original article

[\textsuperscript{18}F]2-fluoro-2-deoxy-D-glucose positron emission tomography (FDG PET) as a diagnostic tool for neurofibromatosis 1 (NF1) associated malignant peripheral nerve sheath tumours (MPNSTs): a long-term clinical study

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Background: Malignant peripheral nerve sheath tumours (MPNSTs) are difficult to detect in neurofibromatosis 1 (NF1) individuals. The purpose was to evaluate [\textsuperscript{18}F]2-fluoro-2-deoxy-D-glucose positron emission tomography (FDG PET) and PET computed tomography (CT) as a diagnostic tool for MPNST in NF1 patients with symptomatic plexiform neurofibromas and to verify the diagnosis by pathology and clinical follow-up.

Patients and methods: NF1 individuals with symptomatic plexiform neurofibromas underwent clinical evaluation and magnetic resonance imaging. Qualitative FDG PET and PET CT associated with semi-quantitative maximum standard uptake value (SUV\textsubscript{max}) assessed possible malignant change. Excision/biopsy verified the diagnosis when possible and clinical follow-up was undertaken in all patients.

Results: In all, 116 lesions were detected in 105 patients aged 5–71 years, including 80 plexiform neurofibromas, five atypical neurofibromas, 29 MPNST and two other cancers. Biopsy confirmed the findings in 59 tumours and no MPNST was diagnosed on clinical follow-up of 23 lesions diagnosed as benign on FDG PET and PET CT. FDG PET and PET CT diagnosed NF1-associated tumours with a sensitivity of 0.89 [95% confidence interval (CI) 0.76–0.96] and a specificity of 0.95 (CI 0.88–0.98), but the SUV\textsubscript{max} level did not predict tumour grade.

Conclusion: FDG PET and PET CT is a sensitive and specific diagnostic tool for NF1-associated MPNST. Other PET tracers will be required to solve the problem of predicting tumour grade.

Key words: FDG PET, malignant peripheral nerve sheath tumour, neurofibromatosis 1, plexiform neurofibroma

introduction

Neurofibromatosis 1 (NF1) is a common neurocutaneous disorder that predisposes affected individuals to developing benign and malignant tumours [1]. Neurofibromin, the NF1 gene product, acts as a tumour suppressor by promoting the inactivation of the proto-oncogene p21RAS and by controlling the mammalian target of rapamycin [2, 3].

The characteristic lesions of NF1 are neurofibromas, benign, peripheral nerve sheath tumours that develop as focal cutaneous or s.c. lesions, spinal nerve root tumours and plexiform neurofibromas [4]. Most plexiform neurofibromas are congenital and have been detected clinically in 27% of NF1 individuals and on imaging in ~50% of patients [5, 6]. They are a potent cause of neurological deficit and disfigurement.

Malignant peripheral nerve sheath tumours (MPNSTs) occur with increased frequency and at an earlier age in NF1 compared with the general population [7]. An individual with NF1 has a lifetime risk of 8%–12% of developing an MPNST [8]. MPNST arise predominantly from pre-existing plexiform neurofibromas, they have also been associated with s.c. and spinal nerve root neurofibromas, but malignant change has not been reported in a cutaneous neurofibroma [1]. MPNSTs are difficult to diagnose, as patients do not regard the appearance of a lump as unusual in the context of NF1 and the tumours are often internal and deep seated. MPNSTs metastasise widely and frequently herald a poor prognosis [1, 7].
The clinical manifestations of malignancy are persistent pain that disturbs sleep, rapid increase in size of a neurofibroma, change in texture from soft to hard and new or unexplained neurological deficit [1]. However, these clinical manifestations are experienced commonly by patients with benign neurofibromas. The extensive nature of plexiform neurofibromas often precludes complete excision [1]. Magnetic resonance imaging (MRI) delineates the site and extent of the tumour, but is not a reliable indicator of malignancy [1]. Histopathology is the final arbiter of malignancy, but blind biopsy may miss the focus of malignancy or the highest grade of a heterogeneous tumour.

\( ^{18}\text{F}-\text{fluorodeoxyglucose} \) positron emission tomography (FDG PET) and PET computed tomography (CT) are a dynamic imaging technique that visualises and quantifies glucose uptake in cells and mirrors the increased glucose metabolism in malignant tumours [9–11]. Apart from isolated case reports, only two small studies have addressed the role of FDG PET in the diagnosis of the site and grade of MPNST [12, 13]. In this paper, we report the first major evaluation of FDG PET and PET CT as a diagnostic tool for NF1-associated MPNST and verify the diagnosis by histopathology in 59 of 116 tumours. We assess the clinical indicators of malignancy and monitor the long-term outcome in 105 NF1 individuals undergoing investigation for ‘symptomatic plexiform neurofibromas’ from 1996 to 2005.

patients and methods

patients

The participants attended our national neurofibromatosis clinic at Guy’s and St Thomas’ NHS Hospital Trust, comprising 750 NF1 patients. Eighteen patients from our preliminary series were included in the current study [12]. Approximately 60% of this cohort has plexiform neurofibromas. Patients with classical NF1 or mosaic NF1 and symptomatic plexiform/s.c./spinal neurofibromas were included [14, 15]. Individuals with one or more of the following symptoms associated with a plexiform neurofibroma/s.c./neurofibroma/spinal nerve root neurofibroma underwent clinical assessment: persistent pain lasting longer than a month or causing sleep disturbance; rapid increase in size of the neurofibroma; change in texture from soft to hard; new or unexplained neurological deficit or sphincter disturbance.

Patients were questioned about a personal history of malignancy, radiotherapy and were examined for a neurofibromatous neuropathy [16]. Family history of MPNST, optic pathway glioma and other cancers in first-degree relatives was ascertained.

Fifteen individuals with known MPNST underwent repeat FDG PET or PET CT for new symptoms from lesions in different sites. These were identified as new primary lesions and not metastatic disease and were included in the analysis. Yearly follow-up FDG PET or PET CT was used to detect second tumours and recurrent MPNST in six patients who had been diagnosed with MPNST within the previous 5 years. These scans were not included in the statistical analysis.

ethics

Approval was granted for this study as a multidisciplinary clinical audit of the continuing use of FDG PET and PET CT in Guy’s and St Thomas Trust for this group of patients.

magnetic resonance imaging

MRI was carried out on either a 1.5 Tesla Phillips Intera scanner or a 1.5 Tesla Siemens Avanto. An extremity coil or a phased array coil was always used to identify the site and extent of the tumour. 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 Short Tau Inversion Recovery images were carried out and axial T1 images were carried out before and following the administration of gadolinium-meglumine-triamine-pentacetic acid contrast medium at 0.2 ml/kg. Fat-suppressed T1 scans were carried out postcontrast to identify the extent of local infiltration.

FDG PET and PET CT

From 1996 to 2004, FDG PET was carried out using an ECAT 951R whole body system (Siemens/CTI, Knoxville, TN). From 2004 to 2005, a GE Discovery ST PET/CT was employed. All body images acquired on the Discovery ST were reconstructed using OSEM (ordered subset expectation maximisation) (30 subsets, 1 iteration, 5.14 m postfilter, 4.69 mm loop filter). Images acquired on the ECAT 951 were also reconstructed using OSEM. Comparison of SUV was carried out by assessing recovery curves from the DST and the ECAT 951.

Imaging was carried out in all patients following a 6 h fast. An i.v. injection of 350 MBq of \([^{18}\text{F}]2\text{-fluoro-2-deoxy-D-glucose} \) (FDG) was administered. (The injected activity was calculated on a weight basis and for children the body weight of the child was divided by 70 kg and multiplied by 350 MBq.)

Half body scans were carried out 60–90 min after injection of FDG and delayed local views of the tumour were carried out 240 min following injection of FDG. The acquisition time at 240 min was 10 min per bed position. (A half body scan is a scan carried out from the cerebellum to the mid thigh. If the clinical problem is below mid thigh then separate views of the lower limb are obtained to the feet.)

Scans were evaluated both qualitatively by visual inspection and semi-quantitatively by means of the calculation of the maximum standard uptake value (SUVmax). The SUV is the normalised measurement of FDG 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. Blood glucose was measured in all patients and was normal. The SUV was calculated using the activity per gram of tissue divided by the body weight of the individual in grams and multiplied by 100. The cameras are cross-calibrated and daily quality control and quality assurance measured. The abnormal sites were all larger than twice the full width half maximum of the cameras. The SUVmax was derived as the highest SUV within the mass and was measured at the time of the 4-h scan.

Qualitative assessment was made by a senior nuclear physician (with extensive experience in assessing sarcomas) to establish if the mass was benign or malignant. Qualitative assessment determined whether uptake appeared higher on the delayed image compared with the early image when the local views were carried out. Quantitative assessment was made by the calculation of the SUVmax for the tumour. The uptake was higher than surrounding tissue and greater than liver uptake with no reduction in uptake on the 4-h scan. All scans were reported blind and before a definitive histological diagnosis of the mass.

PET was carried out on the index lesion that caused clinical concern at 240 min. The other lesions identified were those that had high uptake visually and raised concern on the early scan.

statistical analysis

The SUVmax results for malignant and benign tumours and for comparison of the grade of tumour were compared using parametric \( t \)-test and nonparametric chi-square and Mann–Whitney test as appropriate and two-tailed \( P \) values have been quoted. Sensitivities and specificities were calculated using the standard formulae [17].
biopsy/excision and histology
The biopsy was carried out percutaneously using a tru-cut needle with astrocar and cannula which were MRI compatible. This enabled the surgeon to make several passes, thereby obtaining representative sampling of the lesion. Imaging with FDG PET or PET CT was used to direct the biopsy to the site of the highest SUV value. This allowed the surgeon to target areas of localised high uptake, as well as sampling other areas of the lesion.

The histological diagnosis and grading of the tumour were carried out using the criteria of tumour differentiation, vascular invasion, necrosis and the mitotic count to determine whether the tumour was low, intermediate or high grade [18]. Atypical neurofibroma was defined as a neurofibroma exhibiting hypercellularity and nuclear atypia, without mitosis or necrosis [19].

follow-up
All neurofibromas that were reported as positive on FDG PET were excised or biopsied and patients were followed clinically. Individuals with negative FDG PET underwent excision of the neurofibroma if clinically indicated, unless the lesion was inaccessable, and removal would cause unacceptable neurological deficit or the patient refused permission. All patients continued under clinical monitoring. If there was no clinical evidence of malignant change after follow-up for 60 months, the neurofibroma was classified as benign.

results
There were 51 males and 54 females aged 5–71 years [mean age 30.8 years, standard deviation (SD) 13.49]. One hundred individuals fulfilled the NF1 diagnostic criteria and five patients had mosaic/segmental NF1. One hundred and sixteen new lesions were detected and included benign and malignant lesions (Table 1).

Excision/biopsy was carried out on 59 lesions including 23 plexiform neurofibromas, five atypical neurofibromas, 29 MPNSTs and two other cancers (oesophagus and thyroid). There were multiple, simultaneous lesions in 21 individuals. Fifteen individuals underwent between two and six serial scans (mean three scans) and 3 of 15 patients had multiple tumours. The tumours included an atypical neurofibroma and 17 MPNST (eight low-grade, two intermediate grade and seven high-grade tumours). Six asymptomatic individuals had serial scans for known MPNST. Follow-up scans showed no progression or recurrence of tumours, and no new lesions were detected.

Clinical manifestations of malignancy revealed significant differences in change in size and texture between benign and malignant lesions. Visible change in size was noted in 39 of 47 benign neurofibromas and 25 of 25 malignant tumours, $P = 0.044$. Change in texture developed in 4 of 47 benign lesions and 9 of 23 malignant tumours, $P = 0.006$. There was no significant difference in pain or neurological deficit between benign and malignant lesions.

The commonest site for MPNST was the proximal leg, whereas plexiform neurofibromas were found predominantly in the proximal leg, pelvis and abdomen and head and neck. There was no significant difference between patients with benign and malignant lesions with regard to family history of malignancy, personal history of MPNST, optic pathway glioma, other cancers or neurofibromatous neuropathy.

Qualitative assessment of $^{18}$FDG PET revealed four false positive and three false negative scans (Table 2). Sensitivity of FDG PET in diagnosing NF1-associated MPNST was 0.89 [95% confidence interval (CI) 0.76–0.96] and the specificity was 0.95 (CI 0.88–0.98). Other cancers and atypical neurofibromas were excluded from the analysis due to the small numbers (see discussion).

The mean SUVmax was significantly greater in MPNSTs compared with plexiform neurofibromas. The mean SUVmax for 74 plexiform neurofibromas was 1.5 (SD 1.06, 95% CI 1.3–1.8); mean SUVmax for 26 MPNSTs was 5.7 (SD 2.6, 95% CI 3.9–7.7), ($t = 7.2$, df = 97, $P < 0.001$, two-tailed plexiform neurofibromas versus MPNST).

No malignant tumours were detected with SUVmax <2.5 and there were three benign tumours with SUVmax >3.5. Between SUV 2.5 and 3.5, seven benign plexiform neurofibromas and six MPNSTs were detected. Statistical comparison of SUVmax between high-grade and low-grade MPNSTs was significant ($t = 2.05$, df = 18, $P = 0.055$, two tailed) but there was considerable overlap between the groups.

One hundred and five patients were monitored clinically for 0–110 months (mean 40.6 months, SD 2.55 months; see Table 1. Benign and malignant tumours identified in 105 NF1 patients 1996–2005

<table>
<thead>
<tr>
<th>Tumour</th>
<th>N</th>
</tr>
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<tbody>
<tr>
<td>Plexiform neurofibroma</td>
<td>80</td>
</tr>
<tr>
<td>Atypical neurofibroma</td>
<td>5</td>
</tr>
<tr>
<td>Low-grade MPNST</td>
<td>12</td>
</tr>
<tr>
<td>Intermediate grade MPNST</td>
<td>3</td>
</tr>
<tr>
<td>High-grade MPNST</td>
<td>14</td>
</tr>
<tr>
<td>Other cancers (oesophagus, thyroid)</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>116</td>
</tr>
</tbody>
</table>

MPNST, malignant peripheral nerve sheath tumour; NF1, neurofibromatosis 1.

FDG PET/PET CT in the diagnosis of plexiform neurofibromas, atypical neurofibromas, MPNST and other cancers in NF1 patients 1996–2005

<table>
<thead>
<tr>
<th>Type of tumour</th>
<th>Negative on FDG PET</th>
<th>Positive on FDG PET</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plexiform neurofibroma</td>
<td>76</td>
<td>4</td>
</tr>
<tr>
<td>Atypical neurofibroma</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>MPNST</td>
<td>3</td>
<td>26</td>
</tr>
<tr>
<td>Other cancers (oesophagus)</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>

Benign versus malignant tumours chi-square $= 76.5$, df $= 1$, $P < 0.001$. Atypical neurofibromas and other cancers were excluded from the analysis due to small numbers.

FDG PET, $^{[18]}$F-2-fluoro-2-deoxy-D-glucose positron emission tomography; MPNST, malignant peripheral nerve sheath tumour; NF1, neurofibromatosis 1.
Benign plexiform neurofibromas were confirmed on biopsy in 23 cases. There were no new clinical symptoms of malignancy in patients deemed to have benign lesions and only eight of these individuals had persistent symptoms. The symptoms were found to be due to scoliosis and spinal degenerative disease (four patients), spinal hooks causing impingement on the thoracic cord in (two patients) and large tumour burden (two patients).

One individual with intermediate grade lower limb MPNST developed recurrent disease, one patient with a high-grade buttock tumour developed lung secondaries and seven patients with high-grade tumours have died from metastases 5–26 months after diagnosis (median 12 months). A high-grade pelvic MPNST was diagnosed in a 35-year-old man, 2 years after diagnosis of a cervical atypical neurofibroma.

**Discussion**

Based on our unit’s initial experience with soft tissue sarcomas and neurofibroma assessment, we used FDG PET and PET CT from 1996 to 2005 to evaluate symptomatic plexiform neurofibromas in 105 NF1 patients [9, 10, 12]. FDG PET and FDG PET CT diagnosed NF1-associated MPNST with a sensitivity of 0.89 (95% CI 0.76–0.96) and a specificity of 0.95 (95% CI 0.88–0.98). It should be emphasised that the three patients with false negative scans were assessed with FDG PET (not PET CT), all had low-grade MPNSTs and the sensitivity for high-grade MPNST was 1.0.

We were unable to verify our findings by pathological diagnosis in 56 individuals who were deemed to have benign lesions because of inaccessibility of the neurofibroma. However, no patient has developed clinical evidence of malignant disease. Although the study period ended in 2005, monitoring has continued and all patients have been followed up for >2 years and 31 of 56 individuals have been followed for >5 years.

We observed that FDG PET and PET CT was helpful in diagnosing asymptomatic second primary tumours in addition to the symptomatic lesion. A young man complained of severe pain in the buttock due to a high-grade MPNST and PET CT revealed asymptomatic lung and pelvic metastases at presentation in this patient.

Although FDG PET or PET CT identified asymptomatic primary tumours and metastases at presentation, it was not useful for serial monitoring of individuals with known MPNST, who had no symptoms. We did not detect any progressive, recurrent or new tumours on serial follow-up FDG PET or PET CT in six asymptomatic patients with known MPNST, irrespective of tumour grade.

In a previous study, we concluded that the optimum time for measuring SUV in patients with symptomatic plexiform neurofibromas is 240 min after injection of $^{18}$FDG [12]. There was a significant difference between the mean SUV of benign and malignant tumours. However, there was an overlap between benign plexiform neurofibromas and MPNSTs from SUVmax 2.5 to 3.5. When we used FDG PET CT, we did not detect any malignant tumours below SUVmax 2.5, but there were three false positive scans above SUVmax 3.5 (4.1, 4.8 and 6.4). We advocate that symptomatic neurofibromas with SUVmax 3.5 and above should be excised and lesions with SUVmax 2.5–3.5 should be reviewed clinically. Based on clinical experience, we advise that FDG PET CT is repeated in 3 months to determine progression.

We accept that there will be inevitable false positive results. There was considerable overlap in SUVmax between low and high-grade MPNSTs and we were unable to confirm the findings of a small study on 16 NF1 patients that reported that SUV level predicts grade of malignancy of the tumour [13]. Knowledge of tumour grade pre-operatively would facilitate timing of surgery and decisions about the need for postoperative treatment. Further studies using tracers such as methionine, looking at amino acid transport, might be helpful in discriminating between benign plexiform neurofibromas, atypical neurofibromas and low-grade MPNST.

Rapid increase in size and change in texture of a neurofibroma were significantly more prominent in MPNSTs than in benign plexiform neurofibromas. However, there was considerable overlap between the two groups and we could not use these features to differentiate between benign and malignant lesions.

The possibility of other malignancies should be considered when clinicians assess NF1 individuals with plexiform neurofibromas. Two of our patients were referred with symptomatic plexiform neurofibromas in the neck and thorax, respectively. However, $^{18}$FDG PET detected other cancers in adjacent anatomical regions to their neurofibromas in the thyroid and oesophagus. Atypical neurofibromas were detected in five individuals and histology showed cytological atypia with hypercellularity but no mitosis. Two of the lesions were positive on FDG PET/CT PET (SUV max 5.2 and 5.5). It was not possible to draw firm conclusions about the nature of atypical neurofibromas on the basis of five tumours. However, we speculate that the lesions that were positive on FDG PET CT might have malignant potential. We have encountered one patient with a symptomatic plexiform neurofibroma in the thigh, which was positive on FDG PET CT and histology showed changes of a benign plexiform neurofibroma, atypical neurofibroma and MPNST within the same lesion. We have investigated another patient who has had serial atypical neurofibromas and then developed a high-grade MPNST in another part of the body. The PET negative lesions could reflect senescent neurofibromas, but further clinical, pathological and molecular studies are needed to determine the true nature and possible heterogeneity of these lesions.

An international consensus group proposed that patients with plexiform neurofibromas in the brachial plexus, lumbosacral plexus, spinal nerve roots and abdomen/pelvis have an increased risk of developing MPNST and merit careful surveillance [1]. However, in this study MPNSTs were found predominantly in the proximal lower limb, whereas symptomatic plexiform neurofibromas were preferentially located in the proximal lower limb, abdomen/pelvis and head and neck.

Patients with a personal or family history of MPNST or other malignancy, neurofibromatous neuropathy and individuals previously treated with radiotherapy, might have an increased propensity to develop MPNST. We have previously assessed nine individuals as part of a study on neurofibromatous neuropathy and two of them had MPNST [16]. However, we...
were unable to corroborate any of these risk factors in this study and a longitudinal assessment of neurofibromatous neuropathy is required to address this issue. Individuals with whole gene deletions have been reported as having a higher risk of MPNST [20]. We did not do systematic mutational analysis in our patients or address the underlying molecular changes in NFI-associated MPNSTs, but a variety of mutations apart from whole gene deletions were found in this study (and by other researchers) in individuals with MPNST [21].

Five of our patients had MPNST and mosaic NF1, which has been regarded as a milder form of NF1. However, our findings indicate that individuals with plexiform neurofibromas due to mosaic disease require the same careful surveillance as patients with classical NF1.

This study has demonstrated that FDG PET and PET CT is a sensitive and specific diagnostic tool for MPNST in NF1 individuals and constitutes a significant advance in the diagnosis and management of this complex condition. FDG PET and PET CT identifies both symptomatic and asymptomatic primary and metastatic MPNST. Furthermore, the technique permits the surgeon to biopsy the area of maximum uptake of FDG and ensures that the biopsy reflects the highest grade of the tumour in a heterogeneous lesion. Further research with different tracers might differentiate the grade of MPNST. Early identification of patients at risk of MPNST is of paramount importance, and NF1 individuals should be educated about the clinical features of MPNST and instructed how to contact a specialist NF1/MPNST unit.

acknowledgements
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references