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Pilot study of F^{18}-Fluorodeoxyglucose Positron Emission Tomography/computerised tomography in Wilms' tumour: Correlation with conventional imaging, pathology and immunohistochemistry

Joanna Begent [a], *Neil J. Sebire* [b], *Gill Levitt* [c], *Penelope Brock* [c], *Kathy Pritchard Jones* [d], *Peter Ell* [e], *Isky Gordon* [f], *John Anderson* [g,*]

[a] *Department of Paediatrics and Adolescents, University College Hospitals NHS Foundation Trust, 250, Euston Road, London NW1 2PQ, United Kingdom*
[b] *Department of Histopathology, Great Ormond Street Hospital for Children NHS Trust, London WC1N 3JH, United Kingdom*
[c] *Department of Oncology, Great Ormond Street Hospital for Children NHS Trust, London WC1N 3JH, United Kingdom*
[d] *Institute of Cancer Research, 15 Cotswold Rd., Belmont, Sutton, Surrey SM2 5NG, United Kingdom*
[e] *Institute of Nuclear Medicine, University College Hospitals NHS Foundation Trust, 250, Euston Road, London NW1 2PQ, United Kingdom*
[f] *Unit of Radiology and Physics, University College London Institute of Child Health, 30 Guilford Street, London WC1N 1EH, United Kingdom*
[g] *Unit of Molecular Haematology and Cancer Biology, University College London Institute of Child Health, 30 Guilford Street, London WC1N 1EH, United Kingdom*

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ABSTRACT

Wilms' tumour is the second most common paediatric solid tumour. Prognosis is good although higher stage disease carries significant mortality and treatment related morbidity. In the UK, risk stratification is based on histological response to pre-operative chemotherapy. F^{18}-Fluorodeoxyglucose Positron Emission Tomography (F^{18}FDG-PET) is an emerging functional imaging technique in paediatric oncology. Little is known about the relationship between F^{18}FDG-PET images and the disease process of Wilms' tumour. We performed F^{18}FDG-PET/CT scans in seven children with Wilms' tumour after induction chemotherapy, immediately before surgery. The standard uptake values (SUV) of F^{18}FDG-PET/CT images were related to conventional imaging and histopathological findings. In total seven children were studied. F^{18}FDG-PET/CT was consistently safely performed. All tumours showed F^{18}FDG activity. Four tumours had activity with SUV/bw max >5 g/ml. Histological examination of these active areas revealed viable anaplastic Wilms' tumour. Furthermore, in these four tumours GLUT-1 and Ki67 immunostaining was strongly positive. Three further tumours demonstrated lower uptake (SUV/bw max <5 g/ml), which represented areas of microscopic foci of residual viable tumour mixed with post chemotherapy change. Metastatic disease was F^{18}FDG avid in two of four children with stage four diseases. In conclusion, following chemotherapy, active Wilms' tumour is F^{18}FDG avid and higher SUV was seen in histologically high risk disease.

* *Corresponding author:*
E-mail address: J.anderson@ich.ucl.ac.uk (J. Anderson).
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1. Introduction

Wilms' tumour (nephroblastoma) is the second most common solid tumour of childhood. There is 94% overall survival in stage I tumours and 75% in stage IV disease (United Kingdom Wilms' Tumour 2 study).[1] Recommended imaging at diagnosis typically relies on conventional cross sectional anatomical imaging using ultrasound, CT and MRI, which provide little functional information about the tumour.

Treatment in Europe consists of pre and post-operative chemotherapy. Prior to surgery, ultrasound or CT reassessment of the tumour is required. This imaging provides information about change in tumour size and can potentially identify features such as tumour necrosis. However, although change in tumour size is important for surgical management it correlates poorly with histological features,[2] which may be of prognostic significance. Functional information about the presence of active disease within the primary tumour or residual metastases remains elusive.

^{18}F-Fluorodeoxyglucose Positron Emission Tomography (^{18}F-FDG-PET) detects metabolic activity of malignant cells and reflects increased activity as increased avidity.[3–5] There is limited access to PET scanners and the procedure itself is long and complex making acquisition of ^{18}F-FDG-PET images in children problematic. Urinary tract scanning is additionally complicated by the renal excretion of ^{18}F-FDG, resulting in visualisation of collecting systems and bladder, which may obscure underlying disease. The addition of fused CT images in the new generation of PET/CT scanners has helped to resolve some of these issues; the CT component not only shortens scan acquisition time, as the scan is used for attenuation correction, but also allows accurate anatomical location of areas of ^{18}F-FDG uptake.

Shulkin et al. have looked at the role of ^{18}F-FDG-PET scanning in three cases of Wilms' tumour[6] and suggested it to be FDG avid. We have performed a series of PET/CT studies to investigate the technique's potential in children with Wilms' tumour. We hypothesised that ^{18}F-FDG-PET/CT, if positive, would provide additional functional information to conventional imaging post induction chemotherapy and immediately prior to surgery, in Wilms' tumour. Such information could aid clinical decisions related to treatment response and local therapy (e.g. pulmonary radiotherapy, resection of lung metastases and nephron sparing surgery for bilateral Wilms' tumour). To investigate this we compared the ^{18}F-FDG-PET/CT with CT or US scan and tumour pathology. Misch et al.[7] have demonstrated an increased standard uptake values (SUV) in one case of anaplastic Wilms' tumour when compared with eight cases with intermediate histology when assessing the role of ^{18}F-FDG-PET in 12 cases of Wilms' tumour. We hypothesised that the standard uptake value on ^{18}F-FDG-PET/CT would relate to tumour pathology. If this where the case, ^{18}F-FDG-PET/CT might be able to highlight active tumour. A further objective was to determine whether immunohistochemical staining for GLUT-1 (a marker of increased glucose uptake) and Ki67 (an indicator of cellular proliferation, known to correlate with ^{18}F-FDG uptake in several tumour types) corresponded not only to tumour histological type but also to SUV on ^{18}F-FDG-PET/CT. These data would further confirm the association between ^{18}F-FDG positivity and Wilms' tumour allowing the integration of this tool into clinical practice.

2. Patients and methods

2.1. Patients

All children over the age of one year with Wilms' tumour at Great Ormond Street Hospital were eligible for the study which ran from June 2004 to June 2005. One additional child was recruited from The Royal Marsden Hospital, Surrey. Ethical approval was obtained from Great Ormond Street Hospital Research and Ethical Committee and permission from the Administration of Radioactive Substances Advisory Committee (ARSAC) was obtained. All parents provided written informed consent. The F^{18}-FDG-PET/CTs were performed at the Institute of Nuclear Medicine, University College Hospital London.

Once diagnosed the children were treated with induction chemotherapy on the relevant International Society of Paediatric Oncology (SIOP) Wilms' protocol. Standard repeat imaging (CT/US) and ^{18}F-FDG-PET/CT were performed in the five days prior to surgery.

2.2. PET/CT scans

^{18}F-FDG-PET/CT scans were performed in children using the following protocol. Sedation was with melatonin and temazepam as required. 6 MBq/kg ^{18}F-FDG (minimum 100 MBq) was injected at 45–75 min and 0.5 mg/kg frusemide (furosemide) at 30 min prior to the scan. Image acquisition using a GE Discovery Light Speed PET-CT scanner involved a scout CT (5 mA) then attenuation correction CT at 40 mA followed by the PET acquisition. Scans included neck to thighs as tumour spread outside this area is rare.

Maximum standard uptake values (SUV/bw) were recorded in each individual ^{18}F-FDG avid region within the tumour. To determine whether ^{18}F-FDG-PET/CT would provide additional information to conventional imaging post chemotherapy and prior to surgery, the ^{18}F-FDG-PET/CT was compared with the most recent CT or US. To provide appropriate data to compare the ^{18}F-FDG-PET/CT with histopathological features, immediately following surgical removal, the specimen was photographed and handled as per the appropriate pathology protocol. Sections of the entire tumour were obtained for H&E staining, diagnostic histological reporting and tumour mapping. Samples were labelled and compared using the macroscopic photograph and ^{18}F-FDG-PET/CT scan sections.

2.3. Immunohistochemical staining

Formalin fixed paraffin embedded tissue sections from the areas of interest within the tumour underwent immunohistochemical staining for GLUT-1 glucose transporter (DAKO GLUT-1 polyclonal antibody) and Ki67 (DAKO Ki67 monoclonal antibody), using standard staining protocols and 5% diaminobenzadine (DAB) detection system was used with haematoxylin

counterstaining. The relevant sections were scored positive for GLUT-1 where there was definite tumour cell staining of equal or greater intensity than red blood cells. Ki67 staining was recorded as either negative, 1+ positive when <100 positive cells per high power field (hpf) (over an average of 10 hpf) were present and 2+ when an average >100 positive cells per hpf were present. Statistical analysis was performed using exact non-parametric testing.

3. Results

3.1. *Feasibility of performing FDG-PET-CT scans on young children with WIlms' tumour*

Between June 2004 and June 2005 there were 15 eligible children of whom seven were recruited (average age 57 months [range 20–72 months], three girls, four boys). The other eight children were approached to enter the study however either declined or were unable to undergo a scan because of lack of availability of the scanner. One child had each of post surgical stages 1 and 3, 4 children had metastatic disease, and one patient had bilateral non-metastatic disease. They all underwent PET scanning between 6 and 7 weeks after diagnosis, 7–14 days after the last chemotherapy. All received preoperative vincristine and actinomycin chemotherapy, five also received doxorubicin (stages 3 and 4).

All children successfully completed the scan, including the four requiring sedation. Blood glucose concentrations ranged from 4.5 to 6.2 mmol/l at the time of injection of ^{18}F-FDG. There were no significant adverse events as a result of undergoing ^{18}F-FDG-PET/CT. One child who received sedation had temper tantrums and a disturbed night's sleep after the scan. Another child who had surgery the day after the ^{18}F-FDG-PET/CT had reduced urine output during the operation (<0.5 ml/kg/h). It is possible this was a consequence of frusemide the previous day.

Table 1 – Distribution of ^{18}F FDG on PET-CT, compared with Conventional Imaging and Pathology in children with Wilms' tumours after chemotherapy.

Patient	Region of tumour	CT/US appearance	^{18}F FDG-PET/CT avidity of region	Microscopic appearance of region/tumour
1	Superior region	Residual kidney	Avid uptake	Collecting system
	Medial region	Tumour	Background uptake	Necrotic tumour
	Inferior region	Tumour	Avid uptake	Anaplastic tumour
2	Tumour (non-nodule)	Homogenous tumour	Background uptake	Necrotic tumour
	Nodular lesions	Homogenous tumour	Increased uptake	Post chemotherapy change with some residual tumour cells
	L lung lesion	Largest lung lesion seen on CT	Avid uptake	Post chemotherapy change with some residual tumour cells
3	Superior region	Necrosis	Photopenic	Necrotic haemorrhage
	Medial region	Residual kidney or tumour?	Avid	Collecting system in residual tumour
	Inferior region	Residual kidney or tumour?	Avid	Focal anaplastic tumour within residual blastema
	Mediastinum	Bulky tissue	Background uptake	Not biopsied
4	Superior region	Residual kidney	Avid uptake of collecting system	Residual kidney with collecting system
	Inferior region	Tumour	Avid uptake in tumour	Anaplastic tissue
	Mediastinum	Bulky tissue	Avid uptake	Not biopsied (site of relapse)
5	Tumour (non-nodule)	Homogenous tumour	No FDG uptake	Necrosis
	Nodular lesions		FDG avid	Post chemotherapy change with some residual tumour cells
	Right lung lesion	Small lesion	No FDG uptake	No active tumour
6 (bilat)	Left superior	Kidney	Normal renal uptake	Partial nephrectomy – non-resected pole
	Left inferior	Tumour	No uptake	No active tumour
	Right lesion	Large lesion with necrotic centre	Avid uptake with photopenic centre	Anaplastic tumour with necrotic centre
7	Tumour (non-nodule)	Homogenous tumour	No increased FDG uptake	No active tumour
	Peripheral nodular lesions		Increased FDG uptake	Islands of residual triphasic tumour

3.2. *FDG-PET-CT avidity measurements in Wilms' patients correlate with the presence of macroscopic viable tumour*

^{18}F-FDG-PET/CT showed Wilms' tumour to be ^{18}F-FDG avid and, when compared with the five CT and two ultrasound scans, added more functional information in all cases (Table 1). The accuracy of the functional information was confirmed by comparison of appropriate ^{18}F-FDG-PET/CT slices with macroscopic and microscopic appearances. CT/US was able to demonstrate large areas of presumed tumour necrosis (patients 3 and 6) but CT/US could not reliably distinguish active tumour from necrosis. On ^{18}F-FDG-PET/CT, necrotic tumour showed a mixed pattern comprising areas with minimal ^{18}F-FDG activity and other photopenic areas (patients 3 and 6 [Fig. 1]). Patchy necrosis with small intervening residual (patient 2 [Fig. 2], 5, 7) had a predominantly blastematous or triphasic histology intermixed with necrosis. In four patients (1, 3, 4, and 6 [Fig. 1]) larger highly ^{18}F-FDG avid lesions were seen within the tumour (SUV/bw max>5) and the lesions corresponded histologically with anaplastic Wilms' tumour.

3.3. *FDG-PET avidity in chest lesions corresponds with active disease*

Four children had metastatic disease within the chest at diagnosis.[2–5] This was re-imaged at the time of surgery. Patient 2 had multiple 1–2 mm pulmonary nodules on CT with one 14 mm lesion in the left lung. This larger lesion was ^{18}F-FDG avid (Fig. 2a). On resection it showed post chemotherapy change with some residual tumour; the smaller ^{18}F-FDG negative nodules were not detected at surgery. Patient 3 had non-^{18}F-FDG avid mediastinal metastatic disease visible preoperatively on CT (resection was not attempted). An isolated lesion seen on the chest CT of patient 5 was resected although it was not ^{18}F-FDG avid; histopathological analysis proved it to be necrotic tissue. None of these children have relapsed to date. In contrast patient 4 (who had anaplastic renal disease) had a mediastinal lesion present on preoperative CT which showed ^{18}F-FDG uptake (SUV/bw max 5.28); this was not resected for technical reasons but was irradiated; the child subsequently relapsed at this site. Patient 2 (Fig. 2) had an unusually ^{18}F-FDG avid spleen (Fig. 2). This was examined at operation but appeared macroscopically normal.

3.4. *FDG-PET avidity correlates with histological makers of viability and anaplasia*

The correlation between PET/CT and histopathological findings is shown in Table 2. This shows a comparison of regional SUV on ^{18}F-FDG-PET/CT with morphology and with GLUT-1 and Ki67 immunohistochemistry from the same area. We define Type 1 lesions as having anaplastic morphology, type 2 have residual viable nephroblastoma with no

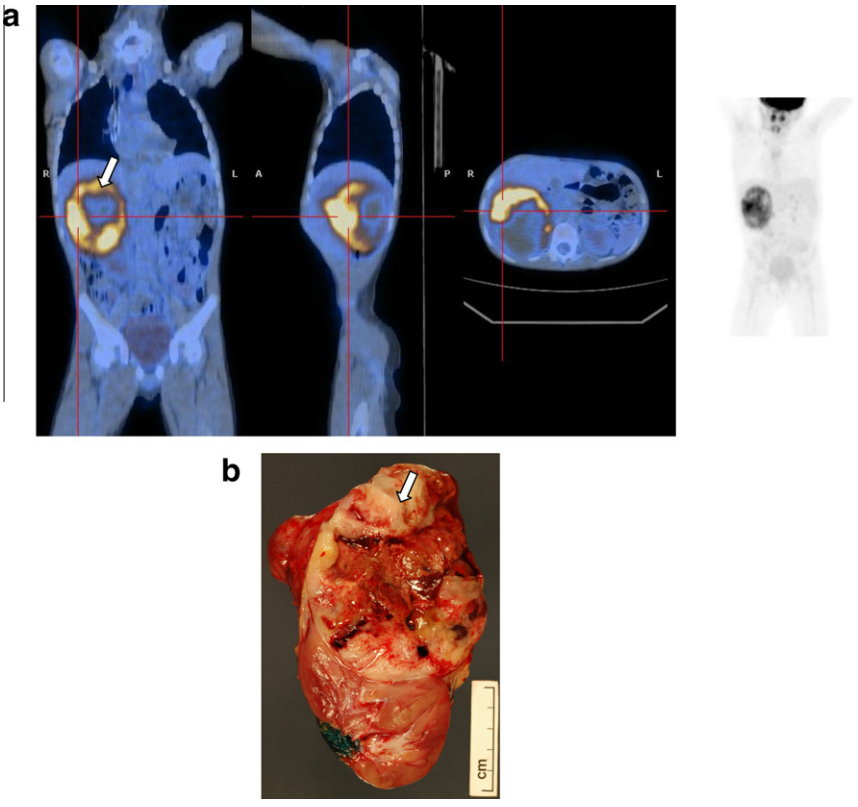

Fig. 1 – Imaging and histology of Patient 6; right sided tumour. (a) Coronal, sagittal and transaxial fused ^{18}F FDG-PET-CT scan and coronal FDG-PET scan (black and white) showing right sided Wilms' tumour. Fused ^{18}F FDG-PET-CT scan shows large FDG avid right sided Wilms' tumour arising in the superior pole. The necrotic centre with minimal uptake is surrounded by an FDG-avid rim of tumour (arrowed). (b) Resected specimen showing viable rim of tumour (arrowed) with necrotic centre and residual inferior normal kidney.

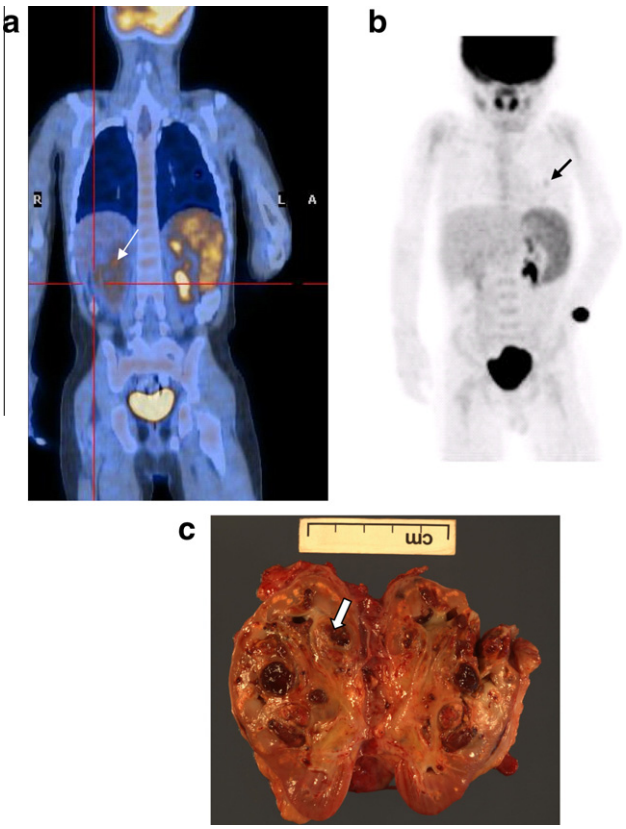

Fig. 2 – Imaging and histology of Patient 2. (a) Coronal, sagittal and transaxial fused ^{18}F FDG-PET-CT scan and coronal FDG-PET scan showing right sided Wilms' tumour with areas of low grade increased uptake (especially upper pole, arrowed) correlating with residual tumour and decreased uptake (especially laterally) reflecting necrosis. The spleen is noted to have increased patchy uptake. (b) Lung lesion identified in the same patient. (c) Bisected pathological specimen of right Wilms' tumour showing areas of necrosis (especially laterally) and haemorrhagic nodules (arrow), some containing residual tumour (the residual normal kidney is inferior).

anaplasia, and type 3 represent extensive post chemotherapy, fibrotic or necrotic change with no viable tumour. Anaplasia correlated with high SUV; SUV values >5 were seen in the 4 tumour regions corresponding with areas of anaplasia. None of the other 11 tumour regions had SUV >5. When comparing the SUVs of the anaplastic regions with all other regions there was a significant difference (Fig. 4; $p = 0.002$, Mann Whitney U test). No other histological type comparisons were found significantly to correlate with SUV values.

We assessed whether highly PET avid areas showed immunohistochemical evidence of increased metabolic activity. Strongly ^{18}F-FDG positive areas with anaplastic histology highly expressed GLUT-1 (Fig. 3a) predicted to correlate with increased uptake of the glucose analogue. In all cases, staining appeared in large focal patches within the anaplastic tumour. The anaplastic areas were also highly proliferative as assessed by Ki67 positivity (with >250 positive cells/hpf, Fig. 3b). Areas with viable non-anaplastic blastematous or triphasic histology did not show significant GLUT-1 positivity detectable by immunostaining, but low level Ki67 positivity was seen (<100 positive cells/hpf, Fig. 3c); the SUV in these areas was 1.5–2.5. Absence of GLUT-1 or Ki67 positivity was seen in necrotic tumour, which was correspondingly ^{18}F-FDG negative.

4. Discussion

In adult oncology practice the role of PET is increasingly well established, providing functional information for staging, treatment planning and response monitoring in several tumours. PET imaging in the paediatric oncology setting has mainly concentrated on Hodgkin's lymphoma and bone tumours. These diseases occur more commonly in older children and are also seen in adults. Published work in exclusively paediatric tumours is limited. Wegner et al concluded that ^{18}F-FDG-PET was a useful clinical tool in a heterogeneous group of tumours, 75% of studies being verified by either histological examination or clinical follow up. Clinicians felt that 75% of the 237 scans added useful information to management decisions. Management was changed in 24% of cases.[8] Daldrup-Link et al. have compared ^{18}F-FDG-PET with conventional imaging for bone metastases in a range of paediatric tumours. They concluded that despite an increased false positive rate, ^{18}F-FDG-PET is the most sensitive tool for detection of bone metastases.[9]

Our study adds detail to the relationship between conventional imaging, ^{18}F-FDG-PET/CT and histopathological characteristics in Wilms' tumours following chemotherapy. We successfully and safely completed ^{18}F-FDG-PET/CT scans in seven children with Wilms' tumour. We also demonstrated that Wilms' tumour is ^{18}F-FDG avid, and ^{18}F-FDG-PET/CT provides additional clinically applicable information to conventional imaging. ^{18}F-FDG-PET/CT highlights FDG avid areas within the tumour and metastases which correspond to active disease, confirmed on histology.

The first study of ^{18}F-FDG-PET in Wilms' tumour was published by Shulkin et al.[6] They reported three patients who underwent ^{18}F-FDG-PET scanning (two bilateral, one unilateral); all scans were positive at diagnosis and resulted in treatment alteration. They concluded that ^{18}F-FDG-PET scanning may be helpful for planning surgery in bilateral cases. More recently Misch et al. have looked at 23 ^{18}F-FDG-PET scans in 12 Wilms' tumour patients for staging, pre-operative assessment and post-therapeutic evaluation, particularly comparing them with conventional imaging. They suggested that FDG-PET was advantageous in ruling out residual disease after completion of first line treatment and in staging of relapse patients. A good correlation of initial SUV and histological differentiation was demonstrated. Their study found that ^{18}F-FDG-PET did not provide additional information to conventional imaging, in contrast with the current study using ^{18}F-FDG-PET/CT. Moinul-Hossain et al. studied 27 patients, mostly with metastatic disease and/or recurrence, with ^{18}F-FDG-PET/CT and demonstrated positive PET avidity in the majority of tumours and metastatic deposits.[10]

^{18}F-FDG-PET/CT imaging of the kidneys is problematic due to the renal excretion of FDG. This results in areas of FDG

Table 2 – ^{18}F FDG-PET/CT, histology and immunohistochemistry.

Patient site K = kidney L = lung M = mediastinum	Area of ^{18}F FDG-PET/CT	^{18}F FDG uptake	SUV/bw (max) (g/ml)	Histology	Immuno histochemistry	
					GLUT-1	Ki67
1 K	Superior region	Normal collecting system	>20	Collecting system	n/a	n/a
K	Medial region	Background	No count	Necrotic tumour	–	–
K	Inferior region	Avid	6.68	Anaplastic tumour	+	++
2 K	Tumour (non-nodule)	Background	No count	Necrotic tumour	–	–
K	Nodular lesions	Increased	2.31	Post chemotherapy change with some residual tumour cells	–	+
L	Left lung lesion	Increased	1.58	Post chemotherapy change with some residual tumour cells	–	+
3 K	Superior region	Photopaenic	No count	Necrotic haemorrhage	–	–
K	Medial region	Normal collecting system	>20	Collecting system in residual tumour	–	+
K	Inferior region	Avid	8.52	Focal anaplastic tumour within residual blastema	+	++
M	Mediastinum	Background	0.43	Not biopsied	n/a	n/a
4 K	Superior region	Normal collecting system	>20	Residual kidney with collecting system	–	–
K	Inferior region	Avid	9.66	Anaplastic tissue	+	++
M	Mediastinum	Avid	5.28	Not biopsied (site of relapse)	n/a	n/a
5 K	Tumour (non-nodule)	None	No count	Necrosis	–	–
K	Nodular lesions	Avid	2.17	Tumour with favourable post chemotherapy changes	–	+
L	Right lung lesion	None	0.49	No active tumour	–	–
6 K	Left superior	Normal collecting system	>20	Partial nephrectomy – not resected	n/a	n/a
K	Left inferior	Background	1.27	Necrosis	–	–
K	Right tumour	Avid with photopaenic centre	6.23	Anaplastic lesion with necrotic centre	+	++
7 K	Tumour (non-nodule)	Background	0.52	Post chemotherapy change	–	–
K	Peripheral nodular lesions	Some areas of increase	2.7	Islands of residual triphasic tumour	–	+

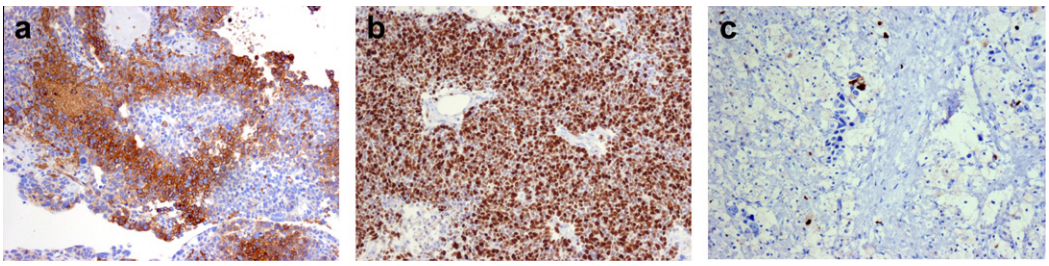

Fig. 3 – Wilms' tumour Immunohistochemistry. (a) Focal GLUT-1 positivity seen in anaplastic Wilms' tumour. (b) High Grade Ki67 positivity seen in anaplastic Wilms' tumour. (c) Low Grade Ki67 positivity seen in residual triphasic Wilms' tumour.

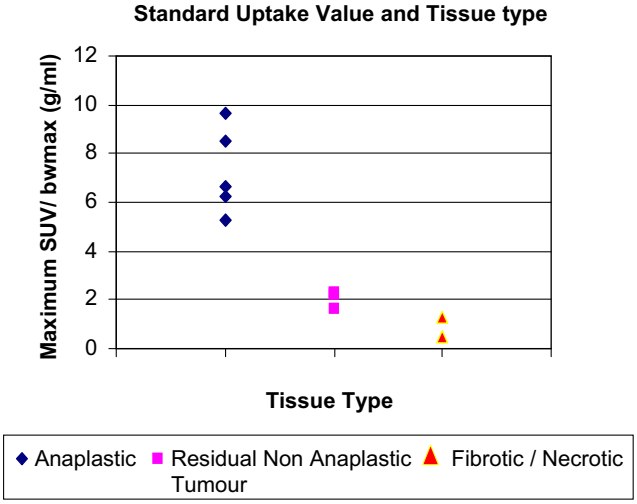

Fig. 4 – Correlation between regional tumour and metastases Standard Uptake Value (based on body weight) and tumour histological type. Anaplastic regions had significantly higher SUV values than other regions ($p = 0.002$ Mann Whitney *U*).

avidity within the collecting systems, which may be distorted by coexistent tumour or disguise uptake due to tumour. The computerised tomography element of ^{18}F-FDG-PET/CT images makes the interpretation easier as the collecting systems can be delineated. Further enhancement of the CT image using intravenous contrast may help delineate the renal anatomy more clearly. A delay in imaging time may also improve the renal scan as theoretically the tumour will retain tracer whilst any FDG within the renal tract will be excreted. This technique however is problematic for nervous children or those requiring sedation. New tracers which are not really excreted would address this problem.

Interpretation of ^{18}F-FDG-PET/CT is additionally complicated in paediatrics by brown fat, lymphoid tissue and the thymus. The timing of ^{18}F-FDG-PET/CT during treatment is important. False positive results follow due to macrophage activation and bone marrow recovery,[11] a possible explanation for the increased splenic and bone marrow activity in patient 2. There was no concern about the child's splenic function and bone scintigraphy was normal and follow-up confirmed the absence of bone metastases. These issues suggest that a diagnostic scan could be a useful baseline.

There is a wide variation in SUV for normal tissues and benign disease. It is well-recognised however, that active tumour has greater ^{18}F-FDG uptake via transmembrane glucose transporters (GLUT) resulting in a higher SUV of radioactivity on PET imaging.[4] GLUT-1, one member of this large family of transporters, is present on all cells but expression levels vary. Expression is known to be high in some tumour types – particularly ovarian and breast carcinomas.

In our subjects, the areas within the tumours with high ^{18}F-FDG uptake (SUV/bw max >5 g/ml) related to high levels of GLUT-1 uptake. In all these cases GLUT-1 expression was seen in a focal distribution, possibly related to areas of hypoxia since GLUT-1 expression is known to be up-regulated in hypoxic tumours.[12] The GLUT-1 positive areas were also highly proliferative. Our data appears to suggest that in this aggressive tumour both GLUT-1 and Ki67 are increased. Other ^{18}F FDG positive areas, with lower SUVs, did not demonstrate identifiable GLUT-1 immunostaining. It is possible that other members of the GLUT receptor family may be utilised by tumour cells.

The reported incidence of anaplasia in Wilms' tumour is 5–10%.[13] Interestingly, of our seven cases, four with high SUV and GLUT-1 and Ki67 expression, contained anaplastic tumour. This histological subtype is known to convey a poor prognosis, probably due to chemotherapy resistance.[14] The diagnostic needle biopsies of these children did not demonstrate anaplasia. However the anaplastic cells which survived chemotherapy targeted at the less aggressive tumour cells may have been missed initially. All these cases were older children (mean age 66.5 months, versus sample mean 57 months), a trend previously reported.[15]

Our data shows that ^{18}F-FDG-PET/CT imaging predicts the presence of residual viable Wilms' tumour. The standard uptake value (SUV) appears related to GLUT-1 expression, mitotic index and histopathological phenotype, in viable anaplastic tumour in both primary and metastatic tumour sites. We propose therefore that ^{18}F-FDG-PET/CT scanning could provide a useful tool for staging and disease monitoring in Wilms' tumour. These data suggest ^{18}F-FDG-PET/CT at diagnosis could highlight the small group of children with high risk anaplastic tumour type. Biopsy may then be accurately directed to any focal areas of increased SUV.

The role for ^{18}F-FDG-PET/CT may therefore be in planning local therapy for metastatic and bilateral Wilms' tumour and providing additional information in non-chemotherapy responsive disease. Both surgical and radiotherapy treatment of lung disease remain complex multidisciplinary decisions, assessing projected late side effects in young children.[16–18]

^{18}F-FDG-PET/CT may assist by delineating residual active metastatic disease and may be a useful tool to assist in primary surgical planning when nephron sparing surgery is desirable.[19] Further studies to determine the role of ^{18}F-FDG-PET/CT scanning in Wilms' tumour management are justified.

Conflict of interest statement

None declared.

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