Guidelines for the use of PET–CT in children

Sally F. Barrington, Joanna Begent, Thomas Lynch, Paul Schleyer, Lorenzo Biassoni, William Ramsden, Thomas Kane, Sara Stoneham, Margaret Brooks and Sharon F. Hain

Background

The use of positron emission tomography (PET) in adult oncology, neurology and cardiology is well established. The most common tracer used in clinical PET is $^{18}$fluorine fluorodeoxyglucose (FDG). Experience with PET in the field of paediatric imaging is, however, limited. Data can be extrapolated from adult studies for conditions that are found in adult and paediatric populations alike such as lymphoma, sarcoma and temporal lobe epilepsy. It would seem reasonable to use PET for such indications where sufficient evidence exists to justify the use of PET in adult patients [1–3]. It is unlikely, however, that robust data will emerge for many conditions that are limited to childhood, which are often rare diseases. Therefore, it is not possible to apply the same selection criteria for adult and paediatric imaging. In rare conditions, the routine use of PET [and PET–computed tomography (CT)] cannot be recommended, but PET may be able to assist in individual management by answering clinical questions that are difficult to answer using anatomical imaging alone.

The optimal use of PET in children relies on tailoring the scan acquisition and the scan environment to the needs of the child, with proper attention to safety and appropriate risk management [4–6]. As with any imaging modality, familiarity with normal variation and appearances of pathological conditions experienced in childhood are important when interpreting scans, which should be undertaken by individuals who regularly report paediatric PET studies.

In the face of these limited published data and experience, this report was compiled by individuals with experience in scanning children with PET and CT in the UK and paediatricians involved in the clinical management of the type of conditions for which PET is likely to be used. It represents a consensus reached among the authors of what is desirable ‘best’ practice. The guidance has been endorsed by the British Nuclear Medicine Society, Royal College of Radiologists, Royal College of Physicians, Royal College of Surgeons and the British Society of Paediatric Radiology.

Issues specifically relating to children are discussed in this report. It is assumed that guidance relating to ‘best practice’ in scanning adults with PET and PET–CT will also be applied in children.

Indications for PET/computed tomography in children with known/suspected malignancy

Small studies have demonstrated many paediatric tumours to be FDG avid; to date no paediatric tumour has been identified as ‘non-FDG avid’.

With the exception of Hodgkin’s lymphoma (where a clinical study involving the use of FDG-PET is underway), no clear guidelines exist; however, data suggest that FDG-PET/CT can be used to enhance the care of children with cancer [1].

The overall survival rate in paediatric malignancy is approximately 75%. For some cancers, for example, Wilms’ tumour, the survival rate will be above 90%; however, for a significant number of patients, for example, stage 4 neuroblastoma, there remains a less than 50% chance of survival. When planning a child’s care, it is important to consider the long-term effects of treatment that many children live with for the rest of their lives.

FDG-PET/CT is now used routinely in the management of Hodgkin’s lymphoma and can significantly alter management [7]. Many data have shown it has improved sensitivity and specificity when compared with conventional imaging (CT/MRI). When performed at staging and after therapy, FDG-PET/CT allows more accurate
assessment of response to treatment. Current data demonstrate that PET is a strong predictor of prognosis after initial chemotherapy and progression-free survival. There has been concern about late second malignancies in children who have received radiotherapy for Hodgkin's lymphoma and FDG-PET/CT may allow reduced treatment burden in those who have responded well to chemotherapy. Conversely, in poor responders early treatment intensification may be beneficial.

Therapy modification based on FDG-PET/CT may be possible in other tumour types as more data are acquired. Currently, PET/CT can be helpful in cases where additional information may assist in difficult clinical decisions, for example, giving radiotherapy to a growing child, planning minimally invasive surgery and withholding further cardiotoxic chemotherapy. To this end, PET/CT can be considered in many paediatric malignant conditions and the advice of experienced physicians in paediatric PET/CT may be valuable.

When a child or young person is diagnosed with an adult-type tumour, for example, malignant melanoma, relevant, existing adult guidelines should apply. Magnetic resonance techniques are further developed in paediatric brain tumours and therefore the main functional imaging techniques which are used for this tumour group. PET/CT with FDG and other tracers including 11C methionine may prove to have an additional role.

**Diagnosis/staging/restaging**

The ability of PET–CT to answer clinical questions during a patient’s treatment course may be greatly enhanced by the presence of a scan at the time of diagnosis, before treatment. It is, however, clearly not appropriate for all children to have a pretreatment scan.

Pretreatment PET/CT scans should be considered in any child with:

- Hodgkin's lymphoma (on or off trial);
- Non-Hodgkin’s lymphoma with unusual primary or metastatic sites;
- Extramedullary leukaemia;
- Malignancy with unknown primary;
- Soft tissue sarcoma – for staging;
- Bone sarcoma with extrapulmonary metastatic disease;
- Metastasized medulloblastoma (MBG)-negative neuroblastoma;
- Opsclonous myoclonus syndrome with no identified primary;
- Germ cell tumours (especially when tumour marker is negative, with retroperitoneal lymphadenopathy or mediastinal primary);
- Langerhans cell histiocytosis ( multisystem);
- Relapsed disease (where data suggest the primary is FDG avid as above);
- who may undergo radiotherapy,
- where accurate biopsy is essential (e.g. heterogeneous tumours where treatment may be determined by highest grade of tumour; e.g. ganglioneuroma vs. ganglioblastoma, necrotic Wilms’ tumour);
- Definite or equivocal stage 4 disease on other imaging, whose treatment may include mutilating or life-threatening surgery, for example, parameningeal rhabdomyosarcoma and hepatoblastoma requiring liver transplant.

**Treatment related indications**

Before local therapy, scans should be considered in:

- Children who are candidates for radiotherapy (for conditions known to be FDG avid),
- Hepatoblastoma requiring liver transplant,
- Wilms’ tumour considered for bilateral renal surgery (to assist nephron sparing),
- Stage 3 neuroblastoma after initial chemotherapy (if further chemotherapy is being considered to further reduce the tumour),
- Mutilating sarcoma surgery.

Treatment response scans should be considered in any child with:

- Hodgkin’s lymphoma (as per Euro-NET protocol, for children on and off trial);
- Non-Hodgkin's lymphoma with poor response on conventional imaging;
- MIBG-negative neuroblastoma;
- Langerhans cell histiocytosis;
- Soft tissue sarcoma.

Residual mass assessment may be appropriate in:

- Hodgkin’s lymphoma,
- Some soft tissue sarcomas,
- Neuroblastoma.

**Follow-up**

Scans for follow-up are only advisable if prompt further life-saving treatment is planned in the event of relapse/progression.

**Relapse**

Scans may be considered in any child with confirmed or suspected relapse of above conditions.

**Indications for PET/computed tomography in children in neurology**

In the investigation of epilepsy, PET scanning should be considered if the child has focal epilepsy that is
potentially amenable to surgical intervention where MRI is negative or discordant with other investigations. Additional supportive evidence from PET may then justify more invasive procedures such as invasive electroencephalogram (EEG) monitoring to localize seizures with sufficient certainty to warrant surgical resection. In practice, where the clinical, EEG and structural data are all concordant, PET is likely to be unnecessary.

Judicious use of PET/CT scans may be considered in the management of patients with neurofibromatosis 1 with symptoms suggestive of malignant transformation of a plexiform or subcutaneous neurofibroma [8]. These include one or more of the following: persistent pain, rapid increase in size, change in texture or new or unexplained neurological deficit related to the lesion. Currently, there is no indication to use PET/CT to screen for malignant change in asymptomatic plexiform neurofibromas.

**Indications for PET/computed tomography in children with cardiological diseases**

PET/CT may be useful in imaging myocardial perfusion and in assessing the functional significance of anatomical abnormalities in coronary arteries or coronary flow reserve in selected cases, including:

- Kawasaki’s disease with or without anatomical evidence of coronary artery involvement.
- Children who have undergone coronary artery surgery for congenital malformations such as arterial switch operations, pulmonary valve autograft procedures or reimplantation of anomalous coronary arteries.
- Congenital coronary artery anomalies with aberrant coronary artery anatomy or course of the coronary artery where impairment of perfusion is suspected or there is potential for impaired perfusion.
- Postcardiac transplantation where coronary artery disease continues to be a major contributor to graft failure.
- PET/CT assessment of perfusion and glucose metabolism may be useful for cardiological risk assessment in patients with Duchenne’s or Becker’s muscular dystrophy and undergoing spinal surgery [9].

**Scan protocols in children**

**Scan planning and preparation**

As soon as a request has been received and the indication for the scan is agreed, the procedure should be discussed with the parents or caregivers verbally. Then a written explanation of the scan preparation and procedure should be provided. Where a child is likely to require sedation or anaesthesia, the admitting paediatric physician and/or paediatric anaesthetist should be contacted. Further information may be requested at this stage including recent blood tests or imaging results.

Sedation is a continuum and in accordance with American College of Radiology Practice Guidelines and Scottish Intercollegiate Guidelines [10,11], all paediatric patients requiring sedation for scanning, which includes patients receiving benzodiazepines orally should be monitored. This includes children who are given diazepam for suppression of FDG uptake into brown fat. Hence, scans performed with any form of sedation/anaesthesia should be performed at centres with facilities, such as personnel and equipment available immediately to manage paediatric emergency situations. It is often preferable to give a short-duration anaesthetic than to administer sedation, as sedation can be unpredictable in children. In centres performing scans using anaesthesia, the scanning room should have access to piped gases. There should be adequate recovery facilities within the scanning centre and inpatient beds should be close by for children to be admitted into and returned to. After general anaesthesia (GA), it is recommended that paediatric patients suitable for day-case anaesthesia should be admitted postoperatively to a paediatric ward for a minimum of 3h before discharge to home to ensure they have tolerated fluids/food without nausea or vomiting and have fully recovered from GA.

Sedation or anaesthesia should be administered to cover the period of the scan. Unless there are exceptional circumstances, children can be satisfactorily managed during the uptake period without the need for sedation or anaesthesia. Where sedation is administered, formulations including glucose should be avoided.

Scans in some children who do not require sedation may be performed in hospitals without direct access to paediatric services. As a guide, it is recommended that children younger than 13 years should be imaged at static sites with access to full paediatric support services. This is based on requirements for paediatric resuscitation equipment in this age group but individual assessment is required on a case-by-case basis. Children older than 13 years with special requirements, including children with developmental problems or behavioural difficulties and children with severe systemic illness will also need to be imaged at a centre with direct access to paediatric services. If intravenous (i.v.) contrast is to be used during the scanning session as part of a separate contrast-enhanced CT examination, the examination should be done in centres with access to full paediatric support services owing to the risk of contrast reaction.

Children aged 8–12 years not requiring GA or sedation or i.v. contrast could be imaged at sites without paediatric provision at the discretion of the referring paediatrician. In this case, a suitably qualified person from the paediatric referring team trained in advanced paediatric life support (APLS) should be available within the vicinity where the scan is being performed. This responsibility could be transferred to a member of a local paediatric team by the referring paediatrician if desired.
Full paediatric resuscitation equipment should be immediately available within the PET scanning area to include paediatric defibrillator, intubation equipment and resuscitation drugs. The individual trained in APLS and the resuscitation team should be aware of the exact location of the PET scan department within the hospital.

If imaging is carried out in sites without paediatric services, staff should still be experienced in the care and imaging of children including paediatric cannulation [12]. The difficulties in paediatric imaging in an environment that is not designed for imaging children should not be underestimated. A scan of good diagnostic quality relies on a cooperative child, which is more likely in a child-friendly environment where staff are imaging children on a regular basis [4]. Advice and involvement of specialists in play may be helpful in planning [5]. A sympathetic child-centred approach may render sedation unnecessary. Timing of scanning during a baby or infant’s usual sleep time during the day may also help to avoid sedation.

Imaging should be performed in paediatric sessions separate from those used by adults. There should be a separate area where girls can be sensitively questioned about the possibility of pregnancy. All staff involved in the care of children should have criminal records bureau checks and child protection training appropriate for their level of involvement [4,5,13].

Written protocols should be in place for imaging children, and the PET and CT parts of the examination should be optimized to reduce the radiation dose, including reducing the administered dose of radiotracer according to weight and the tube current according to patient size and imaging requirements [14].

Independent of the site where the scan is performed, the scan should be reported by individuals skilled in reporting paediatric scans of the type requested (oncology, neurology or cardiology).

**Oncology studies**

Before attendance, information relating to chemotherapy, radiotherapy and surgery should be obtained to ensure optimal timing of the visit to the PET facility. Children should fast for 4–6 h before scanning. Children undergoing general anaesthetic or sedation should remain nil by mouth for 6 h after an intake of solids, cow’s milk or formula milk feeds; 4 h after breast milk and 2 h after clear fluids (water or any clear fluid that you can read print through). Opaque juices, sparkling water, soup, sucked (or swallowed) sweets and gum are regarded as solids.

Consideration should be given to the administration of i.v. hydration during the uptake period with 0.9% normal saline not dextrose infusion. Children who are not being administered anaesthesia or sedation should drink water to maintain good hydration and reduce the radiation dose to the bladder. Infants that are not being administered anaesthesia or sedation should be injected as close to the next milk feed as possible. A feed may be given 30 min after tracer injection. Blood glucose should be measured before FDG injection and the doctor responsible for scan supervision should be informed if the level is more than 7 mmol/l/l in a nondiabetic patient or more than 10 mmol/l/l in a diabetic child. It is then up to the supervising doctor to decide whether it is appropriate to continue with the tracer injection. Insulin should never be administered to reduce the glucose level as this can result in a nondiagnostic scan owing to redistribution of tracer into skeletal and cardiac muscle. The child should also be weighed so that a standardized uptake value can be measured over a region of interest if required. Patients should be kept warm during the uptake period that will last 1–2 h (or longer for soft tissue tumours). Oral diazepam may be required to reduce uptake in brown fat. The use of music, DVDs, reading or electronic games may be helpful in distracting children. Electronic games should be avoided though if disease involves or is likely to involve the upper limbs. Most studies will involve scanning from below orbits to below the pelvis but in some tumour types total body scans may be appropriate, for example, Ewing’s sarcoma, MIBG-negative neuroblastoma and lymphoma with marrow involvement.

**Neurology studies**

Children should fast for 4 h before scanning. Children with epilepsy should have EEG monitoring during the uptake period. Studies involving children or young people with epilepsy should be performed in centres with paediatric neurology services, with a documented emergency management protocol for prolonged seizures. For brain oncology studies the child or young person needs to be quiet and relaxed without stimulation during the uptake period.

**Cardiology studies**

For perfusion studies involving pharmacological stress, a person skilled in paediatric resuscitation and management of arrhythmias should supervise the stress part of the examination. The child’s medication should be reviewed before attendance to determine the stress agent. For studies with FDG, children should fast for 4 h, prior to a glucose load given 1 h before the FDG part of the scan. Additional insulin may be given before FDG injection according to blood glucose in accordance with individual departmental protocols. These studies should be performed in centres with access to full paediatric support services. Should an insulin clamp be required, patients should be observed in hospital for a minimum of 6–8 h after procedure to ensure normalization of blood sugar.
Administration of radiotracer

Children should be offered local anaesthetic cream before tracer injection. Problems can be experienced with radioactive tracer sticking to a Hickmann line. Use of a Hickmann line is, however, reasonable in children, provided the line is flushed well after administration of tracer, aseptic nontouch technique is used and the site of suspected disease for assessment is away from the line. Portacaths should be accessed before attendance at the scanning centre.

The principle of As Low As Reasonably Achievable (ALARA) should always apply and the administered activity should be reduced in paediatric studies. In the experience of this group, good-quality images can be obtained by scaling the dose according to body weight using 70 kg as a reference level and the Administration of Radioactive Substances Advisory Committee diagnostic reference level of 400 MBq of 18fluorine FDG for oncology studies and 250 MBq for brain studies [15]. Administered activities as low as 35 MBq result in good diagnostic images for oncology and brain studies and therefore, no lower limit for administered activity is recommended. 13N ammonia dose should be scaled according to body weight using the diagnostic reference level of 555 MBq.

Scan acquisition

All paediatric patients should be scanned according to the most recent evidence protocols, whether routine clinical or research orientated. In accordance with the ALARA, dose-optimization procedures should be agreed, as discussed above. The tube current may be reasonably reduced to 25–35 mAs (pitch 1.5) in most children where the CT is used for attenuation correction and localization only [14,16]. CT scans acquired with imaging parameters typically used in separate ‘diagnostic’ CT examinations should be performed only if this will avoid the need for a separate CT scan. Until it is established whether there is an effect of i.v. contrast on attenuation correction and semiquantitation of PET data in children, if a diagnostic CT scan with i.v. contrast is acquired at the same scanning session, consideration should be given to acquiring a separate low-dose (5 mAs) CT scan before the injection of contrast for attenuation correction purposes. For response assessment scans where i.v. contrast may not be required, a PET–CT examination may obviate the need for a separate ‘diagnostic’ CT scan.

For brain and cardiac imaging, and where the CT is required for attenuation correcting the PET only, the tube current can be reduced to as low as 5 mAs (pitch 1.5). The minimum tube current on some cameras is higher than this and centres performing paediatric brain and cardiac imaging should ideally use a PET–CT camera that is capable of reducing the dose in accordance with the ALARA principle.

It is recommended that brain studies in children are acquired as dynamic studies or in-list mode (where available), so that frames with excessive movement can be rejected. Brain and cardiac images should be acquired in 3D. Other images should be acquired in 2 or 3D depending on patient size, according to local protocol.

Immobilization aids may assist in positioning the patient and distraction with music or story tapes can be helpful. The nappy of infants should be changed immediately before the scan to reduce the amount of tracer visualized in the nappy on the scan.

Scan interpretation

Interpretation of scans in children can be challenging. Reasons for this include the variety in the normal variation that occurs during development, including the variable distribution of FDG uptake in the brain at different ages, uptake in brown fat, thymus and lymphoid tissue in the head and neck. Paediatric conditions as discussed above may be rare conditions and experience may be built up by reporting these centrally. It is important that wherever a scan is acquired, a radiologist or nuclear physician regularly reporting paediatric PET scans interprets the scan findings. The person should also be prepared to liaise with the referring clinician directly and provide scan data in a format that can easily be shown at multidisciplinary meetings.

Radiation protection aspects

It should be stressed that siblings or friends who are children should not be brought to the PET facility where they may come into contact with injected patients. If the mother of a child to be scanned is pregnant, another member of the family should accompany the patient for the scan. On the basis of measurements taken of dose rates and models of behaviour, if normal contact is resumed in 2 h after the injection, the dose to an individual should not exceed recommended dose constraints [17]. Therefore, there is no requirement for restrictions to be placed on contact with family members after this time. The dose during the uptake period and the scan procedure received by a caregiver is unlikely to exceed the dose constraint of 3 mSv recommended by European guidance [18].

Audit and review

PET facilities should have an agreed method of audit for scan procedures, scan interpretation and patient satisfaction. The number of scans aborted where patients were unable to comply with the scan procedure and the number of nondiagnostic scans should be reviewed regularly. Cases where patient motion required repeat CT scans and additional radiation exposure should also be monitored. It is recommended that these data are collected as part of the national audit of PET in the UK being developed by the UK PET-CT Advisory Board.
Service delivery
It is recognized that a balance needs to be achieved between providing local access for children and their families to PET-CT and the establishment of centres of excellence in paediatric imaging. Given the complexity of PET/CT scanning in children, and the need to develop and maintain expertise in the reporting of sometimes rare conditions in children, it is recommended that specialist regional centres are established in the UK. Studies that require direct access to paediatric services as outlined above should be carried out at these centres. Other scans could be performed at sites more local to the patient including mobile scanners but should be performed according to protocols developed at the regional centre with reporting carried out at the regional centre. Links should be forged between the regional centre and referring clinicians in paediatrics.

Summary
1. It is reasonable to scan children with conditions where there is good evidence for the use of PET in adults.
2. In other conditions the use of PET needs to be assessed on a case-by-case basis where it may be useful for individual management.
3. Liaison with parents/caregivers in advance of the scan is required.
4. Any examination requiring anaesthesia or sedation should be carried out in centres with personnel and equipment immediately available to manage paediatric emergency situations.
5. Neurology and cardiology examinations for children requiring monitoring need to be carried out in centres with paediatric services.
6. Examinations, where a CT scan is performed with i.v. contrast at the same scanning session as the PET–CT scan, should be carried out in centres with paediatric services.
7. Patients under the age of 13 years should ideally be scanned in specialist regional PET units with experience in scanning children and who have direct access to paediatric inpatient services. Children older than this with developmental problems and children with severe systemic illness will also need to be scanned in specialist units.
8. Children aged between 8 and 12 years could be scanned in sites without paediatric services, however, at the discretion of the referring paediatrician provided an individual trained in APLS is in the vicinity and the paediatric resuscitation kit is available within the scanning facility.
9. Studies should always be performed by staff who scan children on a regular basis with experience in paediatric cannulation. All staff should be criminal records bureau checked and have appropriate child protection training.
10. PET and CT protocols should be optimized in accordance with the ALARA principle.
11. Scans should be interpreted by nuclear physicians or radiologists who report regularly the type of paediatric study being performed.
12. Regular audit and review of scan procedure, quality and interpretation are mandatory.
13. Given the complexity of requirements for PET/CT scanning in children, and the need to develop and maintain expertise in the reporting of sometimes rare conditions in children, specialist regional centres should be established in the UK.
14. Scans could be performed at sites more local to the patient in circumstances outlined above but according to protocols developed at the regional centre with reporting carried out at the regional centre.

Acknowledgements
The authors acknowledge significant contributions to the document from the following: Caroline Davies, Consultant Anaesthetist, Guy’s and St Thomas’s NHS Trust, Rosalie E Ferrier, Consultant Neurologist, Guy’s and St Thomas’s NHS Trust, Elaine Hughes, Consultant Paediatric Neurologist, Kings College Hospital and Evelina Childrens Hospital, Ruth Williams, Consultant Paediatric Neurologist, Evelina Childrens Hospital and Robert Yates, Consultant Paediatric Cardiologist, Great Ormond Street Hospital for Sick Children.

References

Copyright © Lippincott Williams & Wilkins. Unauthorized reproduction of this article is prohibited.