Positron Emission Tomography and Radioimmunotargeting

General Aspects

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To optimize radioimmunotherapy, in vivo information on individual patients, such as radionuclide uptake, kinetics, metabolic patterns and optimal administration methods, is important. An overriding problem is to determine accurately the absorbed dose in the target organ as well as critical organs. Positron Emission Tomography (PET) is a superior technique to quantify regional kinetics in vivo with a spatial resolution better than 1 cm^3 and a temporal resolution better than 10 s. However, target molecules often have distribution times of several hours to days. Conventional PET nuclides are not applicable and alternative positron-emitting nuclides with matching half-lives and with suitable labelling properties are thus necessary. Over many years we have systematically developed convenient production methods and labelling techniques of suitable positron nuclides, such as $^{110}In(T_{\frac{1}{2}} = 1.15$ h), $^{86}Y(T_{\frac{1}{2}} = 14$ h), $^{76}Br(T_{\frac{1}{2}} = 16$ h) and $^{124}I(T_{\frac{1}{2}} = 4$ days). 'Dose planning' can be done, for example, with ^{86}Y- or ^{124}I-labelled ligands before therapy, and ^{90}Y- and ^{131}I-labelled analogues and double-labelling, e.g. with a $^{86}Y/^{90}Y$-labelled ligand, can be used to determine the true radioactivity integral from a pure beta-emitting nuclide. The usefulness of these techniques was demonstrated in animal and patient studies by halogen-labelled MAbs and EGF-dextran conjugates and peptides chelated with metal ions.

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Targeted therapy, nuclear oncology and radioimmunotherapy are new scientific terms to describe an increasing interest in tumour-specific ligands labelled with radionuclides suitable for tumour diagnosis or therapy. Recently, three thematic editions of leading journals (J Nucl Med 37: 6, J Nucl Med 37: 9 and Phys Med Biol 41: 10), reviewed the current international interest in the field. The background to this increasing interest is that about 50% of all malignant tumours are difficult to treat successfully by surgery, external radiotherapy and chemotherapy, often due to metastatic growth. The new targeting-based methods focus to a large extent on the diagnosis and treatment of spread tumour cells and metastatic growth.

Considerable effort is made to utilize tumour-associated antigens and overexpressed or mutated receptors as targets for specific directed tumour therapy. Targeting agents can be simple ions, such as ^{131}I for thyroid, ^{89}Sr for bone metastases or antibodies, antibody fragments or other receptor-specific ligands for most other malignancies (1–3). Such tumour-seeking compounds can be loaded with radionuclides, stable nuclides for activation or other toxic substances. The goals are to concentrate the cell-toxic compound in the tumour specifically and to obtain a therapeutic effect. Systems presently under consideration in our own group are the overexpression of epidermal growth factor (EGF) receptors in several cases of malignant gliomas, bladder cancers, squamous carcinomas and malignant gliomas (4). Overexpression of somatostatine receptors is present in neuroendocrine-differentiated tumours as well as several other tumours like hormone-refractory prostatic cancer, cancer of the kidney, malignant lymphomas and breast cancer (5).

Targeted tumour therapy is a complex strategy that involves a number of separate scientific problems, such as receptor concentration and specificity, transport of tumour cell-specific ligands, the targeting principle, i.e. single, double or triple targeting and the choice of proper cytotoxic agent. The specific topic of this paper is how to measure

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the regional absorbed dose delivered by radionuclide therapy. In external therapy advanced calculation of the dose distribution, dose planning, and dose monitoring during therapy are prerequisites for successful therapy. It is our belief that in targeted therapy the same approach is needed, although the task is more difficult since many more factors are involved.

Positron emission tomography (PET) is a superior modality to quantify the distribution of radionuclides in vivo. PET has mainly been associated with short-lived positron-emitting nuclides, such as ^{15}O ($T_{\frac{1}{2}} = 2$ min) and ^{11}C ($T_{\frac{1}{2}} = 20$ min) and has been considered a rather sophisticated research tool (6–8). In oncology the main applications have been to characterize tumours and to evaluate effects of therapy. The aim of this paper is to describe how PET can be used directly in radionuclide therapy for dose planning and as a tool for accurate determination of regional absorbed doses in the individual patient.

GENERAL ASPECTS

PET is an excellent tool for quantitative kinetic measurements in vivo using short-lived positron emitters, such as ^{11}C and ^{18}F. A time resolution better than 10 s and a volume resolution of better than 1 cm^3 can be obtained in modern instruments. The commonly used short-lived positron emitters can be used to label and to measure the kinetics of molecules carrying therapeutic radionuclides. However, if ^{131}I is used for therapy and ^{18}F for PET, the physical half-lives and the metabolic fate of the two labels will be different. Therefore one has to be cautious when estimating absorbed doses from such measurements.

Matching physical and physiological times

Several positron-emitting nuclides exist with varying half-lives that can be used to label biomolecules. Pagani et al. (9) recently published an extended review paper about the production and potential use of non-conventional positron emitters. Over many years our group has developed economical and practical methods for the production of such positron-emitting nuclides, with the intention of making available suitable PET nuclides, such as ^{76}Br (10), ^{61}Cu (11), ^{66}Ga (12), ^{62}Zn (13) and ^{110}In (14) for the labelling of targeting molecules, both for diagnostics and therapy (Fig. 1).

The use of positron-emitting nuclides in therapy

An ideal situation in nuclide therapy is to measure the therapeutic nuclide itself and to obtain the integrated radionuclide distribution with as high accuracy and spatial resolution as possible. Usually, radionuclides for internal therapy do not emit positrons, but planar scintigraphy or Single Photon Emission Computed Tomography (SPECT) are used for single gamma or bremsstrahlung detection. However, there is no fundamental objection to use

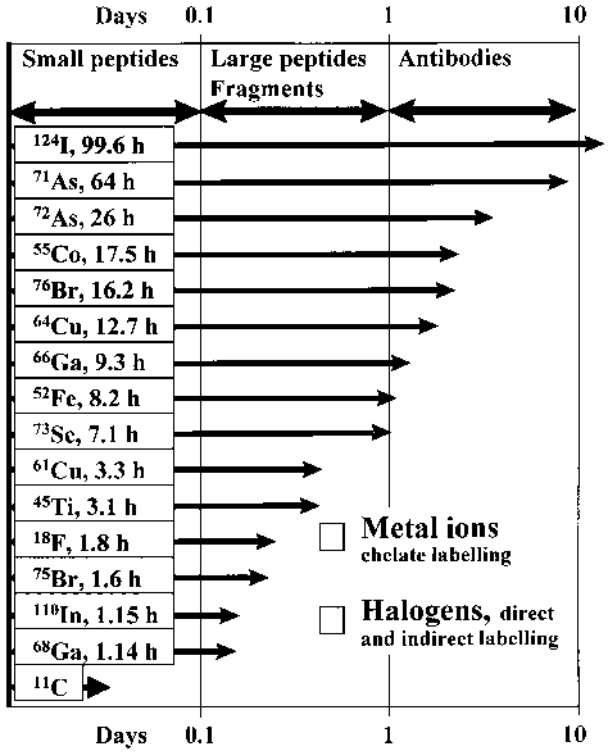

Fig. 1. The diagram shows different positron-emitting nuclides produced and studied within our programme. Their half-lives and possible use for the labelling of different biomolecules are compared with two commonly used PET nuclides, ^{11}C and ^{18}F.

positron-emitting nuclides in therapy. ^{52}Fe has actually been used for bone marrow ablation before bone marrow transplantation (15). More long-lived positron-emitting nuclides often have a competing branch of electron capture (EC) decay. ^{124}I (23% β^+, 77% EC) could be a favourable candidate for Auger therapy (16) using ^{124}I-IUdR instead of ^{123}I or ^{125}I as labels. Economic considerations and availability are largely behind the use of reactor-produced nuclides, such as ^{131}I, ^{89}Sr and ^{90}Y.

It is also an advantage if the positron-emitting nuclide is of the same element as the therapeutic nuclide, since they will follow the same metabolic pathway (Table 1). A PET investigation may be performed in advance to plan the therapy (dose planning) under identical conditions to the

Table 1

Examples of paired radioisotopes of different elements for therapy and for dosimetry with PET

Therapy nuclide	$T_{\frac{1}{2}}$ (days)	PET nuclide	$T_{\frac{1}{2}}$ (days)	β^+(%)
^{89}Sr	50.5	^{83}Sr	1.35	24
^{131}I	8.04	^{124}I	4.18	23
^{90}Y	2.67	^{86}Y	0.61	33
^{67}Cu	2.58	^{64}Cu	0.53	18
^{47}Sc	3.35	$^{43,44}Sc$	0.16, 0.16	84, 93
^{111}In	2.81	^{110}In	0.05	62

therapy. From the quantitative information obtained by PET, one may foresee the uptake (and absorbed dose) to the tumour and critical organs during therapy, and can accordingly adjust the administered amount of therapeutic radioactivity. The positron-emitting isotope may also be mixed with the therapeutic dose to verify the outcome of the therapy.

The use of the interesting nuclide pair $^{86}Y/^{90}Y$ has been evaluated and reported by the Julich group (17, 18). Four half-lives of ^{86}Y, which is a reasonable measuring time, covers about one half-life of ^{90}Y. A protocol for ^{90}Y-therapy could be as follows:

- *Dose planning*. The targeting ligand is labelled with ^{86}Y. PET is used prior to therapy to quantify radioactivity distributions in tumour and critical organs and to calculate expected dose integrals of ^{90}Y during therapy.
- *Dosimetry*. The ligand for therapy is double-labelled with ^{86}Y and ^{90}Y. PET can measure ^{86}Y for about two days (close to one half-life of ^{90}Y) with negligible disturbance from the pure beta emitter ^{90}Y. Only a minor redistribution of the radioactivity is expected at late times. ^{90}Y can be measured with a gamma camera to obtain a relative value of the last day's kinetics with a coarse spatial resolution.
- *Calculation of regional absorbed dose*. At administration, the radioactivity ratio, $^{90}Y/^{86}Y$, is known and will change in vivo only due to differences in physical decay of the two radionuclides. The macroscopic dose delivered by ^{90}Y to tumour or in critical organs for the first two days' time (about half of the total dose) can then be calculated from direct PET measurements of the time integral of ^{86}Y-concentration multiplied by a constant. The dose delivered at late times may be calculated assuming no change in main regional distribution and with a biological half-life determined by gamma camera measurements of ^{90}Y. In theory, the described technique should allow us to calculate the regional dose with an accuracy of 10% or better. However, the final result will depend on the investigation quality, including the number of measurements and at which level of precision the patient can be positioned for repeated measurements.

^{124}I has an ideal half-life to measure the full radioactivity integral of the commonly used therapeutic nuclide ^{131}I. It has also been frequently used in clinical studies (19–21). Another iodine isotope, ^{120}I, with a half-life ($T_{\frac{1}{2}} = 1.35$ h) comparable with the kinetics of MIBG (22), has been suggested as well. However, for an accurate determination of the dose integral, the half-life of this isotope is too short. Other halogens, such as ^{76}Br, have been suggested by Lövqvist et al. as suitable to follow the kinetics of antibodies and from this derive dosimetric information (23–25).

Combining PET and gamma camera technology as described above utilizes the best part of each system. PET is used in dose planning and in some quantitative measurements during therapy, while the cheaper gamma camera technology, with large field of view, can be used to follow most of the whole-body radioactivity distribution.

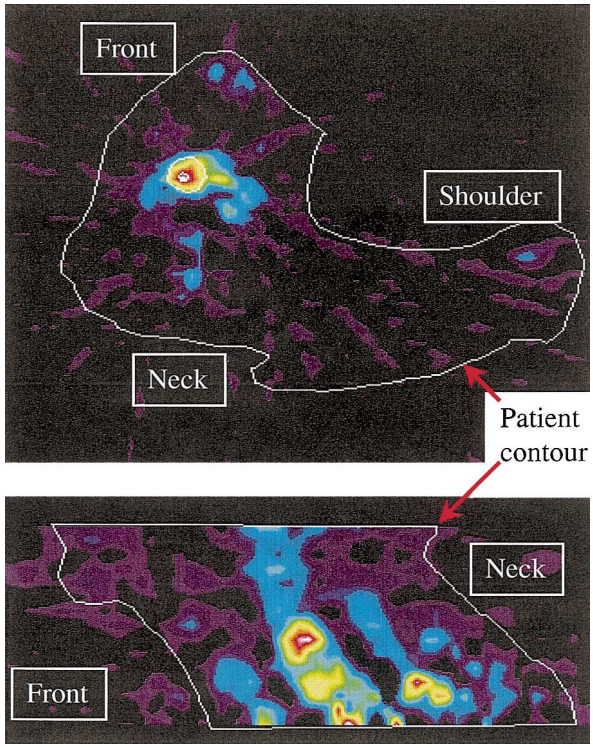

Fig. 2. A PET scan taken 24 h after injection of 50 MBq ^{86}Sr into a patient with primary prostate cancer and known bone metastases in the head-neck region. The patient was not placed symmetrically in the tomograph, but with one shoulder sticking up into the field of view. The picture shows a colour-coded map of radionuclide concentration (Bq/cm^3). Tumours are readily distinguished and have an uptake 3–4 times higher than in normal bone.

CLINICAL PILOT STUDIES

Within our research program, several suitable PET-nuclides for in vivo dosimetry have been produced and labelled to various targeting molecules. Some PET investigations that have demonstrated their eventual clinical usefulness are presented briefly below. The measurements were made with a tomograph (GEMS 4096+, whole-body, Uppsala, Sweden) consisting of 8 detector rings (512 BGO crystals each) that are separated by not-retractable septa, producing 15 image planes. Emission scans were taken for correction of attenuation and to verify proper positioning. The images (128×128 pixels with a pixel size of 4×4 mm^2) were reconstructed using standard scatter corrections and a 4.2-mm Hanning filter.

Case study using ^{83}Sr

A patient with primary prostate cancer and known bone metastases in the head-neck region was given 50 MBq ^{83}Sr

before therapy with ^{89}Sr. Figure 2 shows a colour-coded map of the radionuclide concentration (Bq/cm^3) 24 h after injection. Tumours are readily distinguished from normal bone, and a strontium uptake three to four times higher in tumours than in normal bone can be seen. The density distribution obtained from the transmission scan can be used to calculate the concentration in Bq/g.

Rösch et al. (26) reported phantom measurements to evaluate the use of ^{83}Sr in the context of pharmacokinetic studies and dosimetry of ^{89}Sr. In principle, the same protocol can be used for ^{83}Sr/^{89}Sr as for ^{86}Y/^{90}Y. ^{89}Sr is also a pure beta-emitter and the dosimetry calculation is equally simple. The main difference is in the physical half-lives. The first 5 days, which can be followed by ^{83}Sr ($T_{\frac{1}{2}} = 1.35$ days), account for only 5–10% of the integrated ^{89}Sr-radioactivity concentration. However, it would be expected that the main clearance and distribution of the radionuclide would take place during these days, and that the slow kinetics could be followed by the gamma camera.

^{110}In-octreotide

Octreotide is a small peptide of eight amino acids acting as an analogue to the hormone somatostatine. It has been used for radiotherapy labelled by ^{111}In, and some effort has been made to determine the absorbed dose using gamma camera measurements (27). To one patient suffering from a tumour in the upper thorax region, 140 MBq of ^{110}In-octreotide was administered intravenously. Repeated PET scans of the upper thorax region were made for 50 min after administration to obtain the fast distribution kinetic. The patient was moved and the lower body, including kidneys and liver, was scanned for 2×10 min. The patient was then moved back to the initial position and 3×10 min-long scans were made covering the time interval 100–130 min after administration. At each new position, a 10 min-long transmission scan was made for attenuation correction and to verify proper positioning.

Figure 3 shows a PET image of the tumour 2 h after administration of the radioactivity. PET can be used to study the initial fast dynamic period of tumour uptake and the clearance of normal organs like the kidney. It can also give important quantitative information for dose planning about the number of tumours, their size and ligand uptake. The short half-life of ^{110}In allows repeated injections to study receptor up- and downregulation. The technique also allows quantification of the receptor concentration. A drawback of the short half-life is that from these measurements alone, it is difficult to estimate the expected time-activity curve of the more long-lived ^{111}In, but the PET measurements can help to calibrate subsequent gamma camera measurements.

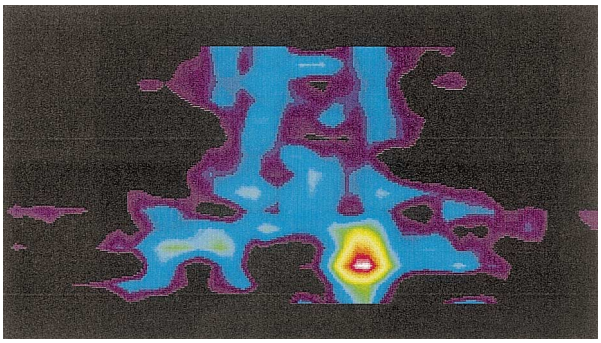

Fig. 3. This shows an uptake of ^{110}In-labelled OctreoScan (octreotide with DTPA as chelator) into a tumour metastases with somatostatine receptors. The tumour is situated below the neck of the patient and has a diameter of about 2 cm.

Patient studies with ^{52}Fe

Here we illustrate the case when PET follows the actual nuclide used for therapy. Iron is taken up to a great extent in red bone marrow, and ^{52}Fe has been used for bone marrow ablation before bone marrow transplantation (15). Iron can also be used to label biomolecules by chelating techniques. The results presented here are from a clinical study of iron metabolism (28). The images (Fig. 4a) show a marked iron uptake in the liver and in the red bone marrow (indicated in the figure with arrows). The kinetics are shown of three organs: the liver, the bone marrow and the heart (left ventricle), in some detail. The uptake in the liver is fast and stabilizes at a constant level, whereas the uptake in the bone marrow is slower, but still increases at later times. The blood radioactivity decreases during the experimental time.

In the iron measurements, the regional time-activity curve is obtained directly. The precision in this determination is mainly due to the repetition rate of the measurements. For the final dose calculations, the photon contribution has to be considered.

Determination of bone marrow dose

Iron and strontium both show high uptake in the bone marrow area. However, while strontium is taken up in bone structures, iron is taken up in the soft tissue, in the red marrow. PET measurements thus underestimate the true concentration of these two nuclides, since both are diluted by structures that do not take up radioactivity. The true absorbed dose to the bone marrow, which is often the critical organ in radionuclide therapy, is therefore difficult to calculate directly from the PET measurements.

This is a general problem in all radionuclide therapy. However, a more elaborate PET protocol may give a more accurate estimate. A tracer, such as ^{15}O-water, that is evenly distributed in blood and in tissue can be used to measure the fraction of soft tissue and blood in the bone. Bromide ($^{75}Br^-$ or $^{76}Br^-$) can measure the vascular space (23) and ^{11}CO-labelled blood the blood volume in the bone marrow area. Measurements of this type can be used to calculate a more accurate bone marrow dose.

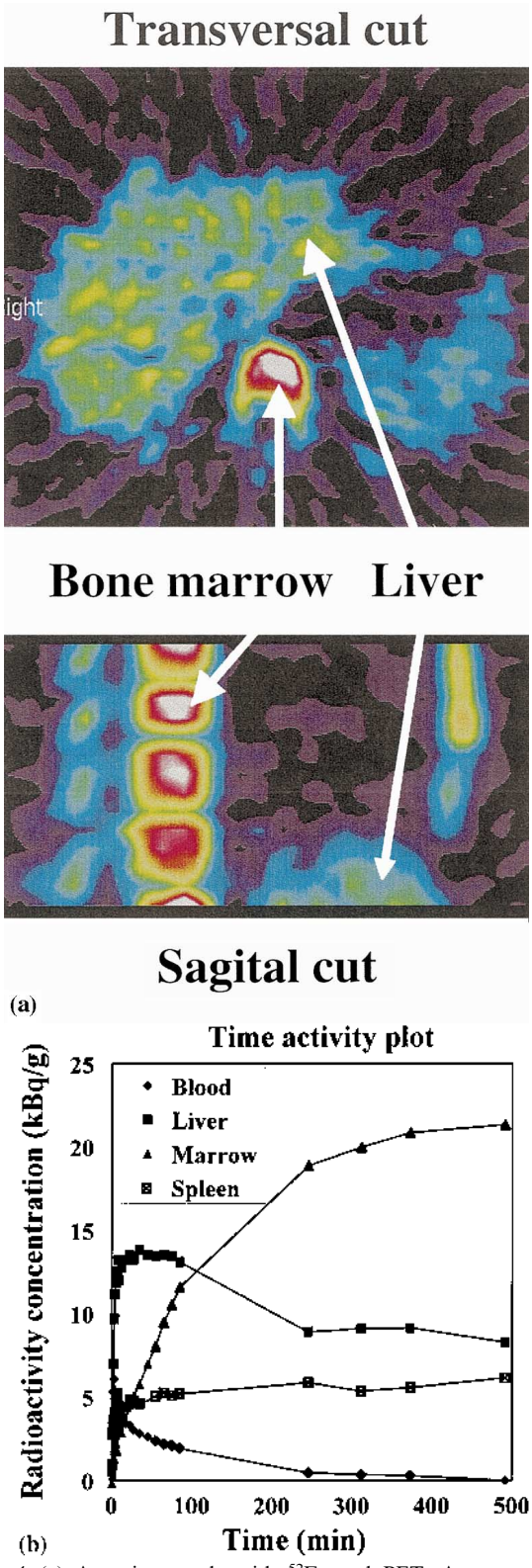

Fig. 4. (a) A patient study with ^{52}Fe and PET. A transversal cut through the liver, spleen and bone marrow is shown (left) as well as a sagittal cut through the bone marrow (right). (b) The radionuclide kinetics followed for 8 h in the blood, liver, bone marrow and the spleen. The radioactivity is rapidly cleared from the blood and a fast uptake in the liver and in the bone marrow is seen.

Such an elaborated PET protocol is not likely to be used in all patients undergoing radionuclide therapy. A simpler and more practical method to calculate the bone marrow dose has been suggested by Sgouros (29). The idea is that the major bone marrow dose is given by the radioactivity in blood. The integrated radioactivity concentration of a sampled blood curve is multiplied with a factor containing the relative blood volume of the bone marrow and the dosimetric constant of the radionuclide, to obtain the absorbed dose. The suggested PET protocol above can be used, in animals or patients, to verify such a simplified approach for different radionuclide treatments.

Antibodies labelled with ^{76}Br

The use of ^{76}Br for dosimetry is not obvious. It is not likely than any bromine isotope will be used in therapy, although ^{77}Br-BrUdR has been suggested (16). However, various bromine-labelled ligands have been shown to have high specific radioactivity, to be biologically active and stable in vivo and thus clinically interesting. ^{76}Br can be used to follow the fate of the targeting molecule, but the metabolic difference from the used therapeutic nuclide must always be compensated for. It is therefore more likely that ^{76}Br-labelled targeting ligands will be used more for diagnostic purposes and dose planning than dosimetry.

We have studied a monoclonal antibody (anti-CEA MAb 38S1) labelled with ^{76}Br. The distribution of this labelled antibody was studied in an animal model (nude rats bearing subcutaneous tumours expressing the antigen CEA). This is described in more detail in references (23) and (24). We have also studied the pharmacokinetics in pigs using PET (25). Some of these results are shown in Fig. 5.

Bromide also has some interesting features, since it is only present in the extracellular space, not in intact cells. $^{76}Br^-$ can thus be used to measure the relative volume of intact tumour cells in a tumour with necroses, which will be of value in a more elaborate dose calculation.

THE FUTURE

There are a few hundred PET systems around in the world today, mainly concentrated in the USA, Europe and Japan. Few of these centres are engaged in clinical investigations only; they also have scientific programmes in drug development, neurological disorders, stimulation studies, oncology, etc. The development of PET has so far depended on the fact that the scientific use of PET needs the best available technology, the highest resolution and sensitivity, accurate quantification, i.e. the best possible PET scanner performance. These PET research centres have also been able to pay the price: two million dollars for a scanner, about the same for a cyclotron and the costs for nuclide production, premises and qualified personnel.

The time is coming when we will see more dedicated PET systems for different applications. The cancer clinics that want to run ^{18}F-FDG to look for tumour metastases in the whole body will have different demands on the equipment than the dedicated brain research centres. They need a system with a large field of view to cover the whole body as fast as possible. They do not need a resolution of 2 mm, but one closer to 5 mm, since body and organs move due to breathing, heartbeat, etc. They need to relate function and morphology, a difficult task in whole-body studies, since moving the patient from a CT or MRI investigation to the PET facility may cause displacements of as much as centimetres for organs such as the liver and kidneys. They may not want a cyclotron next door, since many of the ligands they use can be labelled with more long-lived nuclides, such as ^{18}F ($T_{\frac{1}{2}} = 1.9$ h), ^{75}Br ($T_{\frac{1}{2}} = 1.6$ h), ^{76}Br ($T_{\frac{1}{2}} = 16$ h), ^{86}Y ($T_{\frac{1}{2}} = 14$ h) and ^{124}I ($T_{\frac{1}{2}} = 100$ h), which may be distributed from a centralized cyclotron supporting several clinics.

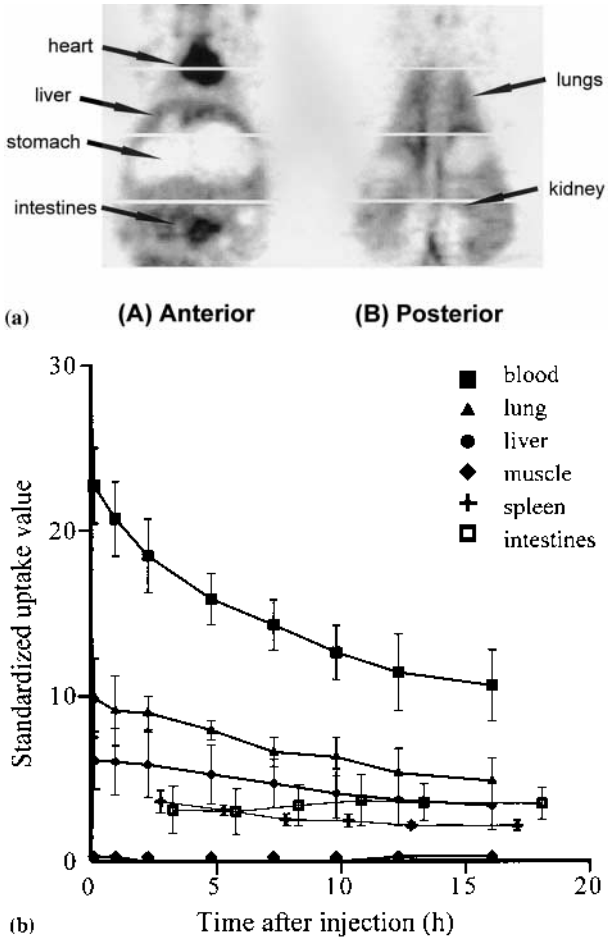

Fig. 5. (a) Coronally reconstructed PET images of the antibody ^{76}Br-38S1 distribution in a pig at 15–19 h post-injection. Consecutive regions of the anterior (A) and posterior parts (B) are shown. (b) The kinetics in different organs are also shown. Kinetics of ^{76}Br in selected pig tissues as measured by PET (n = 3). Lung SUV represents air-free lung volume.

The need for clinical PET systems in oncology is rapidly increasing. It was recently announced that the health security system in the USA is going to pay for ^{18}F-FDG PET investigation for the diagnoses and staging of lung cancer. This alone will increase the number of such PET investigations from about 25000 to 150000 a year (30). This need for cheap clinical equipment has revived an old idea: the rotating dual-head gamma camera. It is the same technique suggested and tried by Anger more than 40 years ago. The technique has improved somewhat, but the dual-head Anger camera is still a poor system for 511 keV, either with a high-energy collimator or in the coincidence mode (31). Its main drawback is the large thin NaI(Tl) crystal. The coincidence efficiency is low ($< 0.1\%$) and the single count rate high. Although modern systems have segmented the crystal to allow for parallel data processing, the radioactivity viewed by the open detector has to be low to avoid pile-up in the detector, which makes the coincidence count rate painfully low.

The future will see a gamma camera based on a faster and more efficient crystal, such as LSO, competing in price with conventional systems. Instead of one single large crystal, the detector will be composed of small crystals in the order of 4*4*15 viewed by a number of PM tubes identifying the hit crystal. The Phoswich principle can be applied to identify the depth of interaction (DOI) in the crystal (32). Such a system should then be able to work as a SPECT system with ^{99m}Tc using the standard collimator, and as an efficient PET system by rotating two open detector systems concurrently.

Rotating systems are already available, but since they are based on BGO, their energy resolution forbids the use of the low-energy gamma from ^{99m}Tc and they can only be used as PET systems (33). An interesting idea now being implemented is to combine such a rotating PET system with a CT scanner. Thus, functional and anatomical information can be obtained in the same investigation session without moving the patient. Experiments to combine PET and MRI are also under way (34).

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REFERENCES

1. Handbook of targeted delivery of imaging agents. Torchilini VP, ed. Boca Raton, FL: CRC Press, 1995.
2. Gaze MN. The current status of targeted radiotherapy in clinical practice. Phys Med Biol 1996; 41: 1895–903.

3. Zweit J. Radionuclides and carrier molecules for therapy. Phys Med Biol 1996; 41: 1905–14.
4. Carlsson J, Gedda L, Grönvik C, et al. Strategy for boron neutron capture therapy against tumor cells with over-expression of the epidermal growth factor-receptor. Int J Radiat Oncol Biol Phys 1994; 30: 105–15.
5. Wängberg B, Nilsson O, Johansson V, et al. Somatostatin receptors in the diagnosis and therapy of neuroendocrine tumors. Oncologist 1997; 2: 50–8.
6. Watson JD. Images of the working brain: understanding human brain function with positron emission tomography. J Neurosci Methods 1997; 74: 245–56.
7. Beanlands R. Positron emission tomography in cardiovascular disease. Can J Cardiol 1996; 12: 875–83.
8. Rubin RH, Fishman AJ. Positron emission tomography in drug development. Q J Nucl Med 1997; 41: 171–5.
9. Pagani M, Stone-Elander S, Larsson SA. Alternative positron emission tomography with non-conventional positron emitters: effects of their physical properties on image quality and potential clinical applications. Eur J Nucl Med 1997; 24: 1301–27.
10. Tolmachev V, Lövqvist A, Einarsson L, Schultz J, Lundqvist H. Production of ^{76}Br by a low-energy cyclotron. Appl Radiat Isot 1998; 49: 1537–40.
11. Tolmachev V, Lundqvist H, Einarsson L. Production of ^{61}Cu from a natural nickel target. Appl Radiat Isot 1997; 49: 79–81.
12. Tolmachev V, Lundqvist H. Rapid separation of Gallium from Zinc targets by thermal diffusion. Appl Radiat Isot 1996; 47: 297–9.
13. Tolmachev T, Lundqvist H, Einarsson L. Diffusion based separation methods: dry distillation of zinc, cadmium and mercury isotopes from irradiated targets. Appl Radiat Isot 1997; 48: 565–9.
14. Lundqvist H, Tolmachev V, Bruskin A, Einarsson L, Malmborg P. Rapid separation of ^{110}In from enriched Cd targets by thermal diffusion. Appl Radiat Isot 1995; 46: 859–63.
15. Ferrant A, Cogneau M, Leners N, Jamar F, Martiat P, Michaux JL. ^{52}Fe for additional marrow ablation before bone marrow transplantation. Blood 1993; 81: 3435–9.
16. O'Donoghue JA, Wheldon TE. Targeted radiotherapy using Auger electron emitters. Phys Med Biol 1996; 41: 1973–92.
17. Herzog H, Rösch F, Stöcklin G, et al. Measurement of pharmacokinetics of yttrium-86 radiopharmaceuticals with PET and radiation dose calculations of analogous yttrium-90 radiotherapeutics. J Nucl Med 1993; 34: 2222–6.
18. Rösch F, Herzog H, Plag C, et al. Radiation doses of yttrium-90 citrate and yttrium-90 EDTMP as determined via analogous yttrium-86 complexes and positron emission tomography. Eur J Nucl Med 1996; 23: 958–66.
19. Dghighian F, Pentlow KS, Larson SM, et al. Development of a method to measure kinetics of radiolabelled monoclonal antibody in human tumour with applications to microdosimetry: positron emission tomography studies of iodine-124 labelled 3F8 monoclonal antibody in glioma. Eur J Nucl Med 1993; 20: 402–9.
20. Flower MA, Al-Saadi A, Harmer CL, McCready VR, Ott RJ. Dose-response study on thyrotoxic patients undergoing positron emission tomography and radioiodine therapy. Eur J Nucl Med 1994; 21: 531–6.
21. Pentlow KS, Graham MC, Lambrecht RM, et al. Quantitative imaging of iodine-124 with PET. J Nucl Med 1996; 37: 1557–62.
22. Zweit J, Flower M, Brown A, et al. Iodine 120-mIBG: production and NCA labelling of a new PET radiotracer. J Nucl Med 1996; 37: 191.
23. Lövqvist A. On the use of ^{76}Br for radioimmuno-PET [dissertation]. Uppsala: Uppsala University, 1996.
24. Lövqvist A, Sundin A, Roberto A, Ahlström H, Carlsson J, Lundqvist H. Comparative PET imaging of experimental tumors with ^{76}Br-labeled antibodies, (^{18}F)fluorodeoxyglucose, and (11C)methionine. J Nucl Med 1997; 38: 1029–35.
25. Lövqvist A, Sundin A, Ahlström H, Carlsson J, Lundqvist H. Pharmacokinetics and experimental PET imaging of a Bromine-76-labeled monoclonal anti-CEA antibody. J Nucl Med 1997; 38: 395–401.
26. Rösch F, Blessing G, Linse KH, et al. Production of the positron-emitting strontium isotope Sr-83 and PET phantom measurements preparatory to the evaluation of Sr-89 pharmacokinetics and dosimetry. J Nucl Med 1996; 37: 166.
27. Stabin MG, Kooij PPM, Bakker WH, et al. Radiation dosimetry for indium-111-pentreotide. J Nucl Med 1997; 38: 1919–22.
28. Beshara S, Lundqvist H, Sundin J, et al. Pharmacokinetics and red cell utilization of ^{52}Fe/^{59}Fe-labelled iron(III) hydroxide-sucrose complex in anaemic patients. Br J Haematol. In press.
29. Sgouros G. Bone marrow dosimetry for radioimmunotherapy: theoretical calculations. J Nucl Med 1993; 34: 689–94.
30. Coleman ER, Tesar RD. Clinical PET: are we ready? J Nucl Med 1997; 38: 16N.
31. Jarritt PH, Acton PD. PET imaging using gamma camera systems: a review. Nucl Med Commun 1996; 17: 758–66.
32. Dahlbom M, MacDonald LR, Eriksson L, et al. Performance of a YSO/LSO Phoswich detector for use in a PET/SPECT system. IEEE Trans Nucl Sci 1997; 44: 1114–9.
33. Dale LB, Young H, Bloomfield PM, et al. ECAT ART—A continuously rotating PET camera: performance characteristics, initial clinical studies, and installation considerations in a nuclear medicine department. Eur J Nucl Med 1997; 24: 8–15.
34. Shao Y, Cherry SR, Farahani K, et al. Development of a PET detector system compatible with MRI/NMR systems. IEEE Trans Nucl Sci 1997; 44: 1167–71.