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Forward to the Past:

the Case for Quantitative PET Imaging

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ABSTRACT

Positron emission tomography (PET) was developed in the 1970's as an *in vivo* method to measure regional pathophysiological processes. In the 1990's the focus moved to the detection of local increases in uptake, first in the brain (activation studies) and later in oncology (finding metastases), where ^{18}F-FDG emerged as a highly sensitive staging technique. This focus on sensitivity has overshadowed the other main characteristic of PET, its quantitative nature. In recent years there has been a new shift. PET is now seen as a promising tool for drug development and precision medicine, i.e. a method to monitor or even predict response to therapy. For precision medicine quantification is essential, but nowadays many studies use simplified semi-quantitative methods without proper validation of those methods. In this review several examples are provided to illustrate that simplified methods may lead to less accurate or even misleading results. Simplification is important for routine clinical practice, but it requires careful studies to find the optimal balance between accuracy and simplicity. It is argued that the use of simplified approaches without proper validation not only may give rise to a waste of time and resources, but that it also may raise ethical questions, especially when used in drug development studies.

KEY WORDS:

Positron emission tomography, quantification, dynamic scanning, static scanning, ethics.

NOTEWORTHY

- The working principle should be “simplicity through complexity”; where possible simple methods should be used, but only after validation against fully quantitative, more complex methods – page 15.
- The level of simplicity should depend on the underlying clinical or research question, finding the right balance between simplicity and accuracy – page 16.
- Use of simplified scanning and data analysis protocols without proper validation may raise ethical questions, especially in drug development studies – page 17.

BACKGROUND

Although there had been earlier attempts, a major step forward was brought about in 1974, when the first PET scanner using a Fourier-based reconstruction algorithm, proper sampling and exact attenuation correction was described *(1,2)*. The final version, the PET-III, was the first whole-body tomograph specifically designed for human studies *(3,4)*. From this design came the first commercial tomograph, the ECAT *(5)*, which was produced by EG&G Ortec, a company that was specialised in nuclear physics measurement equipment. To date, these early scanners may look rather primitive with single detector rings that contained large NaI(Tl) detectors and provided a spatial resolution of just below 2 cm full width at half maximum. In addition, stepping motors were needed to move detectors in both translational and rotational directions in order to obtain both reasonable spatial resolution and sufficient angular information for accurate reconstruction of radioactivity distributions. Nevertheless, it should be realised that these scanners were developed as novel quantitative tools to measure human physiology *in vivo*. This is clearly illustrated by a series of early papers from the UCLA group on "Quantitation in positron emission computed tomography", discussing general quantification issues that are still relevant to date. Here, only references to the first four papers of this series are given *(6-9)*. It should be emphasized that the development of PET as a molecular measurement technique involved efforts from many scientists from many different centres. A complete description of the history of

technical developments in PET is beyond the scope of the present review. Instead, the reader is referred to a very recent dedicated review on this topic *(10)*.

EARLY APPLICATIONS

Initially, studies focussed on measurements of blood flow and metabolism, simply because of the availability of suitable tracers, such as oxygen-15 labelled water and gases and the glucose analogue ^{18}F-FDG *(11,12)*. In fact, the use of ^{18}F-FDG to measure regional cerebral glucose metabolism was one of the very first examples where PET measurements were used to map a physiological process *(12-14)*. Another example from the early 1980's is shown in Fig. 1, providing parametric images of cerebral blood flow (CBF), oxygen extraction fraction, cerebral oxygen utilisation and cerebral blood volume for 2 consecutive patients with a high grade glioma, as derived from ^{15}O-CO_2, ^{15}O-O_2 and ^{11}C-CO scans *(11,15)*. Despite the poor image quality of the images (acquired using an ECAT-II with a spatial resolution of 16 mm full width at half maximum), according to today's standards, this (quantitative) example clearly illustrates that, even in the same condition, underlying pathophysiology (in this case CBF) can be completely different. In addition, these quantitative parametric images also illustrate that oxygen extraction fraction in tumours is lower than in normal brain irrespective of perfusion *(16)*, a finding that still is not fully understood.

In the early days, PET was used primarily for studies of the brain and heart *(17,18)*. In cardiology, mismatch between flow and metabolism actually became the most important diagnostic criterion in the assessment of myocardial viability *(19)*. In neurology, the field progressed into two completely different directions. On the one hand, PET progressed to become a unique molecular imaging tool. Based on its high sensitivity and the development of an ever increasing number of radiolabelled ligands, it became possible to assess various neuroreceptor systems *(20)*, an application that sometime later also became a valuable tool in drug development *(21)*. The other application was more phenomenological, namely the detection of activated areas (CBF) in the brain following a stimulus *(22)*. These studies were carried out using multiple ^{15}O-H_2O runs in a single scanning session. Initially, arterial blood sampling was used to quantify CBF *(23)*. After a thorough assessment of the relationship between ^{15}O-H_2O uptake and CBF, however, the uptake interval was optimised (to obtain the optimal signal to noise ratio, as a shorter interval is more related to CBF, whilst a longer interval allows for more counts and thus less noise) and studies were performed without arterial sampling, often by normalising to uptake in whole brain (proportional scaling), as it was assumed that global CBF would not change between conditions *(24)*. In most cases this approach was sufficient, as the main interest was the site of activation, not its magnitude. This is, in fact, a clear example where thorough knowledge of the kinetics of a tracer allowed for optimal simplification of scanning and analysis protocols for the clinical research question at hand.

THE SECOND WAVE

In the 1990's, when most scanners were still located in dedicated research centres, PET was discovered in oncology. Although it had already been used to study the pathophysiology of tumours as illustrated in Fig. 1, the emerging possibility to perform whole body scans provided an opportunity to survey the entire body *(25)*. Based on the unsurpassed sensitivity of PET and the increased glycolytic rate of many tumours (Warburg effect), PET (and later PET/CT) became an indispensable method for staging. In an overall low level of uptake, one only needed to search for unexpected areas of abnormal, high uptake. This had an enormous impact on the field, as evidence was gathering rapidly that PET had an important role to play in managing patient care, e.g. by indicating that local surgery would be futile given the presence of distant metastases *(26)*. A further boost was given by the development of PET/CT, which made it possible to relate functional information to the exact anatomical location *(27)*.

Unfortunately, there was also a downside to this rapidly increasing interest in PET. Scanner manufacturers competed on the basis of image quality and because of this so-called "image beautification" the other key characteristic of PET, its quantitative nature, was somewhat neglected. For example, iterative image reconstruction algorithms were implemented to improve image quality, but at the same time they

could compromise quantitative accuracy, especially for low count frames in a dynamic study *(28)*.

THE NEED FOR QUANTIFICATION

Clearly, image quality is important if the main purpose is to find hot spots such as metastases. Nowadays, however, the focus has shifted towards precision medicine, monitoring response during therapy or, preferably, even assessing potential response prior to therapy (for example using radiolabelled drugs). As a result, there is renewed interest in quantification of tracer uptake, which is also apparent from the literature where a steep rise in the use of words such as “quantitative” and “quantification” can be seen. Often these quantitative claims are based on the measurement of Standardised Uptake Values (SUV; uptake normalised to injected dose and body weight) or, when a reference region is available, SUV ratios (SUVr). Yet, measuring radioactivity concentrations (uptake) quantitatively is not the same as measuring a (patho)-physiological process quantitatively. To illustrate this point, Fig. 2 shows two ^{11}C-R116301 scans, reflecting NK1 receptor status *(29)*, in a normal human subject, the first at baseline and the second after an oral dose of aprepitant, an NK1 antagonist. Both scans are expressed as SUV for the interval from 60 to 90 minutes after injection. Suppose the dose of aprepitant was not known and one was asked what level of occupancy had been achieved, what would be the logical answer? Presentation of this

case at conferences, workshops and courses over the last 2 to 3 years has shown that the vast majority of people, including experienced PET scientists, estimate the level of occupancy at somewhere between 25 and 75%.

In fact, the scans shown in Fig. 2 represent a static portion (60-90 minutes post injection) of a dynamic scan. The dynamic scanning sequence also allowed for calculating binding potential BP_{ND} (the ratio at equilibrium of specifically bound to nondisplaceable tracer in tissue) on a voxel-by-voxel basis *(30)*. The result of that calculation is shown in Fig. 3 where near complete occupancy (97%) in the striatum of the second scan can be seen. Clearly, for an accurate assessment of the underlying receptor status, the parametric images shown in Fig. 3 are essential and the SUV images in Fig. 2 are, in fact, misleading.

So, why is there such a big difference between the images of Figs. 2 and 3? Fig. 2 shows uptake images at a certain time (60-90 minutes) after injection. Net uptake at any given time, however, is a complex interplay between delivery, uptake, retention and clearance of the tracer. For example, increased uptake can be due to increased delivery (either increased plasma concentration or increased flow), decreased clearance, or a combination of these physiological processes. From a single static scan it is impossible to separate the various components that contribute to the total signal, e.g. specific binding, non-specific binding and free tracer in tissue. In contrast, with a dynamic scan it is possible to follow kinetics (uptake, retention, clearance) of the tracer and from

these kinetics it is possible to tease out the various individual components. By comparing Figs. 2 and 3, it will be clear that all activity in the post-aprepitant uptake scan (Fig. 2) is entirely due to non-specific binding.

THE PRICE AND BENEFITS OF ACCURATE QUANTIFICATION

There are many reasons for not performing (complex) dynamic scans. First, for full quantification, dynamic scanning alone is not sufficient. The input function, i.e. the metabolite corrected arterial plasma input function, also needs to be measured. This requires arterial cannulation, an invasive procedure with a (very small) risk of complications. A potential solution is the use of image derived input functions *(31)*, but no generally applicable method is available yet. Second, dynamic scans typically last 60 minutes, sometimes even longer, and some patient motion during such a long scanning protocol is inevitable. Although several methods have been developed to correct for patient motion *(32)*, they require additional processing time. Third, dynamic scanning, arterial sampling and especially metabolite analysis are time consuming procedures. Fourth, all these issues together mean that patient throughput is reduced compared with simple static scanning. The logical consequence is that (quantitative) dynamic scanning is substantially more expensive than (qualitative or semi-quantitative) static scanning. So, why would one even consider performing complex dynamic studies? The

answer to this question is given by the example of Figs. 2 and 3. To show that this is not an exception, a few more examples of common applications are provided below.

Receptor Occupancy

One application of PET in drug development, and in the future possibly also in precision medicine, is the measurement of receptor occupancy. For example, based on PET studies, it is known that occupancy of D_2 receptors in the striatum by antipsychotic drugs has to be at least 65% to have any effect, but it should be less than 85% to avoid side effects *(33,34)*. This means that, for a novel antipsychotic drug, PET can be used to determine the optimal dose, i.e. the lowest dose for the level of occupancy needed. This avoids overdosing, which is a genuine risk with the classical approach where the initial dose in a trial is based on the toxicity profile of the drug under study. The beauty of PET is that test-retest variability of quantitative parameters such as binding potential BP_{ND} often is in the range of 5 to 10% *(35-37)* and therefore the optimal dose can be found using only a limited number of scans. An early example is shown in Fig. 4a, where the optimal dose was established using data from only 8 healthy volunteers *(21)*. In a follow-on study *(38)*, the biological half-life of the drug (binding to the receptor) was measured. Again, using a limited number of healthy volunteers, each one scanned at a different time after drug administration, it was established that therapeutic levels (i.e. receptor occupancy) could be maintained by administering the drug twice daily (Fig. 4b). Of course, these studies were less complex than other drug development studies,

as it has been shown that, for ^{11}C-raclopride, data can be analysed using the simplified reference tissue model *(39)*. In other words, neither arterial cannulation nor the associated labour intensive metabolite measurements were needed. However, even if such measurements would have been necessary, the costs of both PET studies together (and possibly similar studies in a relevant cohort of patients) are negligible compared with the costs of a clinical trial, and those PET studies guarantee that a subsequent trial can be performed using the most appropriate dose and dosing regimen of the drug.

Global Changes

Global changes provide another example where absolute quantification is essential, even for diagnostic purposes. Fig. 5 presents ^{15}O-H_2O derived myocardial blood flow (MBF) images at baseline and after adenosine induced hyperaemia in both a healthy volunteer and a patient with triple vessel disease. Both subjects show normal perfusion at rest, although baseline MBF is somewhat higher in the patient with triple vessel disease. More importantly, however, the hyperaemia scan in the patient appears to have a normal distribution, the only indication of pathology being that, globally, MBF is much lower than that in the healthy subject. A qualitative assessment of the hyperaemia scan would have labelled this patient as normal. For this application, the overall time of the entire procedure, including rest and stress dynamic ^{15}O-H_2O scans and CT angiography, is less than 1 hour. The input function can be derived from the

dynamic scan itself and generation of the parametric MBF images is essentially automatic *(40)*.

Drug Targeting

An issue in both drug development and precision medicine is whether a certain drug reaches its target at sufficient concentrations. This can be addressed by labelling the drug. The treatment strategy can then be based on the level of uptake (or lack of it) in the lesion. One example to illustrate this principle is the use of tyrosine kinase inhibitors in lung tumours. It is known that only tumours with an activating epidermal growth factor receptor mutation respond to tyrosine kinase inhibitor therapy. It is, of course, possible and indeed routine practice to determine the mutational status on the basis of a biopsy, but this is an invasive procedure and not feasible for all tumours. A study with ^{11}C-erlotinib showed that uptake in tumours with an activating mutation was significantly ($p<0.016$) higher than that in tumours with wild type epidermal growth factor receptors *(41)*, at least when the volume of distribution V_T derived from full kinetic analysis was used (Fig. 6). In contrast, for the best simplified method based on a single static scan, in case of ^{11}C-erlotinib the tumour to blood ratio for the interval 40 to 50 minutes post injection (TBR_{40-50}) *(42)*, the difference between groups did not reach significance ($p<0.070$) due to substantial overlap (Fig. 6), possibly because of a relatively large variability in the metabolic profile of ^{11}C-erlotinib. In other words, within the context of drug development, the same answer can be obtained using smaller

patient populations, which would not only compensate for the higher costs of a fully quantitative dynamic scan, but which would also mean smaller, better controllable trials and probably more definitive information. More importantly, if this method would proceed to clinical practice (the right drug for the right patient), the quality of care would be substantially better with fully quantitative scans.

Amyloid Load

As a final example, amyloid imaging in Alzheimer's disease can be used, an application that is gaining rapid popularity as it provides an *in vivo* method to establish amyloid load in the brain. Clearly, for most diagnostic purposes (amyloid positive versus amyloid negative), quantification will not be useful. For future therapeutic interventions, however, there is a need to identify patients at very early stages, i.e. those who would not be identified as clearly positive, but who are also not entirely negative. Therefore, much effort is being put in quantifying uptake using SUVr, which essentially is the ratio of uptake in a target (cortical) region and a reference tissue, usually the cerebellum. In principle this is fine, but the method is now also being used in large clinical trials investigating novel anti-amyloid therapies. This latter use of SUVr is questionable, as for most amyloid ligands SUVr has not been characterised very well. The limitation in using SUVr for longitudinal studies has been demonstrated for ^{11}C-PIB *(43)*, the results of which are summarised in Fig. 7. In this study no (anti-amyloid) treatment was given and patients were followed for 2 to 4 years. Yet, SUVr showed a small, but significant

counterintuitive decrease in amyloid load, whereas BP_{ND} remained unchanged. In an attempt to explain these findings, simulation studies were performed. These simulations showed that the reduction in SUVr most likely was due to a decrease in CBF, a phenomenon that is known to take place in Alzheimer's disease. In contrast, BP_{ND}, derived from fully quantitative analysis (simplified reference tissue model), is independent of blood flow. As a reduction in perfusion may result in delayed equilibrium conditions, SUVr, taken at a predefined time, may be affected to a degree that depends on the kinetics of the actual amyloid ligand. It should be noted that not only changes in perfusion, but also changes in clearance rates may result in bias *(44)*.

FORWARD TO THE PAST

The examples given above demonstrate that there are various applications where dynamic scanning with full kinetic analysis is superior over semi-quantification based on a static scan. It should be noted that these examples represent only a few of the many applications that could be mentioned. Unfortunately, over the 40 years that PET has been around, there is an increasing incidence of reports based on a qualitative or semi-quantitative analysis of data without proper validation of the simplified analysis method being used. Obviously, there is a strong temptation to use these shortcuts. Apart from patient throughput, it is easier and much faster to publish a paper that is based on exciting images with corresponding simplified semi-quantitative analyses,

such as SUV or SUVr, than one that is based on a thorough, fully quantitative study, especially if the latter also demonstrates potential limitations of the semi-quantitative indices (i.e. images). Clearly, this attitude is promoted by the present publication pressure of citation and H indices. Science, however, is more than populism and there is an urgent need to return to quantification as the basis of PET imaging, i.e. forward to the past when this was the common approach. There is nothing against simplified methods for routine clinical applications, but these methods should be validated before they are being used to draw (otherwise potentially misleading) conclusions. In other words the working principle should be "simplicity through complexity", i.e. aiming to use simple methods for clinical applications, but only after they have been validated using fully quantitative, more complex methods.

FINDING THE RIGHT BALANCE

Having made a plea for quantification, one should also not be too dogmatic. Clearly, many applications only require limited or even no quantification. For example, for both staging in oncology and assessing amyloid status in the memory clinic, a visual read of the scans usually suffices. There are also applications where simplified analytical methods are more than adequate (e.g. ^{18}F-FDG SUV for monitoring response to classical chemotherapy). The issue is that such a simplification should first be validated for the specific application (e.g. ^{18}F-FDG SUV for monitoring response to novel biologicals may

not necessarily be valid) *(45)*, taking into account what the purpose of the study is. If different validated methods of analysis (and acquisition) are available, the level of simplicity should depend on the underlying clinical or research question. The aim should be to find the method that provides the maximum level of simplicity without compromising accuracy, i.e. the capability to measure a difference (from normality or in a longitudinal sense) that is clinically relevant.

ETHICAL CONSIDERATIONS

Finally, in the debate about quantitative versus semi-quantitative studies, little attention has been paid to ethical issues. Of course, everybody will agree that methods that provide incorrect or misleading results should be avoided, even more so if they are used for clinical decision making, where they actually could be harmful. In that sense, it is very strange that so many shortcuts are being made given that, without validation, incorrect results cannot be excluded. Another issue is that in clinical trials the number of patients required can be reduced if more accurate techniques are used (see the ^{11}C-erlotinib example above). In addition, in amyloid imaging trials, it is known that test-retest variability of BP_{ND} is better than that of SUVr *(43)*, again implying that with a fully quantitative method fewer patients need to be enrolled. That also means that fewer patients will undergo the entire study protocol with an experimental drug that may have some degree of toxicity and that may also not be effective. Even from a radiation

protection point of view (ALARA: as low as reasonably achievable), it also means that fewer patients (and possibly normal volunteers) are exposed to the radiation associated with a PET scan (or repeat PET scans). Taking these considerations together one could argue that use of a simplified scanning and data analysis protocol without proper validation not only may give rise to a waste of time and resources, but that it also may raise ethical questions, especially when used in drug development studies.

DISCLOSURE

There are no potential conflicts of interest relevant to this article.

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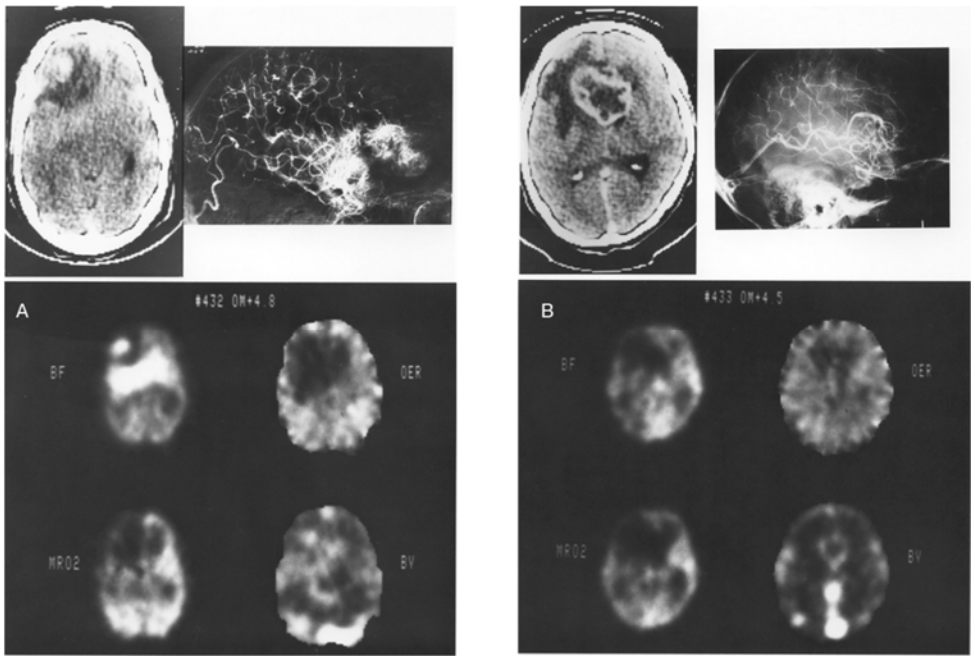

FIGURE 1. Parametric cerebral blood flow (BF), oxygen extraction fraction (OER), oxygen metabolism (MRO2) and blood volume (BV) images of (A) an astrocytoma, Kernohan grade IV, and (B) a glioblastoma multiforme, Kernohan grade IV. CT images and angiograms are shown above these parametric images. BV in both tumours is increased, which corresponds with the pattern seen in the angiograms. BF, however, is very different between the two tumours. Despite this difference in perfusion, oxygen extraction is reduced in both tumours as compared with normal cerebral tissue.

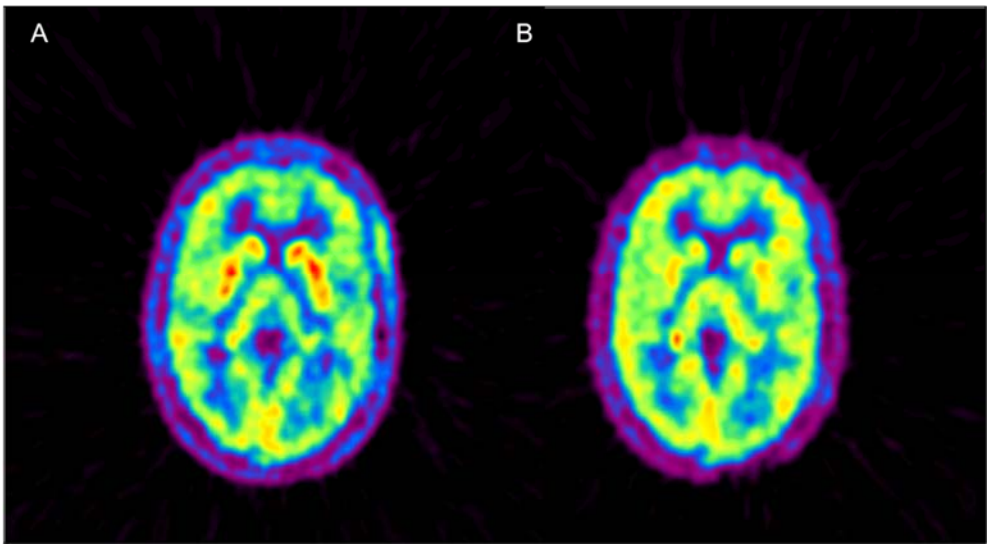

FIGURE 2. ^{11}C-R116301 uptake images, 60-90 minutes after injection, for a normal subject (A) before and (B) after an oral dose of 125 mg of aprepitant.

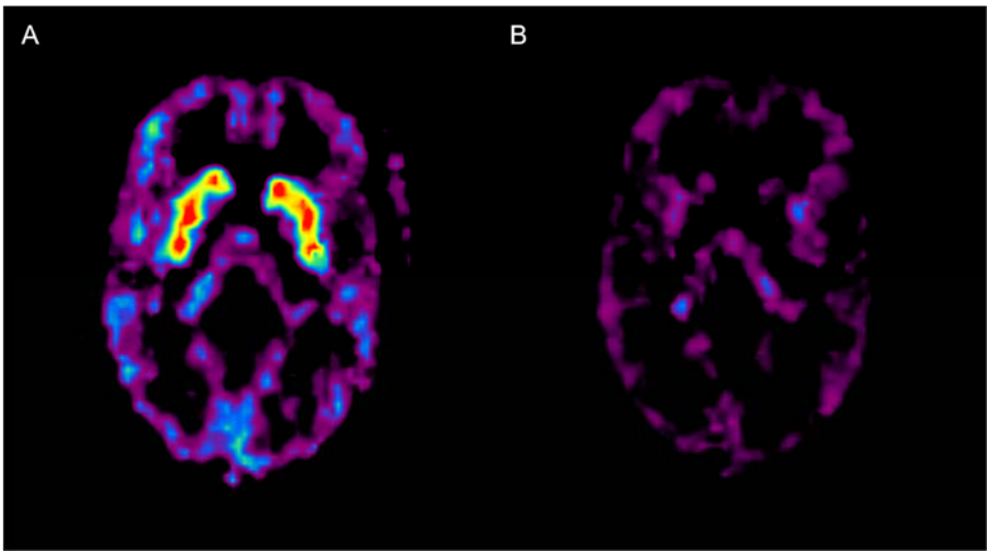

FIGURE 3. Parametric ^{11}C-R116301 binding potential BP_{ND} images for a normal subject (A) before and (B) after an oral dose of 125 mg of aprepitant. These images are based on kinetic analysis of 90 minutes dynamic scans. The uptake images shown in Fig. 2 are derived from the same scans (i.e. summed images from 60 to 90 minutes post injection) and both sets of images together illustrate that there is a significant contribution of non-specific binding in the uptake images. Only the BP_{ND} images show near complete blocking (97%) by aprepitant.

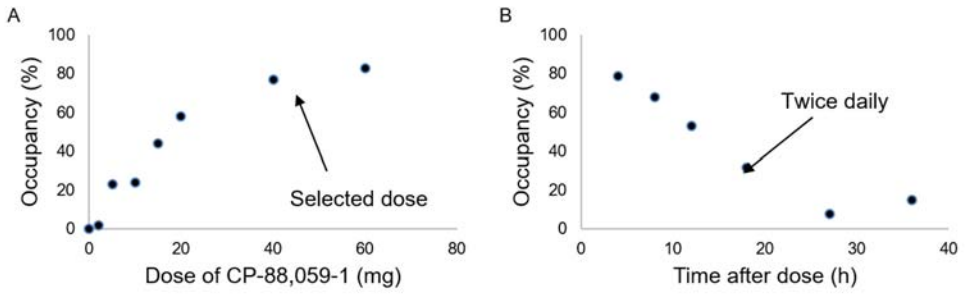

FIGURE 4. D_2 receptor occupancy (derived from ^{11}C-raclopride BP_{ND}) in healthy subjects following oral administration of CP-88,059-1 (a) 5 hours after a variable dose of CP-88,059-1, illustrating that a dose of 40 mg of CP-88,059-1 would be a good starting point for a clinical trial, and (b) at various times after 40 mg of CP-88,059-1, suggesting that occupancy would stay within the therapeutic range when given twice per day.

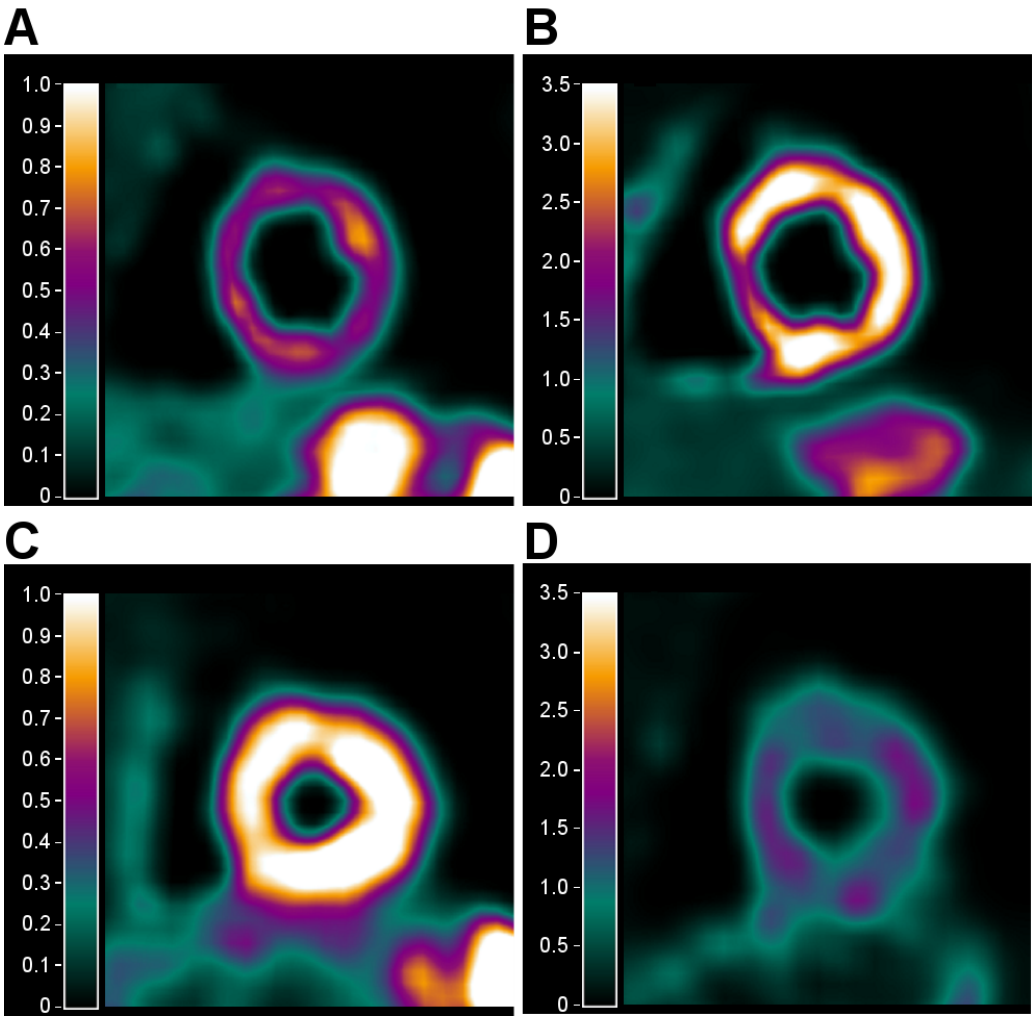

FIGURE 5. Parametric images of myocardial blood flow (MBF) in (A, B) a healthy subject and (C, D) a patient with three-vessel disease, at both (A,C) baseline and (B,D) hyperaemia (adenosine infusion).

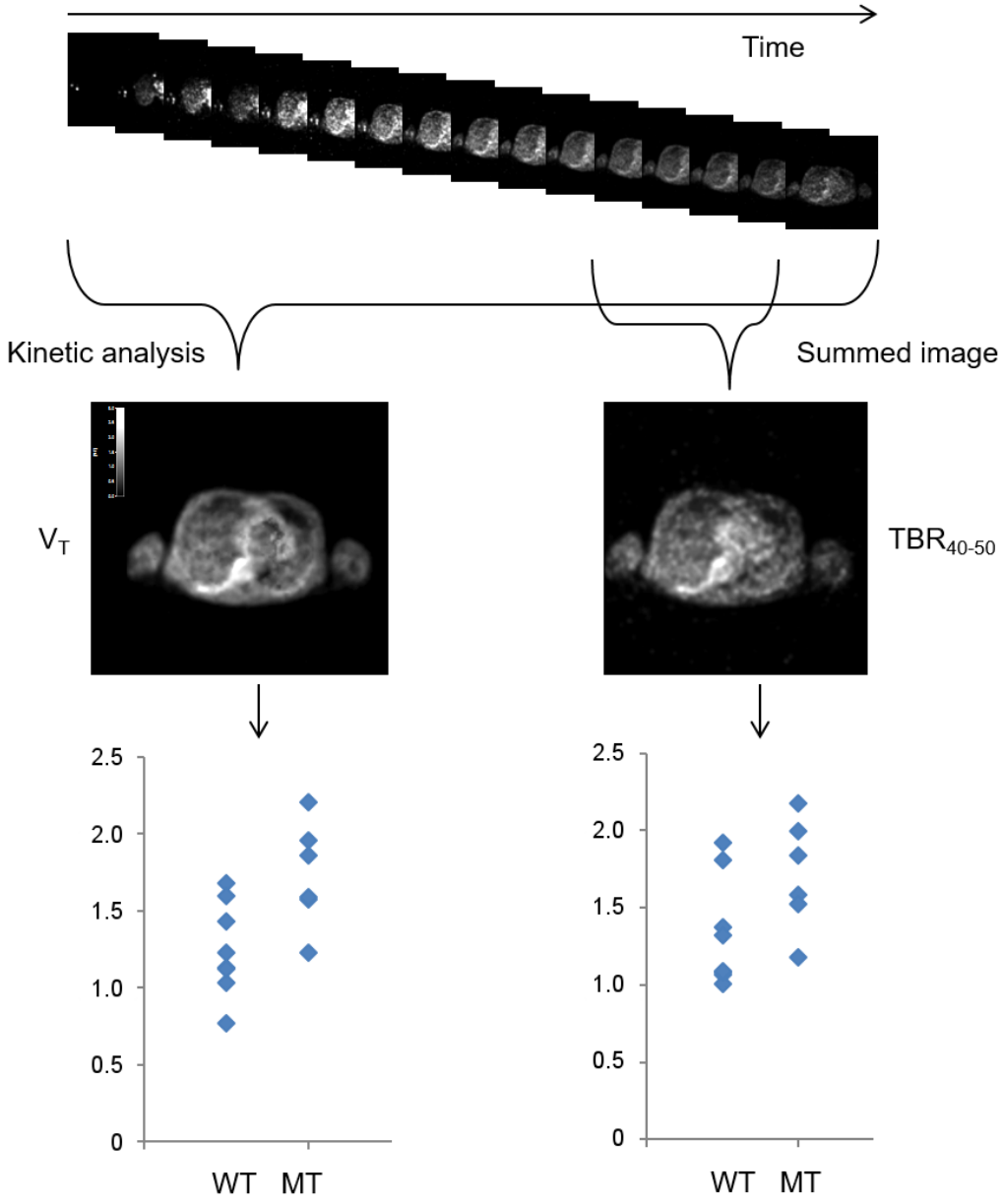

FIGURE 6. Schematic diagram of both kinetic and static analyses of ^{11}C-erlotinib data in lung tumours. For kinetic analysis the entire dynamic scan is used and data are fitted to obtain the volume of distribution V_T. In case of ^{11}C-erlotinib, the best static method

is the tumour to blood ratio applied to a summed image from 40 to 50 minutes after injection ($TBR_{40\text{-}50}$). The difference between tumours with (MT) and without (WT – wild type) an activating epidermal growth factor receptor (EGFR) mutation was significant for V_T ($p<0.016$), but not for $TBR_{40\text{-}50}$ ($p<0.070$).

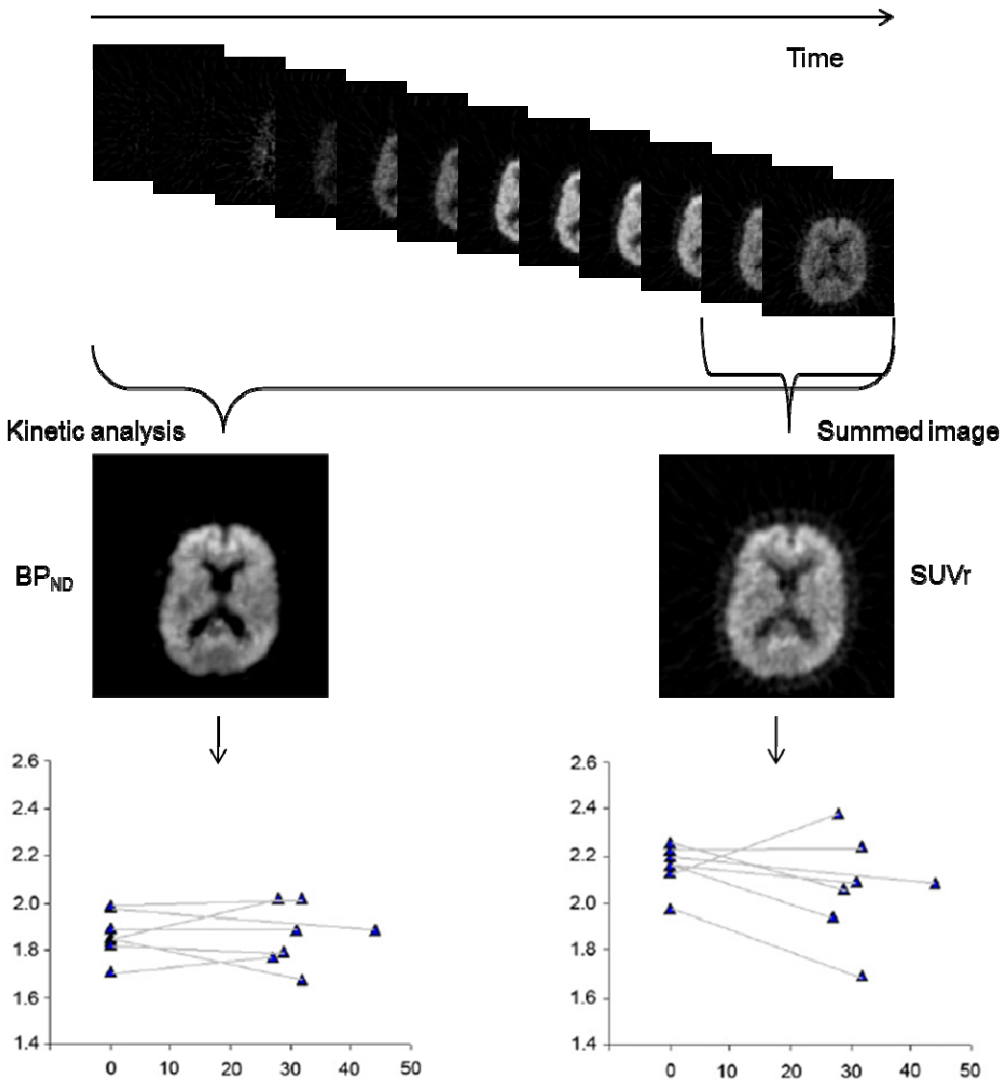

FIGURE 7. Binding potential (BP_{ND}) and uptake (SUVr, 60-90 minutes after injection) for ^{11}C-PIB scans in patients with Alzheimer's disease at two different time point separated by 2 to 4 years (horizontal axes represent months after baseline scan). Patients did not receive anti-amyloid therapy during the interval between scans.