% (95% CI: 1–12%) and the CSF false-negative rate was 16% (95% CI: 9–28%). The differences between the MRI and CSF cytology false-negative rates were not statistically significant ($p=0.07$). Representative examples are demonstrated in Figs 1–3.

The number of patients in which the 3D T1W+C VIBE images increased the number of lesions detected was 42% (5/12) cases. After reviewing the 3D T1W+C VIBE images, the reviewers changed their diagnosis 22% (12/55) of the time. Interobserver agreement improved from moderate agreement ($\kappa = 0.49$) to good agreement ($\kappa = 0.79$) following review of 3D T1W+C VIBE. There was similar good agreement for imaging performed at 1.5 T ($\kappa = 0.79$) compared to imaging performed at 3 T ($\kappa = 0.78$). Subjective image quality assessment of the sagittal 2D T1W+C images was 3.63 compared to 3.84 for the 3D T1W+C VIBE and the difference was statistically significant ($p=0.03$). There was no significant difference in image quality for the sagittal 2D T1W+C images or axial 3D T1W+C VIBE images performed at 1.5 T versus 3 T (3.55 versus 3.73, $p= 0.194$; 3.77 versus 3.79, $p=0.930$).

Among patients who had a final consensus diagnosis of drop metastases on the contrast-enhanced MRI, drop metastases were detected in 83% (10/12) of these patients on the 3D T2W SPACE images. The 3D T2W SPACE images were considered more conspicuous (representative Figs 2 and 3) for demonstrating drop metastases in 25% (3/12) of these cases and involved primary diagnoses of atypical teratoid rhabdoid tumour (ATRT), medulloblastoma, and juvenile pilocytic astrocytoma (JPA), while the remainder were considered similar, or less conspicuous, or not visible. Two cases in which drop metastases were not identified on the 3D T2W SPACE images occurred in patients with supratentorial primitive neuroectodermal tumour (PNETO) and cerebellar medulloblastoma, with one patient having leptomeningeal metastases coating the cauda equina and another with tiny foci of nodular enhancement along the cauda equina.

Table 1
Detection of drop metastases with three-dimensional (3D) spinal magnetic resonance imaging (MRI) and cerebrospinal fluid (CSF) cytology.

Pathology	Patients (%)	MRI positive (%)	CSF positive (%)
Medulloblastoma and PNET	16 (29%)	6 (38%)	3 (19%)
Ependymoma	11 (20%)	2 (18%)	2 (18%)
Brainstem tumour[a]	9 (16%)	1 (11%)	0 (0%)
JPA	7 (13%)	2 (29%)	0 (0%)
GBM	5 (9%)	0 (0%)	0 (0%)
Germinoma	4 (7%)	0 (0%)	0 (0%)
ATRT	2 (4%)	1 (50%)	0 (0%)
Pineoblastoma	1 (2%)	0 (0%)	0 (0%)
Total	55	12 (22%)	5 (9%)

PNET, primitive neuroectodermal tumor; JPA, juvenile pilocytic astrocytoma; GBM, glioblastoma multiforme; ATRT, atypical teratoid rhabdoid tumor.
[a] Brainstem tumours consisted of tectal glioma ($n=1$), pontine glioma ($n=6$), and medullary glioma ($n=2$).

Table 2
Comparison of cerebrospinal fluid (CSF) cytology and spinal magnetic resonance imaging (MRI) diagnosis of drop metastases.

	Positive MRI	Negative MRI	Total
Positive CSF cytology	3	2	5
Negative CSF cytology	9	41	50
Total	12	43	55

Discussion

Both CSF cytology and MRI spine imaging are used for detecting drop metastases; however, neither possesses 100% accuracy.[2–4] Among patients with histological proof of leptomeningeal disease, no more than 59% demonstrate positive post-mortem CSF cytology.[7] Conversely, patients may have positive CSF cytology without apparent abnormalities on spinal MRI. A false-negative MRI may be secondary to micrometastases, CSF flow artefact obscuring a metastasis, patient motion, or lack of identification by the interpreting radiologist. A spectrum from subtle to obvious drop metastases may be encountered, as well as a wide range of image quality, which likely represents the primary detractors from interobserver agreement in clinical practice. Interestingly, only the spinal MRI results demonstrated significant correlation with patient survival in a study comparing spinal MRI versus lumbar CSF cytology versus intracranial CSF cytology for detection of drop metastases in paediatric patients with medulloblastomas, supratentorial PNET, and ependymomas.[3] Therefore, MRI spine techniques that ultimately improve the reproducibility and accuracy of the detection of drop metastases are extremely valuable for patient management and prognosis. In the present study, the 3D spinal MRI sequences improved interobserver agreement from good to nearly excellent, which may reduce the variability of radiological diagnosis, as well as improved image quality by reducing CSF artefacts, which allows a radiologist to confirm a drop metastasis in two orthogonal planes of imaging, subsequently increasing the confidence in radiologist diagnosis of drop metastases.

In a large series of 106 paediatric patients with medulloblastomas and PNETs spanning nearly a 9-year period published over 15 years ago, Fouladi *et al.*[2] reported a false-

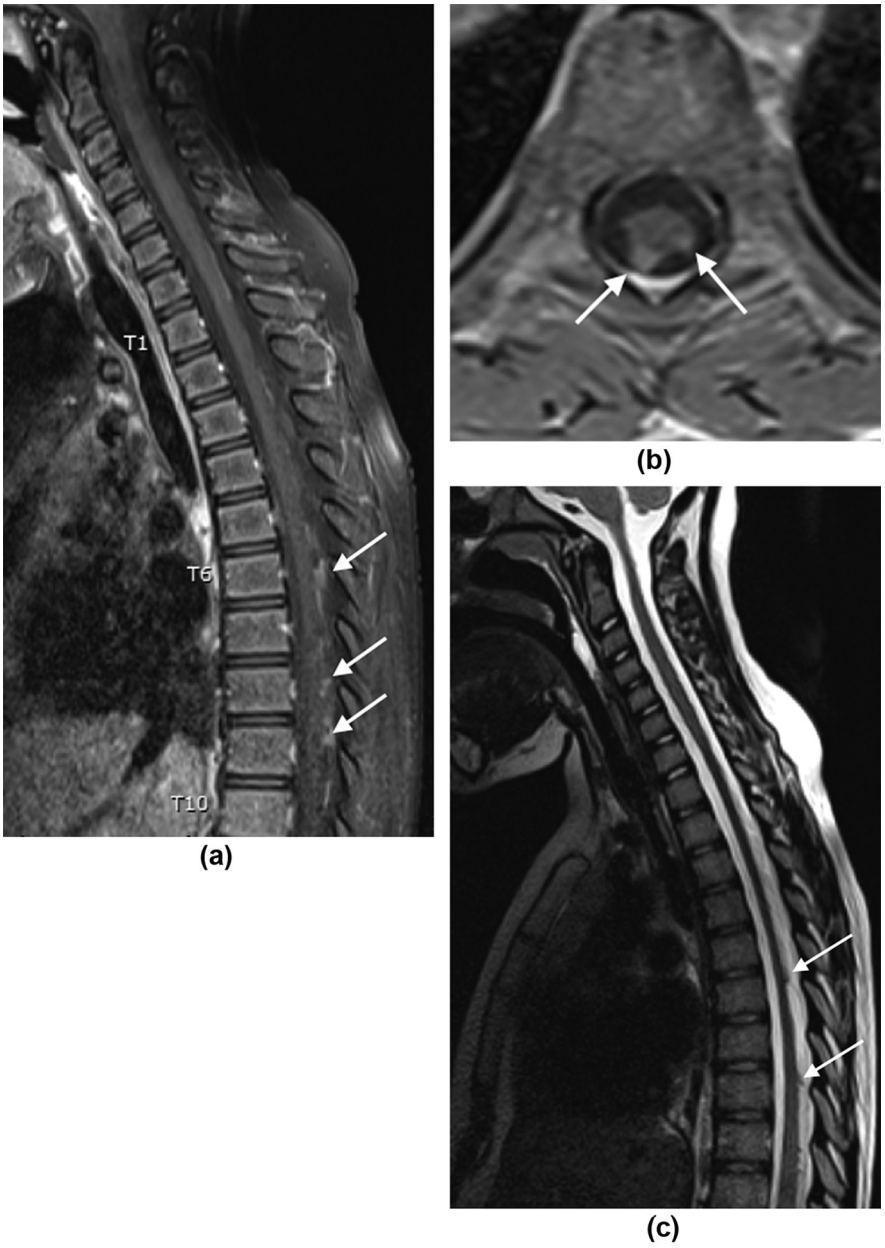

Figure 1 A 7-year-old patient with a history of supratentorial PNET. (a) Sagittal 2D T1W+C with fat-saturation image demonstrates nodular enhancement along the dorsal thoracic spinal cord suspicious for leptomeningeal metastases, which is less likely to be a CSF flow artefact. (b) Axial 3D T1W+C VIBE image demonstrates enhancing leptomeningeal nodules along the dorsal thoracic spinal cord, which are more discrete compared to the sagittal 2D T1W+C image, and confirming leptomeningeal metastases. (c) Sagittal 3D T2W SPACE image demonstrates less conspicuous leptomeningeal nodules compared to 2D T1W+C and 3D T1W+C images.

negative CSF cytology rate of 8.5% (with a 95% upper bound of 14.4%) and a false-negative MRI rate of 11.3% (95% upper bound 17.7%), and concluded CSF cytology outperformed MRI for detection of drop metastases.[2] In the present study, MRI with 2D and 3D sequences performed better than CSF cytology, although still within the 95% CI, which may be due to smaller sample size resulting in a wider 95% upper bound. The present study also included a much wider spectrum of primary paediatric brain tumour diseases, as would be typically encountered in the general paediatric population. One false-negative MRI occurred in a patient with an ependymoma with positive CSF cytology. In this patient, a follow-up MRI performed within 2 months did not demonstrate MRI evidence of drop metastases and follow- up CSF cytology was negative for malignancy. Potentially, such a false-negative result may be secondary to micrometastases. Another explanation for a false-negative MRI result in the present study is the potential for tumour dissemination arising from tumour resection, as CSF cytology was obtained postoperatively. To the authors' knowledge, no prior study has analysed the possibility of tumour dissemination arising from surgery as a confounder

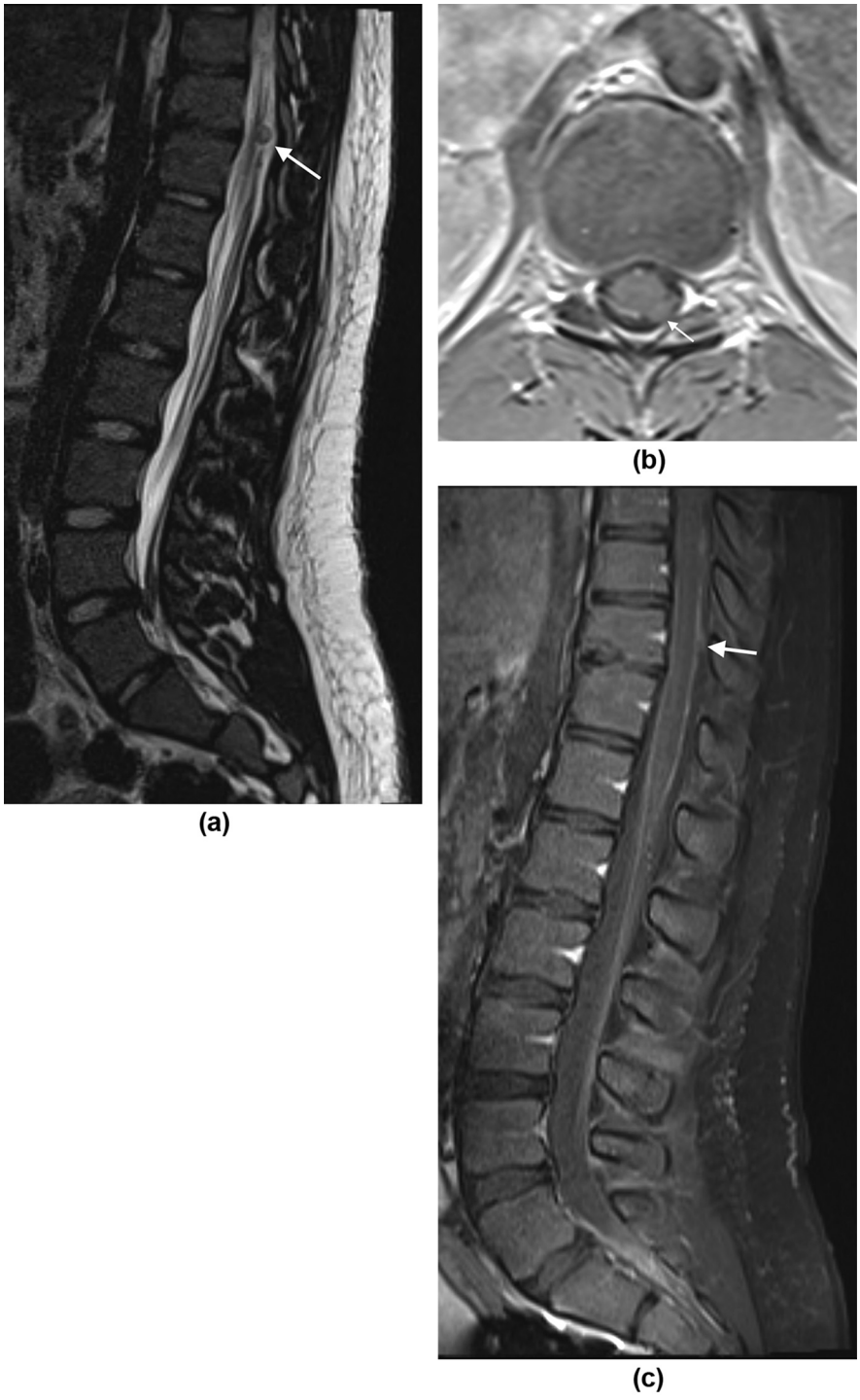

Figure 2 An 11-year-old patient with a history of medulloblastoma. (a) Sagittal 3D T2W SPACE image demonstrates a leptomeningeal nodule along the dorsal thoracic thecal sac. (b) Axial 3D T1W+C VIBE image demonstrates an isointense leptomeningeal nodule along dorsal thoracic spinal cord. (c) Sagittal 2D T1W+C with fat-saturation image demonstrates subtle leptomeningeal nodular enhancement that is less conspicuous compared to 3D T2W SPACE.

in this regard. Obtaining CSF cytology either before or after surgery is standard practice at the authors' institution, which precludes eliminating this limitation from the methodology; however, if CSF dissemination arising from surgery is a possibility, this would suggest that the false-negative MRI rate may be even lower. The present study demonstrated the continued limitations of CSF cytology for the detection of drop metastases. It is uncertain whether the CSF obtained through lumbar puncture is a limitation of the present study given that there are conflicting data regarding whether lumbar CSF or intracranial CSF is more reliable for diagnosis of drop metastases.[3,8,9]

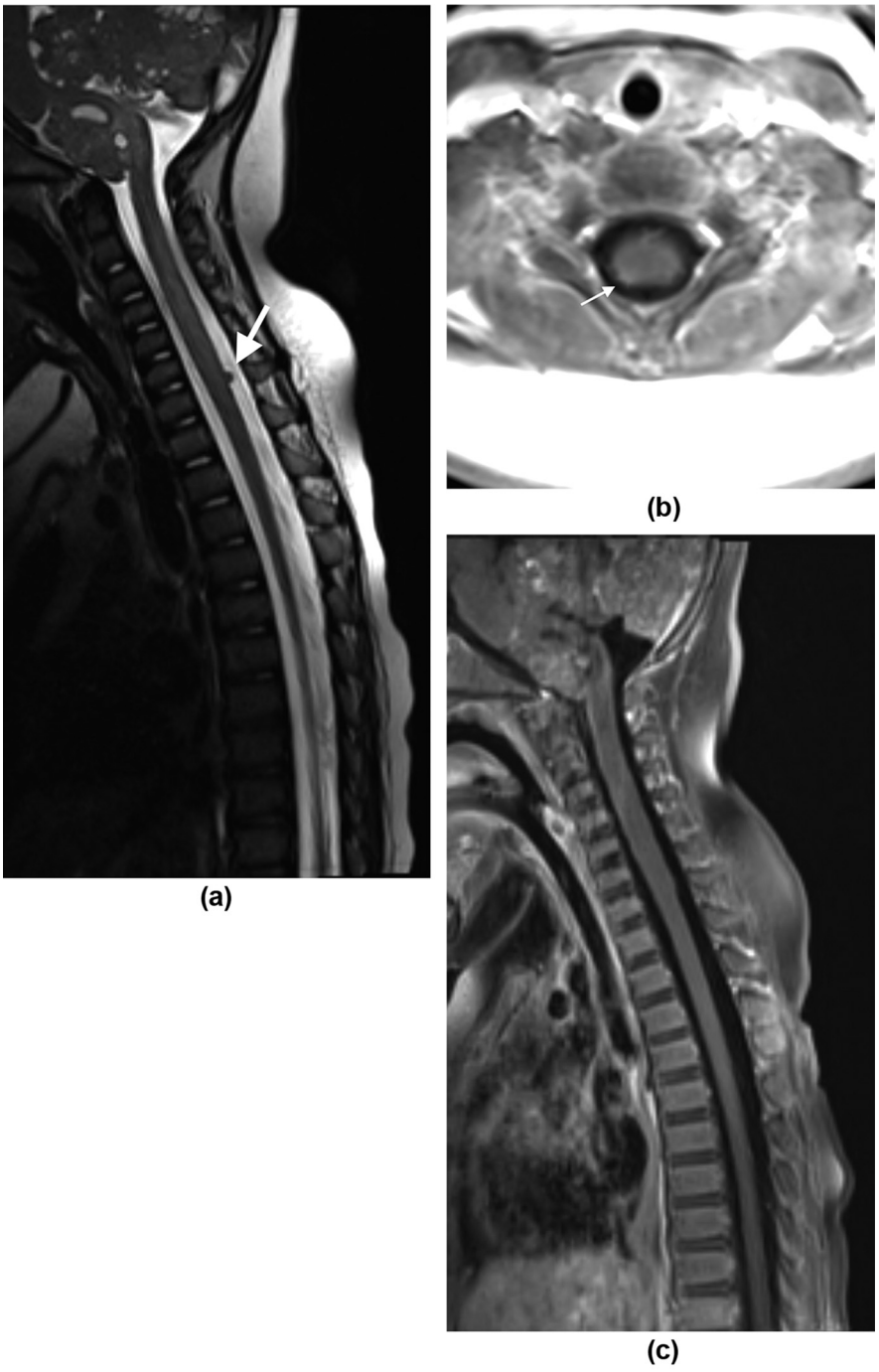

Figure 3 A 15-month-old patient with history of ATRT. (a) Sagittal 3D T2W SPACE image demonstrates a well-defined leptomeningeal nodule along the dorsal cervical spinal cord. (b) Axial 3D T1W+C VIBE image demonstrates a subtle leptomeningeal nodule along right dorsal cervical spinal cord, although less conspicuous compared to 3D T2W SPACE image. (c) Sagittal 2D T1W+C with fat saturation image does not demonstrate the leptomeningeal nodule.

As current standard of care does not include routine resection of spinal drop metastases, the lack of histological confirmation remains a limitation for confirming MRI results in this regard. A spectrum ranging from subtle to obvious MRI findings of drop metastases in the spinal canal may be encountered, such that a positive or negative MRI result can depend on the confidence of the interpreting radiologist. Improvements in imaging techniques for the diagnosis of drop metastases should be able to demonstrate increased interobserver agreement, improve image quality, and increase conspicuity of drop metastases. At many institutions with multidisciplinary paediatric tumour conferences, more than one radiologist may be involved in determining the presence or absence of drop metastases such that improvements in interobserver agreement diminish the possibility for discordance regarding the

diagnosis of drop metastases. The results of the present study indicate improvement in interobserver agreement and improved image quality when including 3D spinal MRI sequences. To the authors' knowledge, this research effort represents the first report of interobserver agreement of radiologists in the detection of spinal drop metastases in addition to demonstrating imaging techniques that may improve image quality. The improvement in interobserver agreement and increased number of drop metastases detected with 3D sequences may likely reflect the improvement in image quality resulting from CSF flow artefact reduction and the reduced section thickness.

The primary imaging artefact encountered using 3D T1W+C VIBE is a wrap artefact at the top and bottom of the series that can be counteracted by overlapping the coverage in the mid-portion of the spine as well as acquiring a few image sections above and below the desired cranial and caudal coverage areas. An important notable difference for a radiologist who may be inexperienced with the axial 3D T1W+C VIBE appearance is the improved visualisation of small vessels extending along the spinal cord surface, which can readily be distinguished from drop metastases by their linear, winding pattern and craniocaudal continuity. Radiologists may consider a short period of utilising both 2D and 3D sequences to develop familiarity with the increased anatomical detail and potential imaging artefacts.

Although the 3D T2W SPACE sequence may not replace contrast-enhanced sequences, the significant CSF to parenchyma contrast with 3D T2W imaging provided a complementary aid in the detection of drop metastases and improved lesion conspicuity of drop metastases compared to contrast-enhanced imaging in a few of the present cases. Analogous to this potential complementary role of 3D T2W imaging for the detection of drop metastases, is the reported detection of spinal drop metastases with diffusion-weighted imaging.[10] Diffusion-weighted imaging was not included in the present protocol due to frequently encountered imaging artefacts; however, this could be included if institutions are able to perform this sequence with routine high-quality imaging. Ultimately, the MRI sequences used for evaluation of drop metastases are impacted by the sequences available and clinical performance including respect for imaging time. In the authors' experience, 3D T1W+C VIBE can has a similar imaging duration to a conventional axial 2D T1W+C sequence and 3D T2 SPACE can be added without compromising image quality and radiological diagnosis.

There are some limitations to the present study. The spinal MRI examinations of paediatric brain tumour patients were examined upon initial presentation to avoid the potential confounding variable of radiation therapy. An unavoidable potential limitation of this retrospective study surrounds the unknown impact of treatment initiation (e.g., steroids or chemotherapy) on the CSF cytology results. Further evaluation of 3D MRI spine techniques in detecting drop metastases could also be considered among patients with recurrent tumour, prior spinal radiotherapy, and adult patients with brain tumours. A combination of 2D and 3D spinal imaging was chosen because of previously reported cases of reduced conspicuity of intracranial contrast-enhancing lesions in 3D imaging compared to 2D TSE techniques, and to utilize the complementary value of both techniques for detecting spinal drop metastases.[11] Further investigation of spinal MRIs for diagnosis of drop metastases, which only utilize 3D MRI sequences, may be helpful to compare to the combination of 2D and 3D imaging MRI protocol used in the present study.

In conclusion, spinal MRI examinations including 2D and 3D sequences demonstrate characteristics that may improve radiological diagnosis of drop metastases.

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