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Radiologic imaging plays a pivotal role in the diagnosis of pediatric malignancies. In many cases the radiologist is the first to suggest the possibility of a malignancy based on imaging findings. Imaging features of primary malignancies are invaluable in providing a differential diagnosis and often direct the subsequent clinical and imaging work-up of the patient. Diagnostic imaging is also crucial in detecting metastatic disease in both solid and hematologic malignancies and, therefore, impacts therapeutic decision making. The currently available imaging modalities include plain-film radiography, ultrasonography (US), computed tomography (CT), magnetic resonance imaging (MRI), and nuclear medicine. Each of these modalities has a unique and important role in the assessment of children with cancer. Because the potential detrimental effects of ionizing radiation are compounded in children relative to adults, when choosing an imaging modality it is essential to minimize radiation exposure as much as possible and to adhere to the “as low as reasonably achievable” or ALARA principle [1–3]. In this chapter I will review the advantages and limitations of each imaging modality relative to the initial assessment of children with cancer. Tumor-specific imaging findings are presented in detail within the chapter devoted to each malignancy.

Plain-Film Radiography

Plain-film radiography is usually the first imaging procedure performed when a child is diagnosed with cancer. Plain radiographs have the advantage of being relatively quick to obtain, easy to perform, generally available at all hours, usually well tolerated, and relatively low cost and producing only low radiation exposure. However, relative to

cross-sectional imaging modalities, the spatial resolution of plain radiographs is limited and additional imaging is required. Despite this limitation, X-ray examinations can provide invaluable information regarding an area of clinical concern. For example, when the evaluation of a child with bone pain includes plain-film radiography the aggressiveness of a bony process is reflected by specific radiographic findings. Signs of malignancy include sunburst or lamellar periosteal reaction, cortical destruction, a Codman triangle, and evidence of a soft tissue mass (Fig. 2.1) [4]. Although MRI provides superior soft-tissue detail of bone and soft-tissue tumor correlation with the plain radiograph remains essential to the diagnosis of these malignancies. Abdominal radiographs of a child with abdominal pain might reveal organomegaly, abdominal mass effect, or abnormal abdominal calcifications due to intraperitoneal or retroperitoneal malignancies (Fig. 2.2). Plain radiographs of the chest can reveal mediastinal or hilar adenopathy, splaying of the ribs, or rib destruction due to malignancies such as lymphoma, neuroblastoma, or Askin tumor. Such information guides the subsequent imaging and laboratory work-up and can be useful to the pathologist when arriving at a final diagnosis.

Ultrasonography

Medical ultrasonography (US) utilizes handheld transducers that are placed on the body surface and emit and receive sound waves ranging from 2 to 20 MHz. Higher frequencies provide higher resolution images but have only limited tissue penetration while lower frequency waves penetrate deeper but provide less image resolution. Modern broadband ultrasound transducers are designed to allow the operator to adjust the emitted sound wave frequency for visualization of a structure of interest. In general, frequencies in the range of 8–20 MHz image structures near the transducer and frequencies in the 2–6 MHz range image deeper structures [5, 6]. Tissue harmonic imaging and pulse inversion harmonic imaging allow the transducer to

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Fig. 2.1 These (a) anterior-posterior (AP) and (b) lateral femur radiographs of a patient with osteosarcoma reveal features typical of a malignant bone tumor including Codman triangles (*arrows*) and sunburst periosteal reaction (*curved arrows*)

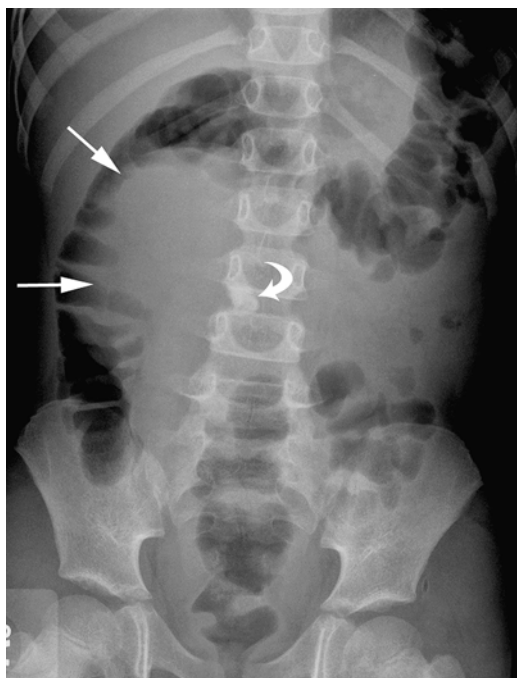
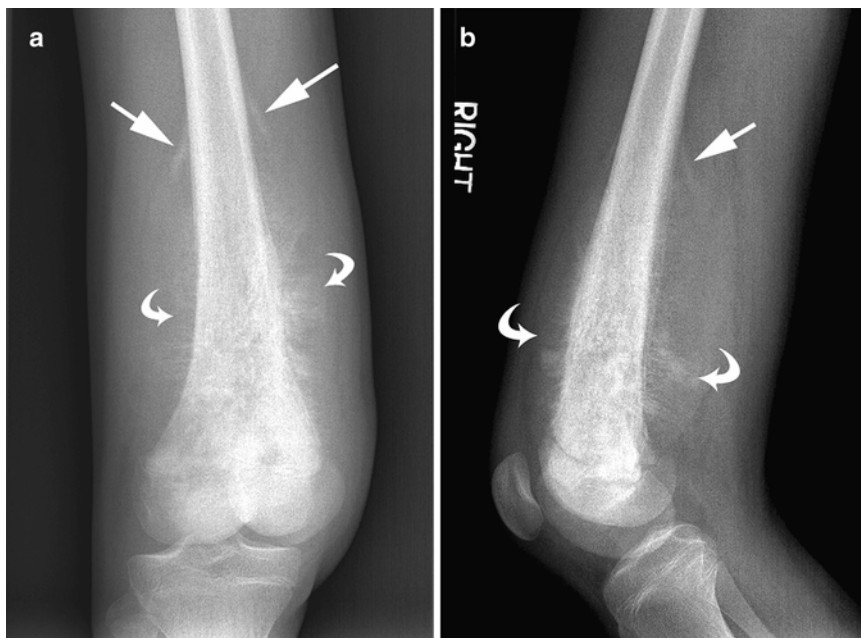


Fig. 2.2 This AP abdominal radiograph of a girl with *right* ovarian teratoma reveals mass effect on the *right* colon (*arrows*) and a toothlike abdominal calcification (*curved arrow*), features suggestive of this diagnosis

receive both the fundamental transmitted frequency and its harmonic frequencies and have become standard in many applications. These techniques increase the contrast of lesions while reducing the effect of some artifacts, but are limited to shallower depths [6].

Children are ideal candidates for US because their small body habitus, relative to adults, allows placement of the US transducer near the structure of interest, thus reducing signal attenuation. Ultrasound has numerous other advantages that make it particularly useful in the pediatric population. Perhaps most importantly it does not expose the patient to the potential harmful effects of radiation, a topic of considerable concern in this age group. It has the added benefits of being portable, does not require sedation, has Doppler capabilities to dynamically assess vascularity, allows real-time visualization of the movement of abdominal structures relative to each other and is less costly than CT and MRI. Additionally, US is usually readily available and does not require pre-procedure preparation. Drawbacks of US are that it is operator dependant, lacks image resolution compared to CT and MRI, is limited by artifact caused by bowel gas, and it can be difficult to visualize deep-seated structures in obese or adult-size patients.

Despite these potential limitations US remains the modality of choice for the initial assessment of a suspected abdominal mass in children and can provide important clues to the diagnosis. For example, real-time assessment of a right upper quadrant mass allows visualization of the mass relative to the liver and kidney during respiration. During continuous dynamic US imaging, masses separate from these solid organs move independently during breathing whereas masses arising within them move in union with their organ of origin. Ultrasound can reveal the solid or cystic nature of a mass, information that can be extremely useful. Cystic structures appear anechoic or sonolucent on US while solid tissue appears echogenic (Fig. 2.3). Regarding liver masses, US

can reveal whether the tumor is solitary or multifocal as is seen with multifocal or diffuse hepatic hemangiomas of infancy, metastatic neuroblastoma, and multifocal hepatoblastoma [7]. Ultrasound can detect calcifications within tumor which appear as bright echogenic foci with posterior shadowing. This finding might suggest an ovarian teratoma when seen in association with an abdominal or pelvic mass in an adolescent girl or neuroblastoma when associated with a retroperitoneal mass in a young child [8]. With the use of high-resolution transducers, US is ideal for assessment of superficial structures such as the thyroid, the scrotum, the eyes, and soft-tissue masses in the head, neck, or extremities

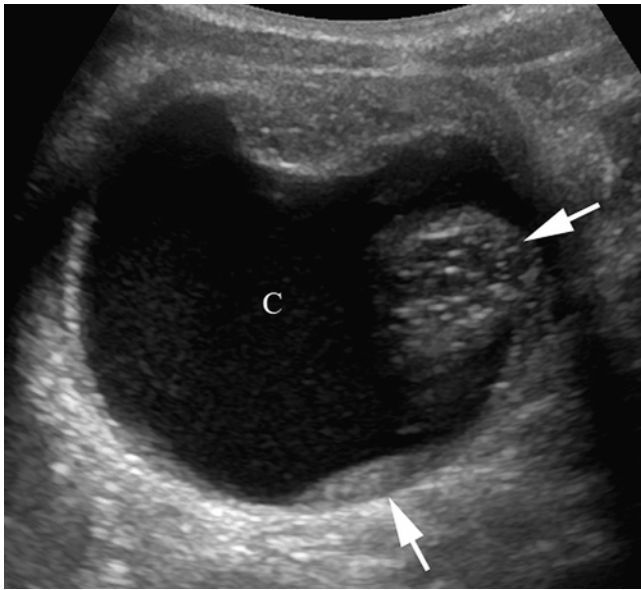


Fig. 2.3 This transverse ultrasound (US) image of an ovarian teratoma reveals the cystic (C) and solid (*arrows*) components that are typical of this tumor

(Fig. 2.4). Taken together with the clinical presentation and age of the patient, US imaging features of abnormalities of these structures can often provide a specific diagnosis or greatly narrow the differential diagnosis [9–12].

Doppler evaluation has numerous applications in the assessment of pediatric tumors. It can show increased blood flow and disorganized vasculature in tumors such as in testicular lymphoma or primary gonadal germ cell tumors [12]. Doppler of hepatic hemangiomas typically shows both arterial and venous waveforms with minimal systolic-diastolic variation in contrast to primary liver malignancies that show high-velocity blood flow [7]. Doppler is also useful in detecting vascular invasion, such as invasion of the renal vein and inferior vena cava by Wilms tumor or the hepatic or portal veins by hepatoblastoma [7, 13].

Because it does not involve ionizing radiation and does not require sedation, ultrasound is particularly appealing for screening patients with syndromes that predispose them to developing abdominal tumors. For example, patients with Beckwith-Wiedemann, Denys-Drash, WAGR (Wilms tumor, aniridia, genitourinary anomalies, mental retardation), Fanconi anemia, and several other syndromes have a risk of developing Wilms tumor (WT). However, the utility of US screening in these patients remains controversial [14]. Due to the rarity of these syndromes no randomized trials have been performed to compare the outcome of screened versus unscreened patients. Furthermore, because survival of patients with WT is greater than 90 % for those with localized disease and over 70 % for those with metastatic disease the benefit of early detection is debatable. Regardless, current efforts are aimed at identifying patients at the earlier and more treatable stages of disease [15, 16]. While there is no physical harm from sonography the emotional stress caused by vigilant screening should not be ignored. Current recommendations for screening children with

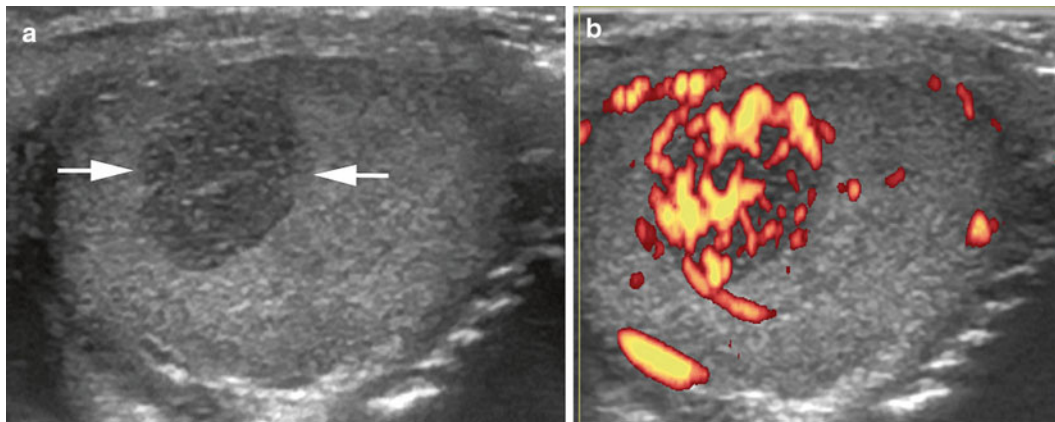


Fig. 2.4 This (a) transverse US image of the testicle reveals a well-defined, small, solid, hypoechoic mass (*arrows*) that on (b) power Doppler imaging appears hypervascular (*orange structures*) in this boy with a testicular Sertoli-Leydig cell tumor

various syndromes that predispose them to Wilms tumor have recently been published. The kidneys should be imaged with a high-resolution transducer; generally a 7–10 MHz transducer for infants and 6–8 MHz transducer for toddlers. When suspicious lesions are identified the imaging should be repeated within 1 week at a specialist center [14]. Children with other cancer predisposition syndromes also benefit from abdominal screening US to detect associated tumors in other organs. This subject is beyond the scope of this chapter but has been recently reviewed [17].

In the pediatric oncology setting US is valuable for guiding biopsy of newly diagnosed masses. In experienced hands US can safely be used to guide biopsy of a wide variety of tumors including rhabdomyosarcoma, non-rhabdomyosarcoma, soft-tissue sarcomas, neuroblastoma, hepatoblastoma, peripheral pulmonary lesions, and even anterior mediastinal masses requiring core biopsy [18–23]. Ultrasound guidance has the advantage of allowing real-time assessment of tumor vascularity and the relationship of the tumor to major vessels. This information can alert the interventional radiologist to the potential for post-procedural hemorrhage and help direct biopsy away from vascular structures. Additionally, because US machines are portable they can be used as a secondary guidance device in conjunction with CT or fluoroscopically directed biopsies [18, 23].

Computed Tomography

In pediatric oncology, cross-sectional imaging modalities (CT and MRI) are essential tools in patient management. These modalities provide valuable information for formulating a differential diagnosis, staging the tumor, monitoring treatment response, and detecting recurrences. However, with regard to CT, it is important to consider that the developing tissues of pediatric patients are more sensitive to the harmful effects of ionizing radiation than those of adults. Additionally, relative to adults, children have a longer lifespan in which to develop adverse sequelae of radiation exposure, which can occur decades later [24]. The pediatric radiologist must have knowledge of the proper use of these imaging modalities so that they can assist oncologists, surgeons, and radiation oncologists in developing rational and appropriate imaging guidelines for therapeutic protocols.

Since the sentinel article by Pierce and Preston in 2000 describing the effects of low-dose radiation exposure [25], there has been an increasing awareness of the detrimental effects of ionizing radiation in children, especially from CT scans. Since then significant progress has been made in reducing the number of CT scans performed, particularly in the pediatric emergency setting. Advances have also been made in optimizing the scanning technique to reduce radiation dose while maintaining image quality [26–28]. However,

children with cancer are particularly at risk because they undergo repeated exposure to radiation and the effects are cumulative over time. Modern cancer therapies have resulted in an overall survival rate of 83 % in children [29] and, therefore, the long-term effects of cancer therapy, including radiation exposure, are now being fully realized. Late effects from cancer therapy are becoming the driving force in tailoring pediatric cancer therapies and challenge the radiologist to apply the ALARA principle whenever possible.

The primary ways to minimize radiation exposure from CT are to require justification for the scan being done and optimization of the technique. In general, a CT is not indicated if the same information can be obtained from a modality that does not involve radiation. Many pediatric cancer therapy protocols consider CT and MRI to be equivalent in terms of assessing local disease. However, there is little scientific data on which to base a decision regarding the use of CT versus MRI in pediatric abdominal imaging [30]. Although it exposes the patient to radiation, CT offers the ability to cover a large anatomic area, provides excellent spatial resolution with minimal motion artifact and high-quality reconstructed multiplanar images, and is not operator dependant. In contrast, MRI requires substantial technical expertise and long scan times that often necessitate sedation. However, MRI has the important benefit of not utilizing radiation while offering multiplanar imaging with inherent tissue contrast, the ability to characterize tissue with various pulse sequences, and the added potential of providing functional information. The decision to use CT or MRI will depend on the local institution's standard of practice, the availability of pediatric sedation, and the radiologist's confidence in performing and interpreting the imaging examination.

Current-day multidetector helical CT (MDCT) scanners allow very rapid image acquisition while maintaining image resolution. These scanners comprise a gantry containing multiple detectors arranged in rows opposite the X-ray tube. The gantry rotates continuously around the patient acquiring data from multiple slices simultaneously as the patient moves through the scanner. Because data are acquired volumetrically, the scan time is shortened while ensuring that small lesions are not missed between slices. Additionally, the quality of multiplanar reconstructed images is greatly improved (Fig. 2.5). Relative to single-slice scanners, MDCT images provide a more accurate assessment of tumor size and a better depiction of the relationship between the tumor and vital structures [5, 31]. Recent advances in MDCT technology include faster gantry rotation times, increased number of detector rows, and dual X-ray tube sources. It is now possible to scan entire body sections in a few seconds or even less than a second. This technology has resulted in a dramatic decrease in the need for sedation while diminishing problems with motion artifact.

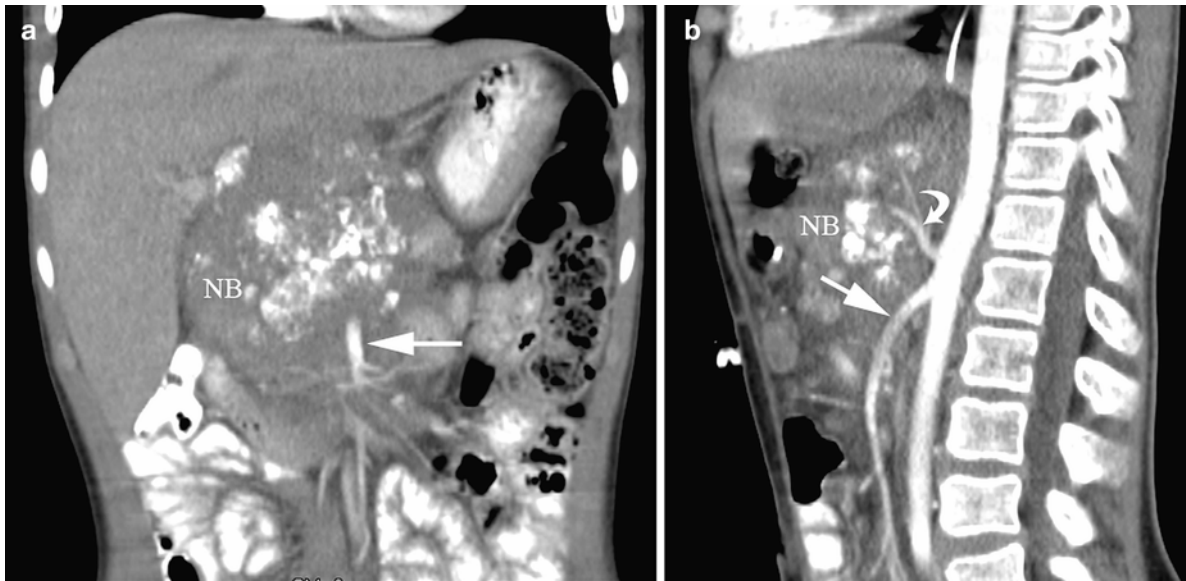


Fig. 2.5 These (a) coronal and (b) sagittal reconstructed computed tomography images provide valuable information regarding the relationship of this neuroblastoma (NB) to the superior mesenteric (*straight*

arrows) and celiac axis (*curved arrow*) arteries which it encases. Such information is crucial for surgical planning

In the past CT scanning protocols designed for adults were not modified for use in children. With increased awareness and education regarding the harmful effects of radiation from CT scanning in children, significant efforts to minimize radiation dose have been undertaken by industry and the radiology community. Parameters that should be modified for pediatric CT scanning include the tube current (milliamperes, mA), tube voltage (kilovoltage peak, kVp), gantry rotation time (second), and pitch.

Tube current has a significant impact on radiation dose and image noise; increases in tube current result in a proportional increase in dose while decreasing current results in increasing image noise. Modern MDCT scanners are equipped with automatic tube current modulation (ATCM) devices that dynamically adjust tube current during scanning in response to the geometry and density of the body part being scanned. The goal of ATCM is to maintain an acceptable image noise level while minimizing radiation dose from tube current [32]. It should be noted that specific pediatric ATCM settings are not universally available on modern scanners and scientific literature regarding appropriate weight, age, body region, and indication-based reference settings is lacking. Therefore, ATCM should be used with care in children [33].

The kVp has an exponential relationship with radiation dose and can substantially reduce radiation dose if optimized. Lowering the tube voltage also lowers the production of scattered radiation. In children weighing ≤ 45 kg, a tube voltage of 80–100 kVp is usually adequate. For adolescents,

a kVp of 100 for the chest and 120 for the abdomen is recommended. Areas with high intrinsic contrast, such as the chest and bones, can be scanned at 80–100 kVp. Recent studies in pediatric phantoms have shown that even lower kVp (approximately 60) may be sufficient for some indications. However, scanner-related parameters, such as tube filtration and scanner geometry, can sometimes negatively impact image quality with lower kVp [33].

Most modern MDCT scanners use rotation times of 0.3–0.5 s resulting in a reduction in radiation exposure, the need for sedation, and motion artifact. Shorter scan times, however, can result in a decrease in the number of profiles that can be used for image reconstruction and, subsequently, an increase in image noise. For optimal image resolution a rotation time of 0.5 s is recommended [32, 33].

The pitch is the ratio between table movement and number of detectors multiplied for section width (collimation). An increase in pitch can result in a reduction in scan time and, in some scanners, a reduction in dose. However, in modern MDCT scanners increasing the pitch can cause a dose increase due to overranging and can also reduce spatial resolution. In general, a pitch of 1–1.5 is currently recommended [32].

Oral contrast material is usually indicated for CT imaging of the abdomen or pelvis and the use of oral contrast material for MDCT is not different than for single-slice CT. Iodinated intravenous (IV) contrast agents should always be used for imaging the neck, abdomen, and pelvis. The use of IV contrast in the chest will depend on the indication for the examination. In our practice, if there is a concern for adenop-

athy or when there is a primary solid tumor arising in the chest, IV contrast material is used. When chest CT is performed solely to evaluate for pulmonary metastatic disease we do not administer IV contrast material. Due to the very rapid scan times attainable with MDCT scanners it is essential to adjust scanning to allow the IV contrast agent adequate time to reach the area of interest as the area is being scanned. In general, scanning should begin later with MDCT scanners compared to single-slice scanners. Pre-contrast imaging has no role in pediatric oncologic imaging and should not be performed [34]. Post-contrast, multiphase imaging in children is rarely indicated and is also strongly discouraged. An exception is in the evaluation of newly diagnosed liver tumors. The pattern of tumor enhancement on immediate- and delayed-phase post-contrast images can help distinguish hemangiomas from hepatoblastoma. At our institution, we have found that the relationship between a liver tumor and the hepatic and portal veins is best defined when imaging is performed during the arterial and portal venous phases of enhancement. Such information is crucial in determining which Couinaud's segments are involved and helps guide surgical planning. Specific guidelines for the administration of IV contrast agents and injection techniques (including volume, injection rate, hand injection versus power injector) in children, using MDCT technology, are available in the literature [31].

Magnetic Resonance Imaging

Magnetic resonance imaging plays a pivotal role in the evaluation of newly diagnosed cancer in children. This modality incorporates a strong magnetic field to align hydrogen nuclei within the body. Once aligned the nuclei precess or “wobble” at a frequency proportional to the

magnetic field strength. Pulsed radiofrequency (RF) waves are then applied which alter the spin of hydrogen nuclei. When the RF pulse is turned off the nuclei return to their original alignment and energy is released. The released energy is converted to an electrical impulse in a wire within a receiver coil. Spatial encoding is used to localize the site within the body from which the signal originated and, using Fourier transformation (the same mathematical model used to produce a CT image), an MR image is created. Each sampled voxel is assigned a shade of gray that depends on the amount of hydrogen nuclei within it and the rate of equilibrium of hydrogen nuclei back to the original, pre-RF pulse, alignment [5].

Conventional MR imaging relies on several scanning parameters. The RF pulse repetition time (TR) occurs with a time constant, T1. The signal produced in the receiver coil decays exponentially at time constant T2. The time between the initial RF pulse and data collection is the echo time, TE. These parameters can be manipulated so that a T1-weighted (T1W) or T2-weighted (T2W) image is produced. Images acquired with a short TR (300–600 ms) and short TE (10–20 ms) are T1 weighted. On T1W images tissue with short T1 relaxation times (e.g., fat, melanin, gadolinium contrast agent) have high signal intensity and those with longer T1 relaxation times (e.g., water, hemosiderin) have intermediate or low signal intensity. T2W images are produced by using longer TR (>2,000 ms) and a longer TE (>80 ms). On T2W images substances with short T2 relaxation times (e.g., white matter, fibrosis) have low-to-intermediate signal intensity and tissues with longer T2 relaxation times (e.g., edema, tumor, fluid) have higher signal intensity (Fig. 2.6a, b). Additional pulse sequences, beyond these conventional spin-echo sequences, are continually being developed. The inversion recovery sequence (IR)

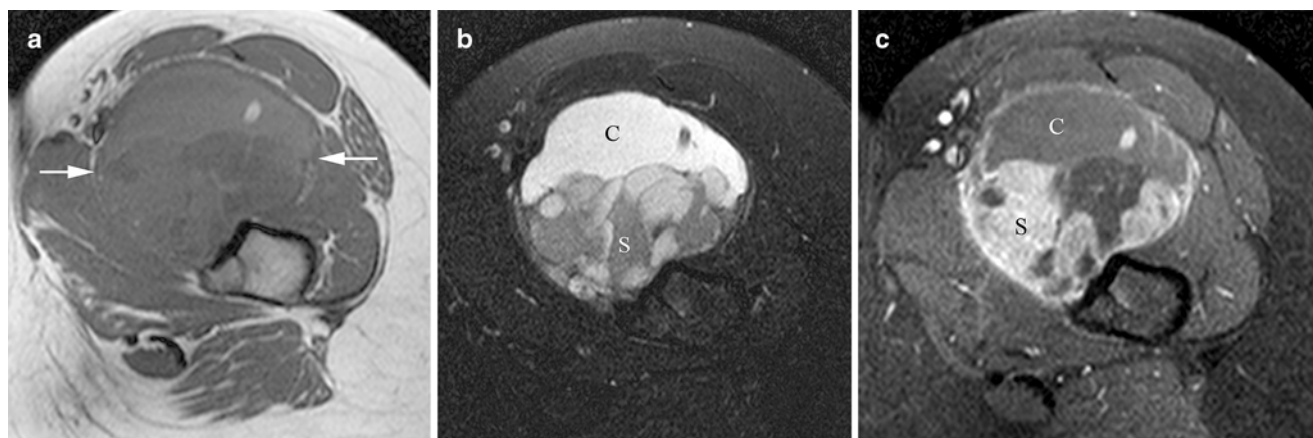


Fig. 2.6 In this patient with a synovial sarcoma the (a) non-contrast-enhanced T1W axial magnetic resonance image shows mixed signal intensity of the tumor (arrows) while the (b) T2W fat-saturated image

reveals its partially cystic (C) and solid (S) nature. (c) Post-contrast imaging further delineates the enhancing solid (S) and non-enhancing cystic (C) components

selectively nullifies signal from tissue based on its T1 relaxation time and a selected inversion time (TI). A variant of the IR sequence, the short tau inversion recovery (STIR) sequence, selectively suppresses fat and enhances fluid signal. This sequence has proven valuable in oncologic imaging because tumors, which have high water content, are generally readily visible [5].

Using various pulse sequences MRI can delineate between normal and abnormal soft tissues better than CT and with the advantage of not exposing the patient to ionizing radiation. In addition to improved soft tissue characterization, with MRI the beam hardening artifact caused by bone on CT imaging is eliminated [5]. These features make MRI the ideal modality for imaging the brain, spine, neck, and extremities. In the past, the multiplanar capabilities of MR, which allow assessment of structures in the axial, coronal, and sagittal planes, were an additional advantage over CT. However, with the advent of MDCT and improved image resolution of coronal and sagittal reconstructed CT images, this advantage no longer holds. A limitation of MR is the long scan times which often require sedation of young patients. Distraction techniques, such as video goggles and audio systems, can help minimize patient motion and avoid the use of sedation in some patients [35]. Long image acquisition times make MRI of lesions in the trunk very susceptible to degradation from respiratory movement, cardiac and vascular pulsations, and bowel peristalsis. Techniques to reduce artifact from bowel peristalsis include keeping the patient from ingesting food or fluid for 4 h before the study and administration of glucagon [35, 36]. Rapid scanning techniques can also help minimize motion artifact. These include low flip angle gradient echo sequences, turbo spin-echo sequences, single-shot sequences, echo planar imaging, and periodically rotated overlapping parallel lines with enhanced reconstruction (PROPELLER) [5, 35]. These faster sequences allow image acquisition during breathholding and coverage of a larger body area in a shorter time period and reduce the potential for motion artifact. Besides the long scan times, other disadvantages of MRI include its high cost, limited availability, relative insensitivity to calcification, and limited ability to assess lung parenchyma [5].

Intravenous gadolinium-based contrast agents are often used in MRI, similar to iodinated contrast agents for CT imaging. These agents are paramagnetic and cause shortening of the T1 and T2 relaxation times. Most gadolinium agents diffuse freely across the vascular membrane and, therefore, reflect both perfusion and diffusion [5]. These agents tend to make tumors more conspicuous and are useful for identifying intra-tumoral necrosis or confirming solid components of partially cystic tumors (Fig. 2.6c). The combination of various pre-contrast-enhanced MR sequences and post-contrast T1W, fat-suppressed imaging allows assessment of tumor margins, determination of extension

across fascial planes, invasion of bone and joints, and involvement of the neurovascular bundle [5, 37]. Gadolinium contrast agents are well tolerated and allergic reactions in children are very rare. However, these agents have been associated with development of nephrogenic systemic fibrosis (NSF) in patients with acute or chronic renal insufficiency. NSF is characterized by progressive tissue fibrosis, usually beginning in the skin of extremities, progressing over weeks to months to involve extra-cutaneous structures including bone, muscle, heart, lungs, and esophagus. This process can be transient, with clinical improvement, or progressive causing severe joint contractures, loss of ambulation, and even death. Therefore, patients should be screened for evidence of renal disease prior to administration of gadolinium-based contrast agents. Patients with an estimated glomerular filtration rate below 30 mL/min/1.73 m² are at high risk of developing NSF. A detailed discussion of the association between gadolinium contrast agents and NSF, and recommendations for gadolinium use in patients with renal disease, has recently been published [38].

An emerging technology for staging solid tumors and lymphoma is whole-body MRI (WBMRI). The development of multichannel coils, fast turbo sequences, the parallel acquisition technique (PAT), and moveable tables are enabling this technology to become more feasible in clinical practice. The goal of WBMRI is to image the entire body in the shortest possible time using the minimum number of sequences, preferably only one. This technique was initially developed as a method of assessing for skeletal metastases but has proven to be valuable in detecting extraskelatal sites of disease [39]. Most recently, the IR sequences, either STIR or turbo inversion recovery magnitude (TIRM), have been recommended [40, 41]. These sequences employ a combination of proton density, T1 and T2 contrast with inherent fat suppression [40]. STIR has been reported to be more sensitive than T1-weighted sequences for the detection of metastases because metastases appear bright on STIR sequences [39].

When using WBMRI in children, knowledge of the MR appearance of normal bone marrow is crucial to interpreting the images. Throughout childhood bone marrow converts from hematopoietic to fatty marrow in a peripheral to central fashion (feet to hips and hands to shoulders) and from the central diaphysis to the metaphysis within each bone [42]. Some investigators caution that STIR may mask lesions in very young children with hematopoietic marrow because it is very cellular and normally appears bright on this sequence. Those investigators suggest in-phase and out-of-phase pulse sequences and the use of reticuloendothelial system-specific contrast agents which suppress the signal intensity of normal marrow but not of neoplastic marrow [43]. Depending on the method employed, whole-body MRI can be accomplished in 15–50 min [41]. In a recent study, using STIR sequences and

PAT technology, WBMRI in children with small-cell tumors had a sensitivity for skeletal metastases of 97.5 % and specificity of 99.4 % compared to skeletal scintigraphy with a sensitivity of 30 % and specificity of 99.4 % and PET-CT with a sensitivity of 90.0 % and specificity of 100 % [44]. The obvious benefit of WBMRI in this setting is the lack of ionizing radiation.

Conventional WBMRI incorporates a large amount of data including that of normal structures such as fat and muscles. As a result image interpretation can be time consuming and subtle lesions can be overlooked. Recently diffusion-weighted (DWI) whole-body MRI has been introduced as an alternative to conventional WBMRI. This technique utilizes a spin-echo sequence and two strong gradients (motion-probing gradients) on either side of the 180° refocusing pulse. This is basically a T2W sequence with the application of two strong MPG's resulting in a decrease in signal intensity of all structures. The amount of signal decrease is not the same for all structures and depends on the degree of apparent diffusion that occurs between the MPG's. Structures with low diffusivity are less suppressed than those with a high degree of diffusion or perfusion (e.g., vascular structures, cerebrospinal fluid, urine). Because most lesions, both benign and malignant, have relatively impeded diffusivity, they lose less signal than adjacent normal background tissue resulting in a high lesion-to-background contrast. This approach to WBMRI has the potential to improve lesion detection while decreasing interpretation time [45]. A DWI whole-body examination can be performed in about 20–30 min. A comprehensive review of DWI in pediatric malignant lymphoma was recently published [45].

Nuclear Medicine

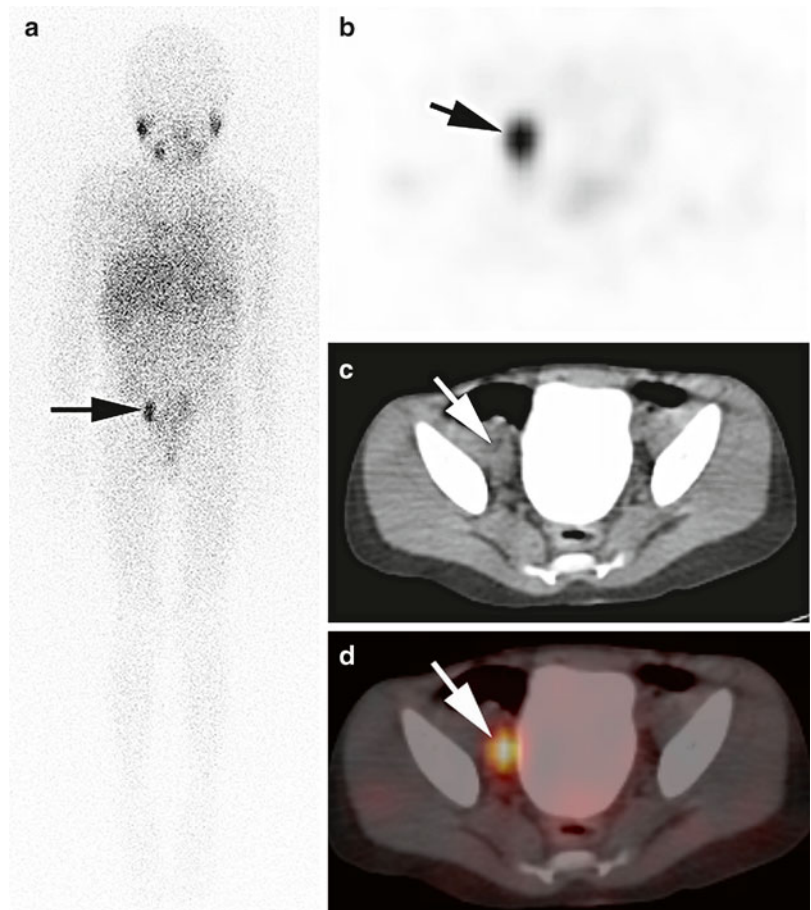
Nuclear medicine employs radiolabeled isotopes that are designed to interact with specific organs or cellular processes. Studies are performed by intravenously injecting the radiotracer and then waiting for an appropriate period of time to allow the desired distribution of the radiotracer within the body. As the radioisotope decays the emitted radiation can be detected by cameras designed to detect a specific level of energy. In general, there are two types of radioisotopes in clinical use, single-photon emitters, detected with a gamma camera, and positron emitters, detected with positron emission tomography (PET) cameras. Because the detection sensitivity of the cameras is very high, radiopharmaceuticals can be administered in very small doses that do not perturb normal physiologic processes. Nuclear imaging is quantitative, or at least semiquantitative; therefore, image intensity (or counts) corresponds to the concentration of the radiopharma-

ceutical. While nuclear medicine studies provide valuable functional and metabolic information, the resulting images have coarse spatial resolution, expressed as the full-width half-maximum of the system point or line-spread function. Resolution ranges from about 5 mm for PET imaging to 10 mm for single-photon emission computed tomography (SPECT) cameras. Therefore, relative to CT and MRI, anatomic definition on nuclear medicine images is poor. The ability to co-register and fuse nuclear medicine images with conventional imaging studies helps to overcome this limitation. An additional drawback of nuclear medicine imaging is the inherent radiation exposure. Although radiation doses from nuclear medicine imaging procedures are low, they are not negligible [46]. Also, because nuclear medicine imaging studies can be lengthy, sedation is often required for young patients.

In pediatric oncology, nuclear medicine imaging is essential in the evaluation of patients with neuroblastoma, bone and soft-tissue sarcomas, and lymphoma. The most commonly used radioisotopes are the single-photon emitters, iodine¹²³-labeled metaiodobenzylguanidine (I¹²³ MIBG) and technetium^{99m}-labeled methylene diphosphonate (Tc^{99m} MDP), and the positron emitter, F¹⁸-labeled fluorodeoxyglucose (F¹⁸-FDG). I¹²³ MIBG is a norepinephrine analog that concentrates in adrenergic storage vesicles of neural crest tissues and is used to assess patients with neuroblastoma. Tc^{99m} MDP is taken up in sites of osteoblastic activity and is useful in identifying sites of bony metastatic disease in patients with bone and soft-tissue sarcomas. F¹⁸-FDG is a nonspecific glucose analog that is taken up in all sites of metabolic activity and is used to assess patients with a variety of malignancies including lymphomas and solid tumors.

Gamma cameras (also known as scintillation or Anger cameras) have been the predominant imaging device in nuclear medicine for many years. These cameras have large detector areas (usually rectangular in shape) that allow fairly rapid data acquisition from a large area of the body. Gamma camera crystals are made of NaI(Tl) that vary in thickness from one-quarter of an inch (with the best spatial resolution but lowest sensitivity) to 1 in. (with the highest sensitivity but coarsest resolution). Most cameras comprise three-eighths inch thick crystals, which provide the optimum balance between sensitivity and resolution. The energy arising from decay of single-photon emitters strikes and may produce a scintillation within the crystal. The scintillation results in the production of light that is detected in a photomultiplier tube backing the crystal and is used to generate an image [46]. During static imaging, the injected patient lies on a table over the gamma camera until a sufficient number of counts (signals) are collected from that body area to gen-

Fig. 2.7 On this (a) whole-body planar I^{123} -metaiodobenzylguanidine image the focus of activity in the *right* pelvis (*arrow*) is difficult to localize to bone, lymph node, or other soft tissues. These transverse (b) SPECT, (c) CT, and (d) fused SPECT-CT images accurately localize the activity to an iliac lymph node (*arrow*)



erate a planar image. Typically, the patient is sequentially moved over the camera in contiguous increments until the entire body is imaged.

Single-photon emission computed tomography (SPECT) imaging utilizes a gamma camera to acquire projection images from multiple angles as the camera rotates around the body. These tomographic images allow more accurate localization of sites of radioactivity within the body, compared to planar images [47]. The acquired data is corrected for non-uniform scanner response and other signal-degrading effects and then reconstructed into 5–10 mm thick transverse tissue-section images. In general SPECT imaging requires 20–30 min of acquisition time to obtain 60–120 projection images at 6° to 3° angular increments, respectively. Because of the lengthy acquisition time, whole-body SPECT imaging (from skull vertex to toes) remains impractical at the present time [46]. More recently, SPECT imaging systems have been combined with conventional computed tomography to produce hybrid SPECT-CT scanners, similar in concept to PET-CT scanners. The co-registered SPECT and CT images provide both functional and anatomic information and allow

more accurate localization of sites of radioactivity (Fig. 2.7). These hybrid images have been shown to improve the sensitivity and specificity of SPECT imaging by improving lesion conspicuity, reducing false negatives and clarifying indeterminate findings [47]. In pediatric oncology SPECT-CT imaging has proven valuable for I^{123} MIBG imaging of patients with neuroblastoma, for I^{123} and I^{131} imaging to localize neck activity in children with papillary thyroid cancer, and for Tc^{99m} sulfur colloid sentinel node lymphoscintigraphy of patients with melanoma [48–50].

PET imaging is based on the annihilation coincidence detection of two collinear (180° apart) 511 keV gamma rays resulting from the mutual annihilation of a positron and electron. PET cameras comprise a series of rings containing individual, small-area detectors that completely encircle the patient and typically span a longitudinal distance of 10–20 cm. When the PET camera detects two 511 keV photons of energy coming from opposite directions, at the same time, a signal is produced. The most recent development in PET imaging is time-of-flight (TOF) scanning which utilizes the measured difference between detection times of the two

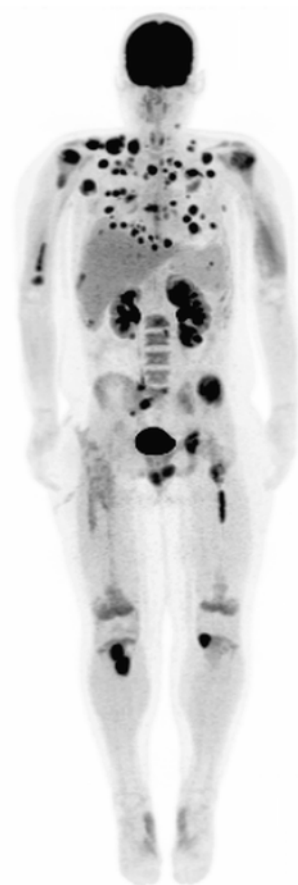


Fig. 2.8 This whole-body maximum intensity projection F^{18} -fluorodeoxyglucose (FDG) positron emission tomography image reveals extensive metastatic disease from adrenocortical carcinoma evidenced as innumerable foci of FDG avidity, throughout the lungs and bones and in lymph nodes

annihilation photons arising from a specific positron decay. TOF imaging allows approximate spatial localization of the event along the line of response with approximately 5–10 ns of coincidence time resolution. This approach reduces the random coincidence rate and improves the signal-to-noise ratio [46]. The most common clinically used positron-emitting radioisotope is fluorine-18-fluorodeoxyglucose (FDG) which is a radiolabeled glucose analog that is transported across cell membranes and phosphorylated but cannot be dephosphorylated. The trapped FDG appears as a focus of activity on the PET image and the intensity of the activity reflects the amount of trapped FDG. In oncology, FDG-PET imaging capitalizes on the fact that tumors are highly metabolically active and accumulate more glucose (and FDG) than normal tissue (Fig. 2.8) [51].

PET imaging requires a technique for soft-tissue attenuation correction. Hounsfield unit intensity measurements, obtained with CT, directly correlate with soft-tissue attenuation of the X-ray beam. Hounsfield unit measurements can also be used

to correct the soft-tissue attenuation effects of the 511 keV photons emitted by radioisotopes used for PET scanning. Therefore, modern PET scanners almost universally integrate CT scanners that serve two purposes. First, the low-dose CT imaging provides the attenuation correction factors for PET imaging. Secondly, and equally important, these hybrid systems allow co-registration of PET and CT images, thus allowing accurate localization of sites of radioactivity within the body. The ability to co-register the anatomic and functional imaging also allows for more accurate distinction between sites of normal metabolic activity, such as brown fat, and pathologic processes.

Although low-dose CT scans are generally performed for PET-CT scanning, there continues to be growing concern regarding radiation exposure in children, especially those requiring repeated radiologic examination during cancer therapy. This has spurred the development of PET-MRI scanners which have recently reached the clinical arena. MRI has the ability to provide superior characterization of soft-tissue structures, particularly in the head and extremities, compared to CT. Furthermore, MRI can provide metabolic and functional information with the use of diffusion-weighted and dynamic contrast-enhanced imaging. The challenge with the development of PET-MRI has been in translating MRI signal intensities into attenuation correction factors for the PET images. This is a major challenge since signal intensities from anatomic structures vary depending on inherent T1 and T2 properties, magnetic field strength, choice of pulse sequence, use of gradients, and choice of radiofrequency coil. An additional challenge is the incorporation of PET scanners into high-strength magnetic fields. Despite these limitations, the development of PET-MRI scanners could revolutionize our approach to clinical molecular imaging since the functional and anatomic information that can be derived from both modalities should be synergistic. Another benefit of PET-MRI in the pediatric setting is that it could allow for acquisition of diagnostic MR images and PET images in one imaging session, thus reducing the number of sedations needed for very young patients. This hybrid modality holds great potential but requires validation in clinical trials and an assessment of its impact on diagnostic accuracy, patient management, and cost efficiency [52].

Conclusion

Diagnostic imaging plays a vital role in assessing children with cancer. Imaging generally begins with planar studies but ultimately cross-sectional imaging is required to fully evaluate both the primary tumor and potential metastatic sites. The radiologist should be aware of the strengths and limitations of each modality with respect to the clinical scenario, tumor location, and suspected histology. Attempts

should always be made to minimize radiation exposure as much as possible without compromising the care of the patient. In the future, molecular and functional imaging modalities will further complement anatomic imaging and likely play a larger and more important role in assessing the biological behavior of tumors.

References

- Brenner DJ, Hall EJ. Computed tomography—an increasing source of radiation exposure. *N Engl J Med*. 2007;357:2277–84.
- Donaldson SS. Lessons from our children. *Int J Radiat Oncol Biol Phys*. 1993;26:739–49.
- Brody AS, Frush DP, Huda W, et al. Radiation risk to children from computed tomography. *Pediatrics*. 2007;120:677–82.
- McCarville MB. The child with bone pain: malignancies and mimickers. *Cancer Imaging*. 2009;9(Spec No A):S115–21.
- Guillerman RP, McCarville MB, Kaste SC, et al. Imaging studies in the diagnosis and management of pediatric malignancies. In: Pizzo PA, Poplack's DG, editors. *Principles and practice of pediatric oncology*. Philadelphia, PA: Lippincott Williams & Wilkins; 2011. p. 216–77.
- Gritzmman N, Evans DH. Recent progress in diagnostic ultrasound techniques. *Ultraschall Med*. 2008;29:320–2.
- McCarville MB, Roebuck DJ. Diagnosis and staging of hepatoblastoma: imaging aspects. *Pediatr Blood Cancer*. 2012;59(5):793–9.
- Epelman M, Chikwava KR, Chauvin N, et al. Imaging of pediatric ovarian neoplasms. *Pediatr Radiol*. 2011;41:1085–99.
- Brennan RC, Wilson MW, Kaste SC, et al. US and MRI of pediatric ocular masses with histopathological correlation. *Pediatr Radiol*. 2012;42:738–49.
- Martinoli C, Valle M, Malattia C, et al. Paediatric musculoskeletal US beyond the hip joint. *Pediatr Radiol*. 2011;41 Suppl 1:S113–24.
- Rosenberg HK. Sonography of pediatric neck masses. *Ultrasound Q*. 2009;25:111–27.
- Sung EK, Setty BN, Castro-Aragon I. Sonography of the pediatric scrotum: emphasis on the Ts-torsion, trauma, and tumors. *Am J Roentgenol*. 2012;198:996–1003.
- Riccabona M. Imaging of renal tumours in infancy and childhood. *Eur Radiol*. 2003;13 Suppl 4:L116–29.
- Owens CM, Brisse HJ, Olsen OE, et al. Bilateral disease and new trends in Wilms tumour. *Pediatr Radiol*. 2008;38:30–9.
- Craft AW, Parker L, Stiller C, et al. Screening for Wilms' tumour in patients with aniridia, Beckwith syndrome, or hemihypertrophy. *Med Pediatr Oncol*. 1995;24:231–4.
- Choyke PL, Siegel MJ, Craft AW, et al. Screening for Wilms tumor in children with Beckwith-Wiedemann syndrome or idiopathic hemihypertrophy. *Med Pediatr Oncol*. 1999;32:196–200.
- Monsalve J, Kapur J, Malkin D, et al. Imaging of cancer predisposition syndromes in children. *Radiographics*. 2011;31:263–80.
- Garrett KM, Fuller CE, Santana VM, Shochat SJ, Hoffer FA. Percutaneous biopsy of pediatric solid tumors. *Cancer*. 2005;104(3):644–52.
- Fontalvo LF, Amaral JG, Temple M, et al. Percutaneous US-guided biopsies of peripheral pulmonary lesions in children. *Pediatr Radiol*. 2006;36:491–7.
- Amaral JG, Schwartz J, Chait P, et al. Sonographically guided percutaneous liver biopsy in infants: a retrospective review. *Am J Roentgenol*. 2006;187:W644–9.
- Chowdhury T, Barnacle A, Haque S, et al. Ultrasound-guided core needle biopsy for the diagnosis of rhabdomyosarcoma in childhood. *Pediatr Blood Cancer*. 2009;53:356–60.
- McCrone L, Alexander S, Karsli C, et al. US-guided percutaneous needle biopsy of anterior mediastinal masses in children. *Pediatr Radiol*. 2012;42:40–9.
- Shin HJ, Amaral JG, Armstrong D, et al. Image-guided percutaneous biopsy of musculoskeletal lesions in children. *Pediatr Radiol*. 2007;37:362–9.
- Hall EJ. Lessons we have learned from our children: cancer risks from diagnostic radiology. *Pediatr Radiol*. 2002;32:700–6.
- Pierce DA, Preston DL. Radiation-related cancer risks at low doses among atomic bomb survivors. *Radiat Res*. 2000;154:178–86.
- Goske MJ, Applegate KE, Bulas D, et al. Image gently: progress and challenges in CT education and advocacy. *Pediatr Radiol*. 2011;41 Suppl 2:461–6.
- Slovits TL. Where we were, what has changed, what needs doing: a decade of progress. *Pediatr Radiol*. 2011;41 Suppl 2:456–60.
- Townsend BA, Callahan MJ, Zurakowski D, et al. Has pediatric CT at children's hospitals reached its peak? *Am J Roentgenol*. 2010;194:1194–6.
- Section 28 Childhood Cancer by Site. Incidence, survival and mortality. http://seer.cancer.gov/csr/1975_2009_pops09/results_merged/sect_28_childhood_cancer.pdf.
- Olsen OE. Imaging of abdominal tumours: CT or MRI? *Pediatr Radiol*. 2008;38 Suppl 3:S452–8.
- Donnelly LF, Frush DP. Pediatric multidetector body CT. *Radiol Clin North Am*. 2003;41:637–55.
- Granata C, Magnano G. Computerized tomography in pediatric oncology. *Eur J Radiol*. 2013;82(7):1098–107.
- Nievelstein RA, van Dam IM, van der Molen AJ. Multidetector CT in children: current concepts and dose reduction strategies. *Pediatr Radiol*. 2010;40:1324–44.
- McHugh K, Disini L. Commentary: for the children's sake, avoid non-contrast CT. *Cancer Imaging*. 2011;11:16–8.
- States LJ, Meyer JS. Imaging modalities in pediatric oncology. *Radiol Clin North Am*. 2011;49:579–88. v.
- Gutzeit A, Binkert CA, Koh DM, et al. Evaluation of the anti-peristaltic effect of glucagon and hyoscine on the small bowel: comparison of intravenous and intramuscular drug administration. *Eur Radiol*. 2012;22:1186–94.
- Stein-Wexler R. MR imaging of soft tissue masses in children. *Magn Reson Imaging Clin N Am*. 2009;17:489–507. vi.
- Kaewlai R, Abujudeh H. Nephrogenic systemic fibrosis. *Am J Roentgenol*. 2012;199:W17–23.
- Mazumdar A, Siegel MJ, Narra V, et al. Whole-body fast inversion recovery MR imaging of small cell neoplasms in pediatric patients: a pilot study. *Am J Roentgenol*. 2002;179:1261–6.
- Darge K, Jaramillo D, Siegel M. Whole-body MRI in children: current status and future applications. *Eur J Radiol*. 2008;68:289–98.
- Goo HW. Regional and whole-body imaging in pediatric oncology. *Pediatr Radiol*. 2011;41 Suppl 1:S186–94.
- Babyn PS, Ranson M, McCarville MB. Normal bone marrow: signal characteristics and fatty conversion. *Magn Reson Imaging Clin N Am*. 1998;6:473–95.
- Daldrup-Link HE, Franzius C, Link TM, et al. Whole-body MR imaging for detection of bone metastases in children and young adults: comparison with skeletal scintigraphy and FDG PET. *Am J Roentgenol*. 2001;177:229–36.
- Kumar J, Seith A, Kumar A, et al. Whole-body MR imaging with the use of parallel imaging for detection of skeletal metastases in pediatric patients with small-cell neoplasms: comparison with skeletal scintigraphy and FDG PET/CT. *Pediatr Radiol*. 2008;38:953–62.
- Kwee TC, Takahara T, Vermoolen MA, et al. Whole-body diffusion-weighted imaging for staging malignant lymphoma in children. *Pediatr Radiol*. 2010;40:1592–602. quiz 1720–1.
- Zanzonico P. Principles of nuclear medicine imaging: planar, SPECT, PET, multi-modality, and autoradiography systems. *Radiat Res*. 2012;177:349–64.

47. Brandon D, Alazraki A, Halkar RK, et al. The role of single-photon emission computed tomography and SPECT/computed tomography in oncologic imaging. *Semin Oncol*. 2011;38:87–108.
48. Kim HY, Gelfand MJ, Sharp SE. SPECT/CT imaging in children with papillary thyroid carcinoma. *Pediatr Radiol*. 2011;41:1008–12.
49. Klode J, Poeppel T, Boy C, et al. Advantages of preoperative hybrid SPECT/CT in detection of sentinel lymph nodes in cutaneous head and neck malignancies. *J Eur Acad Dermatol Venereol*. 2011;25:1213–21.
50. Soderberg M, Mattsson S, Oddstig J, et al. Evaluation of image reconstruction methods for 123I-MIBG-SPECT: a rank-order study. *Acta Radiol*. 2012;53(7):778–84.
51. Rohren EM, Turkington TG, Coleman RE. Clinical applications of PET in oncology. *Radiology*. 2004;231:305–32.
52. Voss SD. Pediatric oncology and the future of oncological imaging. *Pediatr Radiol*. 2011;41 Suppl 1:S172–85.

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