

Quantification of SPECT and PET for Drug Development

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Abstract: Development of a new drug faces multi-faceted sequences in the pipeline. Once a drug candidate is identified, evaluation process can be accelerated by *in vivo* noninvasive imaging because there is a potential to use a smaller number of animals and human subjects. Radionuclide imaging techniques, such as single photon emission computed tomography (SPECT) and positron emission tomography (PET) are directly translatable imaging modalities that can be used in both animal models of disease and humans. In addition, SPECT and PET provide a highly sensitive means to track radiolabeled drugs, for which the imaging process less likely perturbs biological functions of animals and humans. Quantification of SPECT and PET data when used for drug development is elusive. Often times, *in vivo* SPECT and PET images of any drug candidate are used as 'flash' show-and-tell scenarios while actual data are obtained from *ex vivo* analyses. However, once the need and the degree of quantification are defined carefully, quantification of SPECT and PET can play an important role in drug development and evaluation processes.

Keywords: Drug evaluation, radionuclide imaging, SPECT, PET, quantification, biodistribution, pharmacokinetics, kinetic parameters, dynamic imaging.

1. INTRODUCTION

Drug discovery is like finding a needle in a haystack. There could be a large number of candidate drugs that can target a specific disease for either diagnosis or treatment. However, in order to eventually market the drug, investigators should go through multiple phases of the drug development cycle to show its quality, efficacy, and safety [1]. This process takes much time and financial resource [1-3]. Thus, there is a strong need to reduce the time and cost to develop a drug to a point that governmental regulatory bodies (*e.g.*, Food and Drug Administration in the USA) would approve its use.

There have been rapid advances in noninvasive imaging technologies and disease-specific molecular probe developments for both humans and animals [4-6]. These advancements may enable to accelerate many processes in drug development, and potentially reduce the cost significantly.

Among noninvasive imaging techniques, radionuclide imaging methods such as single photon emission computed tomography (SPECT) and positron emission tomography (PET), in combination with nuclear molecular probes that can be imaged by SPECT or PET, are preferred methods when the sensitivity is of the main issue [7-10]. A radiolabeled drug (radiopharmaceutical) can be used at tracer concentrations of the compound (pico- to nano- molar) for detecting molecular signals from targets. At the cost of spatial resolution, functional assessment of a drug is possible with SPECT and PET [11]. SPECT and PET can provide answers to pharmacokinetics, biodistribution, and imaging specific molecular end points. Besides, SPECT and PET are translatable imaging modalities from animal models to humans.

Quantification in SPECT and PET for drug evaluation process is generally considered a challenge [12-14]. Traditionally, SPECT and PET studies in humans have been interpreted with qualitative or semi-quantitative methods (*e.g.*, standardized uptake values or SUVs in PET). The same SPECT and PET techniques applied in imaging animal models of disease during early phases of drug development face the same interpretation dilemmas. There is no true standard for quantification of SPECT in particular for drug development and evaluation processes mainly because SPECT currently does not provide images in the unit of quantitative radioactivity concentrations. Even for PET which is considered as a quantitative

imaging tool, there are still many questions about degrees of quantification. Thus, before proceeding with any quantification issues for drug development and evaluation, one needs to think carefully if quantification is ever needed using SPECT and PET.

The goal of this paper is to describe aspects of quantifications, degrees of quantification necessary for drug development and evaluation, and specific issues of quantification for both SPECT and PET.

2. QUANTIFICATION IN SPECT AND PET FOR DRUG DEVELOPMENT

Radionuclide imaging systems heavily rely on quantitative data processing as sophisticated instrumentations that are used in clinical practice to make very important clinical decisions about diagnosis and treatment. However, the resultant images that are produced from these sophisticated imaging systems are interpreted mostly in qualitative ways. The reason behind this rationale is that it is so easy to find "hot spots" in unconventional regions for given radiopharmaceuticals. In other words, if one knows where the radiopharmaceutical accumulates in normal conditions, it is easy to identify any abnormal regions for detection of the disease.

For the drug development process, small animal models (*e.g.*, mice and rats) of disease are critical to test if the candidate drug goes to the target area and if the drug does not or minimally go to areas that could be biologically harmful and sensitive to the given drug [15-17]. SPECT and PET can image where radiolabeled drug goes to, and in theory can provide *in vivo* biodistribution data. With a serial study capability of SPECT and PET, one animal can serve as its own control so that the total number of animals can be significantly reduced in comparison to conventional biodistribution study for which groups of animals should be sacrificed at each time point. Moreover, in later phases of drug development cycle, SPECT and PET probes can be administered in humans as the same or similar way used in animal imaging.

Using SPECT and PET, one can remove cross-subject variability by imaging same animal or human at multiple time points during drug development processes (*e.g.*, pharmacokinetic studies). However, there is still intrasubject variability because the image data from SPECT and PET cannot be compared with accurately quantified values that do not vary by imaging conditions at multiple time points. Imaging times and subject's physical conditions make different distributions of radiopharmaceuticals. Quantified data in terms of the amount of radioactivity concentrations in selected regions of interest

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are sometimes not sufficient if we consider these variables. Besides, if the imaging studies are performed at different sites or by different imaging systems, there could be another variability when comparing quantified data.

The standardized uptake value (SUV) is based on measured radioactivity concentration by PET systems, and normalized by injection activity and subject's body weight [18-21]. The SUV is a semi-quantitative metric in which there could be significant intrasubject variabilities because of reasons mentioned above. For SPECT, there is not even a SPECT-SUV developed, nor adopted yet. SPECT is still considered a nonquantitative imaging method even if it provides similar or better quality images when dedicated animal SPECT with small pinhole collimators is also considered for comparison [22-25]. With regard to photon statistics, SPECT does not collect as many photons as PET does. Most physical corrections are more difficult in SPECT because of photon statistics and widely varied photon energies that are detected by SPECT cameras.

For drug development, initial preliminary phases to show where the drug goes do not need any degree of quantification. By SPECT or PET, it can easily depict where the drug accumulates at certain time intervals. However, as a robust way of comparison, when SPECT and PET are used to obtain data for biodistribution and pharmacokinetics, the values from SPECT or PET should be quantitative enough so that the studies using *in vivo* imaging should be comparable to the *ex vivo* gamma counting method in calculating %ID (injected dose) /g. For drug development in later stage to evaluate efficacy, both how much of drug is delivered to target and how effective and safe the drug is are preferred information, for which quantified data from SPECT or PET can help accelerate this process significantly.

3. DEGREE OF QUANTIFICATION NEEDED

It is obvious that quantification of SPECT and PET data for drug development is important. Then, one needs to think what degree of quantification is needed for each step of drug development cycles or given studies such as biodistribution that can provide data to toxicity, pharmacokinetics based on kinetic modeling, drug delivery in animals and humans after animal biodistribution data, and diagnostic imaging tests that can show efficacy of the drug delivered.

3.1. Types of Quantifications in SPECT and PET

Types of quantification in SPECT and PET can be sorted into three categories. The first type is to compare relative values between uptake in target versus uptake in background. The target-to-background contrast from images of SPECT and PET can show where the radiolabeled drug is accumulated after administration. The second type is based on correct radioactivity concentrations typically in the unit of Bq/ml which can be also converted into mg/ml of a drug delivered. In SPECT, there is no standard to derive Bq/ml from imaging studies yet. In PET, all images values are obtained as radioactivity concentrations, and they are believed to be sufficiently accurate except extremely high photon counting cases. The third type of quantification, which might be the most important quantification scheme in both SPECT and PET, is a set of kinetic parameters such as tracer flow or metabolic rates, which can be obtained by careful dynamic imaging, in combination with appropriate pharmacokinetic modeling and an arterial input function (AIF) that can be derived from dynamic images or blood samples during imaging sessions [12, 26-29].

3.2. Quantification for Biodistribution and Pharmacokinetics Studies

Biodistribution studies are one of the earlier steps in the drug development cycle. With radiolabeled drugs, biodistribution studies in animals, mostly performed on an animal model of the target disease, can be performed in two ways. One method is to measure

radioactivity levels using gamma counting devices from harvested organs after administration of a radiolabeled drug followed by euthanasia of animals. This method does not require any imaging. The other method is to measure radioactivity *in vivo* using SPECT or PET by calculating values from segmented organs of image volumes [30]. The latter method may enable serial measurements that provide pharmacokinetic data without sacrificing animals at multiple time points for pharmacokinetics studies of a drug.

Quantifications in terms of radioactivity concentrations for both SPECT and PET are required to perform imaging-based biodistribution and pharmacokinetics studies. For SPECT, there is currently no standard method to get radioactivity concentration values from imaging systems. However, relative values can be still obtained assuming there is no significant source of errors such as photon attenuation which could be the case for SPECT imaging of small animals. From small animal SPECT images, the total volume can be analyzed to derive the total activity and relative values in each organ if the injected radioactivity is known.

If the organ in *in vivo* imaging is small, or some organs surrounded by other organs of high radiopharmaceutical concentrations, partial volume errors can be a significant source of errors to obtain accurate values from SPECT and PET images. Partial volume errors will be described in more detail in later sections because they are the most important source of errors in quantification of SPECT and PET when the size of ROI is small, or there are spill-in or spill-out errors by surrounding regions.

3.3. Quantification for Imaging Drug Delivery

After administration of radiolabeled drugs, investigators would like to know whether the drug is delivered to the target. Imaging drug delivery can be combined with biodistribution studies. Quantification requirement for imaging delivered radiolabeled drug is minimal. However, if an investigator would like to know how much or what fraction of drug is delivered to the target, and to the other sensitive organs, the same degree of quantification as for biodistribution and pharmacokinetic studies is required.

3.4. Quantification in Diagnostic Imaging Tests in Conjunction with Drug Delivery Imaging

As well as imaging drug delivery to the target, SPECT or PET with routinely used diagnostic imaging agents to evaluate the efficacy of a therapeutic drug can be performed during a new drug development process. The therapy monitoring with SPECT or PET is one of the most valuable applications for drug development process [31-35].

Since this process involves human imaging at multiple time points, a quantitative verification, not only the size change of disease target such as tumor volumes, is important. Correct radioactivity concentration values might be sufficient in this application. For example, SUV measurements of ¹⁸F-fluorodeoxyglucose (FDG) can be used to monitor disease response to a given drug therapy [36, 37]. However, SUV varies by many factors that are not under the complete control of imaging studies. Injection times, supplies left in arterial blood, and imaging times after injection all can alter SUV values even for a single patient at multiple time points. In order to avoid these problems, one should consider evaluating kinetic parameters of radiolabeled drugs which are believed to be more quantitative, and impose fewer errors caused by intrasubject variabilities.

4. ISSUES OF SPECT QUANTIFICATION

With SPECT, except relative quantification method, there have not been thorough developments in quantification yet. Many investigators have been making efforts to overcome this aspect of SPECT imaging for any purpose including the drug development

application [38-41]. For drug development using SPECT for many phases of the development cycle, one needs to carefully consider what degree of quantification is necessary, and how to overcome at least the known issues.

4.1. Photon Attenuation

Photon attenuation is the biggest source of errors in SPECT reconstruction toward quantification [42]. In clinical SPECT imaging, modern scanners have capabilities of having an x-ray computed tomography (CT) component built in or as in a tandem system [43, 44]. The CT-based attenuation correction has routinely been applied during reconstruction of images from these modern SPECT/CT systems [45]. In animal SPECT imaging using dedicated animal SPECT systems, one could argue CT-based attenuation correction might not be required because the attenuation effect in small objects like rodents is negligible, and thus can be ignored [46]. However, for low energy photons such as those coming from I-125 labeled drug or other imaging agents that can be used in animal SPECT imaging, attenuation effect should not be ignored to obtain quantitatively accurate values of radioactivity concentrations [46].

Physically, precise attenuation correction is difficult in SPECT because unlike PET, attenuation map should be generated for each radionuclide for SPECT imaging with photon energy ranging from 25-30 keV (I-125) to 364 keV (I-131). Attenuation correction for radionuclides that emit photons at multiple energy peaks such as In-111 with 171 and 245 keV energy peaks is not straightforward [47]. However, for drug development and quantification needs described above, photon attenuation correction is the minimum requirement for any quantitative SPECT imaging, and must be considered with significance.

4.2. Scatter and Geometric Blurring by Collimators

Scattered photons easily pass through SPECT collimators, and contribute to actual projection data. An energy window is set to reduce this error, but the energy windowing itself cannot filter all scattered photons. Scatter correction is often performed with various methods [48-52]. Because of its nature, scatter correction may not be accurate and necessary because of SPECT lacking photon statistics. Many scatter correction methods in SPECT will eventually require subtraction in true photon counts, which in return could degrade the imaging quality once reconstructed. However, for quantification method, correction for scatter could be as important as photon attenuation correction [48].

Geometric blurring by collimators especially for parallel-hole collimators that are used in human SPECT imaging is a significant source of errors in reconstructing SPECT images. However, reconstruction algorithms that incorporate corrections for geometric blurring effect are relatively new to the field, and most commercial clinical SPECT manufacturers only recently started to adopt this kind of algorithm. Without correction schemes for geometric blurring, SPECT images cannot be treated as quantitative values [42, 53].

Combined with photon attenuation correction, scatter and geometric blurring corrections can make SPECT images close to quantitative values that can eventually be matched one-to-one as radioactivity concentrations in the unit of Bq/ml. Evaluations to obtain correct radioactivity concentrations in SPECT with corrections for these physical errors should be performed before quantified values in terms of radioactivity concentrations using SPECT can be used in drug development and evaluation processes.

4.3. Partial Volume Errors

When radiotracer uptake is accumulated in a small region such as small tumors, the size small enough to be less than 2-3 times the system spatial resolution, there is an inevitable partial volume error. The same concentration in smaller region looks typically dimmer

than that in larger region. The partial volume error is universal for both SPECT and PET. This error manifests itself as spill in/out of activity between neighboring voxels and the subsequent blurring of boundaries of regions of interest (ROIs). Since this effect is size dependent, it would be crucial to correct for partial volume errors if radiopharmaceutical uptake were used as a quantified metric in either SPECT or PET imaging.

Various techniques exist to correct for partial volume errors, and they can be classified into two categories [54]. The first category utilizes a higher resolution anatomical image from modalities such as CT or magnetic resonance imaging (MRI) to define the boundaries of the tumor. Correction is applied during or after image reconstruction by modeling the effect of the finite spatial resolution. The disadvantage of these methods is that it requires very accurate registration of the SPECT or PET and CT (or MRI) images and subsequent segmentation of the anatomical image. An assumption is also made about the boundaries of the tumor in the functional image even if they do not correlate with the anatomical boundaries such as in the case of necrotic tumors where uptake is inhomogeneous. The second category does not utilize anatomical information but corrects for partial volume errors from knowledge of how partial volume errors affect the quantification of tumors of various sizes and background levels. There is one caveat for this second category of correction technique. An estimate of the tumor size from the PET image is required even though the real tumor extent can be different from its apparent size from the PET image. One best example of the second category of partial volume correction is to use the three dimensional iterative deconvolution technique [55].

4.4. Absolute Quantification and Dynamic Imaging

Unlike PET, conventional SPECT images do not provide absolute quantification values in the unit of Bq/ml. This step would be the first step to use SPECT for providing quantified data to drug development process. Dynamic imaging using SPECT may be possible to derive kinetic parameters with appropriate pharmacokinetic modeling [56]. Once again, unlike PET, there is no routine method of dynamic SPECT imaging because obtaining an arterial input function (AIF), the needed element to derive kinetic parameters, is difficult from slowly rotating SPECT camera. Recent advances in fast SPECT [56], or a technique to derive the AIF from projection data of SPECT can be used for dynamic SPECT imaging [57].

5. ISSUES OF PET QUANTIFICATION

Modern PET scanners typically provide all images in the unit of radioactivity concentrations (*e.g.*, Bq/ml) after corrections for photon attenuation, scatters, and randoms. Because of this advantage over SPECT, PET is considered to be more quantitative than SPECT. However, PET also carries many issues as same as SPECT to provide quantified data for drug development applications.

5.1. Photon Attenuation

Photons of interest in PET imaging all have 511 keV. By coincidence logic, and the way attenuation coefficient is required for correction, photon attenuation correction in PET is relatively easier than that in SPECT [58]. The issue is usually what kind of attenuation map would be used for correction. Before the advent of combined PET/CT scanners, transmission scans to generate attenuation coefficient using a radioactive source (*e.g.*, Ge-68) attached to a rod ring were used to generate an attenuation map [59, 60]. Because of economic reasons, a higher patient throughput is possible using x-ray CT-based attenuation map generation for faster PET data acquisition. Thus, currently attenuation correction for PET is mostly applied from attenuation maps generated from x-ray CT. Although the CT-based attenuation coefficient is generally comparable to transmission based

coefficient, modern CT acquisitions are so fast that CT captures only spontaneous cycle of breathing, which is not consistent with PET acquisition time scale when imaging areas of body affected by respiratory motion (e.g., lungs and heart) [61]. In addition, iodinated contrast agent for contrast-enhanced CT which is often combined in one single PET/CT study creates minor problems when converting attenuation coefficients from contrast-enhanced CT into attenuation coefficients of PET photon energy, 511 keV [62, 63].

5.2. Scatter and Randoms

Inherently in PET acquisition, scatter corrections are applied by energy discrimination as well as count-rate based estimations. However, for some modern PET scanners using a "3D mode" of acquisition without septa between each PET detector row, photon detection efficiency is theoretically a lot higher than the 2D mode. Since the 3D is more sensitive in photon counting and without septa, there are also more scattered photons recorded than the 2D mode with septa. In order to reduce inaccuracies from high scattered photons, either lower dose should be applied, or detection for high count rates must be handled by hardware [64].

With this "3D mode", because of high detection efficiency, and sometimes injection of very high radioactivity in certain studies (e.g., myocardial blood flow imaging with Rb-82), random coincidence rates could go up very high too. In these special occasions, PET most likely cannot deliver accurate radioactivity concentration values, which can affect quantitative accuracy of PET data.

5.3. Physiologic Errors

Physiologic motions, specifically respiratory motions, are significant sources of errors to affect quantification of PET data. These motions also affect SPECT quantification although it was not mentioned explicitly above. For drug development, if the regions of interest (ROIs) are within body areas that are mostly affected by respiratory motions such as lungs and heart, one should consider correction for respiration motion to obtain accurate quantification of the data.

5.4. Partial Volume Errors

As for SPECT, partial volume errors are great sources of errors to make impact on quantified data. PET, because of typically higher spatial resolution (except pinhole SPECT for small animal imaging) than SPECT, partial volume errors is less severe. However, it is also a very important cause to affect significantly quantification of PET. There are many correction methods developed [65]. For detailed descriptions, the previous section, the issues of SPECT quantification should be consulted.

PERSPECTIVES

As clinical imaging tools, SPECT and PET will continue to be used "hot spot" imagers with simple and practical quantitative indices such as SUV for PET. However, for drug development in particular drug evaluation process, SPECT and PET need to be quantified to certain degree during this process. Currently practiced SPECT and PET imaging methods for drug development do not really rely on quantified data from these imaging modalities because the need has not been critically specified. There is no clear evidence that quantified methods of SPECT and PET can actually accelerate the time and cost of drug development yet.

For biodistribution/pharmacokinetics studies, quantification that leads to deriving kinetic parameters is not required. Thus, simply getting absolute numbers in the unit of Bq/ml from SPECT and PET might be sufficient. But, even these approaches are not standardized yet. SPECT suffers a lot from its low detection efficiency in this regard. Higher detection efficiency techniques for SPECT are being

sought, and once developed thoroughly, they can make sizable impacts. Radiolabeling of drug for SPECT imaging is in general less costly because SPECT radionuclides such as Tc-99m and I-123 do not require a medical cyclotron near SPECT camera, as for some PET radionuclides such as C-11, N-13, or O-15. SPECT also does not impose high radiation dose if the detection efficiency is comparable to PET.

For drug evaluation purposes, when diagnostic imaging tests are used to show drug efficacy, or pharmacodynamics of drug is studied, kinetic parameters such as flow or metabolic rates are of great importance when serial studies using same animals or same human subjects are compared against each other. This calls for dynamic imaging capabilities. Dynamic imaging with PET has been an established technique with most modern PET scanners, but suffers a small field of view (FOV) because of the narrow axial width of PET detector rings. For small animals, this is often ignored because some dedicated animal PET systems can cover the entire FOV for mice. Dynamic imaging with SPECT is a greater challenge. There was preliminary work performed for dynamic SPECT imaging. To this end, fast SPECT imaging techniques with high detection efficiency and means to derive input functions that are necessary to extract kinetic parameters, are of key importance in future technological advances.

ACKNOWLEDGEMENTS

The author thanks Stephen Bacharach and Bruce Hasegawa for sharing their expert knowledge of PET and SPECT quantification techniques. This work is supported in part by the National Cancer Institute (grant K25 CA114254).

ABBREVIATIONS

SPECT	= Single photon emission computed tomography
PET	= Positron emission tomography
SUV	= Standardized uptake value
AIF	= Arterial input function
ROI	= Region of interest
FDG	= Fluorodeoxyglucose
CT	= Computed tomography
MRI	= Magnetic resonance imaging
FOV	= Field of view

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