CCR PEDIATRIC ONCOLOGY SERIES

Pediatric Cancer Predisposition Imaging: Focus on Whole-Body MRI

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Abstract

The American Association for Cancer Research convened a meeting of international pediatric oncologists, geneticists, genetic counselors, and radiologists expert in childhood cancer predisposition syndromes (CPS) in October 2016 to propose consensus surveillance guidelines. Imaging plays a central role in surveillance for most, though not all, syndromes discussed. While encompassing the full gamut of modalities, there is increasing emphasis on use of nonionizing radiation imaging options such as magnetic resonance imaging (MRI) in children and adolescents, especially in the pediatric CPS population. In view of rapid evolution and widespread adoption of whole-body MRI (WBMRI), the purpose of our review is to address WBMRI in detail. We discuss its place in the surveillance of a range of pediatric CPS, the technical and logistical aspects of acquiring and interpreting these studies, and the inherent limitations of WBMRI. We also address issues associated with sedation and use of gadolinium-based contrast agents in MRI in children. *Clin Cancer Res; 23(11); e6–e13. ©2017 AACR.*

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Introduction

The use of whole-body magnetic resonance imaging (WBMRI) for surveillance of infants, children, and adolescents with cancer predisposition syndromes (CPS) has grown over the past decade, in line with more widespread adoption of WBMRI for a range of pediatric oncologic indications (1–8). This has been due to a combination of factors including technologic improvements enabling more rapid acquisition, greater access to MRI, as well as increased awareness of its expanding applications (1, 5, 9).

The wide anatomic coverage WBMRI provides is of particular appeal in CPS given the potential for multifocal disease that may have many target organs and tissues and a multiplicity of lesions (9). The lack of ionizing radiation in WBMRI is another key advantage in the pediatric CPS population due to the increasing desire for long-term monitoring, often from a young age. This can result in a large number of imaging studies being performed. With heightened awareness of the potential for increased health risks resulting from radiation exposure in the pediatric population, preferential use of ionizing radiation-free techniques, such as ultrasound and MRI, is paramount when developing strategies for routine surveillance imaging (10, 11).

In performing surveillance WBMRI, consideration should also be given to timing in relation to other imaging, with an effort to minimize unnecessary duplicate studies by harmonizing as many as three different, and potentially overlapping, streams of imaging. These can include other modalities in the surveillance protocol (i.e., ultrasound and MRI of the same region), investigations for diagnosis and staging, and monitoring a known neoplasm. Optimizing the surveillance imaging approach can affect the overall patient experience and reducing the number of investigations can potentially ease patient and caregiver stress; these issues are addressed in the *CCR* Pediatric Oncology Series article by Druker and colleagues (12), which is dedicated to issues related to genetic counseling.

The purpose of this review is to provide a practical approach to performing WBMRI surveillance in pediatric patients with CPS, as recommended in the accompanying syndrome-specific surveillance protocols in this series of articles. This includes discussion of WBMRI technical parameters for basic and more syndrome-specific scan acquisitions, guidelines for image interpretation and reporting, and an overview of risks, in particular sedation issues in the very young and intravenous gadolinium-based contrast agent (GBCA) retention in pediatrics (13–16).

WBMRI Acquisition

WBMRI has the potential to offer a comprehensive assessment of the entire body in a single, integrated examination, with standard protocols providing both anatomic and functional information along with superior soft-tissue contrast resolution. When compared with dedicated region-specific MRI, the spatial resolution attainable by WBMRI may be reduced; however, the whole-body examination can be performed in conjunction with focused regional MRI, such as brain and spine MRI, or targeted MRI of specific organs or extremities, as needed. WBMRI is now successfully employed for CPS surveillance in many pediatric centers, with minor modifications tailored to specific syndromes which is now discussed.

Anatomic coverage

WBMRI is characterized by contiguous multiregion scanning. For surveillance imaging in CPS, extent of coverage of WBMRI

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doi: 10.1158/1078-0432.CCR-17-0515

Table 1. WBMRI surveillance coverage in childhood CPS

Syndrome	WBMRI	Brain MR	Spine MR	NCAP WB	CAP WB + Neck MR
LFS	Q 12 mo from Dx	Q 12 mo from Dx (alternating Q 6 mo with WBMRI unless under GA)			
NF1	Baseline scan between 16 and 20 years				
NF2 and schwannomatosis	Based on Sx and location	Add IAM Q 6–24 mo Q 6 mo if positive	Q 24–36 mo Q 6 mo if positive		
RB	Q 12 mo from 8 y	Q 6 mo to 5 y			
CMMRD (+/− LS)	Q 12 mo from 6–8 y (no anesthesia)	Q 6 mo from Dx			
DICER 1 syndrome	Consider	Q 6 mo from Dx			
RTS	Consider	Urgent if Sx			
HPP syndrome				Q 24 mo from 6–8 y	Q 24 mo from 6–8 y *option
NOT INDICATED	Adenomatous polyposis syndromes (APC, MUTYH), juvenile polyposis coli (BMPR1A, SMAD4, PTEN), Peutz–Jeghers syndrome (STK11/LKB1), RASopathies, NS, NSLAH, NSML, CFCS, CS, LeS, CBLS, Sotos, Weaver, Rubinstein–Taybi, Schinzel–Giedion, and NKX2-1 syndromes; metabolic disorders linked to childhood cancers; rare DNA repair disorders: ataxia telangiectasia, Bloom syndrome, Fanconi anemia, dyskeratosis congenita, Nijmegen breakage syndrome, xeroderma pigmentosum, PHTS, HLRCC syndrome, Gorlin syndrome; leukemia/lymphoma syndromes *unless* part of other syndrome, e.g., LFS, CMMRD; overgrowth disorders and kidney tumors, e.g., BWS, BOS, DDS, FS, HB, IHH, SGBS, PROS, PS, WT; NB; MEN syndromes: MEN1, MEN2A and B, MEN4, HPT-JT; vHL disease				

Abbreviations: BOS, Bohring–Opitz syndrome; BWS, Beckwith–Wiedemann syndrome; CBLS, CBL syndrome; CFCS, cardiofaciocutaneous syndrome; CMMRD, constitutional mismatch repair deficiency syndrome; CS, Costello syndrome; DDS, Denys–Drash syndrome; Dx, diagnosis; FS, Frasier syndrome; GA, general anesthesia; HLRCC, hereditary leiomyomatosis and renal cell cancer syndrome; HPP, hereditary paraganglioma and pheochromocytoma syndrome; HPT-JT, hyperparathyroid-jaw tumor; IAM, internal auditory meati; IHH, isolated hemihypertrophy; LeS, Legius syndrome; LS, Lynch syndrome; MEN, multiple endocrine neoplasia; NB, hereditary neuroblastoma; NF1, neurofibromatosis type 1; NF2, neurofibromatosis type 2; NS, Noonan syndrome; NSLAH, NS like with loose anagen hair; NSML, NS with multiple lentigines; PHTS, PTEN hamartoma tumor syndrome; PROS, PIK3CA-related overgrowth spectrum; PS, Perlman syndrome; RB, hereditary retinoblastoma; RTS, Rothmund–Thomson syndrome; SGBS, Simpson–Golabi–Behmel syndrome; Sx, symptoms; WT, Wilms tumor; vHL, Von Hippel–Lindau; Q, every; mo, months; y, years.

should be tailored to each syndrome based on the expected location of lesions being screened for.

There is much variability in nomenclature surrounding WBMRI in the published literature and, in practice, with terms such as total body MRI, rapid whole-body MRI, and "eyes to thighs" used interchangeably. Similarly, what is meant by WBMRI can be open to interpretation. Even in the same institution, coverage may differ between scans depending on the size of the patient, the choice of scanner and coil complement, and the technologist performing the examination unless the coverage is clearly defined.

Therefore, the authors propose using "Whole-Body MRI"/"WBMRI" to exclusively mean imaging "head to toe" or from the vertex to the heels unless otherwise specified. Where lesser coverage is considered sufficient to screen for a particular syndrome, this should be annotated accordingly, with the following suggested:

"**CAP WBMRI**" = **C**hest, **A**bdomen and **P**elvis MRI
"**NCAP WBMRI**" = **N**eck, **C**hest, **A**bdomen and **P**elvis MRI

Inclusion of the proximal extremities (upper arms to the elbows and lower extremities to the mid-thighs) may emulate conventional coverage in positron emission tomography (PET)/CT; however, it is not advocated for any syndromes discussed in this *CCR* Pediatric Oncology Series.

Tailoring the MRI to the indication has the potential to reduce imaging time. In younger patients this can improve image quality, as shorter scan times typically improve compliance in children, reducing motion artifact. If a dedicated regional MRI is required/desired as part of a CPS surveillance protocol, such as a dedicated brain MRI in Li–Fraumeni syndrome (LFS), this should be separately specified when the examination is ordered. This may be independent of whether the brain MRI is scheduled at the same time as the WBMRI, or as part of a separate examination.

Table 1 summarizes pediatric CPS for which WBMRI surveillance is recommended in the accompanying guidelines, including recommended MRI coverage based on expected tumor sites and any regional MRI requirements proposed in the syndrome guidelines, for example, dedicated regional versus surveillance neck imaging. Importantly, there are a number of pediatric CPS for which WBMRI is not currently recommended, such as the 11p overgrowth syndromes (including Beckwith–Wiedemann syndrome), hereditary Wilms tumor syndromes, Noonan and Noonan-like syndromes, Schinzel–Giedion syndrome, and NKX2-1 syndrome.

Technical factors: Sequences and imaging planes

There is no single "standard" WBMRI protocol. Considerable site-to-site variations arise from differing scanner platforms and technological capabilities, the tumors and syndromes under surveillance, and departmental/radiologist preference. The most recent published protocols specific for WBMRI in pediatric oncology utilize a fluid-sensitive sequence in the coronal plane, with additional optional sequences and imaging planes (1, 6–8, 17–19), and are summarized in Table 2. As documented in the table, scan times vary significantly between protocols depending on number and type of sequences used. Further research and collaboration are necessary to create standard, uniform protocols.

The core WBMRI surveillance sequence is typically acquired as a fluid-sensitive 2D sequence in the coronal plane, primarily because images generated in this plane can be acquired in a shorter time than axial imaging. Increasingly, many centers also routinely obtain images in the axial plane, although the added benefit or even optimal imaging plane is not yet fully established (20). Extending scan times can introduce motion artifact and have an impact on patient throughput, which likely further contributes to variability in sequence and imaging plane choices between

Table 2. Published WBMRI protocols for pediatric oncology

Authors and reference	Imaging plane	Sequences	Approximate scan time[a]
Davis et al. (6)	Coronal	STIR, HASTE, T1 Option: MRA-TWIST	N/A
	Axial	HASTE, STIR	
Eutsler and Khanna (7)	Coronal	STIR	40 minutes
	Axial	STIR, HASTE, DWI (b values: 50, 400–500, 800–1,000 s/mm^2)	
Nievelstein and Littooij (8)	Coronal	STIR, T1 TSE	32 minutes
	Axial	DWI-STIR (b values: 0, 100, 800–1000 s/mm^2), T2 SPAIR	
Villani et al. (17)	Coronal	STIR	18 minutes
Anupindi et al. (18)	Coronal	STIR, T1, HASTE	AVG 72 minutes
	Axial	STIR (head, neck, lower extremities), T2 FS (chest, abdomen ± pelvis), HASTE	
	Sagittal	HASTE	
Jasperson et al. (19)	Axial	HASTE	<1 hour
	Coronal	HASTE	

Abbreviations: AVG, average; DWI-STIR, DWI with background body signal suppression (DWIBS), applying prepulse of STIR for fat suppression; FS, fat suppression; HASTE, ultrafast half-Fourier-acquired single-shot turbo spin echo; MRA, magnetic resonance angiography; MRA-TWIST, dynamic time-resolved MRA; N/A, not available; SPAIR, spectral attenuated inversion recovery; STIR, short tau inversion recovery; TSE; turbo spin echo.
[a]Approximate scan times vary with number of stations, determined by patient height, e.g., average of 5; authors 6–8, 16–18 (see references).

different centers. Sagittal imaging is less frequently performed as part of standard protocols, more commonly used as a supplementary sequence to provide additional information for a detected lesion or to obtain a comprehensive survey of the entire spine in a single longitudinal plane.

Coronal short tau inversion recovery (STIR) is the sequence central to most WBMRI protocols, displaying most pathologic lesions as bright signal against a darker background due to its robust fat suppression (1, 6–8). Fat-suppressed T2-weighted sequences provide an alternative fluid-sensitive sequence; however, these sequences rely on chemically selective fat suppression techniques that can be inhomogeneous in non-axial acquisition planes, resulting in artifacts when transitioning between certain regions of the body (e.g., neck and supraclavicular chest). T1-weighted sequences are also variably applied to aid lesion localization and tissue characterization for certain CPS. Few screening protocols routinely include GBCA-enhanced sequences (1, 6–8).

Whole-body diffusion-weighted imaging (DWI) has only recently been incorporated into pediatric oncology WBMRI protocols, as technologic advances have led to faster acquisitions with fewer artifacts, such as those due to air-filled bowel and motion. Images are typically acquired axially and then reconstructed in the coronal plane to limit artifacts related to applying diffusion gradients in nonstandard (sagittal and coronal) planes. DWI offers greater conspicuity for many lesions and improved lesion characterization (i.e., lesion cellularity, response to therapy), with the potential for acquiring more functional data (i.e., diffusion tensor imaging). These sequences are acquired free breathing with fat suppression. A vendor-specific term, "DWIBS" (diffusion-weighted whole-body imaging with background suppression), is often used to describe this technique. Use of multiple gradient strengths with three or more b-values, both high (800–1,000 s/mm^2) and low ($\leq$200 s/mm^2) values, in conjunction with apparent diffusion coefficient (ADC) maps, improves qualitative assessment of diffusion restriction. This also offers the potential to perform quantitative assessment through calculation of lesion ADC values, which may vary with treatment and serve as a biomarker for therapeutic response (7, 8, 9, 21).

Tissue-specific contrast agents, including ultrasmall superparamagnetic iron oxide particles (USPIO) such as ferumoxytol, which are taken up by the reticuloendothelial system, show promise in improving lesion conspicuity with DWI but are not yet part of standard clinical practice, although ferumoxytol is also being investigated as an alternative intravenous contrast agent (22).

Whole-body MR images are generated from multiple sequentially obtained sets of images, acquired in "stations," at a number of levels from head to toe, dependent upon patient height and desired coverage. For those images acquired or reconstructed in coronal plane, these are later merged or "stitched" into a single whole-body multislice data set for display and analysis. Diffusion-weighted images are often inverted on the viewing workstation, in part to mimic PET and also to improve lesion conspicuity and reduce background signal. Pathologic lesions typically appear dark on this inverted DWIBS image, such as the popliteal fossa lymph node and subtalar joint fluid in Fig. 1. ADC maps (not shown) may show diffusion restriction in solid neoplasms and lymph nodes—typically remaining dark (inverted DWIBS dark—ADC dark). In comparison, uncomplicated fluid does not restrict, instead remaining brighter relative to non-fluid structures on the inverted DWIBS image (inverted DWIBS dark—ADC bright).

It may be desirable in selected CPS to supplement the surveillance WBMRI with additional focused regional MRI to provide higher spatial resolution imaging of a particular anatomic site than WBMRI offers, such as for dedicated brain MRI in LFS. However, targeted small field-of-view imaging can also be acquired *ad hoc* during WBMRI to problem solve or to characterize a new finding. For subtle abnormalities, this may confirm or exclude the presence of a lesion or if more obvious, further characterize a lesion and eliminate the need to return for additional imaging. Note, however, that this level of active monitoring by the radiologist is usually beyond the scope of a routine surveillance imaging examination and may not be possible at all centers.

Technical factors: Hardware and software

WBMRI can be performed satisfactorily on 1.5 and 3 Tesla (T) MRI scanners. Although there is slight increase in artifact at 3T (particularly with DWI, owing to the diffusion gradients being more susceptible to artifact at higher field strengths), with image quality better at 1.5 T, a recent comparison of 21 children undergoing WBMRI at both field strengths within a short time interval showed image quality was still adequate at 3 T (23). This finding was supported by a meta-analysis of the existing literature showing feasibility of identifying lesions in patients with

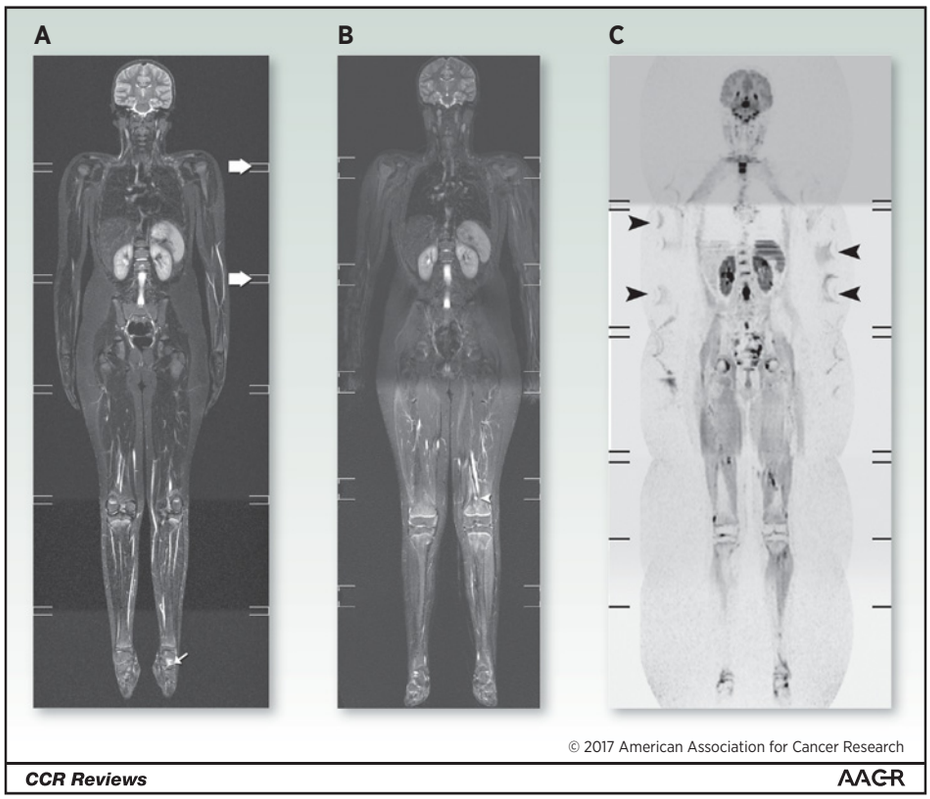

Figure 1.
A–C, WBMRI in a girl genetically confirmed to have LFS, who was undergoing annual surveillance imaging at 9 years old (**A**) and 10 years old (**B** and **C**). Nonspecific findings are seen. **A,** Coronal STIR sequence as 6 "stations" merged (broad arrows) into a single image at 1.5 Tesla (T). The small arrow shows fluid in the left subtalar joint. Coronal STIR (**B**) and inverted coronal DWIBS at b = 1,000 s/mm^2 acquired at 3 T (**C**). Arrowhead (white) in **B** shows left popliteal fossa lymph node. Note incomplete visualization of the left arm compared with **A**, warranting modification of patient position. Arrowheads (black) in **C** show motion artifact from arms.

neurofibromatosis types 1 and 2 and schwannomatosis on WBMRI at 1.5 and 3 T (20).

Many aspects of MRI have benefitted from recent technological developments, resulting in WBMRI now being more widely used in infants, children, and adolescents. These advances have resulted in faster acquisition times and increased signal-to-noise ratio (SNR) for improved visualization of normal and abnormal structures. These include advances in coil technology using multichannel receiver, phased array, surface and in-table coils, and use of multitransmit technology and parallel imaging to reduce acquisition time and increase signal to noise, optimizing 3-T acquisitions in particular (9). Together with continuous table motion, image acquisition is now more streamlined. The patient is usually scanned supine with arms by their side. In larger patients, an additional "station" may be needed, scanning with the patient's upper extremities placed overhead, and thereby closer to the magnet isocenter. For patients with an implanted metallic endoprosthesis, 1.5 T is preferred over 3 T MRI due to decreased distortion of the local magnetic field.

Patient preparation

Generally, for patients with a developmental age of $\geq$6 years, WBMRI can be performed without sedation or general anesthesia (GA) and requires no special preparation. Some infants can also be imaged successfully without sedation using so-called "feed-and-wrap" protocols, although not every center will be prepared for the level of coordination required between the clinical and MRI teams. As standard WBMRI protocols do not use a GBCA, intravenous access is usually not needed. However, this may differ if targeted imaging to troubleshoot requires use of a GBCA, or if a regional MRI scan performed in conjunction with the WBMRI requires contrast.

MRI Risks

MRI safety is of utmost importance in the evaluation of children. MRI risks can be inherent due to the magnetic field or extrinsic, related to complementary techniques such as contrast administration or sedation.

3 T MRI has double the magnetic field and quadruple the energy deposition compared with 1.5 T. Contraindications to MRI include pacemaker and implanted aneurysm clips. Vagal nerve stimulators can be used with some vendors and specific head coils. Educational tools and additional information can be found on MRIsafety.com.

GBCAs are routinely used in diagnostic brain and head and neck MR imaging, and for many body imaging indications. Free gadolinium deposition in the brain following infusion of GBCA has recently become a concern based on the finding of increased T1 signal in various brain nuclei—signal that is thought to represent deposition of gadolinium. The effects of the deposition are unknown. Newer contrast agents based on macrocyclic chelators are considered safer, owing to chemical structures that encase the gadolinium and provide a more stable chelate, thus reducing the free dissociation of gadolinium and limiting its potential for reacting with and depositing in adjacent tissues (13–15).

It is well accepted that diminished renal clearance of free gadolinium puts adults with renal failure at risk for developing nephrogenic system fibrosis (NSF), a rare fibrosing dermatopathy thought to be caused by the deposition of free gadolinium in the

subcutaneous tissues and less commonly in visceral organs. A review of 23 children diagnosed with NSF revealed a history of intravenous gadolinium administration in 17 and renal disease in 10. All children were older than 6 years of age. There have been no reports of NSF in children younger than 6 years of age. In 2007, the FDA instituted a boxed warning for contrast agents that highlighted the risk of NSF with GBCA administration and glomerular filtration rate (GFR) less than 30 mL/min/1.73 m^2. Subsequently, no new cases of NSF have been reported in children. GFR screening is the standard practice in radiology departments in patients with suspected renal disease, solitary kidney, and renal anomalies and renal failure. The Bedside Schwartz equation is the recommended method for the determination of GFR in children (24), although patients with reduced muscle mass and correspondingly low serum Creatinine levels can have falsely normal estimated GFR values, and more direct measures of GFR such as radionuclide (^{99m}Tc-DTPA) clearance techniques may be warranted. Contrast administration is not contraindicated in premature infants and neonates with low GFR due to renal immaturity; however, the benefit should be well reasoned and outweigh the risk (25).

There has been great interest in using USPIO contrast agents due to lack of renal excretion and absence of NSF risk; however, initial postmarket studies in adults have reported a risk of cardiac adverse events and anaphylaxis that is higher than with GBCA (26). In addition, these agents are taken up by the reticuloendothelial system and are retained for weeks to several months and may lead to an additional risk of iron overload with repeat doses. In the pediatric population, ongoing studies are focused on developing protocols for safe administration and minimizing adverse events, assessing optimal imaging time for intravascular visualization and tumor visualization, and defining optimal dose (27, 28).

Although contrast administration is not used for routine WBMRI screening, it is used in the evaluation of the brain in syndromes requiring surveillance of brain and head and neck for tumor detection (29, 30).

Motion Minimization Options

Surveillance of the brain with dedicated MR imaging to detect brain tumors is recommended as early as infancy in patients with constitutional mismatch repair deficiency syndrome, hereditary retinoblastoma, and LFS.

In young children less than 4 months of age, the technique of swaddling and feeding can be used to avoid sedation. "Feed-and-wrap" techniques involve wrapping the baby after feeding to restrict movement, provide reassurance, and encourage sleep. Optimal results require scheduling scan time based on the feeding schedule in combination with sleep deprivation. Skipping feeds and melatonin administration have been shown to increase the success rate. Scan preparation in a warm environment with low light levels and noise cancellation may further increase success (31).

Children between 4 to 6 months and 6 years typically require moderate conscious sedation or GA to reduce anxiety and decrease motion. Due to the risk of hypoxia and aspiration related to sedation and anesthesia and the unknown risk of neurodevelopment impairment (see below), WBMRI recommendations for tumor surveillance do not include this age group unless there are clear data-proven risk of tumor development and evidence that surveillance imaging provides sufficient benefit to offset the risks of anesthesia.

There is increasing concern for neurodevelopment impairment due to the effects of anesthetic medications in infants and young children (32). This is based on data collected in young animals assessing a variety of inhaled anesthetics and sedative drugs, showing both behavioral changes and apoptosis in the developing brain. Data on the effects of sedation or anesthesia on neurocognitive effects in humans are limited. The preliminary international clinical trial, comparing General Anesthesia to Spinal anesthesia (GAS study) in children undergoing hernia repair at less than 6 months of age, found that sevoflurane anesthesia showed no cognitive difference from spinal anesthesia using standard developmental testing at 2 years of age (33). Performance of an intelligence test at the age of 5 will generate more conclusive data regarding long-term effects. It is not yet possible to know whether anesthetic drugs are safe when delivered as a single short administration versus longer duration exposures or multiple repeat episodes. As a result, alternatives to sedation have become increasingly important in a population undergoing repeat surveillance procedures.

In school-age children, child life consultation can decrease the risk of sedation/anesthesia use (34). Preparation techniques used with awake children include child life specialist consultation, practice examinations in mock scanners, and videos of the MRI procedure that can be easily found on the Internet. Carter and colleagues showed a reduced need for GA by almost 50% in children between 3 and 8 years after passing their "mock" scan (35). Distraction techniques during scanning, such as MRI compatible video goggles and audio headphones, are very effective at decreasing anxiety and motion and improving participation (36).

Imaging techniques using motion reduction have largely focused on decreasing motion related to breathing and include respiratory bellows tracking diaphragm motion, navigator pulse detecting respiration, fast free-breathing sequences, or breath hold sequence. Many of these techniques, however, can also increase scan time. Newer data processing techniques [k-space filling techniques such as *BLADE* (Siemens)/*MultiVane* (Philips)/*PROPELLER* (GE)] have also become commercially available and are useful in simultaneously decreasing motion and scan time.

WBMRI Interpretation and Reporting

What to look for?

Interpreting images from a WBMRI can be challenging, but awareness of the tumor types and anatomic sites associated with the syndrome in question is key to performing a systematic review (37). Table 3 provides an itemized checklist to facilitate this review, summarizing locations of tumors relating to the different pediatric CPS undergoing WBMRI. For specific lesions at these sites related to each syndrome, please refer to the relevant syndrome-specific articles in this series.

Depending upon the sequences utilized and lesions under surveillance, consideration must also be given to limits of detectability for small lesions and whether they can be reliably detected by MRI. There are little published data defining this in children or adults undergoing WBMRI cancer screening. One pediatric study by Nievelstein and Littooij compared WBMRI with PET/CT and found MRI was better able to identify bony infiltrates <12 mm (8). Although lung nodules are increasingly identified on WBMRI—some studies showing high sensitivities for lesions between 4 and 10 mm—WBMRI screening for pulmonary metastases is not yet advocated, and chest CT remains the reference standard (5, 6).

Table 3. WBMRI surveillance checklist: Childhood CPS lesion location

	Pediatric CPS disorders and disease groups							
		Neurofibromatoses		Gastrointestinal cancers	Neuroendocrine tumors	Leukemia and lymphoma/DNA repair and immunodeficiency disorders	Miscellaneous disorders	
Anatomic location	**LFS**	**NF1**	**NF2 and Sch**	**CMMRD (+LS)**	**HPP (PHEO and PGL)**	**RTS**	**DICER1**	**RB**
Brain	**X**	**X**	**X***	**X^{L}**			**X**	**X**
Spine			**X**					
Orbits		**X**					X	X
Thyroid	X^{B}						**X**	
Lungs	X^{B}						**X**	
Heart								
Parathyroid								
Liver								
Pancreas								
Adrenals	**X**	X			**X**			
Kidneys	X^{B}			X*^{L}	**X**		**X**	
Urinary bladder		X*		X*^{L}				
Uterus		X*		X*^{L}			**X**	
Ovaries		X*		X*^{L}			X	
Prostate								
Testes								
Bowel	X	X		**X^{L}**	**X**		X	
Breast	**X**							
Bone	**X**					X		**X**
Soft tissue/muscle	**X**	X		X			X	X
Hem/BM^	X	**X**		**X**		X		
Skin	X	X		X		X		X
Other	X	**X**	X	X^{L}	**X**		X	

NOTE: Dark gray columns: WBMRI optional; X (bold), "core" tumors most closely linked to syndrome/disease; Hem/BM^, hematologic = bone marrow/lymph nodes; LFS, Li–Fraumeni syndrome; X^{B}, Brazilian founder mutation, other = neuroblastoma; CMMRD, constitutional mismatch repair deficiency syndrome; LS, Lynch syndrome; X*, genitourinary; X^{L}, common to Lynch syndrome and CMMRD, other = neuroblastoma; RTS, Rothmund–Thomson syndrome; DICER1, other = nasal chondromesenchymal hamartoma; HPP syndrome, hereditary pheochromocytoma (PHEO) and paraganglioma (PGL) syndromes: bowel, gastrointestinal stromal tumor (GIST), other = neck/upper mediastinum—parasympathetic; lower mediastinum/abdomen/pelvis—sympathetic nervous systems; RB, hereditary retinoblastoma; NF1, neurofibromatosis type 1; X*, genitourinary, bowel = GIST, other = nerve sheath tumors; NF2, neurofibromatosis type 2; Sch; schwannomatosis, X* = internal auditory meati, other = where symptomatic; MEN, multiple endocrine neoplasia.

As well as a systematic approach and detailed knowledge improving lesion detection, as Anupindi and colleagues highlighted, it is equally important to carry out "risk stratification" to minimize false positive findings (18). WBMRI is only one part of a surveillance program, and findings should be interpreted in conjunction with other clinical and imaging data (17, 18). Nonspecific findings with a low likelihood of being related to the syndrome in question can likely be managed conservatively in an otherwise asymptomatic patient rather than initiating a more intensive, and possibly invasive, diagnostic pathway.

Who should do it?

This raises the question of who should report WBMRI in pediatric CPS. Anupindi and colleagues (18) state that it is "imperative that the examinations be interpreted by radiologists who are familiar with whole-body MRI." This requires imaging specialists who are skilled both in the interpretation of WBMRI and knowledgeable about the CPS for which the screening examinations are being conducted in order to effectively conduct this risk assessment (18). Options will vary at each site, depending upon specialist and subspecialist radiologist availability (e.g., one radiologist interpreting the entire exam versus a pediatric/body radiologist and neuroradiologist separately reporting respective anatomic regions), the volume of CPS WBMRI scans, as well as overall workload and workflow.

For sites with low volumes of CPS, WBMRI options to consider might include WBMRI being acquired locally and read at a central site or alternately, as in breast cancer screening, double reading, with two readers locally or one local reader and one central reader. However, as shown with breast imaging, even with experienced double readers using a systematic approach to interpretation and standardized reporting, there exists "inherent interpretive variability" (37). This is equally applicable to WBMRI interpretation.

Acknowledging this variability, use of templates in standardized reporting should be encouraged, for both the reporting radiologist and clinician. This allows easier comparison of findings for repeat examinations and, in addition, facilitates the exchange and review of studies and interpretations obtained at different institutions. This is particularly relevant given the long-term follow-up in pediatric CPS patients. Table 4 provides an example.

Future Directions

There is still much to be done to validate the use of WBMRI in the surveillance of all pediatric CPS discussed in this *CCR* Pediatric Oncology Series while also minimizing risk. Indeed, evidence of

Table 4. Report template: WBMRI without contrast

CLINICAL HISTORY: Surveillance for [LFS]

COMPARISON: [None/prior study from]

TECHNIQUE: Coronal STIR, coronal T1, axial T2 FS, optional axial DWI

FINDINGS:
SUPPORT DEVICES: [None]
HEAD/NECK:
[The visualized anatomic structures of the head and neck are grossly normal and no mass is identified. There is no lymphadenopathy in the neck or supraclavicular region. The thyroid gland has uniform signal and no evidence for nodule, cyst, or mass.]
CHEST:
[There is no axillary, hilar, or mediastinal lymphadenopathy. The lungs demonstrate no pleural effusions, focal nodules, or consolidation. Breast tissue is normal. No mass is seen.]
ABDOMEN:
[The liver, spleen, pancreas, adrenals, and kidneys appear normal in signal and morphology. There is no evidence for mass in the solid organs, bowel, or mesentery. There is no abdominal or retroperitoneal lymphadenopathy.]
PELVIS:
[Male: The bladder and prostate are unremarkable. There is no free fluid.]
[Female: The uterus is normal in signal and morphology. The ovaries are not visualized/are visualized and appear normal. The bladder is unremarkable. Free fluid is physiologic.]
BONE MARROW/BONES/SOFT TISSUES: The bones are normal in morphology. There is no abnormal bone marrow signal or focal bone abnormality. No soft tissue masses are identified.

IMPRESSION:
[NO] EVIDENCE FOR SOLID TUMORS
[INCIDENTAL FINDINGS: NONE/INCLUDE]
[ADDITIONAL IMAGING IS/IS NOT RECOMMENDED.]

benefit from imaging surveillance has been shown in only a select few. Villani and colleagues recently showed improvement in survival through early detection in an 11-year prospective review of patients with LFS (17). WBMRI identified almost 30% of malignant lesions, more than any other individual screening tool in this study; however, the combination of surveillance elements—clinical examination, bloodwork, and imaging (including brain MRI, abdominopelvic ultrasound, and mammography)—was most instrumental in tumor detection (17). A pilot study screening for osteosarcoma and subsequent malignant neoplasms in hereditary retinoblastoma showed only moderate sensitivity in tumor detection, with limited data for surveillance effectiveness shared by many pediatric tumors (18, 38, 39). However, as shown by Jasperson and colleagues in comparing WBMRI to biochemical testing in screening for succinate dehydrogenase (SDH)–related tumors, with WBMRI having improved sensitivity and comparable specificity, a high negative predictive of WBMRI has value providing reassurance (19). This needs to be balanced against the low positive predictive value from false positive findings, requiring careful consideration as discussed, and PET/MRI may have a role here. International CPS and specific pediatric tumor registries, such as exists for childhood gastrointestinal stromal tumors (GIST), will help provide data that will undoubtedly lead to protocol optimization and rationalization of those CPS in which WBMRI is shown to be most effective (38, 40). Further WBMRI protocol modifications will arise from advances in MRI, such as techniques for screening for lung metastases (41).

Conclusions

The central role WBMRI now plays in the routine surveillance for many pediatric CPS is primarily due to it providing large field-of-view imaging without the deleterious effects of ionizing radiation, lending itself to serial examination. There is no single "standard" WBMRI protocol. Instead, coverage—"head to toe" unless specified—imaging planes and sequences are tailored to the specific syndromes, as outlined. As more evidence is available, WBMRI protocols, and, indeed, appropriate utilization, will evolve.

A number of factors contribute to variation in existing WBMRI protocols and on its universal adoption. Some issues relate to the patient, including need for sedation/anesthesia in infants and children, and some are site-specific issues such as technical limitations of MRI scanners, technologist expertise for image acquisition, and radiologist experience in CPS image interpretation. A number of these issues have been addressed in this review; others such as access to MRI and availability of WBMRI are beyond its scope. However, in the event that WBMRI is not an option, consultation with diagnostic radiologists can lead to the most suitable alternative imaging solution being found, be that targeted MRI and/or other modalities. This will vary based on local resources and the lesions in question.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Received February 21, 2017; revised March 30, 2017; accepted April 21, 2017; published online June 1, 2017.

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Clin Cancer Res 2017;23:e6-e13.