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POSITRON EMISSION TOMOGRAPHY IN TUMOR DIAGNOSIS AND TREATMENT FOLLOW-UP

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The technique of positron emission tomography (PET) is described. PET is an in vivo imaging and quantitative technique which allows the visualization of various functional and biochemical parameters. PET is a tracer technique in which bioactive tracer substances are labelled with short-lived positron emitting radionuclides. The most important of these are ^{15}O, ^{13}N, ^{11}C and ^{18}F with decay times ranging from 2 min to 2 h. The radiolabelled substance is injected intravenously and the distribution, uptake and binding are registered externally with the PET camera using of the order of 4 000 small detectors. The camera produces simultaneously 15 tomographic slices in which the absolute concentration of the tracer substance can be measured. Using a dynamic imaging sequence starting after the injection of the tracer, the dynamics of the tracer uptake is recorded and can be used to deduce functional parameters, such as perfusion flow, tracer distribution, binding to receptor or enzyme systems, etc. depending on the choice of tracer substance. The great versatility of PET and its potential of direct noninvasive study of tumor function will make it a very important clinical and research tool in oncology. With the choice of substances selective for a certain aspect of a tumor's biochemistry the potential opens for a better diagnosis, improved differential diagnosis and, especially with the use of metabolic tracers, an improved possibility to evaluate the response to treatment.

In oncology, we have since many years learned to rely on a number of indirect signs, such as the patient's clinical condition, hormonal levels in peripheral blood, etc. for the assessment of tumor characteristics, tumor type and response to treatment. With the introduction of computer tomographic techniques, such as CT, MRI, and SPECT, the tumor can be visualized, its relation to surrounding tissues evaluated, and progression of tumor growth or regression during therapy estimated. These computerized imaging modalities have truly been a revolution in oncology. The present imaging techniques are, with a few exceptions, morphologic techniques and usually only indirectly can functional and biochemical parameters be extracted. Thus, for differential diagnosis, features such as for instance occurrence of cysts and infiltrative growth are important signs which can give indications on tumor type. For the assessment of treatment effects, usually tumor size is the parameter of choice.

Positron emission tomography (PET) is a tracer technique which enables a very large number of biochemical and functional parameters to be evaluated in vivo in patients. With the proper choice of labelled substance, good quantitative determinations of metabolism, receptor binding, enzyme activity or drug distribution can be made (1–6). These possibilities can make a significant extension of the potentials for assessment of tumor characteristics and for the evaluation of response to treatment. The present article will attempt to illustrate these potentials of PET in oncology.

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Material and Method

Labelling of tracer substances

Positron emission tomography utilizes tracer substances labelled with a positron emitting radionuclide. These

radionuclides are usually short-lived and must therefore be produced by a cyclotron in close vicinity of the PET facility. The most commonly used radionuclides are:

Radionuclide	Decay time (min)
^{11}C	20
^{15}O	2
^{13}N	10
^{18}F	110

These radionuclides are especially interesting from the point of labelling since the elements are natural constituents in most biologically active compounds. Substituting a natural carbon in a molecule with ^{11}C will have no effect on the compound's biological properties and it will hence behave as a true tracer substance. This is not always true with compounds labelled with e.g. ^{99m}Tc.

The most severe difficulty in positron emission tomography is the requirement for very rapid labelling procedures; the introduction of the radionuclide into a molecule must be made within a few half-lives of the radionuclide, thus with ^{11}C within less than one hour. For this task, special rapid synthesis and labelling procedures have been developed. One trick which is commonly used is to use precursor molecules which are similar to the final compound except that a small group like a methyl- or cyano-group is missing. Under special chemical conditions a ^{11}C-labelled methyl- or cyano-group is introduced into the molecule to finish the labelled compound. At present a very large number of substances can be labelled, including approximately 80% of the registered pharmaceuticals.

Injection of the compound

The labelled substance has a very high specific activity, usually a few Ci/micromol. This means that for the adequate visualization with PET, where a few mCi need to be injected, the carrier substance coinjected is of the order of nanomoles. Thus PET is a true tracer technique and the very low amounts injected allow the use of even relatively toxic substances or pharmaceutical agents in which full toxicology has not been evaluated.

The substance is always chemically analyzed and submitted to sterile filtration before injection. The compound, dissolved in saline, is usually injected as a rapid i.v. bolus injection made with the patient laying on the couch of the PET-camera.

The camera itself contains several rings of detectors in a large number, normally of the order of 4 000 detectors. The PET-camera's external design mimics very much a CT-scanner with a similar type of gantry surrounding the patient.

The radioactivity is continuously decaying by the emission of positrons, the antiparticle of the electron. This positron is stopped by the tissue within about 1 mm. The positron then reacts with an electron, a so called annihilation event, whereby a pair of opposedly directed, high energy gamma rays are created. The gamma rays readily penetrate the tissue, are emitted from the body and recorded by the detector system of the PET-camera.

During a typical PET-investigation several millions of gamma pairs are recorded and utilized for the construction of a large set of tomographic images. There are simultaneously 15 slices recorded, covering an axial distance of 10 cm (Fig. 1). Furthermore, the camera is programmed to produce multiple recordings in time so that each tomographic slice is evaluated dynamically.

Image analysis

The tomographic images produced are quantitative in the sense that in each portion of the image the quantitative amount of the tracer can be evaluated. Furthermore, the images enable the visualization of the anatomical distribution of the radioactivity with a resolution of 5 mm.

In most of the studies, models of tracer behavior are used to extract functional parameters from the dynamics of the uptake (7). From the irreversible trapping rate of amino acids, a parameter can for instance be deduced which is proportional to protein synthesis. Using a glucose analogue, ^{18}F-deoxyglucose, the glucose metabolism can be calculated expressed in micromol/min/g (5). Using ^{15}O-labelled water the blood flow is calculated, expressed in ml/min/g (4).

Results

The potentials of PET are now rapidly being extended, especially with the development of new labelling techniques which allow new substances to be evaluated clinically and in basic research. The possibility of biochemical and functional characterization of tumors can be utilized for different purposes depending on the clinical question.

Diagnosis

Tumors may have special biochemical features which differ from the adjacent tissues and which can be used for the improved diagnosis. An example of this is the usually very high amino acid metabolism in tumors. Thus, in brain tumors we have demonstrated that PET with ^{11}C-methionine is superior to all other imaging modalities in defining the tumor extent (1). With carcinoid tumors the selective irreversible incorporation of ^{11}C-5-hydroxytryptophan allows a good visualization of the metastases. The very high accumulation of ^{18}F-deoxyglucose is used for the identification of colorectal cancer (8). Sometimes metabolic tracers may give similar results, sometimes different (Fig. 2).

One major role of PET for diagnostic purposes is postoperatively or after treatment when conventional imaging modalities have difficulties in discriminating between tumor,

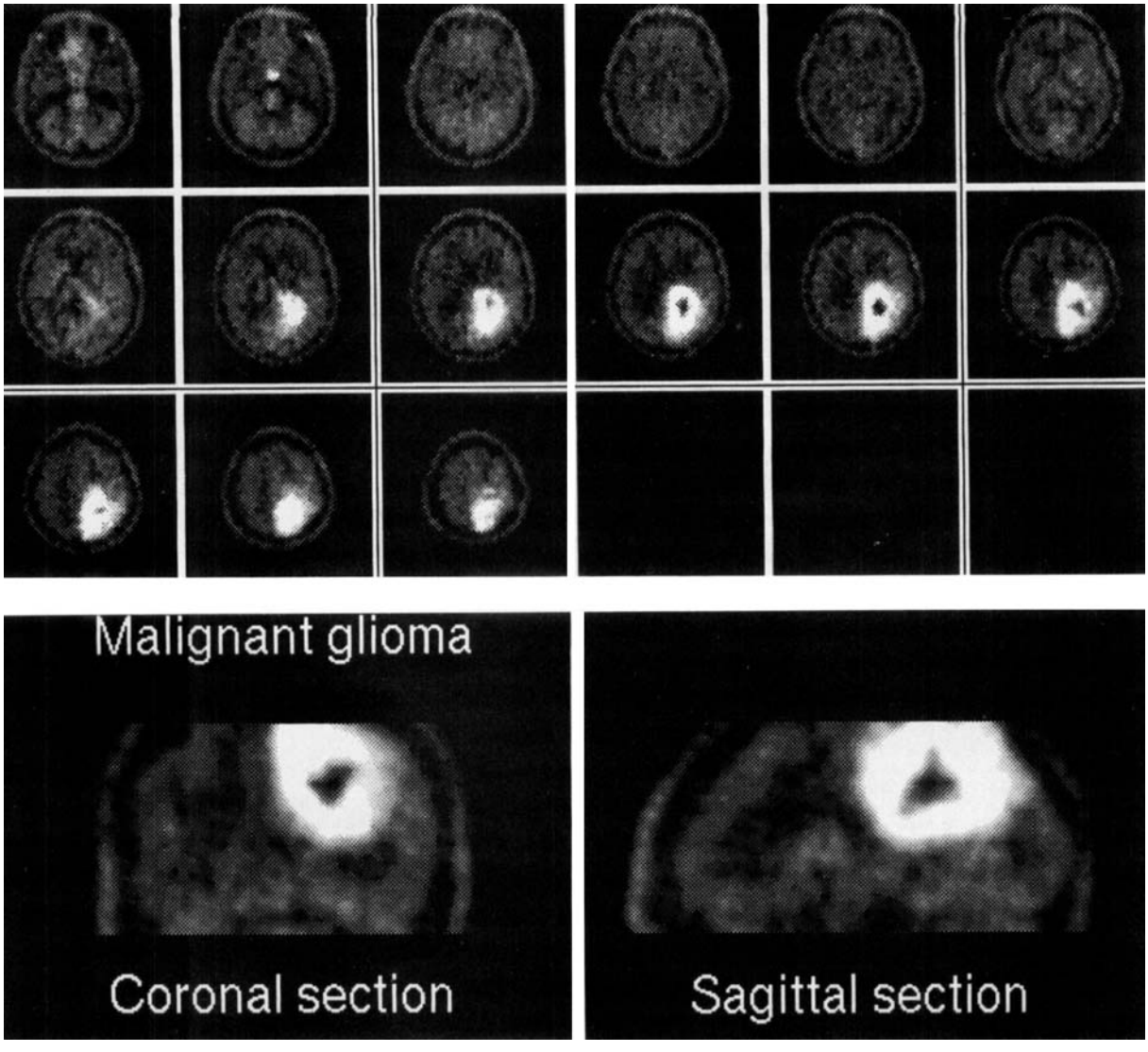

Fig. 1. Patient with malignant glioma examined with ^{11}C-methionine. The camera simultaneously generates 15 axial slices covering about 10 cm. From the set of images the computer may generate coronal and sagittal views. ^{11}C-methionine excellently outlines primary brain tumors.

fibrosis and other changes. The very low metabolism in fibrosis, necrosis etc. as compared to the tumor usually allows a very good discrimination (8).

Differential diagnosis

Some distinct properties of different tumor types allow the use of PET for differential diagnosis. These can include great differences in metabolism. Pituitary adenomas for example have on average three times larger incorporation of ^{11}C-methionine than neurinomas, and the two groups are well separated. A similar mode of differential diagnosis is facilitated by the enzyme binding substance ^{11}C-deprenyl which indicates a very high amount of MAO-B in pituitary adenomas and a very low amount in meningiomas (9).

Characterization of receptor and enzyme systems

By using selective and high affinity substances for receptor and enzyme systems, the amounts of these can be determined in the tumors using PET. This knowledge can in some cases be of great importance as an indication of the potential of treating the tumors with receptor- or enzyme-binding agents. An example of this is the determination of dopamine-D_2-receptors in pituitary adenomas which gives an indication of the possibility to treat the patient with dopamine agonists (10). Furthermore the

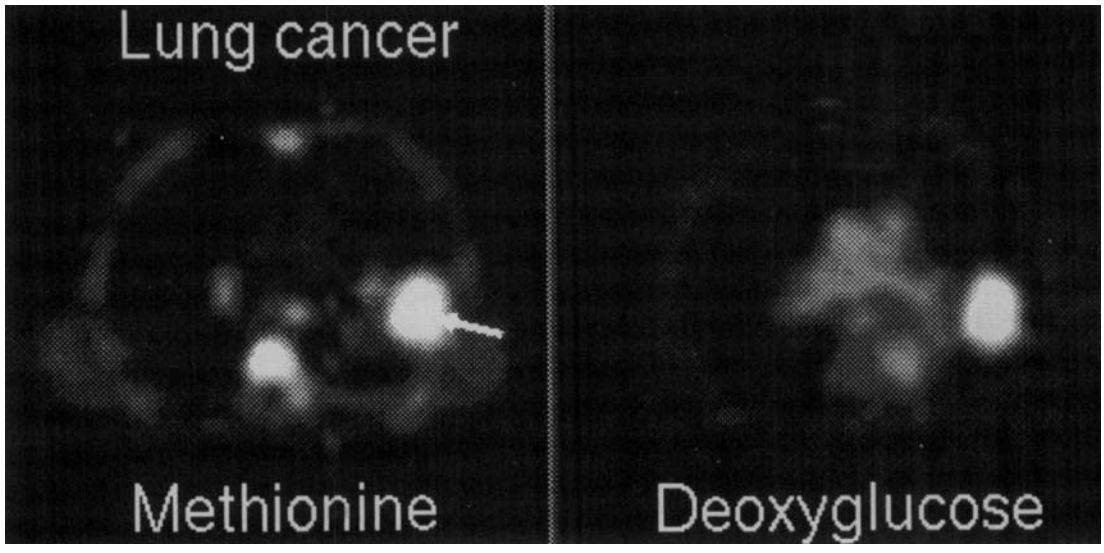

Fig. 2. Patient with lung cancer examined with ^{11}C-methionine and ^{18}F-deoxyglucose. Different tracers may have different merits in the visualization of tumors and normal structures. In this case the tumor is well seen with both substances whereas the visualization of the red bone marrow is good with methionine and the heart with deoxyglucose.

technique allows sequential studies of the amount of free receptors during treatment in order to assess receptor down regulation (10).

Drug distribution

By using a labelled drug, its concentration in the tumor and the pharmacokinetics in the tumor and other organs can be determined. This study can be performed with the injection of the labelled drug in tracer amounts, but more relevant data are achieved by co-injecting the tracer with the drug in pharmacological doses.

Treatment follow-up

Of considerable importance is the potential given by PET to evaluate response to therapy. In this respect it is most promising to use metabolic markers which indicate

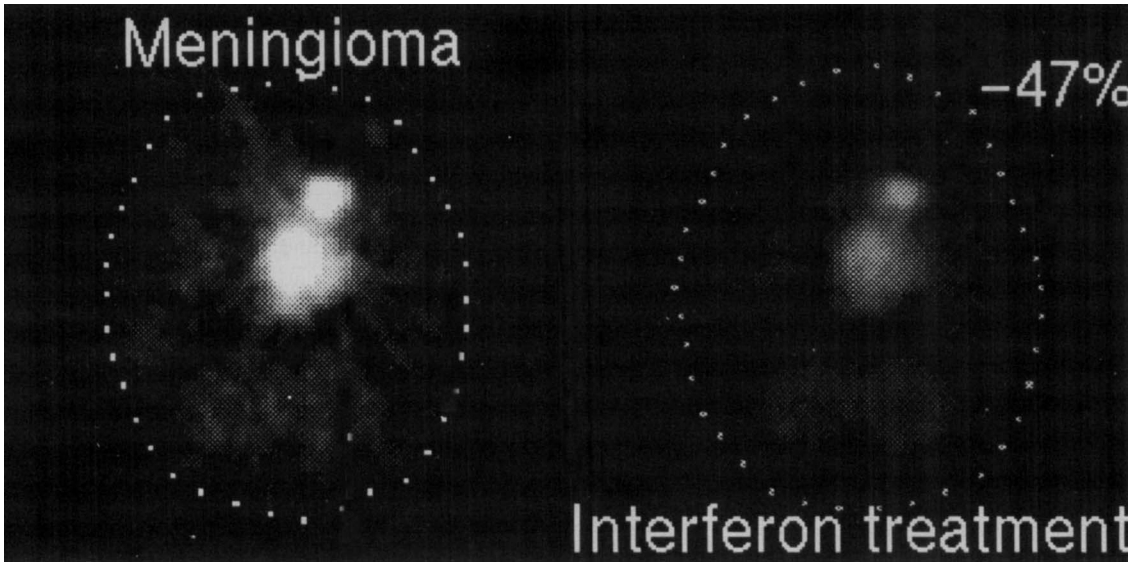

Fig. 3. Patient with meningioma examined with ^{11}C-methionine. During interferon treatment 5 million units/day, the tumor metabolism is decreased by about 50%. This metabolic effect is accompanied by a stop of further growth. In our experience PET is an important tool in the assessment of treatment response.

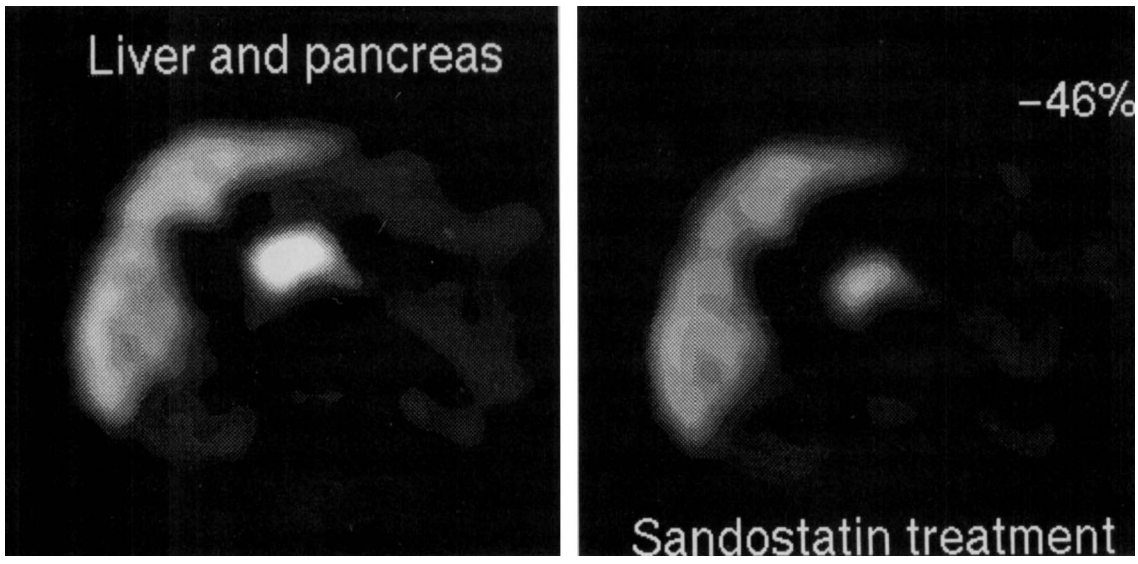

Fig. 4. Patient with ductal pancreas cancer examined with ^{11}C-methionine. The tumor is not visualized with methionine but the remaining normal pancreas has a very high accumulation. Two hours after a therapeutic dose of Sandostatin, the pancreas metabolism is decreased by about 50%. Thus drug effects on different organs can be evaluated with PET.

the tumor cells' functional activity. We have thus in a number of tumor types and with different types of pharmacological treatments attempted to use ^{11}C-methionine and ^{18}F-deoxyglucose to assess the effect of medical treatment. In prolactin secreting pituitary adenomas we see about 50% reduction of the tumor uptake of ^{11}C-methionine already a few hours after the administration of bromocriptine. Within a few days the metabolism decreased by 80% (11). This immediate response to treatment is parallelled by a reduction in the serum prolactin levels and is later, within several weeks or months accompanied by significant tumor size reduction. The present study has clearly demonstrated how a severe metabolic inhibition might occur rather rapidly and that PET can give very early indications as to the effect of treatment. Similar results, however not so dramatic, are observed with somatostatin treatment of GH-secreting adenomas (10) and with interferon treatment of meningiomas. In the latter case, two weeks of treatment with interferon induced 30–50% reduction in the metabolism of the responding tumors (Fig. 3). With long-term treatment these responders could be demonstrated to be stopped or markedly retarded in growth rate. At treatment with cytostatic agents, the metabolic tracers might not always indicate the immediate response since these agents primarily affect DNA-synthesis and replication and not the cellular metabolism of other substances. Still a monitoring of treatment effect with PET is valuable as it provides an accurate method of assessing tumor viability during prolonged follow-up times. With PET it is also possible to demonstrate effects on other organs (Fig. 4).

Discussion

Positron emission tomography is still in its infancy in relation to the vast possibilities that it offers. The driving forces are primarily the development of techniques for labelling of new substances. Secondly, a most important task is to raise clinical and research questions and to develop protocols for PET by which these questions can be answered. Large gains will await a technique that non-invasively can assess biochemistry of the tumor in vivo in humans.

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