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International strategies and experiences in the use of labelled Phase I/II anti-cancer drugs for the *in vivo* study of normal tissue, tumour pharmacokinetics and dosimetry in man. T Jones (UK) and P Price (UK). MRC Cyclotron Unit and Department of Clinical Oncology, Hammersmith Hospital, London W12 OHS, UK.

Position Emission Tomography can be used to measure in man, normal and tumour tissue kinetics and dosimetry of anti-cancer drugs by labelling them with positron emitting radionuclides such as carbon-11 and fluorine-18. The high sensitivity of PET enables tissue pharmacokinetics to be measured without the pertubations associated with administering therapeutic levels of drug. Such measurements when carried out prior to and in parallel with Phase I/II clinical trials offer information on dosimetry, mechanisms of tissue targeting and intertumour variations. To bring together expertise in PET methodology and its clinical application with drug trialists, collaborations are being developed with the EORTC and CRC (UK) new drug committees. This awareness of lead/candidate compounds and the committees' contact with the original drug discoverers, affords specific advice on selective and synthetic routes for radiolabelling. Examples are given of ongoing work involving anti-cancer drugs studied with PET prior and in parallel to clinical trial. Ideas of multiple labelling of anti-cancer drugs are discussed with a view of deriving *in vivo* metabolism and mechanisms of action. The coming together of PET experts and drug trialist in Europe is being enhanced through the EORTC's NDDO and EEC PET concerted action in cellular regeneration and degeneration.

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METABOLIC MARKERS IN THE ASSESSMENT OF TREATMENT RESPONSE - STUDIES IN VIVO AND IN VITRO

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Positron emission tomography with radiolabeled substrates can be used for the in vivo assessment of metabolism in tumors. These characteristics, which sometimes to an advantage can be used for the diagnistic visualization of the tumor, can in many cases be used for the benefit of a quantitative and sensitive evaluation of treatment response.
We have in patients with lymphoma, breast cancer, prostate cancer and bladder cancer used PET with ^{11}C-methionine and ^{18}-FDG for the assessment of treatment response. In general, these markers have early and with significant magnitude revealed a response which only much later have appeared as tumor size shrinkage. Also in several cases a remaining mass after treatment have with PET been disclosed to be metabolically inert; thus probaly mainly consisting of fibrosis.
Markers such as ^{11}C-L-DOPA and ^{11}C-5-hydroxytryptophan, although excellent for the visualization of neuroendocrine tumors, have a much more complicated relation to effect of treatment.
We have developed an in vitro analogue system to PET, which is based on the culture and non-destructive measurement of tumor fragments in organ culture. In this system we have evaluated response to several experimental drugs and also attempted to evaluate mechanisms of uptake of drugs.

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ANTI CANCER DRUGS: THE EFFECT ON TUMOR METABOLISM.

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Positron Emission Tomography (PET) offers the opportunity to quantify biochemical characteristics of tumor tissue in vivo. At present parameters as eg. perfusion, oxygenation state, glycolysis, protein synthesis, DNA synthesis, oxygen consumption, and pH can be measured. The aim of our PET oncology program is 1) to early assess the effect of treatment on glycolysis, protein synthesis rate and DNA synthesis rate with respectively ^{18}FDG, L-[1-^{11}C]tyrosine and [2-^{11}C]thymidine as radiopharmaceuticals and 2) to investigate the pharmacokinetics of anti-cancer drugs in relation to Multi Drug Resistance (MDR). The ultimate goal is to improve the prognosis of the patient. Results will be shown on the effect of regional perfusion with anti-tumor drugs of soft-tissue sarcomas. The advantages and disadvantages of the radiopharmaceuticals and methods will be compared in relation to tumor type and tumor localisation.

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THE *IN VIVO* METABOLIC ASSESSMENT OF BRAIN OLIGODENDROGLIOMAS WITH PET

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We investigated with PET a series of 18 patients with non malignant oligodendrogliomas. 12 of these presented with a primary tumor, whereas the 6 others were operated upon then irradiated several years before the PET study and were suspected to have tumor recurrence. The PET investigation included a ^{11}C-L-methyl methionine (^{11}C-MET) uptake study in all 18 patients, and a ^{18}F-Fluoro-Deoxy-Glucose (^{18}FDG) study in 8 patients. Glucose metabolism investigations were performed just after ^{11}C-MET Scan, or 24 hours later.1) Metabolic pattern. Results were characterized by a parallel pattern of the two markers (^{11}C-MET and CMRglu) in the healthy tissue but not in the tumor where an increase of ^{11}C-MET uptake is associated with a decrease inCMRglu. Moreover, in all patients exhibiting either a primary or a recurrent tumor, a well defined area of the tumor ROI's could be delineated in which the ^{11}C-MET uptake was higher than 200 % of the uptake in the normal tissue. The extent of this area represented the "tumor volume". 2) Differential diagnosis between recurrency and necrosis or scar process. Eight patients had a brain oligodendroglioma surgically removed 2 to 14 years before the PET study, which was aimed at clarifying the mechanism of new or recurrent neurological symptoms. In all 8 patients, the radiological data (CT-scanner and MRI) were unconclusive. Five patients had a definite "tumor volume" on the ^{11}C-MET-scan : 4 of them were reoperated, in all was removed a histologically proven recurrent tumor. The 5th patient with an abnormally high ^{11}C-MET uptake was not reoperated and exhibited evidence of progressive tumor disease both clinically and radiologically. The 3 patients with no abnormally high ^{11}C-MET uptake had no further sign of tumor recurrency. 3) Predicting response to radiotherapy. 5 patients had a post-operative radiotherapy (RT) (60 Gy, 6 weeks) after an incomplete surgical resection of primary oligodendroglioma. They were assessed with PET and ^{11}C-MET before (control study) and after RT, post-PET investigations being performed sequentially 2, 6, and 12 months after the end of the treatment. Effects of the RT were evaluated on both the MET [T]/MET[H] ratio and the "tumor volume", expressed in % of initial (control) values, but also on CT SCAN or MRI and clinical informations. The MET[T]/MET[H] ratio remained relatively stable at the various post-RT times, and uncorrelated to the late clinical evolution; whereas there was an overall and rapid decrease of the "tumor volume" at early and late assessments in 4 patients. The "tumor volume" variation was not correlated to radiological findings, but clearly correlated to the clinical evolution.

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^{11}C-THYMIDINE:A NOVEL APPROACH FOR STUDYING TUMOUR PROLIFERATION INVIVO?

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Positron emission tomography (PET)offers the opportunity to examine organ metabolism in a non-invasive and quantitative way.Studying nucleoside metabolism in the most direct way for evaluation of proliferative capacity of tumours.Therefore,interest developed in using positron-emitter labeled thymidine for use with PET.This tracer,labeled in the ring-2 or ring-5 position,has been shown to be taken up in tumours.This uptake seems to be unrelated to blood flow.However,for quantification we need tot develop a compartimental model,taking into account possible correction factors such as metabolites and blood volume distribution.Much the research at our institute has concentrated on these issues using [Methyl-^{11}C] thymidine compared with $C^{15}O$ or $C^{15}O_2$ and determination of metabolites in blood of patients with head and neck cancer.These results indicate that labeled thymidine disappears rapidly in the blood and after 5min most of the activity is in metabolite form while there is an initial high tumour uptake reaching a plateau between 10-15min with a mean standardized uptake value of 1.33.These results are used to develop a three-compartimental model with adequate quantification.
PET,thymidine,profiferation.

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FASTING IS A PREREQUISITE FOR RELIABLE FDG-PET IN PATIENTS WITH CANCER

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The optimal circumstances for studying oncologic patients with [^{18}F]-fluorodeoxyglucose (FDG) and positron emission tomography (PET) should be defined to facilitate assessment of tumour metabolism and to improve contrast between neoplastic and ambient normal tissues. In the present study, FDG uptake *in vivo* and mRNAs for the glucose transport proteins (GLUT) were measured in the fasting state (FS) in patients with squamous cell carcinoma of the head and neck and lymphoma. FDG-PET was repeated either after oral glucose loading or during euglycemic hyperinsulinemic clamp to study the effect of hyperglycemia or hyperinsulinemia on FDG uptake in tumour and normal tissues. The pattern of the mRNA GLUT expression in FS in tumours as well as the kinetic analyses of tumour-to-muscle contrast ratios during hyperglycemia and/or insulin stimulation clearly favour FS if tumour imaging is the desired goal of the FDG-PET study.