Pergamon

European Journal of Cancer Vol. 31A, No. 12, pp. 1924–1927, 1995

0959-8049/95 $9.50+0.00

0959-8049(95)00421-1

Special Paper

Can Positron Emission Tomography (PET) be Used to Detect Subclinical Response to Cancer Therapy?

P. Price and T. Jones on behalf of the EC PET Oncology Concerted Action and the EORTC PET Study Group

PET Oncology Group, Cyclotron Unit, MRC Clinical Sciences Centre, Royal Postgraduate Medical School, Hammersmith Hospital, Du Cane Road, London W12 0NN, U.K.

At the EORTC NCI New Drug Development Meeting in Amsterdam in 1994, a workshop, suggested by the EC PET (positron emission tomography) Oncology concerted action, was held to bring together many of those European PET centres investigating the use of [^{18}F]FDG ([^{18}F]2-fluoro-2 deoxyglucose) PET scanning as a measure of response to cancer therapy. Of the current 31 PET centres in Europe invited to contribute, 15 centres already had data and others expressed interest. Many of the groups were collaborating with local oncologists to measure tumour response to chemotherapy (12 groups) and radiotherapy (three groups) with this technique. Despite variations of methodology, and difficulties in data interpretation, assessment of tumour [^{18}F]FDG uptake was thought to be a reasonable method for the functional imaging of tumours, assessing metabolic rate and providing a measure of tumour response. Broadly, pooling experience, it would appear that changes in [^{18}F]FDG tumour uptake following one or two cycles of chemotherapy treatment was related to ultimate clinical responses. Patients showing most reduction in [^{18}F]FDG uptake achieved the best clinical responses. Data were also available on the effect of chemotherapy on normal tissues and some data on the effect of radiotherapy and tumour response. It was concluded that changes in [^{18}F]FDG uptake as measured with PET may provide useful information on clinical as well as subclinical response of tumours to anticancer therapy. This could be useful as a guide to early response to therapy as well as providing functional assessment of residual masses of disease. More specific markers of cellular proliferation e.g. [^{11}C]thymidine, or [^{11}C]- amino acids may provide even more accurate information. A strategy was outlined whereby PET scanning protocols could parallel EORTC early clinical trials so that [^{18}F]FDG response information could supplement phase I and II clinical studies. Following these developments, an EORTC study group was formed under the auspices of the EORTC research branch, and the strategy for future development in Europe outlined.

Key words: PET oncology, ^{18}F-FDG response assessment
Eur J Cancer, Vol. 31A, No. 12, pp. 1924–1927, 1995

INTRODUCTION

POSITRON EMISSION TOMOGRAPHY (PET) is a unique technique which allows the measurement of tissue function *in vivo* using compounds labelled with short-lived positron emitting radionuclides. This technique has been used extensively in neuroscience for functional mapping of the brain as well as in cardiology and psychiatry. Its role in oncology has been previously underdeveloped despite the potential of *in vivo* functional assessment of tumours in man, representing a major step forward in our armamentarium for developing anticancer strategies. However, recent innovations in PET methodology have meant that anticancer therapy can now be investigated *in vivo* in man.

PET methodology is multidisciplinary, involving both radiochemistry, quality control, clinical scanning of patients, metabolite analysis, and collection and modelling of data. There are some 31 PET centres in Europe and many are now developing an interest in oncology.

The most widely used radiopharmaceutical for studies of tumour metabolism in oncology is [^{18}F]FDG ([^{18}F]2 fluoro-2 deoxyglucose). [^{18}F]FDG has a low rate of dephosphorylation and so is transported, phosphorylated and metabolically trapped in tumour cells as fluorodeoxyglucose-6-phosphate [1]. It has been reported for use in imaging a number of different types of cancer [2]. There are variations in methodology for quantitation

Correspondence to P. Price.
Received 15 Feb. 1995; accepted 16 May 1995.

of [^{18}F]FDG, e.g. measuring tumour to normal tissue ratio standardised uptake value (SUV), or the kinetic approach using non-linear test-squares fit or graphical methods of analysis. Recognised problems with interpretation of the data include the relationship between [^{18}F]FDG uptake and tumour hexokinase activity, and tumour macrophage uptake of tracer contaminating the signal. Further work is also being carried out on the role of glucose transporters to separate out FDG metabolism from transport.

Potential benefits of this non-invasive *in vivo* functional imaging of tumours include staging of patients, detection of subclinical disease, identification of unknown primary tumuors and the differentiation of tumour recurrence from fibrosis. The advantage of PET–FDG over conventional imaging, such as computed tomography (CT) and magnetic resonance imaging (MRI) scanning, has been explored in a number of sites, for example, head and neck cancer [3]. More recently, PET has been used for the evaluation of tumour viability after chemotherapy for germ cell tumours and malignant lymphomas [4].

However, functional imaging potentially provides far more information about tumours than just imaging the lesion. PET groups are now beginning to explore these areas. The first step has been to investigate whether PET–FDG could provide clinicians with relevant *in vivo* functional information, for example, a guide to the aggressiveness of tumours. Several studies have been undertaken around the world, and tumour uptake of [^{18}F]FDG has been reported to correlate with histological grade in gliomas [5], non-Hodgkin's lymphoma [6], musculoskeletal tumours [7], and liver tumours [8]. However, a lack of correlation has been seen in lung [2] and head and neck tumours [9].

This workshop was convened during the 1994 9th EORTC NCI symposium on new drugs in cancer in Amsterdam to draw together those centres in Europe with data and with an interest in using PET–FDG to measure tumour response to anticancer agents. The workshop was sponsored within the EC concerted action for PET oncology, and aimed to advance this approach in *in vivo* functional imaging in oncology by focusing on the potential use of PET–FDG in measuring tumour response.

PATIENTS AND METHODS

Fifteen PET centres presented data, three further centres attended to observe and 10 replied to the invitation expressing an interest. In general, European PET Groups have been able to generate good collaboration with their clinical colleagues including surgeons, neurologists, radiotherapists and oncologists. However, only one group had an oncologist working as part of the PET group.

PET methodology

PET–FDG methodology varied between groups depending on equipment sensitivity, manpower available and previous experience as a measure of FDG uptake. Most groups recorded data as either a tumour to normal tissue ratio, or provided more quantitative data as accumulation rate of the tracers derived from graphical analysis. All groups except one, studied patients fasting.

Localisation of the tumour on the PET–FDG scan was made using a visual comparison with a CT scan. Coregistration of the PET–FDG and CT image was performed by some groups, and was considered to be important for accurate FDG assessment. Some groups investigating brain tumours used stereotactic localisation of tumours.

The timing of assessment of tumour [^{18}F]FDG was generally after one cycle of treatment. Some groups looked at early response, for example, after 1 day following BCNU treatment for a brain tumour, one group found that supermetabolic tumour reaction at 1 day was predictive of longer survival [10]. Two groups performed serial scans following low grade gliomas, for example, [^{18}F]FDG measurements at 12 and 100 months.

More accurate data were considered to be obtained when patients fasted more than 12 h prior to [^{18}F]FDG assessment and iterative reconstruction of data was considered to provide a much clearer signal. Variations in the signal within tumours was evident, such as in soft tissue sarcomas and brain tumours, and it was often felt that the rim of the tumour gave details of viable tumour, and perhaps provided the clearest measure of response in tumours.

RESULTS

A range of tumours were under investigation: brain tumours (four groups), lymphomas (three groups), colonic metastases (three groups), soft tissue sarcomas (one group), breast cancer (three groups), germ cell tumours (one group) and thyroid cancer (one group).

The specificity of FDG in defining tumours was available from two groups who had the opportunity to study patients prior to surgical removal of the tumour. The specificity of tumour [^{18}F]FDG uptake was recorded at 100% for lymphomas (10 patients) and for germ cell tumours (15 patients).

The sensitivity of FDG in detecting tumour was defined in two groups with access to surgical data. In testicular tumours in 18 patients, the sensitivity was found to be 78%, but 100% in tumours greater than 1 cm. One group recorded a sensitivity of 90% in 14 patients with breast tumours, and felt this was related to tumour density rather than size of tumour.

Staging information was available in lymphoma patients. Histological grading was found to be related to [^{18}F]FDG uptake in lymphomas. In one group of lymphomas studied, [^{18}F]FDG measurement was shown to upstage 3 of the 6 patients with stage 3 disease. Total volume of disease in the patient as measured with [^{18}F]FDG uptake was found to be proportional to the serum LDH (lactate dehydrogenase).

Assessment of residual disease after treatment was available in lymphoma patients using FDG to measure any subclinical residual activities. In a group of 9 patients, a complete response

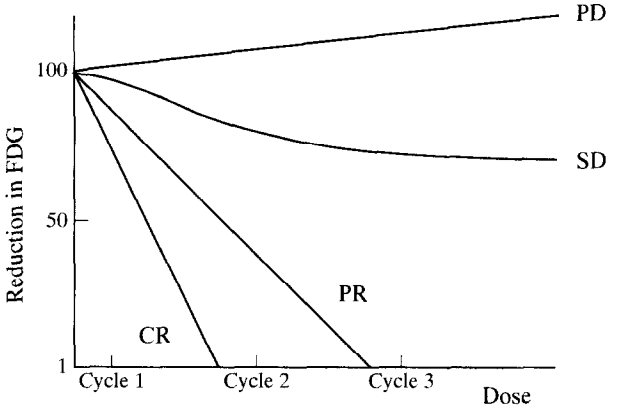


Figure 1. Hypothetical illustration of how percentage change in tumour [^{18}F]FDG uptake may be related to clinical outcome. PD, progressive disease; SD, stable disease; PR, partial response; CR, complete response.

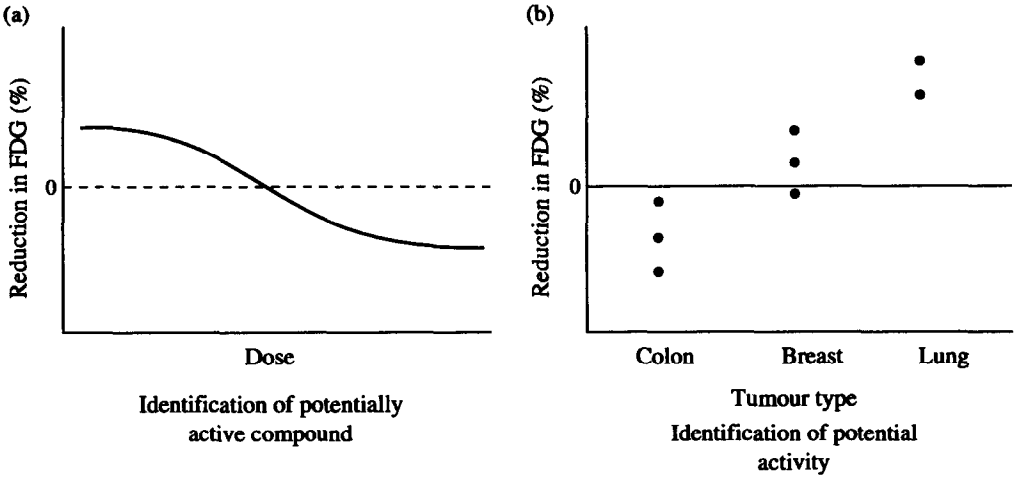
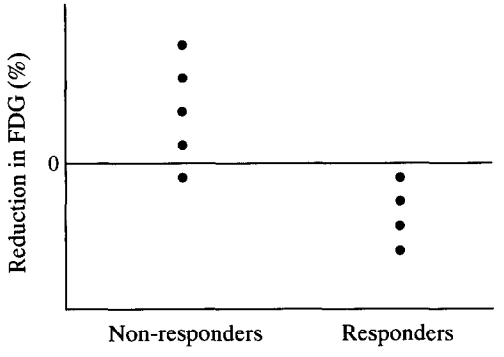


Figure 2. Potential use of FDG–PET in phase I clinical trials. (a) The percentage change in FDG that could be seen at increasing dose levels. A curve as shown, demonstrating a reduction in FDG uptake in tumours with increasing dose level, may indicate an active compound. (b) The percentage change in FDG that could be seen within certain tumour types. The tumour types showing reduction in FDG following treatment may be similar to those identified as potentially responding tumour types at the *in vitro* testing stage.



Use data from non-responders

1. Identification of predictors of response.
2. Alterations in scheduling and changes in all patients.

Figure 3. Potential use of FDG–PET in phase II clinical trials. The patients who show clinical response and those who do not could have their percentage reduction in FDG compared. The conventional clinical response is rigid and may miss the positive effects of changes in scheduling etc. Using a measure of reduction in FDG in patients to further subclassify response, all patients could then be used in analysis, providing more information of predictors or response and measurements of alterations in dose and scheduling.

was evident, but of those, 30% still demonstrated [^{18}F]FDG uptake and these went on to progress, suggesting that FDG may be a good marker of residual subclinical disease.

Dose–response data

This was available in range of tumours. For example, 9 patients with soft tissue sarcomas of the limb were studied with [^{18}F]FDG before and after isolated limb perfusion with cytokines and chemotherapy. PET–FDG response was compared with clinical response and histological response following local resection of tumour. One group looked at response to radiotherapy in low grade gliomas, while another looked at response to lymphomas treated with standard cyclophosphamide, doxorubicin, vincristine and predisolone (CHOP) chemotherapy. Response data were available in sarcomas, lymphomas, breast, colon, melanoma and high grade gliomas. Broadly, there was a trend towards percentage change in FDG uptake before and after treatment, being related to response.

Further information will be available shortly on response in lymphomas and gliomas, and also postradiotherapy changes in radical treatment of the oesophagus.

Other tracers are being investigated, including, meth-^{11}C-methionine and L-[1-^{11}C] tyrosine, to measure amino acid metabolism. Using L-[1-^{11}C] tyrosine, it is possible to quantify a protein synthesis rate. [^{11}C]Thymidine is also being developed, and its rate of incorporation into tumours may be more related to DNA synthesis.

DISCUSSION

It was encouraging that so many European PET groups had been able to form important oncology collaborations, moving on from using PET just as a sophisticated imaging tool and starting to obtain data about the usefulness of functional imaging in assessing clinical response. On the limited data available, it would appear that the percentage change in FDG following treatment (perhaps even after one cycle) may parallel and predict eventual clinical outcome. This is in keeping with the very limited published clinical data. Minn and associates [11] and Ichiya and associates [12] both report a more prominent reduction in [^{18}F]FDG uptake in clinically responding tumours than non-responders in a series of head and neck tumours in miscellaneous patients following radiotherapy treatment. Also, Holthoff and associates [13] noted, in a series of 7 children with posterior fossa and primitive neuroectodermal tumours, that the more marked the decrease in tumour glucose metabolism following chemotherapy, the longer the period of initial clinical improvement.

The timing of assessment of change in FDG uptake may be important. Two published reports have demonstrated an increase in tumour metabolism 24 h after chemotherapy [10,14]. From limited published data and the data presented here, [^{18}F]FDG assessment 1 week after chemotherapy would appear sensible in order to avoid misinterpretation of tumour activity. If such a relationship can be confirmed with larger series, PET–FDG imaging will be of considerable use in early clinical trials where a subclinical measure of response to disease may provide a good indication of drug activity. Figure 1 is a hypo-

thetical illustration of how percentage change in tumour [^{18}F]FDG uptake may be related to clinical outcome. If more studies, particularly in protocols for tumours with a wide range of responses, are performed, this hypothesis could be tested. If true, this may have profound implications for the assessment of subclinical response. For instance, Figures 2 and 3 outline changes in FDG that may be seen in phase I and subsequently phase II clinical trials. In phase I trials (Figure 2), if FDG measurements were made before and after treatment at increasing dose levels, one would hope to see a reduction in FDG tumour uptake following treatment with increasing dose if the drug had any activity. If no activity was anticipated, then no change or an increase in FDG following treatment would be seen for each patient. Changes in FDG in certain tumour types may also parallel the preclinical assessment *in vitro*. In phase II clinical trials (Figure 3) parallel FDG response data may be able to be used to understand more about non-responders. A gradation of FDG with a range of responses may be seen, in which case, it could define those patient groups that had a range of 'conventional non-response' and this may help to stratify future studies and further define potential indicators of response in tumours.

The data presented at the meeting were sufficiently encouraging for the following conclusions to be made:

(1) PET–FDG has potential as a non-invasive *in vivo* tool to measure tumour response to anticancer therapy. This may have important implications for use in early clinical trials and for anticancer drug development.
(2) More data are required paralleling FDG–PET studies with clinical oncology protocols, particularly in tumour types where a range of tumour response is expected e.g. breast cancer etc. The larger the body of data that can be collected, the more the hypothesis in Figure 1 can be tested.
(3) FDG–PET studies paralleling phase I and II clinical trials would be an important strategy for the future.
(4) More data on the sensitivity and specificity of the FDG–PET technique are required as well as continued advancement of PET methodology.
(5) Data comparing clinical response with other newer PET measures of tumour metabolism should be collected, for example, with [^{11}C]methionine, [^{11}C]tyrosine and [^{11}C]thymidine.

To develop this field further, and in recognition of the potential of this powerful technique in oncology, the EORTC has established a EORTC PET study group under the auspices of the EORTC research branch. The aim of the group is to facilitate PET/clinical collaborations within the EORTC and stimulate the clinical direction of this growing field.

1. Gallagher BM, Fowler JS, Gutterson NF, MacGregor RR, Chung-Nan W, Wolf AP. Metabolic trapping as a principle of radiopharmaceutical design: some factors responsible for the biodistribution of [^{18}F]2-deoxy-2-fluoro-D-glucose. *J Nucl Med* 1978, **19**, 1154–1161.
2. Strauss LG, Conti PS. The applications of PET in clinical oncology. *J Nucl Med* 1991, **32**, 623–648.
3. Mancuso AA, Drane WF, Kukherji SK. The promise of FDG in diagnosis and surveillance of head and neck cancer. *Cancer* 1994, **74**, 1193–1195.
4. Bares R, Altehoefer C, Cremerius U, *et al.* FDG–PET for metabolic classification of residual lymphoma masses after chemotherapy. *J Nucl Med* 1994, **35**, 131P.
5. DiChiro G, DeLaPaz RI, Brooks RA, *et al.* Glucose utilisation of cerebral gliomas measured by [^{18}F] fluorodeoxyglucose and positron emission tomography. *Neurology* 1982, **32**, 1323–1329.
6. Leskinen-Kallio S, Ruotsalainen U, Nogren K, Teräs M, Joensuu H. Uptake of carbon-11-methionine and fluorodeoxyglucose in non Hodgkins's lymphoma: a PET study. *J Nucl Med* 1991, **32**, 1211–1218.
7. Kern KA, Brunetti A, Norton JA, *et al.* Metabolic imaging of human extremity musculoskeletal tumours by PET. *J Nucl Med* 1988, **29**, 181–186.
8. Okazumi S, Isono K, Enomoto K, *et al.* Evaluation of liver tumours using fluorine-18-fluorodeoxyglucose PET: characterisation of tumour and assessment of effect of treatment. *J Nucl Med* 1992, **33**, 333–339.
9. Haberkom U, Strauss LG, Rersser Ch, *et al.* Glucose uptake, perfusion and cell proliferation in head and neck tumours: relation of positron emission tomography to flow cytometry. *J Nucl Med* 1991, **32**, 1548–1555.
10. De Witte O, Hildebrand T, Luxen A, Goldman S. Acute effect of carmustine on glucose metabolism in brain and glioblastoma. *Cancer* 1994, **74**, 2836–2842.
11. Minn H, Paul X, Ahonen A. Evaluation of treatment response to radiotherapy in head and neck cancer with fluorine-18-fluorodeoxyglucose. *J Nucl Med* 1988, **29**, 1521–1525.
12. Ichiya Y, Kuwrabora Y, Otsuka M, *et al.* Assessment of response to cancer therapy using fluorine-18-fluorodeoxyglucose and positron emission tomography. *J Nucl Med* 1991, **32**, 1655–1660.
13. Holthoff VA, Herholz K, Berthold F, *et al. In vivo* metabolism of childhood posterior fossa tumours and primitive neuroectodermal tumours before and after treatment. *Cancer* 1993, **72**, 1394–1395.
14. Rozenthal JM, Levine RL, Nickles RJ, Dobkin JA. Glucose uptake by gliomas after treatment. A positron emission tomographic study. *Arch Neurol* 1989, **46**, 1302–1307.

Acknowledgements—PET groups and members present or contributing to the meeting: Dr Karl Herholz, Cologne, Germany; Dr Ulrich Roelcke and Professor Nico Leenders, Zurich, Switzerland; Dr Serge Goldman, Brussels, Belgium; Dr Pat Price and Dr Terry Jones, London, U.K.; Dr Roland Bares, Aachen, Germany; Professor Reske and Dr F. Kocker, Ulm, Germany; Dr Ludwig Strauss, Heidelberg, Germany; Dr Jan Pruim and Professor Willem Vaalburg, Groningen, Holland; Dr Wolfgang Roemer, Munich, Germany; Professor O Eremin and Professor Peter Sharp, Aberdeen, U.K.; Professor Ralph McReady, London, U.K.; Dr Jan-Erik Westlin, Uppsala, Sweden; Dr Cristina Messa and Professor Ferruiccio Fazio, Milan, Italy; Professor Riccabona, Innsbruck, Austria; Dr Preben Anderson, Copenhagen, Denmark; Dr Max Lonneaux, Brussels, Belgium; Dr Bruno Kaschten, Liége, Belgium; Dr Stephen Müller, Essen, Germany; Dr Karl-Josef Langen, Jülich, Germany.