Quantitative Analysis of Tumor Biochemistry Using PET and SPECT

The goals of this conference were to explore the methods of quantitative kinetic modeling currently being used to extract biochemical information from the biodistribution of radiopharmaceuticals and to develop from these approaches simple methods of analyzing data from large clinical trials. The transition from kinetic modeling to practical imaging is a key factor in the performance of rapid clinical trials; therefore, the successful completion of this initiative will greatly accelerate drug development. The presentations covered three areas: kinetic approaches (most of which have been developed for neuroscience applications), translational approaches (which are practical models developed from more complicated analysis), and state-of-the-art clinical studies carried out in the field of oncology.

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General Discussion:

Most of the current work in functional modeling is based on experience in the brain—how do we transform these methods for application to tumors?

Much work has been done demonstrating the utility of functional radiotracer modeling in the brain, yet in this area alone, there remain many questions to be answered. The brain has several imaging advantages, including symmetry, minimal intrinsic motion (with easier alignment algorithms for gross motion), and the blood-brain barrier. The approaches used to develop brain-modeling algorithms should be adapted to account for the problems encountered when imaging outside the brain (intrinsic and extrinsic motion, varying blood supplies, adjacent tissue uptake, lack of barriers to metabolite uptake, etc).

What methods can be used to compensate for patient motion?
Non-physiologic motion caused by voluntary patient movement (stretching, twitching, etc.) causes large errors in quantitation. In the brain, head restraint devices and post-processing algorithms can reduce motion artifacts, but no similar approaches are available for whole-body imaging. These errors may be lessened by standard means—limiting imaging time, ensuring patient comfort, using positioning aids, and clearly informing patient of the negative impact of motion. Although large amounts of non-physiologic motion can invalidate a study, smaller amounts may be either corrected or deleted from the dataset.

Respiratory motion can cause significant problems when imaging the lower lungs and liver. Several methods of respiratory gating have been attempted, including assuming a constant respiratory rate, pre-training the patient to breathe in a pattern, and plethesmography. The latter has shown some success in MR applications. Reliable methods are certainly needed in this area, particularly when evaluating for potentially small post-treatment changes in size.

The bowel is constantly moving, making precise localization and measurement in the abdomen challenging. The variable uptake in portions of the bowel also creates an inhomogeneous background, with areas of increased uptake that may change position from study to study.   Alignment algorithms attempt to focus on the more fixed structures of the abdomen

(aorta, kidneys…) but more work in optimizing these algorithms is necessary. No corrections for such motion currently exist.

How do we ensure proper realignment for multiple imaging sessions, serial studies and correlation with other imaging modalities?
Image fusion technologies are still in their infancy. Use of external skin markers for realignment is unreliable, and computer algorithms have difficulty compensating for multidimensional changes in position (i.e. patient twisting, stretching, varying asymmetries). Limited success has been achieved with the Woods algorithm and other algorithms that employ volume rendering to normalize multiple studies; however, the logistics of implementation are often difficult. Fusion of serial images obtained with the same camera is most successful—needing only correction for patient position/ motion. Using different instruments, acquisition parameters, tracers (fusing different functional volumes) and/or modalities (fusing anatomical and functional volumes) for acquisition increases the complexity and noise in the resulting fused image. In such cases, a decision as to which portion of the study 'target region' is to be aligned may be required. (For example, if the liver is the region of interest, then consider fusing only the right upper quadrant to avoid potential fusion of variable stomach uptake). To be useful, an algorithm must be able to compensate for motion of the target region in all dimensions. Development of robust image fusion solutions is essential for quantitation of small changes in serial studies. CT-PET may prove helpful in this area by providing real-time anatomical imaging.

What is the role of attenuation correction?
Attenuation correction is important for quantitative analysis, as it removes effects from adjacent tissues. It is a more important consideration when making comparisons between patients (as individual attenuation patterns tend to vary) and therefore when making statements about characteristics of a given tumor. For serial imaging of an individual patient, the attenuation pattern is likely to be less variable.

Major concerns over attenuation correction have arisen, as older algorithms added significant noise; however, recent schemes fair much better. Debate over its true value for clinical reading continues, yet most scientists agree that both attenuation-corrected and non-corrected images should be viewed.

What alternatives to arterial blood sampling are available?
With the introduction of an arterial line to obtain an input function, it can be argued that PET imaging is no longer non-invasive. However, the use of surrogate input functions is gaining acceptance, as validation data on surrogate input functions have appeared in the literature. Several techniques have been reported, including normalized population-based input function, ROIs of the left atrium/ left ventricle, aorta and other large vessels, and arterialized venous sampling. Optimally, an arterial input function is preferred, but with proper care and recognition of the noise/error added, use of a surrogate input function is acceptable.

Summary of Recommendations. There was general agreement that the recent guidelines from the European group were the most comprehensive and should be followed:
Young H BR, Cremerius U, Herholz K, Hoekstra O, Lammertsma AA, Prium J, and Price P. Measurement of clinical and subclinical tumour response using [18-F]-fluorodeoxyglucose and positron emission tomography: 1999 EORTC recommendations. European Journal of Cancer 1999; 35:1773-1782.

Acquisition

Patient preparation	1. Patient fast overnight for AM scan, 6 hours for PM study. Measure venous BGL prior to injection (nl 4-7 mmol/l)
	2. Scan type I diabetics in the AM after overnight fast. In type II diabetics insulin may be administered at the discretion of the physician and must be documented
	3. All patients should be well hydrated and drink 500 ml water after injection if possible. 20-40 mg Lasix given within 10 minutes of FDG injection may be used for renal/pelvic imaging.
	4. Record all patient medications
	5. Diazepam may be used at the discretion of the clinician and must be documented.

Timing of PET scans *Insufficient data is available to determine the optimal tumor uptake period and optimal interval between scans*	1. Pre-treatment and post-treatment scan should be acquired 2. Pre-treatment scan should be obtained as close as possible to start of therapy (<2 weeks). Timing of post-treatment scan should be determined by the endpoint under assessment a. For post-treatment images, wait 1-2 weeks after cessation of treatment to avoid transient increases or decreases 3. Changes due to radiotherapy need further investigation 4. Single static image at 50-70 minutes post FDG injection or dynamic imaging of at least 60 minutes
Attenuation correction	1. No standard procedure yet recommended. Document procedure used
^{18}F-FDG dose	1. No standard dose yet recommended; doses of 5 to 20 mCi reported. Document dose used.

Methods of analysis:

Standardized uptake value	1. SUV_{bsa} (normalized to body surface area) is the minimum standard of measurement 2. $SUV_{bsa} = \dfrac{C(T)}{InjectedDose / BSA}$ 3. $BSA = W^{0.425} \times H^{0.725} \times 0.00718$
Kinetic method	1. Patlak graphical analysis is the method of choice 2. Direct arterial or surrogate measurement of plasma input function. 3. Compartmental analysis may be useful to determine the presence of k_4 when direct arterial blood sampling is possible
Tumor sampling	1. Regions defined on pre-treatment scans should include region of peak uptake. Whole tumor uptake should also be recorded. 2. The same ROI volumes should be sampled on other scans. Methods of co-registration should be documented. 3. Mean and maximal uptake measurements should be recorded and calibrated as MBq/l 4. Changes in extent of tumor uptake should be documented 5. Anatomic tumor size should be documented
Reproducibility	1. On the order of 10-20%. Recommend collection of reproducibility measurements for each camera when possible
Defining tumor response	1. **Progressive metabolic disease (PMD):** Increase in SUV >25%, visible increase of extent of uptake (>20% in the longest dimension), or new areas of FDG uptake 2. **Stable metabolic disease (SMD):** Increase in SUV <25% or decrease <15%, no visible extension of FDG uptake (<20% in longest dimension). 3. **Partial metabolic response (PMR):** Decrease in SUV >15-25% after 1 cycle of chemotherapy and > 25% decrease after more than 1 cycle. No reduction in extent of FDG uptake is required.

	4. **Complete metabolic response (CMR):** Tumor no longer identifiable

Table Adapted [1]

Method	Advantages	Disadvantages	Dependencies
Visual	1. Static/whole body image 2. No blood sampling 3. Shorter scan times 4. ± Attenuation correction	1. Non-quantitative 2. Threshold may vary between readers 3. Lower statistics 4. Single "snap-shot" of dynamic process 5. Dependent on background activity	1. Uptake time 2. Glucose levels 3. Partial volume effects
SUV	1. Static/whole body images 2. Semiquantitative 3. No blood sampling 4. Easy computation	1. Numerous methods for calculation in literature 2. Lower statistics 3. Single "snap-shot" of dynamic process 4. Needs attenuation correction 5. Decreased accuracy in detecting small changes	1. Uptake time 2. Glucose levels 3. Body weight 4. Partial volume effects
Kinetic analysis	1. Dynamic data acquisition 2. Quantitative 3. Less dependence on uptake time	1. Requires plasma input function (arterial preferred) 2. Complex computation	1. Partial volume effects 2. Quality of input function

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