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**18-Fluorine Fluorodeoxyglucose positron emission tomography (18F-FDG PET)
in the diagnosis, treatment stratification and monitoring of patients with
retroperitoneal fibrosis (RPF): a prospective clinical study**

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Abstract

Background: The ability to distinguish malignant from benign Retroperitoneal Fibrosis (RPF) and to select the patients who are likely to respond to steroid treatment using a non-invasive test would be a major step forward in the management of patients with RPF.

Objective: To prospectively evaluate the potential of 18F-FDG-PET to improve clinical decision-making and management of RPF patients.

Design, setting and participants: 122 RPF patients have been assessed and managed by a multi-disciplinary RPF service between January 2012 and December 2015. 78 of these patients have undergone 101 FDG-PET scans, as well as CT and blood tests. Management was based on the findings of these investigations. Median follow up was 16 months.

Results and limitations:

0/24(0%) patients with a negative 18F-FDG-PET had malignancy on biopsy (NPV 100%).

18F-FDG-PET identified malignancy in 4/4 (100%) patients prior to biopsy. All 4 patients had a highly avid PET (maximum standardised uptake value ≥ 4) with atypical distribution of avidity.

18F-FDG-PET detected avidity in 19/38 (50%) patients with normal inflammatory markers and demonstrated no avidity in 10/63 (16%) patients with raised markers.

Patients with a highly avid PET were significantly more likely to respond to steroids compared to those with low avidity or negative PET (9/11(82%) vs 3/24(12%), $p<0.01$; and 9/11(82%) vs 0/14(0%); $p<0.01$).

Limitations include the small number of patients and the predominantly tertiary referrals which may represent patients with particularly problematic RPF.

Conclusions: This study has established a promising role for 18F-FDG-PET in optimising and individualising the treatment of RPF patients.

Patient summary: This study shows that a FDG-PET scan could reduce the need for biopsy because it is able to distinguish cancer from non-cancerous RPF, and may be better than blood tests at assessing and monitoring RPF. It also appears to predict response to steroids which should allow more individualised treatment.

69 Introduction

70 Retroperitoneal fibrosis (RPF) can be a challenging disease to manage and there are no
71 published guidelines. Important considerations include the identification of malignancy
72 which can mimic RPF; the management of ureteric obstruction; the role of biopsy and
73 associated complications; minimising side effects from long courses of steroids and reducing
74 morbidity from major abdominal surgery, viz, ureterolysis [1,2]. Other challenges include
75 delayed diagnosis; intractable pain; morbidity from ureteric stents and the operations to
76 change them.

77
78 Helpful in addressing some of these challenges would be a non-invasive, safe and reliable
79 method of firstly, excluding malignancy without the need for biopsy and secondly, predicting
80 and monitoring response to immuno-suppressants. A number of approaches have been
81 investigated but all have limitations.

82
83 CT or MRI are valuable but may not definitively exclude malignancy and the degree of
84 contrast enhancement does not appear to reflect metabolic activity within the RPF or
85 predict response to steroids [3]. This inability to distinguish malignant from benign RPF on
86 imaging necessitates biopsy in many cases. However, RPF does not always produce a
87 discrete mass amenable to biopsy and even if a mass is present, its proximity to major blood
88 vessels may make percutaneous biopsy not feasible. These problems can lead to biopsy
89 being non-diagnostic in up to 33% of cases [4]. Open surgical biopsy has better yields but is
90 more invasive [5]. Furthermore, the clinical implications of a 'positive' biopsy are not clear
91 since the histological characteristics of RPF are not well-defined and the biopsy protocol is
92 not standardised in terms of number of biopsies or immune-histochemical panel needed

[2,6]. In practice these limitations mean that many patients commence drug treatment without prior histological exclusion of malignancy.

RPF, like many other fibro-inflammatory disorders, appears to have both an active inflammatory phase and a more chronic, non-inflammatory fibrotic phase [7]. Distinguishing between these phases could be crucial in guiding clinical management and allowing individualized treatment; for example, if inflammatory RPF responded to steroids better than predominantly fibrotic RPF.

Currently the best surrogates for identifying inflammatory activity within RPF are elevated serum inflammatory markers – Erythrocyte Sedimentation Rate (ESR) and C-Reactive Protein (CRP) - and in most practices form the basis of both decisions to treat with steroids and assessing response. However, these markers are non-specific [8] and their use may be problematic in patients who have other reasons for raised inflammatory markers (e.g. UTI, stents, systemic autoimmune disease). Furthermore, intense inflammatory activity in small but potentially clinically significant plaques may not generate changes in systemic inflammatory markers.

These dilemmas have led to investigations of alternative imaging modalities in RPF. Case reports and preliminary studies have suggested a possible role for FDG-PET (table 1). Interest in FDG-PET for the evaluation of inflammation began with the observation that FDG shows increased uptake not only in malignant cells, but also in inflammatory cells [9]. Subsequent work has addressed its potential value in inflammatory disorders such as vasculitis, sarcoidosis and automimmune conditions [10,11]. FDG-PET is also able to identify actively inflamed joints with higher sensitivity than clinical symptoms or ESR/CRP [12].

Based on these initial reports we hypothesised that ¹⁸F-FDG-PET, because of both the anatomical and functional information that it can provide, might identify the rare instances of malignancy mimicking RPF; might differentiate between inflammatory and fibrotic RPF thereby shaping treatment decisions; and might provide an accurate method of monitoring treatment response.

Methods

A multi-disciplinary RPF service was established at Guy's Hospital in London in January 2012. The protocol for investigation of patients evolved over the first year, with 18F-FDG-PET initially being used only to resolve uncertainties with regard to malignancy. From July 2013 patients requiring imaging were investigated using a combination of standard CT and 18F-FDG-PET. Patients who were asymptomatic and appeared to have no clinical issues related to RPF did not have FDG-PET. Data on all patients undergoing 18F-FDG-PET between July 2013 and January 2016 were prospectively collected. Biopsy was undertaken where technically feasible and safe. Inflammatory markers, ESR (normal value < 20mm/hr) and CRP (normal value < 5mg/L), were measured within 1-14 days of the FDG-PET scan.

18F-FDG-PET images were acquired using either a Discovery DST or VCT scanner prior to October 2014 and one of two GE PET/CT 710 scanners after this date. An injected activity dose of 350 MBq 18F-FDG was injected intravenously. Images were acquired 90 minutes after the injection. Image acquisition was performed with a field of view covering the head to mid-thigh using a setting of 4 minutes per bed position with 5-8 bed positions. Images were reconstructed using the ordered subsets expectation maximization algorithm with a reconstructed slice thickness of 3.27mm and pixel size 4.7mm. The CT component of the scans was acquired at 120 kVp and 65 mAs without administration of oral or intravenous contrast agent.

Each PET scan was reported in consensus by two PET experts firstly with a qualitative analysis comparing to blood pool avidity, then quantitative analysis with measurement of the maximum standard uptake value (SUVmax).

FDG-avidity on PET was categorized as negative, low grade ($SUV_{max} < 4$), and high grade ($SUV_{max} \geq 4$). FDG-avidity was used as a proxy for inflammation based on previous human

and animal studies [13].

Perivascular distribution of RPF was classified as typical.

Data was collected on demographics, clinical presentation, radiological, histopathological and serological parameters, treatments and treatment responses. A hybrid standard had to be used with regard to malignancy – if biopsy (open or percutaneous) was not carried out, follow up was used as confirmation of benign disease. Treatment response was defined as any shrinkage of mass, reduction in SUVmax on PET, or normalisation of serum inflammatory markers where no other cause for raised markers was identified.

In previously untreated patients the starting dose of steroids used was 20mg twice daily.

Descriptive statistics were used to summarise the data. Percentages were used for categorical data. Statistical analysis was with student *t* test for continuous variables and the χ^2 test for categorical variables. Statistical significance was defined as $p < 0.05$.

Results

78 patients underwent 101 PET scans. 78/101(77%) of these scans were performed at the time of first consultation in our RPF service and 23/101 (23%) as part of follow up. Median follow-up: 16 months (range 6-42 months). Baseline characteristics of the patients are outlined in table 2.

Diagnosing malignancy: FDG-PET vs biopsy (table 3)

69/78 (88%) patients had both FDG-PET and a histological diagnosis from image-guided or surgical biopsy. In 9/78(11%) biopsy was felt to be unsafe or not possible.

Negative PET (image 1a) 24/69 (35%); 0/24 (0%) malignant. NPV 100% (95% CI: 0.95-.097)

Positive PET (image 1b) 45/69 (65%):

Low grade FDG-avidity 26/45 (58%); 0/28 (0%) malignant

High grade FDG-avidity typical distribution (image 1b) 11/45 (24%); 0/11 (0%) malignant

High grade FDG-avidity atypical distribution (image 1c) 8/45 (18%); 4/8 (50%) malignant

All 4 malignant cases (2 lymphoma, 1 adrenal cancer, 1 metastatic melanoma) were highly FDG-avid and the avidity was not peri-vascular. All 4 were reported as 'highly suspicious for malignancy' prior to biopsy giving a sensitivity of 100% for diagnosing malignancy. 4 patients with high FDG-avidity and atypical distribution had benign histology; 3/4 (75%) IgG4-related RPF. The PPV of an atypical high avidity PET for detecting malignancy is 50% (95% CI: 0.12-0.43).

Predicting response to steroids (table 4)

209 62/78(79%) patients were prescribed steroids
210 47/62(76%) patients underwent FDG-PET
211 14/47(28%) negative (image 1a); 24/47(49%) low-grade FDG-avidity (SUVmax<4; image 1d);
212 11/47(23%) high-grade FDG-avidity (SUVmax≥4; image 1b)
213 Response to steroids corresponded to degree of initial FDG uptake on PET (table 3).
214 Patients with high-grade FDG-avidity on PET (median SUVmax 9.2) were more likely to
215 respond to steroids than patients with low-grade FDG-avidity (median SUVmax 3.1) or
216 negative PET (high grade 9/11 (82%) vs low grade 3/24(12%), p<0.005 value; vs negative
217 0/14(0%); p<0.005).

218

219 **Diagnosing inflammatory activity: FDG-PET vs serum inflammatory markers (table 5)**

220 CRP was recorded at the time of 101/101(100%) PET scans and ESR for 84/101(83%).
221 Relationship between FDG-PET findings and CRP+/- ESR (if tested) are outlined in table 5. In
222 29/101 (29%) of scans there was discordance between FDG-PET findings and inflammatory
223 markers.
224 Inflammatory markers have a sensitivity of 71% and specificity of 62% for detecting
225 active/inflammatory RPF if FDG-PET is used as a proxy for inflammatory activity within the
226 RPF [13].
227 In 19/38 (50%) scans there was FDG uptake within the RPF despite normal markers. In 17/19
228 (90%) of these the FDG uptake was low grade (SUVmax<4) and in 2/19 (10%) avidity was
229 high grade (SUVmax>8) but localized e.g. over a short segment of the iliac artery (image 3).
230 In these 2 cases patients responded well to steroids with improvement in pain and decrease
231 in FDG-avidity.

232 The 10 patients who had no FDG-avidity despite raised markers had no response to steroids.

233

234 9/101(9%) PET scans showed incidental increase in FDG uptake in other organs; duodenum
235 (3), stomach (1), colon (2), lung (1), axilla (1) and thyroid (1). All 9 patients were referred for
236 further evaluation. Two had very significant findings: one patient was diagnosed with
237 metastatic axillary melanoma (image 4a); and another was diagnosed with Wegner's
238 granulomatosis following lung biopsy (image 4b). Four had no pathology on endoscopy and
239 one was diagnosed with duodenitis. The patient with uptake in the thyroid was diagnosed
240 with a goitre.

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Discussion

This study suggests ¹⁸F-FDG-PET has the potential to improve clinical decision-making in RPF. It appears to be able to identify patients that are at high risk or low risk of malignancy pre-biopsy; it may help guide decisions regarding commencement or cessation of steroid treatment; and it can reveal plaques of inflammatory RPF not detected by serum inflammatory markers.

The existing literature on PET in RPF consists mainly of case reports and small heterogeneous retrospective analyses. These are outlined in table 1. They are essentially preliminary studies that have pointed to a possible role for FDG-PET in RPF but have not been able to fully explore or define this role. In common with many other rare diseases, specialised clinical services are lacking making it difficult to study different aspects of the disease in a systematic manner. Our aim with this study was to evaluate FDG-PET prospectively in a larger cohort of RPF patients.

None of the 24 patients with a negative FDG-PET proved to have malignancy on biopsy or developed malignancy during follow up. This suggests that a biopsy may not be required when there is no uptake within the RPF mass. It is however known that not all cancers, particularly if small, generate a positive FDG-PET, but it would seem that cancers of the type and volume that might mimic RPF are very rarely FDG negative [14,15].

Malignancy in the retroperitoneum was identified in 4 cases, all of whom had both a highly avid FDG-PET and non-typical distribution of avidity. Idiopathic RPF tends to have a perivascular distribution of avidity whereas the avidity of malignancy is more dispersed (image 1b vs 1c).

279

280 Half the patients with high avidity and atypical distribution on FDG-PET proved to have
281 malignancy. Of the others, 75% had features on biopsy in suggestive of IgG4-related RPF.
282 IgG4-related RPF is a complex disorder [16] whose clinical significance is debated but it may
283 represent a more aggressive subtype of RPF [2,17].

284

285 Two further points are worthy of mention about the clinical utility of FDG-PET. Firstly, it may,
286 on occasion, be more accurate than biopsy for detecting malignancy. In one case (image 2)
287 two biopsies at the referring hospital had shown fibrosis; PET appearances led to a third
288 targeted biopsy diagnosing lymphoma. Secondly, PET may reveal clinically significant extra-
289 abdominal disease; high volume axillary melanoma in one patient (image 4a) and Wegener's
290 granulomatosis (image 4b) in another.

291

292 To date no cancer has been identified in patients with avid FDG-PET and typical peri-aortic
293 distribution of avidity suggestive of peri-aortitis. This finding may have clinical value because
294 biopsy in these situations can be challenging due to the risk of arterial injury. Currently we
295 would continue to recommend biopsy if technically feasible but it may be in time that biopsy
296 is not required in these cases.

297

298 The presumed basis of steroid treatment in RPF depends on the suppression of inflammation
299 [18]. What has not been clear to date is whether steroids have therapeutic benefit in the
300 absence of inflammation. None of the 14 (0%) patients with negative FDG-PET and only
301 3/24(12%) with low-grade avidity on FDG-PET (SUVmax<4) had a measurable response to
302 steroid treatment. By contrast 9/11 (82%) patients with high-grade avidity responded.

These findings may be of value in decisions regarding initiation or continuation of steroid therapy. The morbidity of oral steroids is considerable with over 80% complaining of ≥ 1 side effect [19] and an individualised approach based on prediction of response is therefore desirable. Our findings will need validation in larger cohorts, particularly of steroid naïve patients but our policy is to avoid continuation or commencement of steroids in patients with a negative FDG-PET.

A noteworthy observation is that inflammatory activity within RPF plaques may not always be associated with elevations in serum inflammatory markers. In 29/101 (29%) PET scans there was discordance between PET findings and serum markers. 19/38(50%) of scans demonstrated avidity despite normal serum markers. Whilst the majority of avidity in these cases was low grade, two patients had intense localised avidity.

By contrast, 10/63 (16%) PET scans were negative despite raised serum inflammatory markers. In these patients, raised markers may be a reflection of systemic autoimmune diseases, infection or the consequences multiple interventions to manage acute complications of RPF. The value of FDG-PET when markers are raised may be the knowledge it provides about the degree of inflammation within the anatomical area of interest. This could have clinical implications as drug treatment may not be worthwhile in patients who have a negative FDG-PET despite raised serum inflammatory markers due to other causes.

By extension, serum inflammatory markers alone are probably not sufficient for monitoring disease activity or evaluating treatment response.

There are a number of limitations to this study. This study is of only 78 patients. However, a cohort of 78 patients accrued over 3 years does represent a high volume RPF practice. The

biggest clinical study of RPF to date accrued 180 patients over 11 years [5]. Clearly though our findings will need to be validated across wider populations.

Secondly, the majority of patients in this study were tertiary referrals; many had been heavily pre-investigated and pre-treated and could represent a group with particularly problematic RPF. Our practice continues to accrue fresh untreated patients in whom our findings can be tested and validated.

Thirdly, due to the evolution of the study over time and the heterogeneity of the clinical scenarios it was not possible to investigate or treat all the patients uniformly. Nevertheless, the patients have been managed by the same multi-disciplinary team in an effort to deliver as consistent an approach as possible.

Conclusion

In this study of RPF patients investigated prospectively with 18F-FDG-PET we conclude that:

- Retroperitoneal malignancy mimicking RPF appears to be highly avid on PET and has an atypical anatomical distribution
- A negative 18F-FDG-PET may be useful in excluding retroperitoneal malignancy – 0/24 patients with negative PET had malignancy on biopsy
- Steroids may not be beneficial if the 18F-FDG-PET is negative – 0/14 patients with a negative PET had a response
- 29% of patients had discordance between serum inflammatory markers and 18F-FDG –PET findings, raising questions about the validity of surveillance schedules based on markers alone

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