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Imaging in Pediatric Oncology

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Preface

When the Series Editors for the Springer Verlag Pediatric Oncology Series first approached us to consider developing a comprehensive text focused on Imaging in Pediatric Oncology, we were enthusiastic. Not since 1992, when Cohen published his text *Imaging of Children with Cancer*, has there been a textbook dedicated to pediatric oncologic imaging. To be sure, there have been numerous clinical pediatric oncology texts with chapters devoted to imaging, as well as a variety of pediatric imaging textbooks with chapters or sections describing the imaging features of particular tumor types, in addition to textbooks focusing on radiology/pathology correlation in pediatric oncology. But a comprehensive reference text that could serve both pediatric oncologists and pediatric radiologists, and that focused primarily on the imaging techniques used in caring for children with cancer, was lacking.

In approaching this project we had two major considerations: firstly, this text was not simply to be focused on providing detailed discussions of the role of imaging and the imaging characteristics for each individual cancer observed in the pediatric age group—while of interest, there are ample other reference materials devoted to these topics. Rather we chose to focus on the imaging techniques available and currently in use, including guidelines for response assessment, use of functional imaging techniques and molecular imaging, as well as newer developments within the field of radiology. Secondly, in an effort to appeal to a broad readership and to provide a balanced perspective, we were encouraged to invite colleagues from both North America and Europe to serve as chapter coauthors, taking advantage of the insights and expertise of pediatric imaging experts active in multiple international consortia, such as the Children's Oncology Group (COG) and the International Society of Pediatric Oncology (SIOP).

The result has been better than we could have anticipated. We were thrilled by the willingness of so many of our colleagues from institutions around the world to contribute their knowledge and expertise in putting together the various chapters contained in this text. In many cases chapters were written together by colleagues from both the USA and Europe, and that is a testament to the close working relationships that have developed among pediatric radiologists with a major interest in oncology. The result is a series of contributions that span the breadth of pediatric radiology as it relates to the imaging of children with cancer. All of the authors are well-known leaders in their respective fields, and most also contribute their imaging expertise and knowledge by being active in ongoing clinical trials. By inviting input from both

North American and European institutions, we feel we have been able to provide a varied perspective on the different approaches to imaging, particularly as it is used in the context of both North American and European clinical trials. In another edition we will endeavor to make this effort an even more global phenomenon with contributions from Australasia and hopefully elsewhere also.

The text initially focuses on technical aspects of pediatric oncologic imaging, and then moves into how the multiple imaging techniques are applied to specific challenges inherent to the imaging of children being treated for cancer, such as assessing response to therapy and treatment-associated complications. Chapters focused on radiation safety considerations and on radiotherapy are necessary in any text such as this, as are the sections related to interventional techniques. We conclude with chapters focusing on emerging techniques (molecular imaging) as well as on the use of imaging to guide new clinical management paradigms, such as for screening patients with a cancer predisposition syndrome, and considerations related to survivorship and imaging surveillance.

Understandably, some topics could not be specifically addressed in this text. For example, the topics of quality of life, ethical considerations, global disparities, and communication with patients are all worthy topics, but beyond the scope of this text. There is no doubt that differences in healthcare economics between countries can and do influence how imaging is utilized and which techniques are deployed in the management of children with cancer. For example, whole body MRI is not currently reimbursed in the USA as there is presently no CPT billing code. As such many institutions must either forgo these exams or develop creative strategies for reimbursement. In most Canadian and European centers, in contrast, whole body MRI is reimbursed as with other examinations and there are no barriers to performing the studies in the majority of patients.

We hope you will agree that a book such as this is long overdue and that you find it to be a valuable reference and resource for imaging and imaging-based therapy used in the care of children with cancer.

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Imaging in Pediatric Oncology: New Advances and Techniques

1

Daniel A. Morgenstern, Carlos Rodriguez-Galindo, and Mark N. Gaze

1.1 Introduction

The discovery of X-rays by Wilhelm Röntgen in 1895 was translated with remarkable speed into routine clinical practice. Less than 1 year later, the world's first radiology department was established at the Glasgow Royal Infirmary. One of the earliest images was of a foreign body lodged in the esophagus of a 6-month-old boy, and thus pediatric radiology was born [1, 2]. Since that time there has been astonishing progress in imaging technology, including the development of medical ultrasound in the 1950s and computerized tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET) from the 1970s to the 1990s. Over time, technological advances coupled with clinical research have led to an expanding array of more sophisticated and sometimes more costly imaging investigations. These include the use of various types of contrast, additional functional MRI sequences such as diffusion weighting and arterial spin labeling, a wider choice of molecular imaging tracers, and image fusion with hybrid imaging platforms bringing together single photon emission computed tomography (SPECT) and PET with CT and MRI. This bewildering range of imaging options brings with it a requirement to choose wisely, to get the most clinically important information from the smallest number of scans.

Radiologists have emerged from an initial role, focused on the technical aspects of obtaining images and their interpretation, to become a vital part of the multidisciplinary team caring for pediatric oncology patients. Imaging is now central to the management of patients with a variety of CNS and non-CNS solid tumors, including for initial diagnosis, staging and risk stratification, treatment response assessment, surgical and radiotherapy planning, and surveillance both after completion of therapy and in patients with cancer predisposition syndromes. In addition, children with all types of cancer are at risk of infective and other treatment-related complications for which radiological investigations are required. The new subspecialty of pediatric interventional radiology is essential to modern pediatric oncology, its practitioners undertaking a range of image-guided minimally invasive techniques

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including core biopsies, central venous catheter placement, fluid drainage, stent placement, arteriography and tumor embolization, and lesion ablation.

Cancer in children is comparatively rare, representing only 1% of all cancer diagnoses, yet the burden of disease is significant, and in North America and Western Europe, cancer remains the leading cause of childhood death by disease occurring after infancy. While breast, prostate, lung, and gastrointestinal carcinomas represent the most common diagnoses in adults, the pattern of disease in children is radically different. Acute lymphoblastic leukemia (26%), brain tumors (21%), neuroblastoma (7%), and non-Hodgkin lymphoma (6%) represent the most common diagnoses in patients aged 0–14 years, with Hodgkin lymphoma (15%), thyroid carcinoma (11%), brain tumors (10%), testicular germ cell tumors (8%), and bone cancers (including osteosarcoma and Ewing sarcoma) most common in the 15–19-year-old adolescent population [3]. Most well-recognized pediatric embryonal tumors such as neuroblastoma, Wilms tumor (nephroblastoma), hepatoblastoma, and retinoblastoma rarely occur in adults. Thus, the varying spectrum of disease across the pediatric age group and in adolescents and young adults is very different from that in older adults, and an understanding of these changing disease patterns within childhood and adolescence is crucial to interpretation of imaging (see Fig. 1.1).

There has been remarkable progress in improving the outcomes for patients with childhood cancer, resulting from various factors, not least of which has been the development of better imaging for diagnosis, risk stratification, treatment planning, response assessment, and surveillance. In addition, the implementation of multi-agent chemotherapy regimens, and more

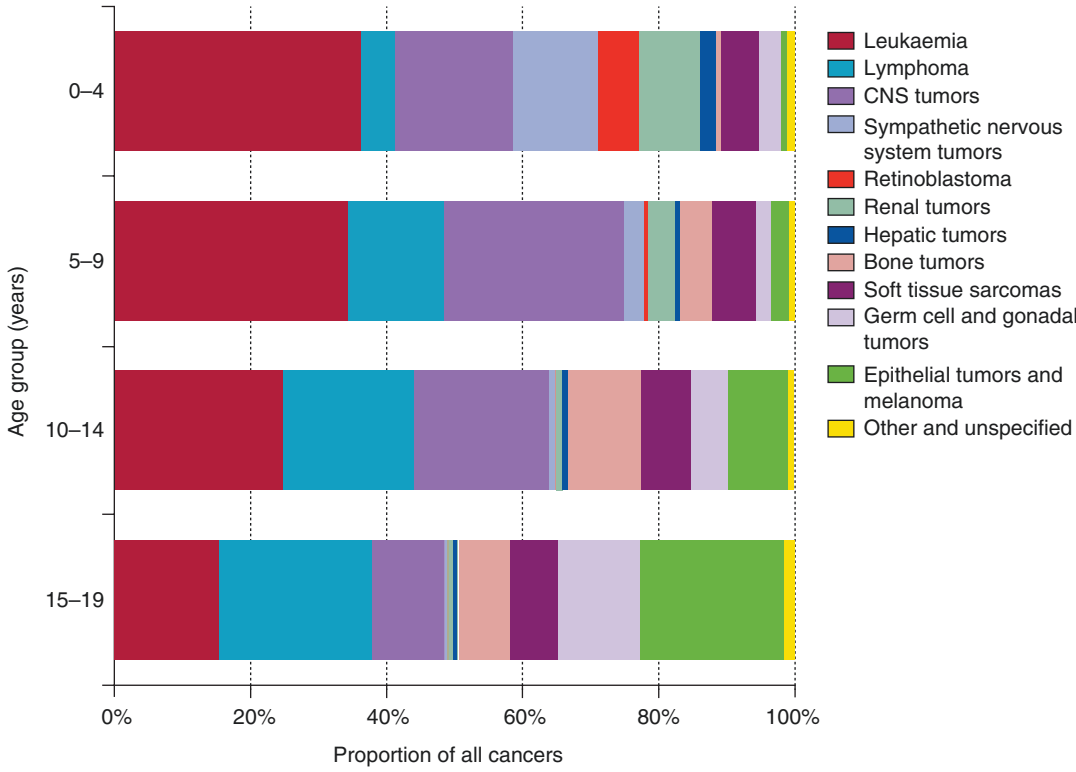

Fig. 1.1 Distribution of cancer types by age group. Summary from multiple international pediatric and general cancer datasets showing the dramatic changes in proportions of different cancer diagnoses depending on age. From [5] with permission

refined use of the local treatment modalities of surgery and radiotherapy, coupled with a strong ethos of clinical research built on national and international collaborations has been transformative. Overall childhood cancer mortality rates have more than halved in the period 1975–2006 from 5.14 to 2.48 per 100,000 [4]. Currently the combined 5-year overall survival (OS) rate is around 80%, although this single figure masks a wide range of outcomes, depending on the underlying diagnosis (see Fig. 1.2). For acute lymphoblastic leukemia (ALL), 5-year OS is nearly 90%, while for non-infant neuroblastoma (>12 months of age), 5-year OS is 65% [4]; for diagnoses such as diffuse intrinsic pontine glioma (DIPG), outcomes remain dire with 5-year OS less than 1%. Overall childhood cancer incidences have been slowly increasing since 1975 (for reasons that are not entirely clear), with a current incidence rate around 170 per 100,000 in North America and Western Europe. However, there is incomplete knowledge on the incidence and epidemiology of childhood cancer globally since large proportions of the world's population are not covered by cancer registries; this is particularly true in the areas of the world where predictions indicate that the cancer burden is growing with the fastest rates, such as in Asia and Africa. Existing data suggest noticeable differences in incidence and patterns of disease by ethnicity, race, and geography [5]. In the United States, it is estimated that 1 in 408 children will be diagnosed with cancer before the age of 15 and 1 in 285 before the age of 20 years [3].

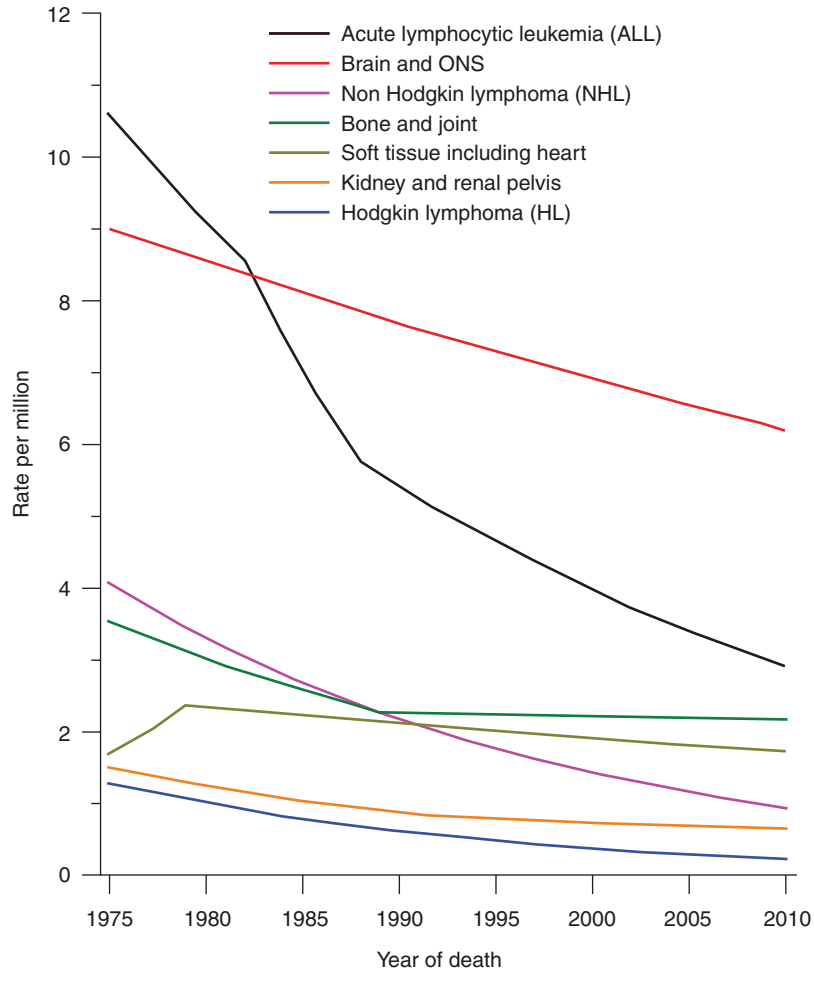

Fig. 1.2 Trends in pediatric cancer mortality rates by site. Data showing changes in pediatric cancer mortality in the United States obtained from National Center for Health Statistics, Centers for Disease Control and Prevention. ONS indicates other nervous system. Overall mortality rates have declined dramatically since 1975, particularly for ALL but also across the range of most solid tumors. From [3] with permission

Improved survival rates have also led to a growing number of adult survivors of childhood cancer, many of whom will be at risk of significant late effects as a result of their original oncology treatment, prompting new considerations related to off-treatment surveillance, both for detecting late relapses and the late effects resulting from the original therapies.

Most children with cancer will initially present to a primary care doctor or general practitioner or to a local hospital emergency department and be referred to a general pediatrician for further investigation. Patients in secondary care settings with suspected or confirmed malignancies will then be referred on to an appropriate regional specialist tertiary center. Those with brain tumors will normally be managed initially by a pediatric neurosurgical service, while those with extracranial solid tumors or leukemia/lymphoma will be referred directly to a pediatric oncology center. Different pathways may exist for adolescents and younger adults suspected to have cancer compared with those for younger children, depending on the local structure of health services. Once at a pediatric oncology center, the care of patients with proven or suspected cancer is usually coordinated by a site-specialized pediatric or adolescent oncologist or hematologist working together with members of a diagnostic and therapeutic multidisciplinary team (MDT). As subsequent care, including imaging, may be shared between the tertiary principal treatment center and local secondary services at the pediatric oncology shared care unit, it is good practice for there to be close communication between radiologists and clinicians regarding any radiological investigations requested closer to home, established protocols for the secure transfer of imaging studies between institutions, and taking steps to ensure that the optimal imaging examinations are performed in order to avoid the need for suboptimal investigations to be repeated.

Initial management is focused on stabilizing the patient, obtaining a diagnosis, and defining risk factors which will guide treatment options. The choice of imaging technique is dependent on the history and clinical examination indicating the body part affected. For suspected brain tumors, contrast-enhanced MRI of the whole central nervous system (CNS) with functional sequences including diffusion weighting will give the best information. For neck, abdominal, pelvic, chest wall, and extremity lesions, ultrasound may be a very useful first step, followed by either CT or MRI. Intrathoracic lesions may be better demonstrated by chest X-ray and CT. These cross-sectional imaging techniques will contribute to determining disease burden and delineate the primary tumor prior to interventional radiology percutaneous (or surgical) biopsy to provide a histological diagnosis and tissue for relevant biological studies. These studies are also essential for demonstrating the presence of lymph node or distant metastatic disease and establishing disease stage. In some cases, such as diffuse intrinsic pontine glioma, retinoblastoma, or Wilms tumor, a presumptive diagnosis may be made on imaging appearances alone. In other cases, typical imaging appearances coupled with elevated blood, cerebrospinal fluid, or urinary tumor marker levels may be sufficient to diagnose, for example, hepatoblastoma, cortical or medullary adrenal tumors, and gonadal, extra-gonadal, and intracranial germ cell tumors. Biopsy may still be required to obtain tissues to complete diagnosis and facilitate risk stratification.

Part of the role of the MDT discussion is to decide on the most appropriate imaging investigations and the order in which they should be performed in individual patients. Because of the carcinogenic risk of ionizing radiation exposure [6], investigations such as ultrasound and MRI are preferred, especially in undiagnosed children who may not, in fact, have cancer. Even in those with a confirmed diagnosis, a balance has to be struck between obtaining the most useful clinical information for disease management and minimizing radiation exposure. The aim of keeping the radiation exposure as low as reasonably achievable (ALARA) can be helped by the selection of optimal technical parameters in imaging protocols, avoiding unnecessary over-investigation, and minimizing the frequency of reassessment and surveillance imaging by following evidence-based guidelines.

Staging investigations depend on an understanding of the likely (or confirmed) diagnosis and anticipated potential sites of metastatic spread. Patients with CNS malignancies typically require imaging of the entire neuraxis. Many extracranial solid tumors (such as sarcomas and Wilms tumor) metastasize preferentially to the lungs requiring CT evaluation, with many sarcomas additionally requiring ^{99m}Tc bone scintigraphy or ^{18}F-fluorodeoxyglucose (FDG) PET/CT evaluation for distant metastases. For neuroblastoma, ^{123}I-mIBG (meta-iodobenzylguanidine) scintigraphy has now largely replaced ^{99m}Tc bone scans for the evaluation of skeletal metastases [7]. This is an important element in the diagnostic process as it can define future therapeutic options with the use of ^{131}I-mIBG for relapsed or refractory disease [8]. FDG-PET/CT has now been routinely adopted for staging and response evaluation in Hodgkin lymphoma and is increasingly used for metastatic evaluation in patients with rhabdomyosarcoma, Ewing sarcoma, and other pediatric sarcomas [9].

There are considerable complexities around the details of primary tumor evaluation and staging that require a detailed knowledge of the underlying diagnosis and relevant clinical trial protocols. Improvements to the resolution of thoracic CT have led to the identification of more sub-centimeter nodules, raising difficult questions about defining lung metastases on the basis of imaging appearances alone [10]. Improving imaging resolution leading to the identification of ever smaller lesions also risks leading to stage migration (i.e., upstaging of patients in whom metastases might not previously have been identified)—the so-called Will Rogers phenomenon [11]. For many pediatric cancers, staging strategies have moved from those based on a surgical evaluation to those based on imaging alone. For neuroblastoma, for example, the International Neuroblastoma Staging System (INSS) definitions are based on tumor surgical resectability and disease involvement of nearby lymph nodes [12]. In contrast, the more recent International Neuroblastoma Risk Group (INRG) staging system focuses on imaging-defined risk factors [13]. Thus, radiological interpretation coupled with a detailed understanding of the relevant staging systems and newly developed imaging-based risk-stratification criteria is crucial to appropriate staging. Other diagnoses have disease-specific staging systems that are based on relevant anatomy and future decisions relating to surgical resectability, for example, the pretreatment extent of disease (PRETEXT) staging system for hepatoblastoma [14].

The role of imaging in pediatric oncology of course extends well beyond the initial diagnostic work-up and staging. For both CNS and extracranial solid tumor imaging, evaluation of tumor response to therapy is crucial for treatment decisions, and again a detailed understanding of relevant diagnoses and treatment protocols is important for appropriate interpretation. In the research context, response of solid tumors is often defined on the basis of the response evaluation criteria in solid tumors (RECIST) guidance [15]. However, for many pediatric cancer diagnoses, disease-specific criteria have been established, often using three-dimensional volume assessments. For example, the European Paediatric Soft Tissue Sarcoma Study Group (EpSSG) guidelines are not interchangeable with RECIST [16], whereas for neuroblastoma, a multinational analysis concluded that none of the methods of primary tumor response assessment was predictive of outcome, and therefore future tumor response assessment will be based on the RECIST guidance [17], together with semiquantitative assessment (such as Curie scoring) of MIBG-positive disease response. Similar issues arise in neuro-oncology, particularly in the evaluation of malignant embryonal tumors such as medulloblastoma that have the propensity to disseminate throughout the neuraxis, leading to the development of disease-specific response criteria [18]. The example of medulloblastoma also further highlights the critical importance of comprehensive disease evaluation and the potential role for central radiology review. The Children's Oncology Group (COG) ACNS9961 study reported significantly inferior EFS for patients with inadequate studies, compared with those with centrally reviewed adequate examinations [19]. Outcome was particularly poor for patients

in whom disseminated disease was only detected retrospectively upon central review. Nuclear medicine modalities also play an important role in response evaluation. In Hodgkin lymphoma, early response assessment based on FDG-PET predicts outcome [20], and resolution of FDG-avid lesions is now used to guide decisions about radiotherapy, while for patients with high-risk metastatic neuroblastoma, post-induction mIBG response predicts outcome [21] and is used to determine adequacy of response for the patient to progress to consolidation therapy.

Imaging also plays an important role in surveillance after the end of therapy for early detection of disease recurrence and the late effects of therapy. Clinical trials that incorporate event-free survival as a primary endpoint have detailed schedules of disease evaluation post-therapy, typically requiring cross-sectional imaging with CT/MRI every 3 months initially. These schedules have frequently been adopted for routine monitoring of patients outside the context of therapeutic trials, although the benefit of intensive surveillance in improving overall outcomes (through the early detection of relapse) has rarely been established. Growing concerns about the risks of exposure to CT-associated radiation [22], gadolinium contrast for MRI [23], and the impact on the developing brain of recurrent general anesthesia often required to facilitate imaging in young children [24] mean that the appropriateness of such imaging needs to be carefully considered.

In summary, the excellent outcomes seen today for the majority of children and young people with cancer, and hope for future improvements for those tumor types where the prognosis is less good, are based in no small part on the wide range of imaging techniques now available and the knowledge and skills of diagnostic and interventional radiologists working as part of the wider pediatric oncology MDT. The selection of the most appropriate investigations for an individual patient should be evidence-based and made in discussion with experienced pediatric radiologists. The radiologist will identify the site, extent, and nature of the primary tumor and demonstrate the presence or absence of metastases. The radiologist may biopsy the tumor for histological diagnosis and molecular pathology subtyping and may well support care by insertion of a central venous catheter and other interventions. The radiologist is an essential supporter of surgeons and clinical oncologists as they plan complex radical tumor surgery and sophisticated modern radiation treatments and provide continuing evaluation with the assessment of response to chemotherapy, surgery, and radiation therapy. Finally, the involvement of the radiologist in the follow-up of the patient after completing therapy is critical in the evaluation of local or metastatic recurrence or treatment-related complications and second tumors.

For future improvements in the care of children and young people with cancer, it is essential that pediatric radiologists are not simply fully integrated as core members of the pediatric oncology MDTs in principal treatment centers but are also involved in national and international clinical trial groups. Further research into imaging biomarkers and the best use of radiological investigations is as fundamental to the progress of pediatric oncology as randomized trials of treatment.

References

1. Sweet E. Paediatric radiology in Great Britain and Ireland. In: Kaufmann HJ, Ringertz H, Sweet E, editors. The first 30 years of the ESPR. Berlin: Springer; 1993. p. 1–2.
2. Thomas AM, Banerjee AK. The history of radiology. Oxford: Oxford University Press; 2013.
3. Ward E, DeSantis C, Robbins A, Kohler B, Jemal A. Childhood and adolescent cancer statistics, 2014. CA Cancer J Clin. 2014;64(2):83–103.
4. Smith MA, Seibel NL, Altekruse SF, Ries LAG, Melbert DL, O'Leary M, et al. Outcomes for children and adolescents with cancer: challenges for the twenty-first century. J Clin Oncol. 2010;28(15):2625–34.
5. Steliarova-Foucher E, Colombet M, Ries LAG, Moreno F, Dolya A, Bray F, et al. International incidence of childhood cancer, 2001-10: a population-based registry study. Lancet Oncol. 2017;18(6):719–31.
6. Linet MS, Kim KP, Rajaraman P. Children's exposure to diagnostic medical radiation and cancer risk: epidemiologic and dosimetric considerations. Pediatr Radiol. 2009;39(Suppl 1):S4–26.
7. Matthay KK, Shulkin B, Ladenstein R, Michon J, Giammarile F, Lewington V, et al. Criteria for evaluation of disease extent by (123)

I-metaiodobenzylguanidine scans in neuroblastoma: a report for the International Neuroblastoma Risk Group (INRG) Task Force. Br J Cancer. 2010;102(9):1319–26.
8. Wilson JS, Gains JE, Moroz V, Wheatley K, Gaze MN. A systematic review of 131I-meta iodobenzylguanidine molecular radiotherapy for neuroblastoma. Eur J Cancer. 2014;50(4):801–15.
9. Norman G, Fayter D, Lewis-Light K, Chisholm J, McHugh K, Levine D, et al. An emerging evidence base for PET-CT in the management of childhood rhabdomyosarcoma: systematic review. BMJ Open. 2015;5(1):e006030.
10. Grundy PE, Green DM, Dirks AC, Berendt AE, Breslow NE, Anderson JR, et al. Clinical significance of pulmonary nodules detected by CT and Not CXR in patients treated for favorable histology Wilms tumor on national Wilms tumor studies-4 and -5: a report from the Children's Oncology Group. Pediatr Blood Cancer. 2012;59(4):631–5.
11. Feinstein AR, Sosin DM, Wells CK. The Will Rogers phenomenon. Stage migration and new diagnostic techniques as a source of misleading statistics for survival in cancer. N Engl J Med. 1985;312(25):1604–8.
12. Brodeur GM, Pritchard J, Berthold F, Carlsen NL, Castel V, Castelberry RP, et al. Revisions of the international criteria for neuroblastoma diagnosis, staging, and response to treatment. J Clin Oncol. 1993;11(8):1466–77.
13. Monclair T, Brodeur GM, Ambros PF, Brisse HJ, Cecchetto G, Holmes K, et al. The International Neuroblastoma Risk Group (INRG) staging system: an INRG Task Force report. J Clin Oncol. 2009;27(2):298–303.
14. Roebuck DJ, Aronson D, Clapuyt P, Czauderna P, de Ville de Goyet J, Gauthier F, et al. 2005 PRETEXT: a revised staging system for primary malignant liver tumours of childhood developed by the SIOPEL group. Pediatr Radiol. 2007;37(2):123–32. quiz249–50.
15. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45(2):228–47.
16. Schoot RA, McHugh K, van Rijn RR, Kremer LCM, Chisholm JC, Caron HN, et al. Response assessment in pediatric rhabdomyosarcoma: can response evaluation criteria in solid tumors replace three-dimensional volume assessments? Radiology. 2013;269(3):870–8.
17. Bagatell R, McHugh K, Naranjo A, Van Ryn C, Kirby C, Brock P, et al. Assessment of primary site response in children with high-risk neuroblastoma: an international multicenter study. J Clin Oncol. 2016;34(7):740–6.
18. Warren KE, Vezina G, Poussaint TY, Warmuth-Metz M, Chamberlain MC, Packer RJ, et al. Response assessment in medulloblastoma and leptomeningeal seeding tumors: recommendations from the response assessment in pediatric neuro-oncology committee. Neuro Oncol. 2018;20:13.
19. Packer RJ, Gajjar A, Vezina G, Rorke-Adams L, Burger PC, Robertson PL, et al. Phase III study of craniospinal radiation therapy followed by adjuvant chemotherapy for newly diagnosed average-risk medulloblastoma. J Clin Oncol. 2006;24(25):4202–8.
20. Furth C, Steffen IG, Amthauer H, Ruf J, Misch D, Schönberger S, et al. Early and late therapy response assessment with [18F]fluorodeoxyglucose positron emission tomography in pediatric Hodgkin's lymphoma: analysis of a prospective multicenter trial. J Clin Oncol. 2009;27(26):4385–91.
21. Matthay KK, Edeline V, Lumbroso J, Tanguy ML, Asselain B, Zucker JM, et al. Correlation of early metastatic response by 123I-metaiodobenzylguanidine scintigraphy with overall response and event-free survival in stage IV neuroblastoma. J Clin Oncol. 2003;21(13):2486–91.
22. Owens C, Li BK, Thomas KE, Irwin MS. Surveillance imaging and radiation exposure in the detection of relapsed neuroblastoma. Pediatr Blood Cancer. 2016;63(10):1786–93.
23. Fraum TJ, Ludwig DR, Bashir MR, Fowler KJ. Gadolinium-based contrast agents: a comprehensive risk assessment. J Magn Reson Imaging. 2017;46:338.
24. Sinner B, Becke K, Engelhard K. General anaesthetics and the developing brain: an overview. Anaesthesia. 2014;69(9):1009–22.

2 Imaging in Paediatric Oncology: Pitfalls, Acceptable and Unacceptable Imaging

Joy Barber and Kieran McHugh

2.1 Introduction

Cancer in the paediatric age group is rare and in most countries is usually managed in a small number of specialist centres in order to maximise expertise. The first presentation of a child with cancer is most frequently however at a smaller local hospital where the initial diagnostic tests are often undertaken. Some follow-up imaging may also be performed locally for patient convenience. This arrangement results in imaging from a wide variety of district hospitals being sent to regional cancer centres for review. Our chapter sets out to illustrate potential errors made in the imaging of children with cancer, from selecting an incorrect modality or using suboptimal protocols to incorrect identification and interpretation of abnormalities. Whilst this chapter illustrates some of the pitfalls in the imaging of childhood cancer we have encountered, it comes with a plea for a collaborative approach to imaging between specialist and general hospitals with an encouragement of an open dialogue and constructive feedback to referring centres.

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2.2 How to Scan

2.2.1 Choosing Imaging Modalities

Survival rates for childhood cancer are very good, with a 5-year survival of 82% for children diagnosed between 2006 and 2010 [1]. For this reason, it is particularly important to minimise potential morbidity due to the side-effects of radiation exposure incurred during diagnosis, treatment and later surveillance. The risks of treatment-dose radiation in children are well established [2]. More controversial currently are the risks attributable to diagnostic level radiation, with arguments both for [3, 4] and against [5] it posing significant hazard. At worst, a lifetime risk of cancer in the order of 1 in 550 has been quoted for a 1 year old child following a CT of the abdomen [6]. Given the uncertainty regarding the risk of diagnostic radiation doses, the ALARA principle is recommended for safety. On the other hand, MRI is not an entirely risk-free alternative, with sedation or anaesthesia required for long scans in young children carrying an associated morbidity [7]. There is growing concern in the literature regarding the effects of gadolinium deposition in tissues albeit without any evidence of harm to children as yet [8]. Certainly, if CT or other techniques involving ionising radiation are to be used, the protocol must be optimised to ensure the maximum useful information will be gained.

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2.2.2 Plain Radiographs

2.2.2.1 Chest Radiographs

Chest radiographs will, quite reasonably, be performed in most patients with a suspected new tumour for staging purposes. With the exception of children with obvious pulmonary metastases, most abnormalities identified on chest radiographs will be inflammatory/infective abnormalities such as round pneumonia or occasionally congenital lesions such as bronchopulmonary foregut malformations. This is largely due to the low incidence of primary thoracic malignancy in children although bronchogenic tumours, carcinoids, pleuropulmonary blastomas and mesenchymal tumours are occasionally seen.

Misidentification of normal structures on plain film is easily done on a rotated radiograph. The thymus can look particularly large in infants and toddlers, however should always maintain its normal gently lobulated contour and not exert any mass effect (Fig. 2.1). Malignant mediastinal masses however do also occur in children. Locating the mass within the anterior or posterior mediastinum can help to narrow the differential, lymphoma being the most common malignant anterior mediastinal mass and neuroblastoma (Fig. 2.2) being a posteriorly located mass often erodes or splays the posterior ribs. Chest radiographs are used as part of follow-up of patients following treatment for cancers with a risk of lung metastatic disease, for instance, Wilms tumour, rhabdomyosarcoma, osteosarcoma and Ewing sarcoma. In addition to the usual sites where pathology is commonly missed on chest radiographs—for instance, behind the clavicles (Fig. 2.3), behind the heart and in the costophrenic recesses projected below the diaphragm—another potential pitfall which is peculiar to paediatrics is misidentification of sternal ossification centres. Although more commonly mistaken for rib fracture on oblique chest

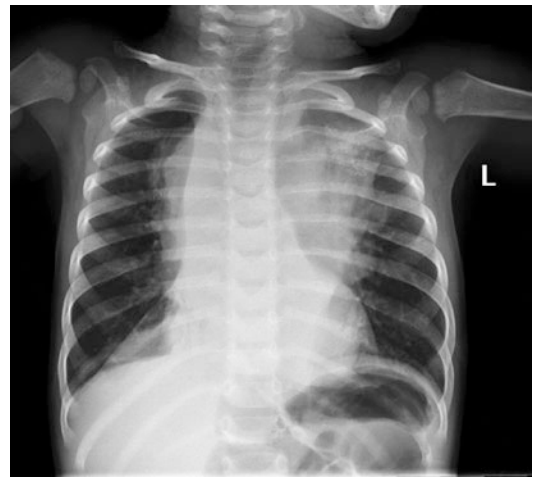

Fig. 2.2 A posterior mediastinal mass (neuroblastoma) on chest radiograph—note the distortion of the posterior ribs, helping to confirm the posterior location

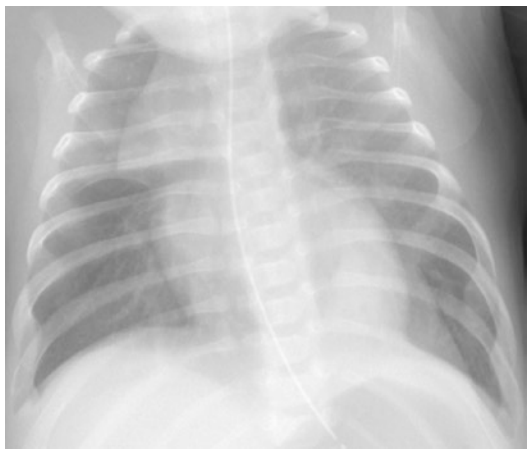

Fig. 2.1 Normal gently lobulated thymic contour on chest radiograph, conforming to the overlying ribs. Note also the added left lower lobe density in this example—a sequestration

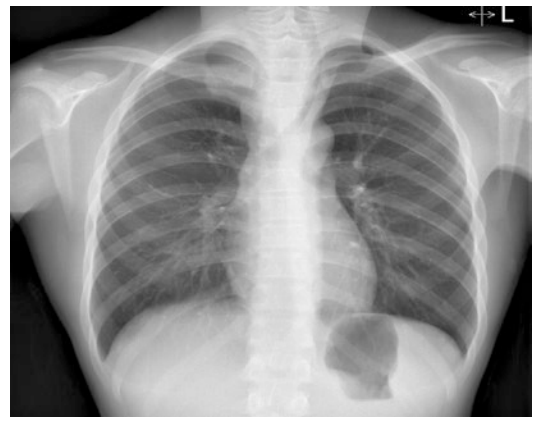

Fig. 2.3 This Ewing tumour is located behind the right clavicle but is also detectable by the deviation it causes to the adjacent trachea—demonstrating the importance of systematic review areas

radiographs, sternal ossification centres may on occasion be mistaken for calcified metastases. Thankfully with patient age and progressive ossification, this becomes a less common pitfall.

The bones imaged on chest radiographs are a minefield for potential missed diagnoses. In addition to the posterior rib distortion and erosion that may help to identify a mediastinal mass as a posterior thoracic neuroblastoma (Fig. 2.2), metastatic bone disease and non-malignant but nonetheless aggressive processes may also be demonstrated. Lucency within the proximal humeral metaphyses may be the first manifestation of metastatic bone disease, for instance, in neuroblastoma, or diffuse marrow space involvement in the setting of haematological malignancy (Fig. 2.4). Whilst metabolic bone disease should also be considered in cases where the abnormality is symmetrical and the margins ill-defined, the imaging features of cupping and fraying of the metaphyses in rickets are well described and quite characteristic and distinct from the bony changes seen in malignancy. It is well recognised that ifosfamide treatment for tumours can also be complicated by rickets. The presence of abnormality elsewhere in the skeleton and the overall clinical picture usually allow differentiation.

The ribs, whilst also a site of potential metastatic disease, may also be affected by primary bone lesions including PNET/Ewings (Fig. 2.5). Non-malignant lesions such as enchondromas, fibrous dysplasia and mesenchymal hamartoma may also be seen (Fig. 2.6). Of note, osteochondromas are the commonest rib tumour induced by

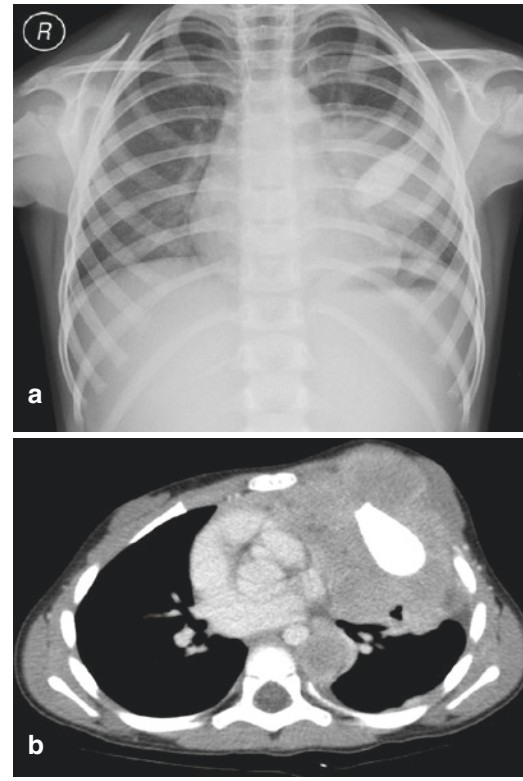

Fig. 2.5 (**a**, **b**) Note the sclerotic, expanded left third rib, with associated soft tissue mass—an Ewing sarcoma

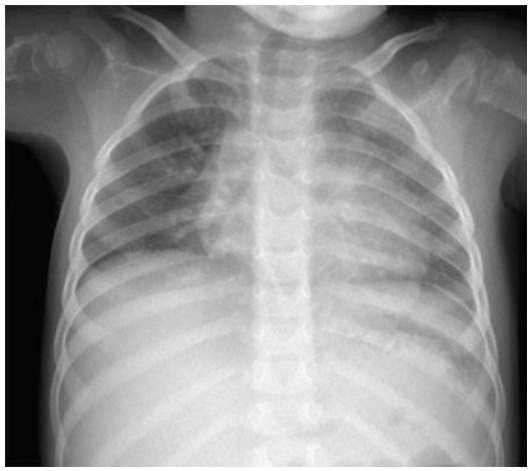

Fig. 2.4 Infiltrative lucency in both proximal humeri was the presenting abnormality in this child with metastatic neuroblastoma

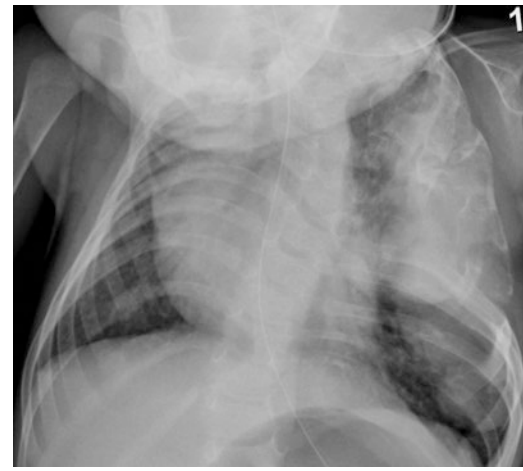

Fig. 2.6 Unusual but characteristic chest radiograph appearance of a mesenchymal hamartoma

radiation, and these were frequently seen in the era when children had total body irradiation prior to bone marrow transplant and are still encountered following mediastinal radiation for Hodgkin lymphoma. The likelihood of each differential is influenced by patient age at presentation and the often distinctive imaging appearances.

Vertebral lesions may also be detectable on chest radiograph although easily missed if not looked for—in particular vertebral collapse which may be secondary to infiltration in haematological malignancy and metastatic disease or secondary to Langerhans cell histiocytosis (LCH) (Fig. 2.7).

2.2.2.2 Abdominal Radiographs

A calcified neuroblastoma mass can often be seen on a plain abdominal radiograph in the upper abdomen or pelvis. Calcification in a germ cell tumour or teratoma of the ovary may also be evident occasionally. These findings may help in the diagnosis of those tumours but seldom provide any other useful information. In addition, these findings are generally evident at initial ultrasound examination also. In rare cases of high-risk metastatic neuroblastoma, lytic skeletal metastases may be visible, but that is an exception rather than the rule. Abdominal radiographs for abdominal masses in children usually show a nonspecific mass in the abdomen, with pelvic masses appearing often identical to a distended bladder. Their role is virtually always superseded by cross-sectional imaging, notably ultrasound. In general an abdominal radiograph at initial presentation of an abdominal mass may be avoided unless there is a concern over bowel obstruction or perforation.

2.2.2.3 Appendicular Radiographs

Whilst they are performed for LCH, extended skeletal surveys are not recommended for routine identification of metastatic disease in children with malignancy, and where clinically required, radiographs should be targeted to a specific indication. Whilst not as sensitive as scintigraphy or

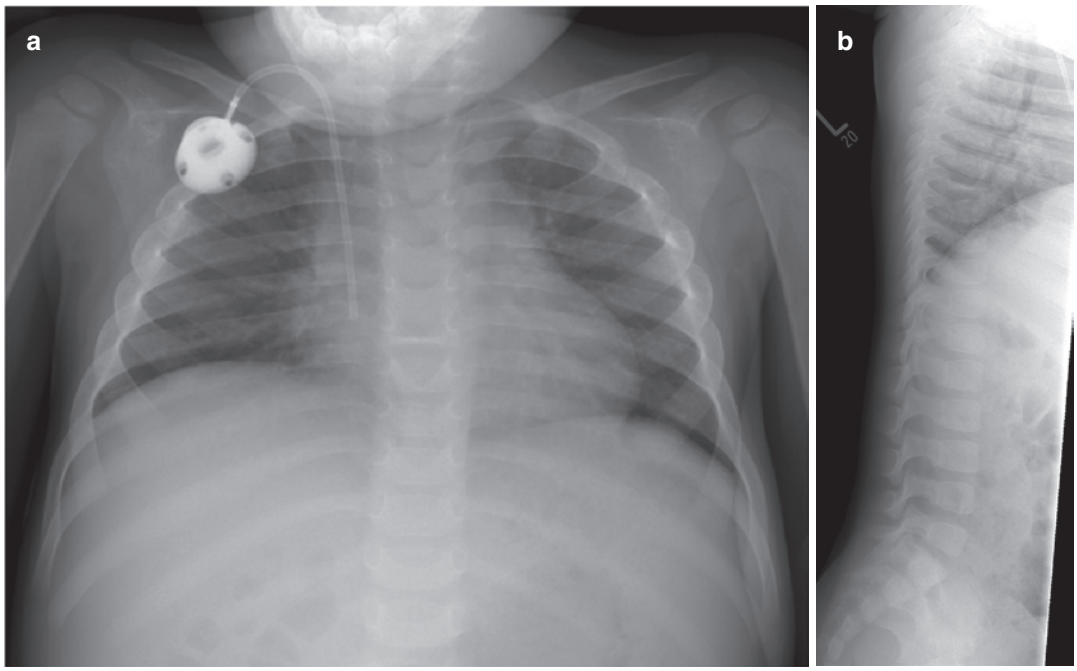

Fig. 2.7 (**a**, **b**) There is collapse of the T7 vertebral body, secondary to infiltration by Langerhans cell histiocytosis

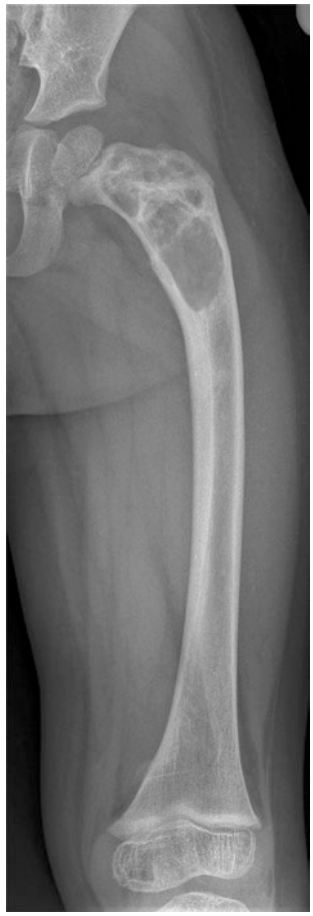

Fig. 2.8 The plain radiograph appearance is sometimes sufficiently distinctive to allow identification of specific patterns of calcification or ground glass changes—such as in fibrous dysplasia shown here

MRI for detecting bone lesions, plain radiographs are particularly valuable in identifying patterns of calcification or typical osseous changes which may assist in identifying 'don't touch' lesions—such as the ground-glass appearance in fibrous dysplasia (Fig. 2.8).

2.2.3 Ultrasound

There are many merits of ultrasound in paediatric oncology. Ultrasound requires neither ionising radiation nor sedation and is low risk and potentially high yield. The dynamic nature of the study and direct patient interaction allow for assessment of mobility of structures relative to each other and on respiration. For instance, ultrasound can allow relatively easy assessment of whether a right upper quadrant tumour is tethered to adjacent liver—allowing the oncologic surgeon to more accurately assess operative risk and take mitigating steps as appropriate. In the authors' experience, this useful information is often overlooked on preoperative ultrasound scanning.

With a distressed or uncooperative child, it can take time and patience to acquire an optimal ultrasound study, sometimes requiring 'time-out' for both child and operator. A systematic approach can help avoid critical components of the study being missed. Colour Doppler should always be applied to lesions—to assist in differentiation between solid and cystic lesions and to help establish the relationship to adjacent vessels (Fig. 2.9). Regional lymph nodes should always be systematically assessed when soft tissue lesions are examined and followed up (Fig. 2.10).

High-frequency linear probes (at least 10–12 MHz) should be used to interrogate the solid organs when metastases are suspected or when fungal infection is suspected in a neutropenic child following treatment. Use of lower-frequency curvilinear probes may mask pathology or at the very least may make it much more difficult to identify lesions which are present (Fig. 2.11).

Ultrasound microbubble contrast (Sonovue/Lumason, Bracco, Milan, Italy) has recently been approved by the FDA in the United States for intravascular use in adults and children for assessment of focal liver lesions. It continues to be used 'off label' in Europe for a multitude of indications in children. There is a paucity of literature currently regarding the accuracy of intravascular ultrasound contrast in assessing paediatric solid organ lesions, although the limited data available is encouraging with one study reporting a specificity of 98% for identifying benign lesions and a negative predictive value of 100% [9]. It is anticipated with the recent FDA approval that the body of evidence surrounding paediatric ultrasound contrast will be significantly expanded in the coming years.

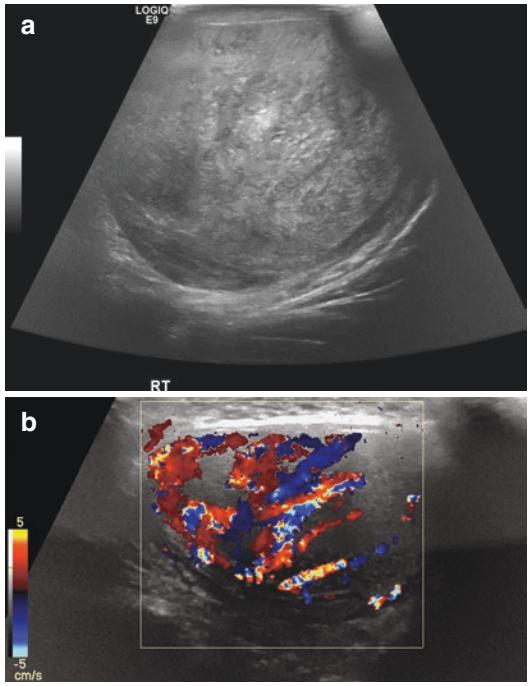

Fig. 2.9 (**a**, **b**) Colour Doppler interrogation allows characterisation of this para-testicular mass as a solid lesion (rhabdomyosarcoma) rather than, for instance, a heterogenous haematoma

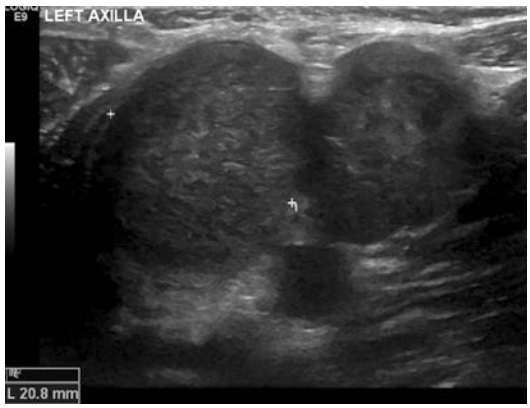

Fig. 2.10 Regional lymph node recurrence of rhabdomyosarcoma, identified at follow-up ultrasound

An easy error on ultrasound is to mistake a calcified left upper quadrant mass for gas in the stomach and vice versa (Fig. 2.12). Similarly a cystic mass in the low midline can be dismissed as bladder. In both of these cases, careful delineation of the surrounding anatomy can avoid these pitfalls. For instance, correct identification

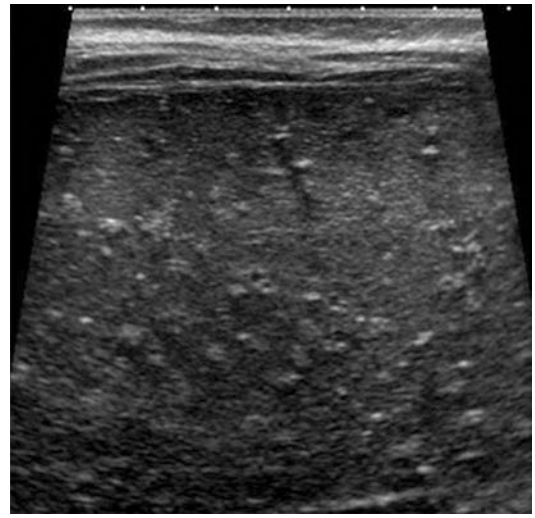

Fig. 2.11 Focal parenchymal lesions in the liver, spleen and kidneys are more apparent on high-frequency ultrasound scanning with a linear probe—such as these hepatic fungal deposits

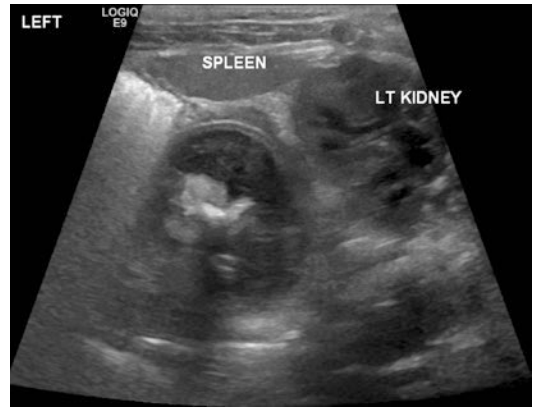

Fig. 2.12 The echogenic foci casting posterior acoustic shadows are not gas within the stomach but calcification within a left upper quadrant solid mass

of the stomach can be confirmed with recognition of the pylorus, and correct identification of the bladder can be confirmed with recognition of the urethral opening.

2.2.4 CT

Whilst the risks of diagnostic level ionisation are debated [3–6], the ALARA principle has driven the development of technology centred around

reducing dose. Choice of scanner plays a role in the dose reduction techniques available, and it would be remiss for a paediatric radiologist to not be involved in specifying the requirements for new acquisitions of CT scanners and establishing paediatric-specific CT protocols. From optimising pitch and collimation to tube current modulation and iterative reconstruction, there are a wealth of techniques that can be implemented to ensure radiation can be minimised without impairing image quality [10]. At our institutions, paediatric chest CT is currently delivered with an effective dose in the range 0.5–1 mSv. Dose reference levels have been developed by Image Gently and the European Society of Radiology through the Eurosafe project [11] and should be used as a guide to optimise departmental protocols. However even a perfectly optimised, paediatric-friendly CT scanner can be used in error if the wrong scan or protocol is performed.

2.2.4.1 Only Perform Necessary Studies

For children with radiation sensitivity syndromes such as Li-Fraumeni, ataxia telangiectasia, Nijmegen breakage syndrome, or Fanconi anaemia, extra effort should be made to avoid CT and substitute with US or MRI whenever possible.

CT imaging of the chest is not required in all tumour types; in particular it has been shown to be unnecessary in neuroblastoma [12], where pulmonary metastatic disease is uncommon, although including the thorax may be helpful in characterising potential supraclavicular lymph node involvement (Virchow's node) identified by MIBG. Chest CT is nonetheless more sensitive for detecting metastatic lung disease than plain radiographs and is invaluable in pathologies with a tendency to spread to the lungs including osteosarcoma, Ewing sarcoma, rhabdomyosarcoma, hepatoblastoma and Wilms tumours.

The frequency of follow-up imaging in children can also be moderated. For instance, most tumour relapses can be detected clinically, and repeated surveillance CT does little to improve outcome in tumour types including lymphoma [13, 14].

CT of the abdomen/pelvis provides poorer soft tissue resolution than MRI, particularly important in young children who have high body water contents and little internal fat to separate organs. New MRI sequences allow excellent spatial resolution, and well-performed MRI is now generally preferable for investigation of a new abdominal mass. The main drawback is regarding the risk of sedation or anaesthesia, which may be required for longer MRI studies and can often be avoided for CT.

2.2.4.2 Do Not Use Thick or Noncontiguous Slices

This should rarely occur; however, where a scanner has acquired thin section data, this needs to be available for review and reformat by the reporting radiologist. Some lesions are much easier to identify and characterize on coronal or sagittal reformats than the standard provided axial images. Indeed, review of properly reformatted images in axial, sagittal and coronal planes using soft tissue, lung and bone windows is considered standard of care and should take place with every examination. Noncontiguous slices are unacceptable in cancer staging.

2.2.4.3 Eliminating Movement

Whilst the increased speed of scanners reduces the severity to which images are degraded due to patient movement, it is not acceptable to repeatedly image a child with CT due to poor immobilisation. Whilst sedation or anaesthesia was previously widely employed to ensure children were sufficiently still for CT, this is less necessary in the era of sub-second scan times. Immobilisation techniques such as trauma evacuation-style 'vacuum' bags are well tolerated by most children, easy to use and compatible with CT and MRI. A small number of children will nonetheless require anaesthetic support for CT, in particular those with neck or mediastinal masses at risk of compromising the airway. In these patients, if the risk of lying supine is felt to be too great, such as in a child with T-cell non-Hodgkin lymphoma and a large anterior mediastinal mass compressing the trachea, lateral decubitus or prone imaging may still be possible.

2.2.4.4 Intravascular Contrast

Iodinated contrast is not inherently safe, with potential risks of extravasation, anaphylactoid reactions and contrast-induced nephropathy. Thankfully these are uncommon in children. Extravasation can be reduced by careful IV line placement, line flushing and auto cut-offs on injector pumps in the case of a rapid rise in resistance. Mild or moderate anaphylactoid reactions occur in up to 0.5% of patients and severe anaphylactoid reactions only in approximately 0.02% [15, 16]. The risk of unexpected contrast-induced nephropathy can be mitigated by checking of renal function in at-risk patients.

With their higher body water content and lower body fat content compared with adults, giving contrast for paediatric CT is rarely an error. With the exception of spotting lung nodules, non-contrast scans in children often result in relatively homogenous shades of grey with poor differentiation between tissues (Fig. 2.13) and should be avoided in the assessment of a new mass [17]. The only useful information gleaned from a non-contrast CT in a child is whether a lesion is calcified or not, but this is also readily apparent after contrast administration (see Table 2.1). Even for CT studies primarily assessing for metastatic lung disease, contrast can be useful to delineate the mediastinal and vascular structures.

There has been some debate in the literature regarding the timing of contrast boluses in oncologic CT [18, 19] with some advocates of a dual-bolus approach—achieving both arterial and portal venous phase contrast in a single pass. This can be helpful in certain scenarios but is not normally required. Arterial phase imaging is generally preferred for the chest.

Ideally, the abdomen and pelvis should be imaged with MRI. Where CT imaging of the abdomen is necessary, the phase of imaging must be tailored to the question. Single-phase imaging at CT is all that is necessary for the majority of abdominal mass lesions in young patients. Triple-phase scanning (arterial, portal, delayed venous) seldom adds useful additional information and triples the effective dose. It should be borne in mind that prior ultrasound with Doppler vascular assessment of any abdominal mass should have been performed before CT. If both arterial and portal venous phase imaging are required simultaneously, the dual-bolus technique can be considered.

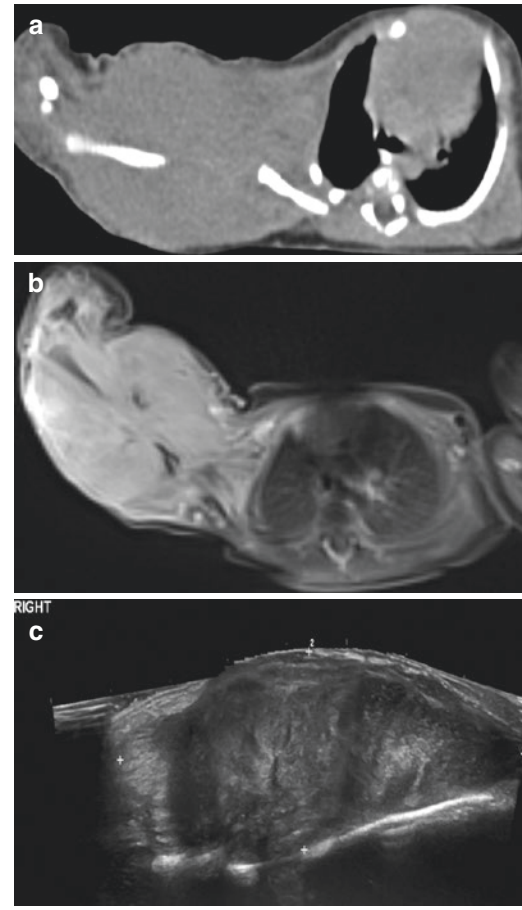

Fig. 2.13 This right upper limb soft tissue lesion is poorly delineated on non-contrast CT (**a**) but much better seen and assessed on both MRI (**b**) and ultrasound (**c**)

2.2.5 MRI

2.2.5.1 MRI Sequences

MRI sequences can generally be grouped into those which aid detection of disease (fat-suppressed T2 imaging/STIR, DWI), those which allow assessment of lesion contents

Table 2.1 Important 'Do's' and 'Don'ts' in paediatric oncology imaging

Don't do non-contrast CT. Post-contrast scanning should generally suffice
Don't do multiphase CT scanning; single-phase scans should be sufficient. Remember that ultrasound to assess vascularity should have been performed before CT
Do perform ultrasound evaluation initially of superficial lesions
Don't forget to assess the regional lymph nodes with ultrasound and MRI. For limb tumours this means assessing the popliteal and inguinal nodes of a leg or the epitrochlear and axillary nodes for an upper limb primary
For MRI do try to perform diffusion weighted imaging (DWI) and ADC maps for all new tumours. This helps assess lesion cellularity and may guide biopsy
At MRI a volumetric sequence is useful for reconstruction in the other orthogonal planes for surgical planning
Don't routinely perform an abdominal radiograph for an abdominal mass; it is seldom useful
Do consider performing MRI instead of CT for all limb, abdominal (particularly pelvic and liver), paravertebral and neck tumours

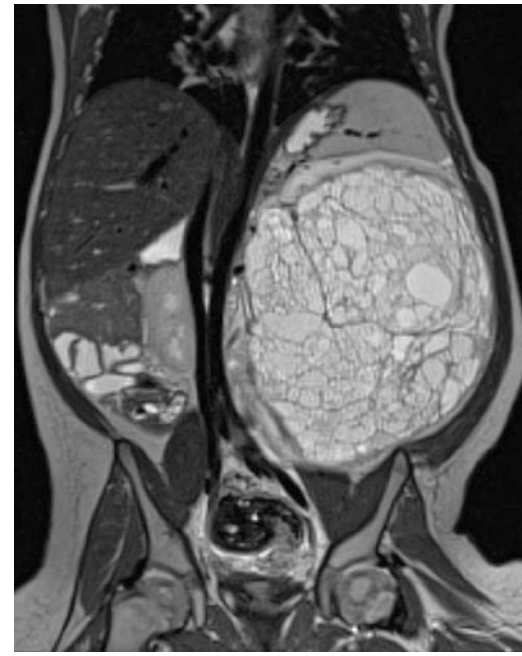

Fig. 2.14 High-resolution T2 SPACE/CUBE imaging provides excellent delineation of a left renal tumour and surrounding vascular anatomy but at the cost of a long study time often requiring general anaesthetic in younger children

(T1, in- and out-of-phase, T2, and contrast-enhanced imaging) and those which are particularly good at anatomic localisation and resection planning (isotropic, small voxel T2 imaging). An oncology protocol needs to satisfy all these demands but will be tailored to an individual institution's machine and coil capabilities and adapted based on the patient and pathology.

The plane of imaging is important. Midline lesions, for instance thymus or prostatic/vaginal lesions, are difficult to delineate on coronal imaging, and sagittal imaging is often a better choice for the second acquired plane.

MRI sequence selection involves trade-offs. High-resolution MR imaging has the ability to replace CT of the abdomen and pelvis in terms of spatial resolution (Fig. 2.14) but takes a long time to acquire in order to maintain an adequate signal-to-noise ratio (10–15 min for a T2-SPACE/CUBE of the abdomen and pelvis) and therefore often requires sedation/anaesthesia.

2.2.5.2 Gadolinium

Although the risk of NSF is low with modern macrocyclic gadolinium agents, it should not be given to children with known renal impairment without a careful risk-benefit assessment [20]. Gadolinium carries lower but non-zero risk of anaphylaxis compared with CT-iodinated contrast. More recently, concerns have increased regarding deposition of gadolinium within brain and bone tissue. Although the long-term effects of this are unknown, it has been found to occur both in patients with normal renal function and with macrocyclic agents previously thought to be more stable [21, 22]. The need to give gadolinium to assess enhancement needs to be weighed carefully against potential risks in each child.

2.2.6 Nuclear Medicine

SPECT and PET/CT are increasingly used in the investigation of childhood malignancies. [^{18}F]fluo-