Prospective observational study on diagnostic accuracy of whole-body MRI in solid small round cell tumours


AIM: To assess the diagnostic accuracy of whole-body magnetic resonance imaging (WB-MRI) for metastatic disease in patients with solid small round cell tumours (SRCT) by comparing it with routine staging procedures (standard of care).

MATERIALS AND METHODS: Eligible cases of neuroblastoma, primitive neuroectodermal tumour, and rhabdomyosarcoma were enrolled in the study after obtaining informed consent. WB-MRI was undertaken using overlapping coronal T1 and short-tau inversion recovery (STIR) sequences. Lesions were classified into skeletal, pulmonary, and soft-tissue types. Conventional staging, which consisted of combined positron-emission tomography & computed tomography (PET-CT), bone scintigraphy & bone marrow biopsy for bone metastases, CT thorax for lung metastases, combined PET-CT, metaiodobenzylguanidine (MIBG) scintigraphy (in neuroblastoma) for soft tissue metastases and clinical evaluation was used as the reference standard. Parameters for diagnostic accuracy were calculated.

RESULTS: Thirty-four out of forty patients enrolled were included in final analysis, half of them having metastatic disease. The sensitivity, specificity, positive and negative predictive value, and the diagnostic accuracy of WB-MRI and PET-CT for skeletal metastases as compared to reference standard were 91.9%, 99.8%, 97.4%, 99.6%, and 95.5% and 99.1%, 99.9%, 99.1%, 99.9%, and 99.9%, respectively. The sensitivity of MRI for soft-tissue lesions was 76.9%.
Introduction

Paediatric malignant small round cell tumours (SRCT) include Ewing’s sarcoma/peripheral neuroectodermal tumour (PNET), rhabdomyosarcoma (RMS), synovial sarcoma, non-Hodgkin’s lymphoma, retinoblastoma, neuroblastoma (NB), hepatoblastoma, and Wilms’ tumour. Of these tumours, PNET, NB, and RMS are common solid tumours that require elaborate staging work-up for appropriate management. Bone marrow aspiration and biopsy (BMA/B; for PNET, NB, and RMS), bone scintigraphy and computed tomography (CT) of the thorax (for PNET and RMS), metaiodobenzylguanidine (MIBG) scintigraphy or bone scintigraphy (for NB) are always performed. In addition, combined positron-emission tomography (PET)/computed tomography (CT) is used if available or required. There are several disadvantages of these studies, such as increased radiation burden (except bone marrow aspiration); inconvenience to the patient as examinations are usually not undertaken in one setting; BMA is a painful, invasive procedure; and bone scintigraphy has low sensitivity.

The ability to evaluate both local and metastatic disease in a single session of sedation or anaesthesia without exposing a child to ionizing radiation makes whole-body magnetic resonance imaging (WB-MRI) attractive for evaluating solid tumours. With the innovations in hardware and software technology of MRI machines, it is now possible to perform WB-MRI in 45–60 min. It can depict skeletal and extra-skeletal abnormalities and can easily detect complications that require early intervention such as spinal cord compression or intracranial extension.

Several studies have compared WB-MRI with bone scintigraphy, radiography, 2-[18F]-fluoro-2-deoxy-D-glucose (FDG)-PET-CT in a heterogeneous group of paediatric patients. The present prospective, observational study was performed to assess the diagnostic accuracy of WB-MRI for metastatic disease in patients with solid SRCT (NB, PNET or RMS) by comparing it with a reference standard based on conventional staging procedures and clinical evaluation.

Materials and methods

Study population

The study was approved by the institutional review board and was conducted in a single institution. All newly diagnosed or suspected cases of NB, PNET, or RMS were considered eligible for trial. Even though the predominant target population was children, adults with these tumours were also considered eligible. Exclusion criteria included patients having received any form of treatment for the same disease, those in relapse, or those who were considered unlikely to lie in the gantry due to disease or age (there were no facilities to sedate children), or those having pacemakers or aneurysm clips. Patients having technically inadequate MRI and incomplete studies were excluded from analysis (six patients). Patients with no histological proof of the primary cancer were also excluded (one patient).

Recruitment

Consecutive patients with suspected diagnosis of SRCT were referred to the radiologists by the oncologists. Those who met the eligibility criteria and gave informed consent were prospectively included in the study. Patients were enrolled between February 2010 to August 2012 and analysed in August 2013 (minimum follow-up of 12 months).

WB-MRI

WB-MRI was performed using a 3 T MRI machine (Signa HDxt, General Electric, Milwaukie, WI, USA). A transmit—receive in-built quadrature body coil with automated sliding table platform was used for imaging. The patients were scanned in a supine position with hands by their sides. They went into the scanner with their feet first to reduce claustrophobia. Small-sized patients had to be positioned on an elevated cushion platform to include the posterior sections of the body. The protocol consisted of coronal T1 and coronal short-tau inversion recovery (STIR) with overlapping stations for the entire length of the body, from the vertex to the toes. Coronal spoiled-gradient recalled-echo (SPGR; T1-weighted (T1W)) images were obtained using parameters of 105 ms repetition time (TR), 2.1 ms echo time (TE), section thickness of 8/1, number of excitations (NEX) = 2, and a matrix of 512 × 192. Coronal STIR images were obtained using parameters of 4000–6000 ms TR, 46–47 ms TE, 160 ms TI, section thickness of 8/1, and a matrix of 128 × 128. Respiratory gating was used for the STIR sequence in the station covering thorax. The images thus obtained were reconstructed to obtain whole-body coronal pictures. Both the T1W and STIR images were read in congruence. Additional sequences such as axial single-shot fast spin-echo (SSFSE)-T2-weighted (T2W) images for the thorax for the evaluation of lung nodules, sagittal sections for the spine, and axial STIR for the bones were also performed when lesions were seen on routine coronal
PET-CT was performed on a dedicated hybrid 16 section PET-CT machine (Discovery ST, General Electric). Patients were injected with 0.5 mCi/kg FDG and were made to wait in the isolation room for 45–60 min. For the purpose of the study, the scans covered the entire length of the body, from head to toe. CT attenuation values (unenhanced) was obtained first at low tube current (between 80–100 mA) followed by a PET acquisition. The acquisition was for 3 min per bed position with an overlap of 30%. It is a routine practice at our centre to perform a plain CT chest examination (with breath-hold whenever possible) for evaluation of lung metastases (thus obviating the need of another investigation). The PET-CT images were read by two nuclear medicine specialists, one with 10 years and the other with 20 years of experience.

Bone scintigraphy

Bone scintigraphy was performed using 99m-tecnitium methylene diprophosphonate (Tc-99m MDP) on a dual-head gamma camera (Infinia Hawkeye, General Electric). The bone scintigraphs were read by the nuclear medicine experts mentioned above.

CT chest

Only those patients who did not undergo a PET-CT examination (four patients) were subjected to a separate CT thorax. These were performed using a 16 slice CT machine (Lightspeed 16, General Electric).

Reference standard

Conventional staging and clinical evaluation were considered as the reference standard. The time interval between the conventional workup and MRI was less than 2 weeks. If the results of conventional staging were ambiguous or equivocal, additional investigations were performed to confirm such results before including them as true positives for the reference standard. For example, a patient with abdominal NB with only sites of suspected metastases being non-regional small FDG-positive nodes in the left supra-clavicular fossa and the para-oesophageal region underwent biopsy of the former to confirm the histology. For marrow metastases, PET-CT and BMA/B was the conventional workup in most of the patients (30 out of 34 cases) and in the four patients where PET was not performed, bone scintigraphy with bone marrow biopsy was performed. CT chest examination was the reference standard for pulmonary metastases. For soft-tissue abnormalities, PET-CT with or without biopsy was the reference standard. Data from MIBG studies was also used for NB. The lesions detected only by MRI warranted follow-up after chemotherapy as we wanted to avoid invasive procedures, such as biopsies, for lesions detected on the experimental arm of the study.

Data collection

The data were recorded electronically. The readers of the MRI studies were blinded to the information obtained from the reference standard and vice versa. For the purpose of easy documentation and correlation of the bone lesions, the skeleton was divided into 83 regions: the midline bones of skull, facial bones, mandible, sternum, individual vertebrae from first cervical to last lumbar and sacrum constituted 29 regions and the duplicated bones of scapula, clavicle, three parts of pelvic bones, acetabulum, all the long bones divided into proximal, mid and distal third, hand bones and foot bones constituted 54 regions of the body. Only the regions that showed abnormality in any of the three imaging techniques—MRI, PET, or bone scintigraphy—were entered and all other regions were negative for a given patient. For the pulmonary lesions, the observer had to note whether there were metastases in the right and/or left lung. The FDG avidity of lung nodules was documented. Soft-tissue abnormalities, such as enlarged nodes and liver lesions, were also recorded.

Patients were then classified as non-metastatic or metastatic by the reference standard evaluation and the sites of metastases were divided into bones, lungs, lungs and bones, soft tissue, soft tissue with lung, soft tissue with bone, and all three. Lesion-by-lesion analysis was performed for the bones and soft tissues.

Analysis

The parameters of sensitivity, specificity, positive and negative predictive values and diagnostic accuracy were calculated for the skeletal lesions. As it is difficult to estimate the number of true negatives for soft tissues, only sensitivity was calculated for these lesions.

Results

Patient flow is summarized in Fig 1. Males comprised 70% (28 out of 40) of the patients. The ages ranged from 3–33 years with a median of 13. Twenty-eight patients had PNET, six had NB, and another six had RMS. Out of these 40 patients, information from 34 patients (27 patients with PNET, four with NB, and three with RMS) was used for final analysis as six patients had to be excluded due to incomplete data. Seventeen patients did not have metastatic disease, whereas the others had metastases to various sites as shown in the Fig 1.

Skeletal lesions

Including the multiple lesions in six patients with metastases to bones and the primary bone lesions of PNET, there were in all 129 bony lesions detected by all imaging
Of the 121 lesions identified on PET-CT, 120 were positive by reference standard. The exception was a patient with PNET of the ulna who had a solitary FDG-avid metastatic-appearing lesion in the calvarium with no correlating lesion at CT and a negative BMA/B. This lesion was considered negative for the reference standard and clinical management and follow-up revealed that the patient was in remission after being treated as a case of non-metastatic PNET. Similarly, of the four lesions that had only bone scintigraphy correlation, only one was considered negative by the reference standard, as it was a solitary skull lesion in a patient with PNET of fibula having negative bone marrow biopsy. One patient had a skip lesion close to the primary, which was detected on dedicated MRI for loco-regional evaluation; this was not resolved separately by PET-CT/bone scintigraphy and was considered as true positive by the reference standard. Thus, in all 124 true-positive lesions were obtained for the reference standard.

MRI correctly detected 114 of 124 skeletal lesions (sensitivity of 91.9%; 95% CI: 85.2—95.8%; Figs 2 and 3). Ten lesions that were missed on MRI were distributed in five patients all of whom had multiple other skeletal metastases that were diagnosed on WB-MRI (status of metastatic disease was already established). The distribution of the 10 missed lesions on MRI was as follows: sternum (3), skull bones (2), scapula (2), rib (1), lumbar vertebra (1), and acetabulum (1). It is interesting to note that most of these missed lesions occurred in flat thin bones of the body and all of these were small focal lesions.

Three skeletal lesions that were positive on MRI but negative on the reference standard occurred in three different patients: one was in the proximal femur and this patient had lung metastases but no other bone lesion. This patient abandoned therapy and was lost to follow-up. Two other false-positive lesions were in the ilium and were attributed to marrow oedema after a recent BMA/B. The parameters of diagnostic accuracy are summarized in Table 2.

All lesions that were seen on T1W images were also seen on STIR (101 out of 117 lesions detected by MRI) and none of the lesions that were missed on STIR were seen on T1W imaging when compared to the reference standard.

BMA/B was false negative in two cases with unequivocal marrow lesions: one was a case of PNET and other was a case of NB (MIBG positive).

### Pulmonary metastases

CT was the reference standard for pulmonary lesions (Table 3). The sensitivities of MRI and the PET only component of PET-CT were 30% and 40%, respectively (Figs 4 and 5). All of the missed lesions were <1 cm in size. However, as plain CT thorax was obtained in all patients undergoing PET-CT, all the FDG-non-avid lung metastases were detected at CT and the overall sensitivity of PET-CT was higher (100%). MRI falsely detected lung metastasis in one patient — the lesions were of infective aetiology as characterized at CT.

### Soft-tissue metastases

MRI missed three out of 13 soft-tissue abnormalities that were positive on the reference standard with a sensitivity of

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Skeletal lesions.</th>
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<tr>
<td></td>
<td>Reference positive</td>
</tr>
<tr>
<td>MRI positive</td>
<td>114</td>
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<tr>
<td>MRI negative</td>
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<td>PET-CT positive</td>
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</tr>
<tr>
<td>Bone scintigraphy positive</td>
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<tr>
<td>Bone scintigraphy negative</td>
<td>1</td>
</tr>
<tr>
<td>Bone scintigraphy not available</td>
<td>105</td>
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</table>

MRI, magnetic resonance imaging; PET-CT, combined positron-emission tomography and computed tomography.
Figure 2 STIR images of WB-MRI section (a) and the individual substations (b–c) show extensive skeletal metastases in the vertebrae, pelvic bones, both femori, left humerus and right tibia along with a sub-carinal nodal metastasis in this known case of right supra-renal NB, which correlates well with the MIP image of the FDG-PET examination (d).

Figure 3 In this case of PNET of left tibia, the STIR image (a) of WB-MRI shows focal hyperintensities in the L3 (long arrow) and L4 (short arrow) vertebrae, which are also seen as a corresponding hypointensity on the sagittal T1 (b) and hyperintensity on the sagittal STIR image (c). The PET-CT (d) image confirms the same.
76.9% (Table 4). All of the three missed lesions were subcentimetre-sized nodal metastases (two supraclavicular and one posterior mediastinal; Fig 6). One of these metastatic supraclavicular nodes was a biopsy-proven lesion, whereas the presence of the other two lesions was confirmed by response to therapy at follow-up.

**Adverse events**

No untoward incident occurred during or immediately after the MRI examinations.

**Discussion**

In the present study, MRI was found to have a high sensitivity and specificity for the detection of marrow metastases. Marrow lesions that were missed on MRI more commonly occurred in the flat bones of the body such as the sternum, scapulae, ribs, and skull. As it is possible to miss these thin bones on coronal sections, it would be useful to incorporate at least an axial STIR sequence for the thorax and pelvis in future protocols. None of the skeletal lesions missed at MRI could have had any impact on management, as they were part of a larger number of metastases in a given patient. MRI showed moderate sensitivity for soft-tissue abnormalities; however, MRI was poor in the detection of lung metastases.

The failure of BMA/B to detect tumour cells in two cases with unequivocal marrow lesions is probably due to sampling error and brings forth the utility of studies such as PET and WB-MRI, which can evaluate the entire marrow.
A recently published ACRIN 6660 trial failed to show non-inferiority of WB-MRI in diagnosis of distant metastasis in patients with common paediatric tumours; however, the study also concluded that WB-MRI was more accurate in the detection of metastases in patients with solid tumours rather than lymphomas.6 Our study, which was initiated prior to this publication, is based on solid tumours. It is interesting to note that the results of our study are comparable to their findings, where they concluded that MRI is more useful in the detection of skeletal metastases rather than those in the lungs and solid organs.

An early study of 39 patients by Daldrup-Link et al.3 compared MRI with skeletal scintigraphy and FDG-PET for the detection of bone metastases in children and adolescents. In their study, the sensitivity of FDG-PET (90%) was much higher than the sensitivity of WB-MRI (82%) and skeletal scintigraphy (71%).2 However, the low sensitivity of WB-MRI could be attributed to the use of only T1W sequences in most of their patients. Use of STIR sequence is known to improve the sensitivity of MRI and this was also reflected in the present study. In a study by Schmidt et al.,7 WB-MRI was compared with PET-CT for the detection of skeletal metastases in 30 patients, and WB-MRI showed a significantly higher diagnostic accuracy than PET-CT (91% versus 78%). Another recent study by Krohmer et al.8 showed that WB-MRI using a combination of STIR and T1W images detected all bone lesions and most of the extra-skeletal lesions (with a sensitivity of 93.8%), all the missed lesions being nodes in 24 children with malignant diseases.

One of the important findings of our study is that metastases were not over-diagnosed. Half of the patients had non-metastatic disease according to the reference standard and none of them had false positive MRI. There is a concern over presence of red marrow in the skeleton of small children leading to difficulty in the detection of marrow metastases, where the red marrow could mimic lesions. The present study cannot eliminate this with certainty, as the red marrow was not mapped in our patients and the median age was 13 years; however, it shows reliable accuracy at least in older children. Marrow oedema is a known pitfall on STIR images and caution should be exercised in patients who undergo MRI post-bone marrow aspiration as seen in two of our cases. A 3 T magnet was used in imaging all patients and this also shows feasibility of WB-MRI at higher field strength.

The most important advantage of MRI is it being radiation-free, thus saving exposure to young vulnerable and curable paediatric cancer patients. The estimated cumulative radiation dose from PET-CT in children with malignancies is about 78.9 mSv when an average number of 3.2 scans per child are performed as quoted in a retrospective study by Chawla et al.9 A study by Pearce et al.10 showed that the use of CT, which delivers cumulative doses of about 50 and 60 mGy, in children might triple the risk of leukaemia and brain tumours, respectively.10 Even though the current PET machines with improved algorithms may not contribute to such large doses of radiation, it is a matter of concern.

### Table 4

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<thead>
<tr>
<th></th>
<th>Reference positive</th>
<th>Reference negative</th>
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<tbody>
<tr>
<td>MRI positive</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>MRI negative</td>
<td>3</td>
<td>NA</td>
</tr>
<tr>
<td>PET-CT positive</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>PET-CT negative</td>
<td>0</td>
<td>NA</td>
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MRI, magnetic resonance imaging; PET-CT, combined positron-emission tomography and computed tomography.
Furthermore, MRI is superior in characterization of soft-tissue lesions; for example, in one of the trial patients suspected to have an orbital RMS, WB-MRI showed an infective appearing lesion in the orbit and a paravertebral abscess associated with a vertebral lesion. These lesions were histologically proven to be granulomatous infection due to tuberculosis and the patient was excluded from the trial. Such lesions are FDG avid and cannot be differentiated at PET.

One of the limitations of our study is lack of histological proof, of lesions detected by MRI. Another limitation is small sample size with unequal distribution of patients in the three histological subsets. As the predominant population in the present study had cases with PNET, the results could be more applicable to this sub-group.

In conclusion, WB-MRI is a useful radiation-free tool with high diagnostic accuracy for the evaluation of metastatic disease to the marrow in solid SRCTs. The sensitivity for detection of smaller soft-tissue metastases, such as nodal lesions, is moderate. As PNET is more likely to metastasize to the marrow rather than to soft tissues, WB-MRI is likely to be more accurate in this sub-group of solid round cell tumours. CT thorax remains essential for the evaluation of lung metastases.

Figure 6 A patient with abdominal NB. The primary supra-renal mass and associated retroperitoneal adenopathy is well seen on the coronal STIR image of WB-MRI (a). However, the sub-carinal node (b) and left supra-clavicular node (c) are not appreciated at MRI. Both of these nodes were true positives as confirmed by follow-up and biopsy, respectively.
Acknowledgements

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References
