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Review

Role of FDG PET in the management of childhood lymphomas – case proven or is the jury still out?

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ABSTRACT

Positron emission tomography (PET) is a novel non invasive functional imaging modality that is increasingly used for the primary staging of lymphomas and assessment of therapeutic response. This review evaluates the published reports of its use in childhood lymphomas, particularly in the primary staging, response assessment and monitoring after completion of treatment. Specific attention is focused on the clinical circumstances in which FDG PET is most likely to have an impact on management and some indications for its use in childhood lymphomas are suggested.

1. Introduction

Accurate disease staging in childhood lymphomas is of critical importance in the stratification of patients into prognostic risk groups and thereby determining the intensity of treatment necessary to achieve optimal response and overall cure. Positron emission tomography (PET) with 2 fluoro– 2 deoxy (18 fluorine)- D-glucose (^{18}FDG) is a distinctive form of non invasive diagnostic imaging that is now considered an invaluable adjunct to conventional imaging modalities (CIM) for staging as well as assessment of response to treatment in adults with Hodgkin's (HL) and non Hodgkin's lymphoma (NHL). ^{18}FDG PET is a functional whole body imaging technique that is more sensitive and specific than conventional CIM as it exploits a distinctive biochemical feature of cancerous cells – increased glucose uptake and elevated glycolyis. This is due to the amplification of glucose transporter proteins on the tumour cell surface and increased activity of multiple intracellular enzymes.[1–3]

In contrast to the extensive data in adults, there have been only a few studies evaluating the role of ^{18}FDG PET in the management of childhood lymphomas. This review article attempts to evaluate the role of PET in the disease staging of childhood lymphomas including its significance in directing

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treatment according to risk stratification and tailoring therapy according to treatment response. It also examines the role of ^{18}FDG PET in the diagnosis of residual disease and in the detection of disease recurrence.

2. Limitations of conventional imaging including gallium scintigraphy

2.1. Conventional cross sectional imaging

Modern conventional imaging modalities (CIM) such as ultrasonography, computed tomography (CT) and magnetic resonance imaging (MRI) are excellent at delineating the extent of disease involvement in childhood lymphomas and have completely supplanted the need for a staging laparotomy. Although pivotal in the staging of lymphomas, their sensitivity in detecting small volume disease including infiltrative disease at extra-nodal sites such as bone marrow or liver is poor. Another major limitation of conventional CIM is its inability to detect tumour involvement in normal sized lymph nodes or discriminate between fibrous scar and necrotic tissue from active tumour in post treatment residual masses.[2,4–6] The Ann Arbor system for HL[7] and the Murphy staging for NHL[8] incorporate CT and/or MRI as standard investigational modalities for disease staging. Clearly there is a need for a more sensitive (the probability that a person having a disease will be correctly identified by a clinical test; i.e. calculated as the number of true positive results divided by the sum of the numbers of true positive and negative results) and specific (the proportion of patients without a disease who are correctly identified by a test; i.e. the number of true negative results divided by the sum of the numbers of true negative plus false positive results) diagnostic tool for accurate disease staging.

2.2. Gallium scintigraphy

The gallium (Ga-67) scan was the standard functional imaging technique in the assessment of response in lymphomas. However, it has many limitations, including the fact that its sensitivity for staging lymphoma varies with localisation, size and cell type[9–12] and its comparative ineffectiveness in evaluating disease in the abdomen due to physiological bowel uptake. Moreover, compared to gallium scans, FDG PET detects more disease sites[12,13] and more accurately defines active disease.[14] In addition, the effective dose of absorbed radiation from a gallium scan is much greater than FDG PET and the majority of other nuclear medicine scans (Table 1). Consequently, gallium scanning has fallen out of favour as a functional imaging modality in the management of paediatric lymphomas.

2.3. Review of evidence

The review of evidence on which this report is based consists largely of the review of published studies on the use of FDG PET in childhood and adult lymphomas. PubMed and Medline searches were done to ascertain relevant references on the use of PET in lymphomas between 2001 and 2007. Attention is mainly focused on clinical situations where FDG PET is expected to have some bearing on therapy or management.

3. Role of ^{18}FDG PET

3.1. Childhood Hodgkin's Lymphoma (HL) at diagnosis

3.1.1. Assessment at diagnosis

Though there are several adult studies[15–24] that have confirmed the importance of FDG PET as a diagnostic tool in the staging of HL, comparable studies of its use in childhood HL are limited. Nevertheless, in the few studies conducted, FDG PET provided important information that was both, sensitive and specific. Its use during the initial diagnostic evaluation was shown to change disease stage in 10 – 23% patients.[25,30,31] In the seminal study by Montavers and colleagues,[26] FDG PET uncovered more disease sites than CIM and resulted in the upstaging of disease in >50% of patients (five out of seven children with HL) although only one patient had treatment modified on the basis of FDG PET. Hermann and colleagues[27] compared whole body FDG PET with CT in the initial staging of 18 children with HL. PET resulted in a change in disease stage in five patients (higher stage – three; lower stage – two). In four of these patients, treatment was modified on the basis of FDG PET. Similarly, in another retrospective study,[28] FDG PET was discordant with conventional imaging in three of 11 patients with HL and altered clinical stage and patient management in two (one patient was down-staged from stage IV to II while the second patient was upstaged from stage III to Stage IV). In their retrospective study, the GPOH group have also reported significant discordance between CIM and FDG PET imaging.[29] There was a discrepancy rate of 8% per region (nine separate regions were evaluated per patient) that affected 54% of their patients ($n = 67$). The results of a more recent report by Miller and colleagues[30] confirm that the use of FDG PET during diagnostic staging was associated with change in approximately one out of three children with HL and NHL. The latter study was a combined FDG PET-CT study compared to the two earlier reports[28,29] in which PET and CT

Table 1 – Effective dose for different radiopharmaceuticals in children (mSv)

Radiopharmaceutical	Administered Activity (MBq/kg)	1 year	5 year	10 year	15 year	Adult
99m Tc MDP (Bone scan)	11.4	3.1	3.0	4.0	4.4	4.6
99m Tc DMSA (Renal scan)	5.7	2.1	2.3	2.7	3.5	3.5
67Ga (Gallium scan)	5.7	37	36	37	41	40
FDG (PET scan)	4.5	4.3	4.3	5.2	6.2	6.0

were performed as separate investigations. However, no significant disparity has been shown between contrast augmented FDG PET/CT and combined evaluation of separately acquired PET and CT imaging in patients with lymphoma.[21] The discordance between PET and CT was highest in the extra-nodal sites. Kabickova and colleagues[31] reported that in children and adolescents with HL ($n = 55$), the sensitivity of FDG PET and CIM for pre-treatment staging was 96.5% and 87.5% respectively and specificity was 100% and 60% respectively. FDG PET changed the stage in 15% (upstaged - seven; down staged - two) of patients (9/55).

Data from Furth and colleagues[32] confirm the excellent value of integrated PET-CT in the initial staging of children with HL. Although CIM and FDG PET were equally accurate in identifying HL involved sites (90% and 92% respectively) there was a lack of sensitivity of either modality in the infra-diaphragmatic and extra nodal sites. With image fusion, the specificity and sensitivity was increased to 95% and 99% respectively with an accuracy rate of 98%. Although most of the published studies above show relatively poor concordance between FDG PET and CIM in the staging of children with HL, two recent reports show complete concordance in the diagnostic staging of children and adolescents.[33,34] Moreover, a report by Hernandez-Pampaloni and colleagues[35] has sounded a note of caution as FDG PET incorrectly under staged two children with lymphoma (HL-1 & NHL-1).

In the detection of extra-nodal involvement, especially bone marrow involvement, reports from adult studies indicate that FGD PET is superior not only to CIM, but also to bone marrow trephine biopsy.[16,36] This also appears to be true in children as the most common sites of discordance between FDG PET and CIM at extra-nodal sites were in the spleen, bone and bone marrow.[26,27,31,32] From these studies it seems that FDG PET improves the detection of disease in the bone marrow compared to an unguided marrow biopsy.

See Table 2A and B showing the concordance rate between FDG PET and CIM in the diagnostic staging of HL.

3.2. *Monitoring of response during treatment*

3.2.1. *Early response assessment*

The guiding principle for patients who show poor or sub-optimal response to treatment has been to intensify therapy. However, assessment of clinical response in children and adolescents with HL is particularly difficult as radiological evidence of response i.e. regression in the size of lymphadenopathy in the involved regions, especially within the mediastinum, may be slow and protracted. The only verifiable measure of tumour or disease status is histopathological examination of nodes. FDG PET has been used as a surrogate marker of tumour response in adult patients with HL both during and after treatment. Changes in FDG uptake occur soon after the initiation of therapy and precede changes in tumour volume.[37,38] In adults, FDG PET has usually been performed after one to two cycles of chemotherapy or at mid treatment[39–41] to assess tumour response and tailor treatment accordingly. Published studies of the use of FDG PET as a strategy for early response evaluation in children with HL are limited. Montravers and colleagues [26] examined FDG PET results in three patients performed during treatment (one patient at mid treatment and in two patients after the end of chemotherapy but prior to radiotherapy) and showed that incomplete resolution at previously known sites were indicative of persistent viable disease in two children. Minson and colleagues[34] evaluated 24 newly diagnosed adolescent patients with HL at diagnosis and after two cycles of OEPA (vincristine, etoposide, prednisolone and doxorubicin) chemotherapy. HL treatment was based on risk stratification at diagnosis and was response adapted according to FDG PET result after two cycles of OEPA. Patients who had a good early response (complete remission or partial remission and FDG PET negative) after two cycles of OEPA did not receive radiotherapy. The results of early response assessment showed that 11/24 patients had a negative FDG PET and all 11 avoided radiotherapy. All but one were in clinical remission at a maximum follow up of 20 months. In contrast, all 24 patients had residual disease on CIM at this stage (partial remission). Miller and colleagues[30] have also shown an interim FDG PET scan to be an excellent prognostic tool in children with both HL ($n = 24$) and NHL ($n = 7$). Of the 20 patients who had a negative FDG PET scan after one or two courses of chemotherapy, nineteen were disease free for an average period of 14.5 months [range, 1–40 months] compared to progression of disease in the three patients who all had an interim positive PET scan. The negative predictive value (the proportion of patients with a negative scan who are free of disease) of an early negative PET in this report was 96%.

3.2.2. *Re-staging after completion of therapy*

A residual mass at the end of treatment is frequent in children with HL and there are no specific CT or MRI criteria that permit differentiation between viable and necrotic or fibrous scar tissue. Being a functional imaging modality FDG PET can provide unique information on the tissue characteristics of residual masses. The utility of FDG PET in the restaging of HL in adults after treatment has been confirmed in many recent publications.[2,42–45] Similar outcomes have also been shown in paediatric studies. The results of Montavers and colleagues,[26] confirm the usefulness of FDG PET as the imaging technique of choice for determining the nature of post treatment residual masses in childhood HL. In the presence of a post therapy residual mass, a negative FDG PET was a reliable indicator of complete clinical remission [13/14; 93% negative predictive value]. Edeline and colleagues[46] prospectively evaluated 16 patients with HL; 14 had CT evidence of residual masses. Two of five patients with a positive FDG PET scan had biopsy proven residual disease (both had residual mediastinal mass by CT). Of the remaining three patients who had positive FDG PET scans, two did not have CT evidence of residual disease at the site of FDG positivity and all three remained in first remission (range, 27 – 46 months) after completion of treatment. All 11 patients with a negative FDG PET have remained in complete remission (range, 28 – 60 months) after end of treatment. The report by Depas and colleagues[28] also confirms the importance of a negative PET at the end of treatment. They used FDG PET for disease evaluation at the end of treatment in children with both HL and NHL. In 15 of 16 patients, FDG PET was true negative while it was falsely positive in only one patient. The specificity was 94% for PET compared to 54% for CIM. Hernandez-Pampaloni and colleagues[35]

Table 2 – FDG PET in the staging of childhood lymphomas

Study	Imaging	Concordance	Upstaged by PET	Downstaged by PET	Management change/Outcome
(A) Hodgkin's lymphoma					
Montravers et al. 2002 [HL = 7]	PET versus CIM	2	5	0	Treatment modified in 1 patient
Wickmann et al. 2003 [HL -67]	PET versus CIM	–	–	–	8% discordance per region (9 regions) affecting 54% of patients
Kabickova et al. 2005 [HL-55]	PET versus CIM	851/887 regions	7 patients	2 patients	PET changed stage in 15% of patients. FDG PET was falsely positive in a further 2 patients
Furth et al. 2006 [HL-33]	PET versus CIM	737/852 regions	–	–	PET was superior to CIM as as only 5 patients were incorrectly staged versus 7 patients with CIM
Minson et al. 2007 [HL-24]	PET versus CIM	100% concordance	0	0	FDG PET did not result in any change in stage in all 24 patients
Mody et al. 2007 [HL = 9]	PET versus CIM	100% concordance	0	0	FDG PET and CT were concordant in all regions in all 9 patients
(B) Combined group of Hodgkin's and non Hodgkin's lymphoma patients					
Hermann et al. 2004 [HL-18, NHL-7]	PET versus CIM	608/652 regions	16% of patients	8% patients	Overall 20% of patients had treatment modified. 4 patients with HL had alteration in therapy
Depas et al. 2005 [HL-14; NHL-5]	PET versus CIM	16/19 patients	1 [HL]	1 [HL]	PET discordant in 3 patients with HL. PET was also false negative in 1 patient with HL
Herndez-Pampaloni et al. 2006[a] [HL + NHL-7]	PET versus CIM	–	–	2	2 out of 7 patients were under staged by PET [HL-1; NHL-1]
Miller et al. 2006[a] [HL-24; NHL-7]	PET versus CIM	21 patients [67.6%]	7/31 patients	3/31 patients	FDG PET changed disease stage in 1 out of 3 patients with HL & NHL
(C) Non-Hodgkin's lymphoma					
Amthauer et al. 2005 [NHL-10]	PET versus CIM	3/6 [17 out of 20 regions were concordant]	1	0	Upstaging & intensified treatment in 1 patient
Mody et al. 2007 [NHL-6]	PET versus CIM	PET, CT and Gallium concordant in 4 patients; PET and CT concordant in 1 patient	0	–	FDG PET falsely negative in 1 patient

a Includes children and young adult patients.

reported in their retrospective evaluation of ten patients with HL and NHL, that a negative FDG PET at the end of treatment was consistent with complete remission (9 /12 were true negative scans while three were true positive scans).

3.3. *Surveillance imaging during follow up*

Children who have completed treatment for HL are commonly followed up for the first 5 years with regular surveillance imaging to monitor for relapse of disease. Residual imaging abnormalities are common in children who have completed treatment for HL, and CT surveillance during follow up to assess disease status is unsatisfactory, as these residual masses persist for a prolonged period.[28,30,47] Residual masses that are not FDG avid usually represent a non viable tumour.[26] Although FDG PET surveillance in their cohort was obtained during or after therapy or for evaluation of residual masses, there was only one false negative PET result out of 18 negative FDG PET scans (26). In fact, all 11 patients who had negative PET results ($n = 15$ PET results) obtained between 3 – 12 months after completion of therapy have remained in continuous clinical remission. Similar findings have also been reported in three other studies that evaluated residual masses after therapy for childhood HL.[30,33,46]

However, the usefulness of FDG PET as a surveillance tool to detect relapse in asymptomatic patients during follow up is compromised by the problem of false positive results as highlighted by Meany and colleagues.[48] In their retrospective study, 23 patients who had completed treatment for HL were followed up with 3 monthly FDG PET scans for a period of 1 to 42 months. 12 patients who had consistently negative PET scans during this period remained disease free without experiencing a relapse. Of the 11 patients who developed a positive PET scan within 6–9 months after end of treatment, only two patients (one patient actually had clinical symptoms suggestive of relapse - fever, night sweats and bone pain) subsequently developed biopsy proven recurrent HL. Levine and colleagues[49] have also shown that FDG PET has a much lower specificity in detecting relapse in asymptomatic patients during routine follow up. Of the 156 surveillance FDG PET scans obtained in 34 children during follow after completion of therapy, only three scans ($n = 2$ patients) were true positives while 25 were falsely positive. The remaining 128 PET scans were true negatives. The positive predictive value of PET (the probability of a positive PET scan to predict persistent disease or future relapse) was only 11%. In a more recent publication that included patients with HL and NHL,[35] FDG PET was again shown to be less specific in detecting relapses during regular follow up. Of the nine PET scans performed during follow up, there were three positive scans of which two were false positives. Similarly, Wickmann and colleagues[29] and Rhodes and colleagues [47] have also shown that the positive predictive value of PET surveillance during follow up in asymptomatic patients was only 25% and 53% respectively.

In contrast, when FDG PET has been performed during follow up for suspected relapse, it has been more accurate. In the report by Mody and colleagues,[33] all three FDG PET ($n = 3$ patients) examinations, done when relapse was strongly suspected, were true positives; all confirmed by biopsy. Concurrent gallium scans were negative in two of the three patients at relapse.

3.4. *Histology and FDG uptake*

It has been suggested that the different histological subtypes of HL show significantly dissimilar levels of FDG uptake; nodular lymphocyte predominant HL and mixed cellularity HL have been reported to have the lowest and highest uptake of FDG respectively.[50] This observation has not been confirmed in other studies.[51] To date, no similar observations have been reported in childhood HL but in the context of mandatory diagnostic biopsy, this is of little practical importance.

3.5. *Childhood Non-Hodgkin's lymphoma*

3.5.1. *Diagnostic staging*

Routine staging of childhood NHL involves the use of CT, MRI, ultrasound and, occasionally, whole body isotope bone technetium-99m methylenediphosphonate (Tc-99m MDP) scintigraphy, while in contrast, the use of FDG PET for staging in childhood non-Hodgkin's lymphomas has only been studied in recent years. As in childhood HL, FDG PET has not always been concordant with CIM and in some studies has led to upstaging of disease but, unlike in childhood HL, this upstaging has not led to substantial treatment alterations (Table 2B and C). This seems to be in direct contrast to the adult studies[52–55] where FDG PET significantly increased disease stage when compared to CIM. In the study by Hermann and colleagues,[27] the use of PET FDG in seven children with NHL resulted in the upstaging of one patient (III → IV). The report of Amthauer and colleagues[56] confirms that the diagnostic utility of FDG PET in children is less than in adults. In their small series of six patients, though additional nodal lesions were detected by FDG PET in three children, this resulted in only one patient being upstaged who subsequently required an intensification of chemotherapy treatment. In another report,[28] FDG PET did not alter the diagnostic stage in their cohort of children with NHL as there was no discordance between CIM and FDG PET. In contrast, the report by Miller and colleagues[30] showed a concordance rate between CIM and FDG PET was only 67% in their mixed group of patients with HL ($n = 24$) and NHL ($n = 7$) and FDG PET upstaged seven (22.6%) out of the 31 patients and down staged a further three patients. There are also reports that suggest FDG PET in childhood NHL may be discordantly false negative when compared to CIM.[33,35]

FDG PET is therefore currently not a standard diagnostic tool in the staging of childhood NHL as it appears to detect additional disease in a small proportion of patients and any alteration of stage has generally not resulted in any modification of treatment. There is a need for larger prospective studies to demonstrate more clearly the observation in these very small series.

3.6. *Response evaluation during treatment*

Studies in adult patients with NHL have shown that an interim FDG PET response after one to two cycles or at mid-treatment

is a prognostic factor[37,40,57–59] and is a valuable procedure in response adapted treatment. In children, there are very few published studies that have explored the role of interim FDG PET. Two of the five published paediatric studies included a mixed population of children with HL and NHL.[28,30] Edeline and colleagues[46] reported that an interim FDG PET obtained after induction chemotherapy (mean - 17.5 days after the last course of chemotherapy) in children with NHL ($n = 10$) was non informative with regard to predicting outcome. Of the ten patients who had an interim PET evaluation, five had negative PET scans; four remained in continuous remission between 45 – 62 months after the FDG PET examination while one patient relapsed 9 months after completing therapy. Of the remaining five patients who had a positive FDG PET scan (all had residual mediastinal disease with uptake in the mediastinal masses), four were false positive scans with histologically negative mediastinal biopsies and they all remained in continuous complete remission 27 – 35 months after the interim PET scan. The fifth patient had a histologically proven true positive PET scan. Depas and colleagues[28] evaluated 19 patients (HL - 11; NHL - 8) during treatment to evaluate early response to therapy. FDG PET was performed at varying intervals during therapy. They observed that early PET scan results were misleading in predicting outcome in three patients with NHL (all three were FDG PET negative) as they either relapsed ($n = 2$) or had histologically proven residual disease. The report by Miller and colleagues[30] suggests that interim FDG PET during therapy is an excellent prognostic indicator for predicting clinical outcome although their patient groups comprised children with HL and NHL (see early response assessment in HL). The findings of Amthauer and colleagues[56] also support the role of interim PET during treatment. In five patients showing unclear residual masses on CIM during therapy, FDG-PET indicated viable residual tumour in one patient. This patient relapsed during follow-up while the four FDG-PET negative patients did not. Similarly, Mody and colleagues[33] reported that none of the four patients with a negative PET scan after two cycles of chemotherapy experienced a relapse and have remained in continuous remission 4–9 years after completion of treatment.

3.7. *Restaging in NHL after completion of treatment*

The few reports published on the use of FDG PET in childhood NHL suggest that the most appropriate indication for FDG PET may be in post treatment restaging.[28,33] As with HL, FDG PET appears to be more accurate than either CT or MRI in evaluating the nature of post treatment residual masses, the absence of FDG uptake in a residual mass appears to be predictive of remission whereas increased uptake indicates refractory or residual viable tumour. Depas and colleagues[28] reported that the specificity of FDG PET in the detection of viable tumour in this setting was superior to CT. Of the eight children in whom FDG PET was performed after completion of therapy, CT was falsely positive in four (50%). No patient had a false positive PET scan. Similarly, in the report by Amthauer and colleagues,[56] FDG-PET at the end of therapy was positive in one out of five patients and this patient subsequently developed disease progression. However, another report[33] questions this conclusion as FDG PET was less accurate in the detection of residual disease at the completion of treatment. In this study; FDG PET, CT and gallium scans were done approximately 4–8 weeks after the last cycle of chemotherapy. Two patients who had a negative FDG PET scan relapsed within 12 months after completion of treatment.

3.8. *Surveillance imaging during follow up or at time of suspected relapse*

Most NHL relapses are identified as result of investigations of overt symptoms. The effectiveness of FDG PET during post treatment surveillance in asymptomatic patients in CR is arguable and unproven. This is exemplified in the report by Rhodes and colleagues[47] where the use of FDG PET was effective in excluding relapse rather than in positively identifying recurrent disease. In a group of 41 patients comprising NHL ($n = 17$) and HL ($n = 24$), the negative predictive value of PET-CT was 99.3% (one relapse out of 155 negative PET-CT scans) compared to a positive predictive value of 53% (18 relapses out of 34 positive PT-CT scans). Similar results have also been reported in two other studies[28,35] where false positive FDG PET results have incorrectly suggested relapse in asymptomatic patients during routine follow up. Nevertheless, it remains an extremely effective method in identifying relapse when it is clinically suspected.[33]

3.9. *Histology and FDG uptake*

FDG PET has been used with some success in adults to differentiate between indolent and aggressive non Hodgkin's lymphoma and also to confirm the clinical suspicion of transformation from indolent to aggressive disease with some success. This has been based on the intensity of FDG uptake which has been shown to be lower in patients with low grade NHL compared to high grade tumours.[52,60] Up till now, there are no comparable data in childhood NHL.

3.10. *Preparation, distribution and radiation dosimetry*

18 Fluorodeoxyglucose (18 FDG) is a glucose analogue that has been labelled with a transitory positron emitter 18-fluorine (18F). The measured uptake of glucose labelled with the positron emitting radionuclide 18-fluorine is proportional to the degree of cellular metabolism of viable tumour cells.

An optimal PET scan requires the patient to lie quietly for the approximately 1 hour uptake phase after administration of FDG and prior to imaging. During this uptake phase, movement can result in muscular uptake unrelated to tumour activity. Administration of a sedative agent or muscle relaxant, such as diazepam, can facilitate muscle relaxation and reduce FDG muscle uptake. Brown fat uptake can be reduced with careful attention to ambient temperature control and in some cases with the use of propranolol, which is thought to alter the adrenergic input to brown fat which is richly innervated by the sympathetic nervous system.[61,62]

The policies governing sedation or anaesthesia for children undergoing PET vary between institutions. If required, sedation should be managed by experienced personnel who

can monitor the patient closely throughout the procedure. Patients should be fasted for at least 4 hours prior to the FDG injection. Blood glucose level should not exceed 11 mmol/l at the time of the injection.

The administered activity of FDG and CT acquisition parameters will vary according to institutional preference and manufacturer specifications. The usual administered activity of FDG is 5–6 MBq/kg body weight. In a heavier child, this is often capped at 80% of the maximum standard adult administered activity (i.e. approximately 360 MBq).

Imaging should begin 60 minutes after injection. A low dose CT scan is acquired in <1 minute. If lower FDG activities are administered, longer acquisitions of 4–5 minutes per bed position will result in acceptable image quality whilst maintaining a total scanning period of approximately 30 minutes.

Whole body acquisitions sampling from skull base to the mid thigh are usually recommended. If pelvic disease is suspected, the preferred scanning direction is caudal to cranial to minimise interference by the filling bladder and discordance in size between PET and CT. Serial studies to evaluate therapeutic response should be done in exactly the same way, at the same institution, on the same type of camera, and using the same administered activity, imaging times, acquisition parameters and reconstruction parameters.[63]

Since administered activity of FDG is based upon body weight, the effective dose from an FDG PET scan is similar across all age groups. The absorbed dose from FDG PET is comparable to other investigations utilising ionising radiation, including nuclear medicine and conventional radiology imaging modalities.

3.11. *Interpretation of PET scans*

Absolute quantification of FDG uptake is possible utilising Patlak analysis[64]; however, this is a demanding technique suitable only in the research environment. The Standard Uptake Value (SUV) is defined as the tissue concentration of tracer as measured by a PET scanner divided by the activity divided by the body weight. The SUV is subject to many influences and can be affected by factors such as body composition and habitus, which can easily change during a course of therapy. Length of uptake period, plasma glucose, recovery coefficient and partial volume effects also need to be normalised in order to make the SUV meaningful. Visual judgment alone appears to be satisfactory for deciding whether the FDG PET scan is positive or negative at diagnosis, response assessment and at the end of treatment. The general definition of an abnormal scan by visual estimation as focal or diffuse uptake higher than the background uptake in an area incompatible with normal anatomy/physiology is appropriate in most situations.

Exceptions to the above are:

1. Mild diffusely increased FDG uptake at a site of moderately sized or large residual masses, regardless of their location with intensity lower than or equal to the mediastinal blood pool structures should be considered negative.
2. Clearly increased focal or multi-focal bone marrow uptake should be considered as lymphomatous infiltration.

3.12. *Misleading FDG PET interpretations*

It is important to realise that FDG PET evidence is not always incontrovertible and there are some specific clinical situations which may give rise to false positive or false negative scans.

3.12.1. *False positive FDG PET scans*

[1] Thymic hyperplasia or rebound is common after completion of therapy and can give rise to a false positive scan.[65,66] CIM, particularly MRI, can easily differentiate thymic rebound from recurrent HL.
[2] Bone marrow activation: Use of colony stimulating factors such as granulocyte colony stimulating factor (G-CSF) especially after myelo-suppressive chemotherapy can lead to increased FDG uptake in the spine, spleen, pelvis and long bones.[67,68] This increased uptake will subside after stopping GCSF treatment but may still be around for up to 4 weeks after G-CSF treatment.[69]
[3] Infections and inflammatory conditions: Increased FDG uptake may be seen in benign conditions such as infections such as infectious mononucleosis or tuberculosis and granulomatous disease such as sarcoidosis.[70,71]
[4] Brown fat: Increased physiological FDG uptake in the brown fat in the neck, intercostal, para-aortic and perinephric regions can lead to false positive PET results.[66,72] This is because brown fat is metabolically active and expresses a mitochondrial uncoupling protein that stimulates the anaerobic pathway of glucose metabolism.
[5] Radiation effect: Radiotherapy can result in an increased FDG uptake and this can last for a few months after treatment. It is therefore recommended that FDG PET scans be performed at least 12 weeks after radiotherapy.[67,73]

3.12.2. *False negative FDG PET scans*

1] Small lesions: Very small lesions or nodules (0.5 – 1 cm) may be undetected as these are below the resolution of the PET scanner.
2] Hyperglycaemia may result in a false negative scan as it may affect FDG uptake within the tumour.

3.13. *Timing of FDG PET scans*

In the animal model, histological post-therapy inflammatory changes may be observed in lymphoma for at least 2–3 months after radiation therapy and for up to 2 weeks after chemotherapy.[42,74,75] These changes can confound the interpretation of PET scans, making it difficult to distinguish with confidence inflammatory response from viable residual tumour.

The optimal interval from completion of therapy to imaging with FDG-PET is not precisely defined. However, the

Consensus of the Imaging Subcommittee of the International Harmonisation Project in Lymphoma (IHPL) recommended that PET should not be performed before at least 3 weeks after chemotherapy. Although data on treatment interval after the completion of radiotherapy are less clear, the IHP consensus recommended an interval of between 8–12 weeks after completion of radiotherapy and PET imaging.[76] If PET is obtained during a course of therapy, it should be performed as close as possible (i.e. within 4 days) to the subsequent cycle; for example on days 17–21 of a 21-day cycle or days 10–14 of a 14-day cycle.

3.14. *Standardisation of PET and CT parameters*

Recommendations related to standardisation of PET imaging parameters such as patient preparation and image acquisition were recently addressed by Shankar and colleagues.[63] These recommended parameters have generally been accepted by the IHPL Imaging Subcommittee.[76] There is limited discussion on issues specific to childhood PET. Hybrid PET-CT scanners use the CT portion of the examination for attenuation correction and anatomical localisation of lesions identified on PET. CT protocols and availability of resources that facilitate the application of diagnostic quality CT including the use of intravenous and oral contrast especially, for staging vary considerably between institutions. However, low dose CT acquisitions minimise the complexity of the procedure and also improve tolerance of the study by the children, and are generally acceptable for the requirements of attenuation correction and lesion localisation in PET.

3.15. *Integration of FDG PET in radiation treatment planning*

As FDG PET-CT is more accurate than CIM in the disease staging in of HL, it will also be more precise in defining the involved regions that require being irradiated. Additionally, the incorporation of FDG PET-CT in radiation treatment planning may allow for reduction in treatment dose and target treatment volume based on response to induction chemotherapy. FDG PET-CT data are gradually being incorporated in radiotherapy planning for adults with HL in many centres.[77,78] This will require pre–treatment FDG PET/CT imaging to be acquired with the patient in the treatment position (i.e. in the same position as the position that will be later used during radiotherapy treatment and on a similar flat couch top) with the use of appropriate immobilisation devices and markers visible in the planning image. It must be emphasised that FDG PET-CT based target volume definitions must be matched up with CT based target volumes to ensure that the targeted radiation fields are clinically appropriate. When used for radiotherapy planning, FDG PET-CT results in larger involved field treatment volumes compared to conventional CT planning.[78] This is because with FDG PET/CT, patients are usually upstaged and this invariably results in larger treatment volumes when applied to radiotherapy planning under prevailing guidelines. Prospective clinical trials will be required to validate the customising of radiotherapy fields using FDG PET-CT imaging before this can be accepted as the benchmark for treatment planning in childhood HL.

4. Summary and conclusions

The application of FDG PET in patients with HL and NHL continues to expand world-wide and its role in the management of childhood lymphomas is gradually gaining acceptance. In HL, PET is currently utilised for pretreatment staging, response assessment after completion of therapy and, to a lesser extent, early response assessment during treatment. In the pretreatment staging of HL in children and adolescents, while it is improbable that FDG PET will replace CIM, it does provide information complementary to CIM, potentially resulting in a modification of disease stage (usually upstaging). Although FDG PET is recognised to be advantageous in the primary staging of adult NHL,[79–81] this has not been demonstrated in childhood NHL. This may be because the majority of children present with advanced disease (stages III or IV) which is easily detectable by CIM. FDG PET appears to have a higher level of sensitivity than MRI in the detection of bone marrow infiltration.

The role of PET for treatment response monitoring is still evolving but may prove to have a potentially important impact on patient management and outcome. In adults with HL, FDG PET appears to be a reliable method of assessing response to treatment and predicting outcome and this strategy is now a component of a number of childhood HL trials designed to minimise treatment burden. The ongoing major European study in childhood and adolescent HL [Euronet PHL C1 trial] is evaluating the role of interim PET in determining the need for involved field radiotherapy in patients who have a good early response to induction chemotherapy (i.e. patients who are in complete remission or in partial remission but PET negative). The clearest role for FDG PET is in the reassessment of patients who have completed treatment for HL. FDG PET is more accurate than CIM in this setting, although a positive PET does not necessarily equate with residual active disease.

Early response assessment to chemotherapy with an interim PET is now routine in the management of adults with NHL; this cannot be regarded as standard practice in children. In childhood mediastinal T-lymphoblastic NHL there is a need to identify useful early prognostic factors and FDG PET may be one. It is therefore important to conduct prospective multi-centre international clinical trials in the use of early PET response to answer some very important questions – What is the optimal time for an interim PET during NHL treatment? Should children with poor early PET response be considered for intensification of therapy? Does NHL histology affect PET response? Without well designed clinical trials in children, it will be difficult to develop new risk adapted treatment strategies for children with NHL.

In both HL and NHL, the role of PET for post-therapy surveillance in asymptomatic children without clinical or radiographic evidence of disease remains controversial, primarily because of the potential for false-positive findings, which will result in increased cost due to re-investigation and emotional distress.

It is clear that the sensitivity and specificity of FDG PET interpretations will be improved with co-relation with morphology based CIM especially as PET is limited by its lack of anatomic detail and additionally, where physiological varia-

Table 3 – Role of FDG PET in the management of childhood lymphomas

Validated evidence
In HL
1. FDG PET is a useful diagnostic tool in the staging
2. It is complimentary to conventional cross sectional imaging
3. Change in staging and treatment modification are justified as a result of FDG PET
4. The nature of the residual tissue at the end of therapy is predicted by FDG PET

Probable indications
1. In the staging of childhood NHL
2. To provide better definition/delineation of radiation fields
3. For the detection of bone marrow disease in HL

Unsettled questions
1. Detection of extra-nodal disease such as renal and bone infiltration
2. Use for response assessment in childhood NHL
3. Routine surveillance imaging for the detection of relapse in childhood lymphomas during follow up

tions of FDG uptake cannot be easily be distinguished from pathology.

In conclusion, based on the evidence from published PET literature, the following suggestions can be made for the use of PET in childhood lymphomas (See Table 3).

1. All children and adolescents with newly diagnosed HL should have FDG PET scan as part of the initial diagnostic work up. This is not the case for B or T lineage childhood NHL outside clinical trials.
2. In HL, FDG PET appears to be a useful component of response based treatment stratification. The role of PET in determining the need for involved field therapy in childhood HL is the subject of an ongoing major European Study (Euronet –PHL-C1 trial). The role of interim FDG PET in children with NHL is less clear.
3. PET imaging may be of value in confirming relapse following treatment cessation but is not an integral part of routine follow up surveillance in either HL or NHL.
4. If PET is obtained during a course of therapy, it should be performed as close as possible (i.e. within 4 days) to the subsequent cycle of chemotherapy.
5. Although FDG PET has the potential to improve radiation treatment planning in children with HL, its use outside clinical trials cannot be recommended.

Conflict of interest statement

None declared.

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