1. INTRODUCTION

Over the past decade positron emission tomography (PET) has become the fastest growing medical imaging technology. This is primarily based on its performance as a diagnostic tool in oncology. In particular, its sensitivity for detecting metastases using whole body scans and 2-[\(^{18}\)F]fluoro-2-deoxy-D-glucose ([\(^{18}\)F]FDG) as a tracer is unrivaled, resulting in reimbursement for a steadily increasing number of indications. The development of PET/computed tomography (CT) scanners has further stimulated the use of PET, as investment in such a scanner is now also feasible for smaller hospitals.

It should be noted, however, that originally PET was developed as a technique for the noninvasive in vivo quantification of functional processes and molecular interactions (1). In fact, many different physiological, biochemical, and pharmacokinetic parameters can be measured with high selectivity and sensitivity in the picomolar to nanomolar range (2). Apart from glucose metabolism, processes that can be measured include blood flow, blood volume, oxygen utilization, presynaptic and postsynaptic
receptor density and affinity, neurotransmitter release, enzyme activity, drug delivery and uptake, and gene expression.

2. SCOPE FOR QUANTIFICATION

The detection of distant metastases using whole body $[^{18}\text{F}]$FDG PET does not rely on quantification. Due to the high glycolytic rate of most tumors (3) and the kinetic properties of $[^{18}\text{F}]$FDG, uptake of $[^{18}\text{F}]$FDG in malignant tissues is increased and, consequently, detection of positive lymph nodes and/or metastases involves identification of areas with increased uptake (i.e., hot spots) within a background (normal tissue) of lower uptake. Clearly, for this purpose, visual assessment of the whole body images will suffice.

Qualitative FDG images can even be useful for assessing response to chemotherapy. It is particularly useful if in repeat whole body scans new sites with increased uptake are detected, indicating progressive disease. In addition, if uptake in a tumor disappears during treatment, there is good reason to believe that the treatment is effective. On the other hand, if there is no change in uptake it can be assumed that there is no response. The difficulty arises in (the majority of) intermediate cases, where some reduction in uptake might be seen. Clearly, a quantitative method would potentially allow for the definition of objective cut-off values for response or, more likely, the definition of response probabilities associated with a certain reduction in $[^{18}\text{F}]$FDG uptake.

In essence, PET is a technique that allows for quantification of functional processes and molecular interactions. This makes it ideally suited as a tool for the objective assessment of therapeutic efficacy, both with respect to monitoring response to an existing treatment in an individual patient and to assessing the efficacy of new drugs (4).

It should be noted that although presently most oncological studies are based on $[^{18}\text{F}]$FDG, PET is not restricted to $[^{18}\text{F}]$FDG. It is likely that in the future, response will be measured using more tumor-specific markers than $[^{18}\text{F}]$FDG. Also in those cases, quantification of the most appropriate tracer parameters will remain important, if response is to be measured objectively.

3. 2-$[^{18}\text{F}]$FLUORO-2-DEOXY-D-GLUCOSE

As mentioned above, most PET studies on cancer therapy are based on $[^{18}\text{F}]$FDG, an analogue of glucose, that is transported into the cell by the glucose transporter. There it is phosphorylated to $[^{18}\text{F}]$FDG-6-PO$_4$ by hexokinase. In contrast to phosphorylated natural glucose, $[^{18}\text{F}]$FDG-6-PO$_4$ is not a substrate for further metabolism. In addition, in most tissues including tumors, the rate of dephosphorylation is negligible. Due to this lack of tissue clearance, $[^{18}\text{F}]$FDG accumulates in proportion to glucose metabolism (5, 6). Together with the long half-life of $^{18}\text{F}$ (~2 h) relative to study duration (1 h), this guarantees a high signal-to-noise ratio, which is ideal for quantitative studies. The main disadvantage of $[^{18}\text{F}]$FDG for monitoring response to therapy is the fact that it is an analogue of glucose with different affinities for the glucose transporter and hexokinase (5). Therefore, irrespective of the method of analysis being used (i.e., even in case of visual inspection), it has to be assumed that the relative affinities of $[^{18}\text{F}]$FDG and glucose for glucose transporter and hexokinase do not change as a result of therapy, i.e., that the so-called lumped constant remains indeed constant.