

Evaluation of ¹⁸fluorodeoxyglucose positron emission tomography (¹⁸FDG PET) in the detection of malignant peripheral nerve sheath tumours arising from within plexiform neurofibromas in neurofibromatosis 1

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Abstract

Objectives—The ability of ¹⁸fluorodeoxyglucose positron emission tomography (¹⁸FDG PET) to detect malignant change in plexiform neurofibromas from patients with neurofibromatosis 1 (NF1) was evaluated.

Methods—Eighteen NF1 patients who presented with pain, increase in size, or neurological deficit associated with a plexiform neurofibroma were assessed. Magnetic resonance imaging determined the site and extent of the lesion. Qualitative ¹⁸FDG PET was performed and the standard uptake value (SUV) measured the regional glucose metabolism. Histological confirmation of the diagnosis was obtained in 10 patients.

Results—Twenty three plexiform neurofibromas were detected in 18 patients. Seven malignant peripheral nerve sheath tumours, four high grade and three low grade tumours, occurred in five patients. In one patient the clinical and radiological characteristics of the tumour suggested malignancy, but histology was inconclusive. Fifteen benign plexiform neurofibromas were identified in 12 patients and these findings were confirmed histologically in five lesions from four patients. Ten plexiform neurofibromas occurring in eight patients were considered benign on ¹⁸FDG PET and the patients did not undergo surgery. They remained stable or their symptoms improved on clinical follow up (median 9 months). The results of qualitative ¹⁸FDG PET were interpreted as indicating that 13 plexiform neurofibromas were benign and 10 were malignant. No malignant tumours were classified as benign, but two benign tumours were reported as malignant. The SUV was calculated for 20 tumours and was significantly higher in five malignant tumours 5.4 (SD 2.4), than in 15 benign tumours 1.54 (SD 0.7), $p=0.002$. There was an overlap between benign and malignant tumours in the SUV range 2.7–3.3.

Conclusions—¹⁸FDG PET is helpful in determining malignant change in plexiform neurofibromas in NF1. Increased separation between benign and malignant lesions could be obtained by calculating

the SUV at about 200 minutes after injection of ¹⁸FDG, when the peak activity concentration is obtained in malignant tumours.

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Neurofibromatosis 1 (NF1) is a common autosomal dominant disease with an estimated birth incidence of 1 in 2500.¹ The cardinal features of NF1 are café au lait spots, neurofibromas, iris Lisch nodules, and skinfold freckling. The diagnostic criteria were formulated by the National Institutes of Health Consensus Development Statement in 1988.² The complications are manifold, may affect any of the body systems, and vary, even within the same family.

Neurofibromas are benign skin tumours arising from the connective tissue of nerve sheaths, especially the endoneurium.³ They are composed predominantly of Schwann cells and fibroblasts, in addition to axons, perineurial cells, mast cells, and extracellular matrix.⁴ They may be discrete dermal or nodular lesions or plexiform neurofibromas. Plexiform neurofibromas differ from discrete neurofibromas because they have an expanded extracellular matrix, grow along the length of a nerve, and may involve multiple fascicles and branches. They interdigitate with surrounding structures, often resulting in diffuse hypertrophy of bone and soft tissues. Superficially visible plexiform neurofibromas were reported in 26.7% of patients with NF1 in one population based study.¹ In a recent study, Tonsgard *et al*⁵ performed CT on 91 adults with NF1 and found that 20% had plexiform neurofibromas in the chest and 40% in the abdomen or pelvis. Plexiform neurofibromas are a potent cause of disfigurement, impaired function, and emotional distress. However, the growth characteristics of these lesions have not been determined and periods of rapid growth may be followed by relative quiescence.

About 4% of patients with NF1 develop malignant peripheral nerve sheath tumours which arise within plexiform neurofibromas and often carry a poor prognosis.⁶ The tumours may metastasise to the lung, brain,

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liver, bone, soft tissue, regional lymph nodes, skin, and retroperitoneum.⁷ Optimal management is dependent on early and accurate histological grading and staging of the disease, but malignant peripheral nerve sheath tumours are often difficult to detect and may metastasise to many different sites. Pain, rapid increase in the size of a neurofibroma, and the development of neurological deficit are clinical indicators of malignancy, but may also be features of benign plexiform neurofibromas. Magnetic resonance imaging locates the site and extent of the plexiform neurofibroma but is not reliable in detecting malignant change.⁸ Malignant peripheral nerve sheath tumours often contain heterogeneous areas, biopsy of a small part of the lesion does not always reflect the overall character of the tumour, and high grade areas may be missed. Total removal of the tumour may not be feasible or may result in significant morbidity because of the involvement of surrounding structures.

Positron emission tomography with the glucose analogue ¹⁸F-fluorodeoxyglucose (¹⁸FDG) is a dynamic imaging technique which permits the visualisation and quantification of glucose metabolism in cells and reflects the increase in metabolism in malignant tumours.⁹ Previous studies of soft tissue sarcomas have suggested that ¹⁸FDG PET successfully detects soft tissue sarcomas and metastases and can give an indication of the histological grade.¹⁰⁻¹⁵ There have been no previous studies using ¹⁸FDG PET to identify malignant peripheral nerve sheath tumours in NF1.

In this study, we evaluated the ability of ¹⁸FDG PET to detect malignant peripheral nerve sheath tumours, arising from plexiform neurofibromas in patients with NF1.

Methods

The patients were recruited between 1996 and 1998 from our multidisciplinary neurofibromatosis clinic and comprised 400 patients.

Overall, 35% of our patients have plexiform neurofibromas. A clinical and neurological examination was carried out on patients reporting pain, increased size, or neurological deficit in a plexiform neurofibroma. We report our experience with the first 18 patients.

MRI

Magnetic resonance imaging was performed on 18 patients with a 1.5 Tesla superconducting system (Philips Gyroscan S15, Philips Medical Systems). Images were taken in the axial and coronal planes with a slice thickness of 5 mm and an interscan distance of 0.5 mm. Coronal STIR images (TR/TE 2000/25, TI 150) were performed and axial T1 images (TR/TE 700/20) were carried out before and after the administration of gadolinium-meglumine-triaminepentacetic acid contrast medium at 0.2 ml/kg.

¹⁸FDG PET PROTOCOL

Imaging was carried out on all patients after a 6 hour fast. Localised imaging of the mass was performed in all patients and whole body or half body scans were carried out on seven patients. Data were acquired using an ECAT 951R whole body system (Siemens/CTI, Knoxville, TN, USA). The scanner has an image resolution of about 8 mm and an axial field view of 10.8 cm (one bed position equalled 10.8 cm). A whole body scan (not corrected for attenuation) was performed for 5 minutes per bed position, about 60 minutes after intravenous injection of 350 Mbq ¹⁸FDG. Localised attenuation corrected views of the mass were undertaken after the whole body study, if this was performed, using a combined protocol of a 10 minute transmission scan and a 15 minute emission scan. This allowed a semiquantitative calculation of the rate of ¹⁸FDG metabolism in the tumour to be made. The images were displayed as coronal, sagittal, and transaxial sections.

Table 1 Clinical features and site of lesions in 18 patients with NF1 with 23 symptomatic plexiform neurofibromas

No	Sex	Age	Site of lesion	Pain	Increase in size	Neurological deficit (sensory and motor impairment)
1	F	49	Prevertebral at L1	Yes	Not visible*	Yes
2	M	37	Pelvis	Yes	Not visible*	No
3	F	19	L brachial plexus	Yes	Not visible*	Yes
4	F	23	L thigh	Yes	Yes	Yes
			R lower limb	Yes	Yes	No
5	F	41	L thigh	Yes	Yes	No
			L axilla	Yes	Yes	No
6	M	62	R thigh	Yes	Yes	Yes
7	M	22	L thigh (medial)	Yes	Yes	Yes
			L thigh (post.)	Yes	Yes	Yes
8	F	26	L supraclavicular fossa	Yes	Yes	Yes
9	F	35	L buttock	Yes	Yes	No
10	F	34	R lower limb	Yes	Yes	No
11	F	12	R thigh	No	Yes	No
12	F	27	L popliteal fossa	Yes	Yes	Yes
13	M	14	R cervical region	Yes	Yes	No
14	M	24	Pelvis	No	Yes	Yes
15	M	14	L popliteal fossa	Yes	Yes	Yes
16	M	26	Retroperitoneum,	No	not visible*	Yes
			R popliteal fossa	No	Yes	Yes
			L popliteal fossa	No	Yes	Yes
17	F	22	L upper limb	Yes	Yes	No
18	M	15	R lower limb	No	Yes	Yes

* Indicates plexiform neurofibromas not visible on the body surface.

Pain was a feature in 17 of 23 tumours; increase in size was present in 19 of 19 visible tumours; neurological deficit was present in 14 out of 23 tumours.



Figure 1 Coronal STIR MRI showing a lesion in the left brachial plexus. The 19 year old patient with NF1 presented with severe pain and neurological deficit in the left upper limb. Histology showed that the lesion was a high grade malignant peripheral nerve sheath tumour (triton tumour).

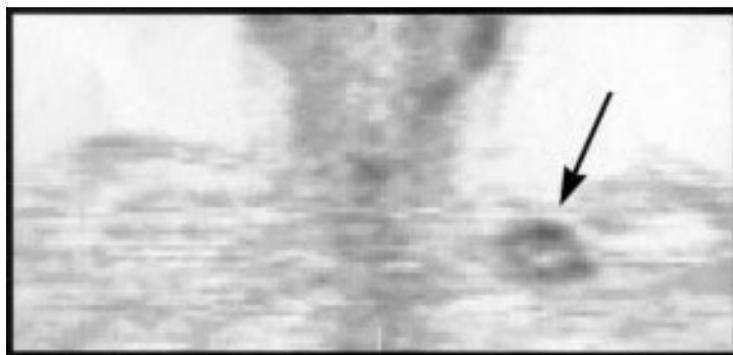


Figure 2 ¹⁸FDG PET in a 19 year old patient with NF1 presenting with severe pain and neurological deficit in the left upper limb. There is a focal area of abnormal ¹⁸FDG uptake in the left brachial plexus with a photopenic centre indicative of necrosis (arrow). Histology showed that the lesion was a high grade malignant peripheral nerve sheath tumour (triton tumour).

DATA ANALYSIS

All scans were evaluated both qualitatively by visual inspection and semiquantitatively by means of the calculation of the standard uptake value (SUV). The SUV is the normalised measurement of ¹⁸FDG uptake which is related to the regional metabolic rate of glucose, provided that the uptake of the tracer into the tumour has reached its maximum value.

QUALITATIVE ASSESSMENT

Qualitative assessment was made by a senior nuclear medicine physician experienced in PET with the specific aim of establishing if the mass was benign or malignant. In addition, the distribution of the uptake of ¹⁸FDG within the tumours was noted. Patients who had symptoms and neurological deficit which could have arisen from more than one site, underwent whole or half body scans. In those patients, the ¹⁸FDG uptake by the tumour was compared with the liver, and those tumours with uptake greater than the liver were deemed to be malignant.

QUANTITATIVE ASSESSMENT

Quantitative assessment was made by the calculation of the SUV (see equation 1) for the

tumour with correction for the partial volume effect. (the smallest spatial resolution is the pixel).

$$SUV = \frac{A_{tumour} \times P}{ID/BW}$$

where A_{tumour} is the tumour activity concentration (MBq ml⁻¹), ID is the injected dose of FDG (MBq), BW is the body weight (g) and P is an experimentally determined partial volume correction. The SUV as a function of time, SUV(t), was calculated according to equation 2:

$$\frac{SUV(t) = C(t)}{A/M} \times G$$

where C(t) is the activity concentration at time t measured using a 4.5 mm circular region of interest, A is the injected activity, M is the body mass, and G is a simple glucose correction factor (blood glucose concentration/4.5 mmol l⁻¹). The SUV time was the time after the injection when the SUV the transmission/emission scan was performed.

All scans were reported blind, without knowledge of any other imaging modality that had been undertaken of the tumour of concern and before a definitive histological diagnosis of the mass.

HISTOLOGY

The histological diagnosis and grading of the tumour was performed using the criteria of tumour differentiation, necrosis, and the mitotic count to determine whether the tumour was low, intermediate, or high grade.¹⁶

STATISTICAL ANALYSIS

The SUV results for malignant and benign tumours were compared with the Mann-Whitney U test and two tailed p values have been quoted.

Table 2 ¹⁸FDG PET Results and histology on 18 patients with NF1 with symptomatic plexiform neurofibromas

No	Site of plexiform neurofibroma	Necrosis	Radiologist opinion	SUV	SUV time (min)*	Histology
1	Prevertebral at L1	No	Malignant	4.5	195	Not diagnostic
2	Pelvis	Yes	Malignant	3.3	53	MPNST (low grade)
3	L brachial plexus	Yes	Malignant	2.7	60	Triton tumour
4	L thigh	Yes	Malignant	6.8	90	Triton tumour
	R lower limb	No	Malignant			MPNST (low grade)
5	L thigh	Yes	Malignant	8.4	163	Triton tumour
	L axilla	No	Malignant			MPNST (low grade)
6	R thigh	Yes	Malignant	5.7	175	Triton tumour
7	L thigh (medial)	No	?Malignant	1.8	60	Benign neurofibroma
	L thigh (post)	No	Benign	1.4	60	Benign neurofibroma
8	L supraclavicular fossa	No	Malignant	3.3	45	Benign neurofibroma
9	L buttock	No	Benign	1.46	77	No surgery
10	R lower limb	No	Benign	1.4	137	No surgery
11	R thigh	No	Benign	0.93	126	No surgery
12	L popliteal fossa	No	Benign	0.56	206	No surgery
13	R cervical region	No	Benign	2.4	121	Benign neurofibroma
14	Pelvis	No	Benign	1.46	77	No surgery
15	L popliteal fossa	No	Benign	1.27	79	Benign neurofibroma
16	Retroperitoneum,	No	Benign	1.67	184	No surgery
	R popliteal fossa	No	Benign	2.14	184	No surgery
	L popliteal fossa	No	Benign	0.56	184	No surgery
17	L upper limb	No	Benign	1.73	45	No surgery
18	R lower limb	No	Benign	0.97	193	No surgery

* SUV time is the time when SUV was calculated after injection of ¹⁸FDG.

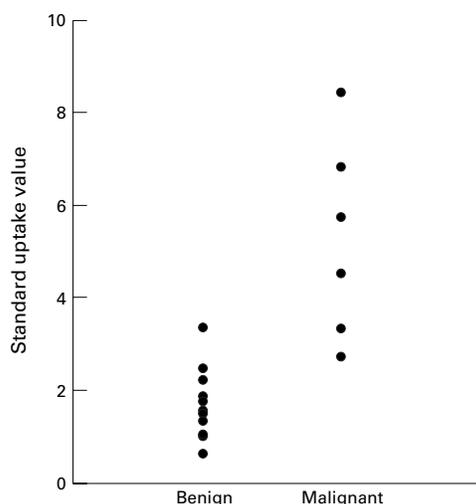


Figure 3 ^{18}F FDG PET comparing the SUV between benign plexiform neurofibromas and malignant peripheral nerve sheath tumours in 18 patients with NF1 (the cluster of data points in the benign group is so close that many of the 15 data points are superimposed).

Results

Between 1996 and 1998, 10 females and eight males with NF1 presented with pain, enlargement, or neurological deficit associated with a plexiform neurofibroma (table 1). The median age of the patients was 23.5 years with an age range of 12–62 years. Twenty three lesions were detected on MRI and four patients had more than one plexiform neurofibroma. Sixteen plexiform neurofibromas were visible in the limbs, eight proximally and eight distally, one was identified on MRI in the brachial plexus (figs 1 and 2), two were detected in the neck and four in the trunk.

Pain persisting for more than 1 month and interfering with daily activities, was a feature in 17 from 23 tumours. Increase in size was present in 19 of 19 visible tumours. Neurological deficit was present in 14 of 23 tumours.

Five patients with NF1 had seven malignant peripheral nerve sheath tumours and histological examination showed four high grade and

three low grade tumours. Three of the high grade tumours were triton tumours exhibiting rhabdomyoblastic features (table 2, cases 2–5). The median age of these patients was 23 years with an age range of 17–62 years. One patient had severe pain (waking her from sleep) and neurological deficit caused by a prevertebral plexiform neurofibroma at the level of L1 and ^{18}F FDG PET indicated that the lesion was malignant (case 1). However, biopsy was technically difficult as the lesion was in close proximity to the aorta and it was not possible to confirm the diagnosis histologically.

Fifteen benign plexiform neurofibromas were diagnosed in 12 patients with NF1 and histology confirmed the findings in four patients (cases 7, 8, 13, and 15, table 2). The median age of patients with benign plexiform neurofibromas was 30.5 years with an age range of 12–35 years.

^{18}F FDG PET: QUALITATIVE ASSESSMENT

The radiologist assessed 23 plexiform neurofibromas from 18 patients and on visual inspection reported 13 plexiform neurofibromas as benign and 10 as malignant. No malignant tumours were classified as benign, but two benign tumours were rated as malignant (cases 7 and 8). Histology was not diagnostic in one plexiform neurofibroma which was deemed to be malignant (case 1).

^{18}F FDG PET: QUANTITATIVE ASSESSMENT

The SUV was calculated in 20 tumours (table 2, fig 3). The mean SUV for five malignant tumours was 5.4 (SD 2.4), range 2.7–8.4, which was significantly higher than the SUV for 15 benign tumours, which was 1.54 (SD 0.7), range 0.56–3.3 (Mann-Whitney U test=1.5, p (two tailed) 0.002 (case 1 excluded from the analysis)).

The mean time after ^{18}F FDG injection to when the SUV was calculated for 20 tumours was 111 minutes, median 105.5 minutes, range 45–206 minutes (case 1 excluded). The mean SUV time for five malignant peripheral nerve sheath tumours was 108 minutes, median 90

Table 3 Clinical follow up of 18 patients with NF1 with symptomatic plexiform neurofibromas

No	Site of lesion	Latest follow up (months) after PET	Clinical outcome
1	Prevertebral at L1	9	Persistent pain and neurological deficit
2	Pelvis	26	Asymptomatic after surgery and DXT
3	L brachial plexus	25	Died of lung metastases after surgery and DXT
4	L thigh R lower limb	8	Died of lung metastases, after surgery and chemotherapy
5	L thigh L axilla	8	Asymptomatic after surgery
6	R thigh	10	Asymptomatic after surgery
7	L thigh (medial) L thigh (post)	15	Asymptomatic after surgery
8	L supraclavicular fossa	3	Neurofibroma excised, histology benign Persistent pain on left side of neck
9	L buttock	12	Pain resolved, no further increase in size of lesion
10	R lower limb	12	Pain on prolonged standing
11	R thigh	9	Pain resolved No further increase in size of lesion
12	L popliteal fossa	4	Pain resolved, no further change in size of lesion or deficit
13	R cervical region	10	Excision of lesion, benign neurofibroma, pain resolved
14	Pelvis	26	Unchanged
15	L popliteal fossa	23	Asymptomatic after excision of benign neurofibroma
16	Retroperitoneum, R popliteal fossa L popliteal fossa	3	Symptoms unchanged
17	L upper limb	8	Pain resolved, neurofibroma reduced in size
18	R lower limb	9	Symptoms unchanged

minutes, range 53–175 minutes and for 15 benign plexiform neurofibromas it was 111 minutes, median 121 minutes, range 45–206 minutes.

Eighteen patients with NF1 were reassessed 6–26 months (median 9.5 months) after ¹⁸FDG PET was performed (table 3). Two of the five patients with malignant peripheral nerve sheath tumours died from lung metastases, 25 months and 8 months after presentation (cases 3 and 4). Three patients are currently asymptomatic 5 months after surgery (case 5), 12 months after surgery (case 6), and 26 months after surgery and radiotherapy (case 2). The patient with a prevertebral plexiform neurofibroma at L1 and inconclusive histology has persistent symptoms of pain and neurological deficit 9 months after presentation.

Five plexiform neurofibromas were excised in four patients and were benign. These patients have remained asymptomatic 15 months, 3 months, 10 months, and 26 months after surgery (cases 7, 8, 13, and 15). Eight patients with 10 plexiform neurofibromas which were thought to be benign on ¹⁸FDG PET did not undergo surgery, either because the patient refused surgery or the risk of morbidity was too high. They were followed up for 3 to 26 months after presentation (median 9 months). Four of these patients originally presented with pain arising from a plexiform neurofibroma (cases 9, 10, 12, and 17). On follow up, the pain had resolved in all patients except patient 10 who experienced aching in her leg after prolonged standing at work. All patients had reported an increase in size of the plexiform neurofibroma on presentation. Subsequently, six patients reported no further change in size, one patient reported a decrease in size (case 17), and in one case the lesion was in the pelvis and not visible to the patient (case 14). Four patients presented with neurological deficit (cases 12, 14, 16, and 18) and the deficit remained unchanged on follow up (table 3).

Discussion

Qualitative assessment identified all the malignant tumours but yielded false positive results in two lesions. Quantitative assessment showed a significant difference in mean SUV between benign and malignant lesions. However, fig 3 shows an overlap between benign and malignant lesions between SUV 2.7 and 3.3. A cut off of 2.5 for the SUV would yield only one false positive result. Cases 3 and 4 were incorrectly thought to have malignant lesions and in these cases the SUV was calculated at 45–60 minutes after ¹⁸FDG injection. We have recently shown that high grade soft tissue sarcomas attain a peak activity concentration about 4 hours after injection of ¹⁸FDG and benign lesions reach a maximum after 30 minutes.¹⁷ Increased separation between benign and malignant lesions could be obtained by calculating the SUV at about 200 minutes after injection of ¹⁸FDG.

Clinical symptoms did not help us distinguish between benign and malignant lesions. Features considered to suggest malignancy, pain, increase in size of the lesion, and

neurological deficit were all found in both benign and malignant lesions. All the malignant peripheral nerve sheath tumours were painful, but eight patients with benign plexiform neurofibromas also complained of pain. Patient 17 noted a temporary increase in size of a plexiform neurofibroma on the left arm. This could be attributed to bleeding within the lesion which subsequently resolved. Conceivably, the presence of pain, increase in size, and neurological deficit in a benign plexiform neurofibroma reflect a period of active growth of the neurofibroma and the symptoms resolve or improve when the plexiform neurofibroma becomes quiescent. The natural history of plexiform neurofibromas has not been determined and we are participating in a multicentre study coordinated by Boston Children's Hospital to consider this issue.

The detection of malignant change in plexiform neurofibromas using clinical characteristics, MRI, and biopsy is extremely difficult. Our study has shown that ¹⁸FDG PET is a useful non-invasive method of identifying malignant change in plexiform neurofibromas in patients with NF1. We are undertaking a prospective study with appropriate timing of the SUV after injection of ¹⁸FDG and histological examination in all cases to confirm the result of our retrospective study.

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