Consensus Recommendations for the Use of $^{18}$F-FDG PET as an Indicator of Therapeutic Response in Patients in National Cancer Institute Trials

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Many therapeutic clinical trials have proposed using a measure of metabolic change to assess therapeutic response rather than relying on conventional anatomic measurements of changes in tumor size on CT or MRI. PET assessment of changes in $^{18}$F-FDG uptake by tumors is gaining acceptance as such a measure.

Despite the increasing use of $^{18}$F-FDG PET as a biomarker for predicting therapeutic response, there are no widely accepted standardized protocols for using $^{18}$F-FDG PET as a tool for assessing response to therapy, nor are there validated criteria for judging response using $^{18}$F-FDG PET. The European PET community, working with the European Organization for Research and Treatment of Cancer, initiated a project to begin defining response criteria for PET and published their preliminary consensus recommendations in 1999 (1). The European Organization for Research and Treatment of Cancer continues to accumulate data in order to more carefully assess the role of $^{18}$F-FDG PET in measuring therapeutic response.

$^{18}$F-FDG PET has become a common imaging modality in oncology, primarily as a result of the widespread availability of PET instruments, an accumulation of clinical data, and the gradual expansion of oncology indications that Medicare will reimburse. With this increasing clinical experience, it is becoming clear that $^{18}$F-FDG PET may have an important role as a surrogate endpoint for assessing the clinical efficacy of novel oncologic therapies. At the same time, it has become equally clear that the potential of $^{18}$F-FDG PET as such a tool will not be achieved unless standard protocols are developed so that data can be accumulated and compared across multiple clinical sites. Today, the methods of obtaining $^{18}$F-FDG PET scans and assessing $^{18}$F-FDG metabolism and uptake vary.

To provide such guidance and to help standardize the acquisition and interpretation of $^{18}$F-FDG PET images in clinical trials sponsored by the National Cancer Institute (NCI), the Cancer Imaging Program of the NCI convened a workshop on January 10–11, 2005, in Washington, DC, at which the current status of $^{18}$F-FDG PET technology and clinical experience—both in diagnosis and in monitoring therapeutic response—was reviewed. The participants focused on patient preparation, image acquisition, image reconstruction, quantitative and semiquantitative image analysis, quality assurance, reproducibility, and other parameters important in $^{18}$F-FDG PET studies before and after a therapeutic intervention. Their discussions were based on the existing medical literature and on their own expertise.

This document represents the outcome of those deliberations. We intend that it serve as the recommended set of procedures for the acquisition and analysis of $^{18}$F-FDG PET scans of patients participating in NCI-sponsored diagnostic and therapeutic clinical trials. We hope that these guidelines will help bring about a future in which $^{18}$F-FDG PET can provide an early metabolic assessment of therapeutic response.

**IMAGE ANALYSIS AND UPTAKE QUANTIFICATION**

$^{18}$F-FDG is a marker of metabolic activity in a variety of tissues and tumors (2). Most malignant tissues have increased $^{18}$F-FDG uptake associated with an increased rate
of glycolysis and of glucose transport. Warburg first described this fundamental aberration of malignant cells in the 1930s (3), and more recently, several groups have described the specific cellular mechanisms associated with glucose uptake in malignant tissue (4–6). The increase in 18F-FDG uptake noted in malignant tissue is related in a complex manner to the proliferative activity of malignant tissue and to the number of viable tumor cells (7–9). For these reasons, investigators have postulated that alterations and changes in 18F-FDG uptake after treatment of cancer should reflect the cellular response to the treatment, likely including effects such as changes in the number of viable tumor cells and altered cellular proliferation. However, a complex mix of different cellular processes determines the rate of glucose metabolism. The precise mechanism by which alterations in these cellular processes with cancer treatment lead to changes in 18F-FDG uptake is incompletely understood and may be different for different tumor types and different treatments.

Numerous approaches have been used to assess 18F-FDG uptake in malignant tissue. There are 3 broad categories: visual interpretation and estimation of relative uptake, assessment of uptake over a defined time using semiquantitative methods, and assessment of uptake from the time of injection to a defined endpoint using kinetic analysis. Table 1 provides an overview of the various methods of assessing tumor 18F-FDG uptake and their advantages and disadvantages. Each method has been shown to have clinical utility but has been applied rigorously only in a few trials assessing response to therapy.

Visual assessment, the easiest method, is subjective and not suitable for clinical trials in which a more objective quantitative measure is desirable, barring the uncommon occurrence of a complete response to therapy. Visual assessment is based on a comparison of 18F-FDG uptake in tumor with 18F-FDG uptake in surrounding tissue, either of which may show the effects of a therapeutic intervention on subsequent scans.

A major issue in monitoring tumor response by determining 18F-FDG uptake is that the uptake depends on the time of measurement. An important aspect of oncologic 18F-FDG PET is whole-body imaging, because it assesses the entire body for malignant disease. However, whole-body imaging complicates semiquantitative and quantitative techniques because various parts of the body are imaged at different times after the injection of 18F-FDG. In reality, whole-body images are a composite of static images obtained sequentially beginning at some defined time after the injection of 18F-FDG. The static images are typically obtained over a defined period and often are corrected for attenuation using a separate transmission scan. When used to assess the response of tumors to therapy, whole-body 18F-FDG PET must be attenuation corrected to allow for accurate kinetic analysis or semiquantitative measurement.

The standardized uptake value (SUV) is the semiquantitative method most commonly used to determine 18F-FDG uptake in attenuation-corrected PET images. With this technique, the tumor 18F-FDG concentration is normalized to the amount of injected activity and total volume of distribution. Numerous indices have been used to represent the volume of distribution, such as body weight, lean body mass, and body surface area (10). Another variable incorporated into the SUV equation is normalization for the serum glucose concentration. When corrected only for body weight, SUV does not take into account the relatively lower 18F-FDG accumulation in fatty tissues (11). Normalization to body surface area or lean body mass potentially reduces the effect of weight loss (which may occur during therapy) on subsequent SUV determinations. Lean body mass may be the better method because of the availability of sex-specific corrections (12).

Full kinetic modeling has been used infrequently for the evaluation of malignancy in clinical practice because of the complexity of such an approach, including patient compliance issues and the requirement for arterial blood sampling or dynamic imaging of a blood-pool structure to obtain a

### Table 1

Methods of Assessing 18F-FDG Uptake (1)

<table>
<thead>
<tr>
<th>Method</th>
<th>Advantage</th>
<th>Disadvantage</th>
<th>Dependency</th>
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<tbody>
<tr>
<td>Visual</td>
<td>Static/whole-body imaging</td>
<td>Subjectivity</td>
<td>Uptake time</td>
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<tr>
<td></td>
<td>No need for blood sampling</td>
<td>Chance of threshold variation between readers</td>
<td>Blood glucose concentration</td>
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<td></td>
<td>Short scan times</td>
<td>Low statistics</td>
<td>Partial-volume effects</td>
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<tr>
<td></td>
<td>± Attenuation correction</td>
<td>Single snapshot of dynamic process</td>
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<tr>
<td>SUV</td>
<td>Static/whole-body imaging</td>
<td>Numerous methods of calculation</td>
<td>Uptake time</td>
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<td></td>
<td>Semiquantitative analysis</td>
<td>Low statistics</td>
<td>Blood glucose concentration</td>
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<tr>
<td></td>
<td>No need for blood sampling</td>
<td>Single snapshot of dynamic process</td>
<td>Body weight</td>
</tr>
<tr>
<td></td>
<td>Ease of computation</td>
<td>Need for attenuation correction</td>
<td>Partial-volume effects</td>
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<td></td>
<td></td>
<td>Inaccuracy in detecting small changes</td>
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<tr>
<td>Kinetic</td>
<td>Dynamic data acquisition</td>
<td>Need for input function (arterial preferred)</td>
<td>Partial-volume effects</td>
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<tr>
<td></td>
<td>Quantitative analysis</td>
<td>Complexity of computation</td>
<td>Quality of input function</td>
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<tr>
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<td>Low dependency on imaging time</td>
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precise input function (13). The advantages of a full kinetic quantitative analysis, however, are that it yields an absolute rate for 18F-FDG metabolism, is independent of imaging time, and provides insight into various components of glucose metabolism such as transport and phosphorylation. Early in the development of PET, absolute quantitative techniques were commonly used for the brain because a dynamic image set of the nonmoving brain could be obtained easily. Even in this context, however, the technique was not widespread as a clinical tool because of its complexity, the time involved, and the need for arterial blood sampling (14). A tremendous amount of research has gone into defining the specific rate constants, lumped constant, and other parameters of 18F-FDG quantitation in brain tissue (15). A critical component in determining the absolute metabolic rate for glucose from 18F-FDG studies is the lumped constant, because it reflects the difference between the affinities of 18F-FDG and glucose for transport and subsequent phosphorylation (16). Some studies have suggested that the lumped constant varies considerably in tumors, leading many investigators to describe the 18F-FDG metabolic rate instead of the glucose metabolic rate in 18F-FDG PET studies of tumors.

Other techniques were eventually developed to determine parameters of interest in studies of neurologic disorders, including graphical or Patlak analysis for irreversibly trapped tracers (17,18). Because 18F-FDG is an irreversibly trapped metabolic tracer, the influx rate constant can be determined from a graphical approach without the nonlinear optimization inherent in the full kinetic approach. As in kinetic analysis, however, graphical analysis requires dynamic scanning and determination of the blood time–activity curve, possibly by arterial blood sampling. This technique has been extrapolated from brain imaging and used in tumor imaging when a tumor is evaluated over a defined period. Whole-body imaging is difficult with this technique because dynamic tissue time–activity data are required for each specific location or tumor (19). The potential value in absolute quantitative PET studies is the ability to determine metabolic rate and the greater robustness of the approach to variations that may affect semiquantitative studies, such as the time from injection to scanning.

In the full kinetic approach, the study reflects transport and phosphorylation of 18F-FDG in both normal and malignant tissues. It is obvious that these approaches, both absolute quantitation with dynamic imaging and Patlak analysis, will be burdensome and difficult to implement routinely in patients with cancer or, indeed, in large phase II and phase III clinical trials. One advantage of 18F-FDG PET is the ability to easily image whole-body distribution of the tracer and look for new metastatic lesions. This advantage would be compromised with the full kinetic and Patlak approaches, which require monitoring of arterial 18F-FDG plasma concentration and, consequently, can be difficult for patients and PET center personnel. To avoid placing an arterial catheter to obtain the arterial input function, investigators have used various surrogate approaches, including dynamic scanning over the heart or a major artery. In addition, techniques have been developed for arterializing venous blood. However, these are fraught with technical difficulties, particularly in patients with poor venous access, as is typical in patients with cancer. Several “simplified kinetic” methods have been proposed and represent a compromise between full kinetic analysis and simple static imaging (20–22). These methods might prove useful in monitoring changes in 18F-FDG metabolism with therapy but, to date, have not been widely tested.

A major difficulty with whole-body 18F-FDG PET is that the patient may have numerous lesions, including both the primary tumor and metastatic lesions, spread throughout the body. 18F-FDG uptake into both primary and metastatic tumors, as well as into other body tissues, is a dynamic process that peaks and plateaus at various time points dependent on the tumor tissue kinetics for 18F-FDG uptake, the method by which the patient is prepared for the study, and other unknown variables. Therefore, it is extremely important that in serial examinations the target lesion or lesions be imaged at exactly the same time after injection of the tracer. An 18F-FDG uptake period of at least 60 min is generally considered most appropriate for patients with malignancy, and this period was used in most of the published clinical studies. However, uptake in the tumors of some patients evaluated with dynamic imaging may not peak or plateau until 90 or 120 min, or longer, after tracer injection. Therefore, in a given patient, image acquisitions should commence at exactly the same time after injection of 18F-FDG and the sequences should be of exactly the same time and length to ensure that each component static image of the whole-body image is obtained similarly. Figures 1 and 2 show the tissue time–activity relationships

![FIGURE 1. Tissue time–activity curves for 10 patients with solitary pulmonary nodules imaged over time with dynamic emission PET (23). Lesions were identified, ROI analysis performed, and SUV determined. 18F-FDG uptake plateaued at various times after injection. Reprinted with permission from the Society of Nuclear Medicine.](image-url)
of various lesions and the resultant variability in SUV
determination as a function of time. If uptake is still in-
creasing, significant variability in SUV determination is
possible unless the patient is imaged at the same time on all
sequential studies used to assess response (23,24). Studies
have shown that in metabolically active tumors, SUV can
change significantly over the course of 10–15 min (25,26).
Comparisons of various kinetic modeling and semiquan-
titative techniques show a good correlation between abso-
lute quantitative metabolic rate and SUV normalized to
body weight, lean body mass, or body surface area. Many
members of the working group expressed a preference for
normalizing to lean body mass, but existing data did not
warrant a unanimous preference for normalizing to lean
body mass over other parameters. Given the complexities
of conducting kinetic analysis, the working group conclud-
ed that a reasonable approach for large phase II or III clinical
trials would be semiquantitative analysis (i.e., measurement
of SUV normalized to either lean body mass or body sur-
face area). If there is a perceived need to obtain the absolute
quantitative metabolic rate or more detailed information
on 18F-FDG kinetics in a protocol evaluating therapeutic
response (e.g., for new therapies that may affect tracer
delivery to the tumor and limit uptake), this need could be
more easily addressed in the setting of a single-institution
phase I or early phase II study.

**FACTORS AFFECTING UPTAKE DETERMINATION**

**Partial-Volume Effects**

Partial-volume effects secondary to scanner resolution
are an important technical factor. Most PET scanners have

FIGURE 2. Tissue time–activity curves for 16 patients. Static
PET was performed at 1, 3, and 5 h after injection of 18F-FDG,
and activity in lesions was determined. 18F-FDG uptake plateaued
at various times after injection and, in several lesions,
was still increasing even at 5 h after injection. (Courtesy of
Karen Kurdziel.)
receiving the injection of 18F-FDG. In general, patients should fast and medications be made if necessary, so that the fasting blood glucose concentration can be brought down to an acceptable range at the time of 18F-FDG injection, that is, 150–200 mg/dL or less. The working group also agreed that diabetic patients should not be excluded from clinical trials but that such patients should be scanned early in the morning before the first meal and that the doses of insulin and hypoglycemic medication should be titrated appropriately the night before and morning of the study. Before scheduling an 18F-FDG PET study, diabetic patients should test their ability to maintain reasonable plasma glucose levels after fasting, while avoiding insulin close to the time that 18F-FDG would be administered.

RECOMMENDATIONS OF WORKSHOP PANEL

These recommendations are summarized in Table 2.

Patient Preparation

Patient preparation is critical to the quality of 18F-FDG PET, both as a diagnostic test and as an assessment of therapeutic response. The following are recommendations to ensure consistency of data across institutions, as well as in the same patient in serial 18F-FDG PET studies:

- Patients should fast overnight for morning scan or 4 h for afternoon scan. Venous serum glucose concentration is measured before injection (<120 mg/dL for nondiabetic patients and 150–200 mg/dL for diabetic patients).
- Diabetic patients are scanned in morning after overnight fast and before first use of medication. Patients are well hydrated and, if possible, drink 500 mL of water after injection and before scanning. For renal/pelvic imaging, furosemide (20–40 mg) may be given 10–15 min after 18F-FDG injection, or urinary catheter may be used.
- All medications being taken by patients are recorded. Diazepam or other mild sedative may be used at clinician’s discretion to decrease uptake in muscle.
- Pretreatment scans are acquired as close to start of therapy as possible (preferably <2 wk).
- Posttreatment scans are acquired no sooner than 2 wk after end of chemotherapy to avoid transient increases or decreases. Timing is determined by endpoint being assessed.
- Timing of scans after changes due to radiotherapy needs further investigation.
- Whole-body imaging begins 60 ± 10 min after injection of 18F-FDG.
- Attenuation correction is used. No standard procedure has yet been recommended. Procedure chosen is documented.
- No standard dose has yet been recommended. Doses of 370–740 MBq (10–20 mCi) are appropriate. Dose injected is documented.

<table>
<thead>
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<td>PET timing</td>
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<tr>
<td>Attenuation correction</td>
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Image Acquisition and Reconstruction

Because the specifications of PET cameras are variable and manufacturer specific, every attempt should be made to use the same scanner (ideally at the same center) or same scanner model for serial scanning of the same patient. Whole-body acquisition is important because it allows for sampling of all areas of interest and can assess whether new lesions have appeared and, thus, the possibility that disease has progressed. Whole-body acquisitions can be in either 2- or 3-dimensional mode with attenuation correction, but a consistent method should be chosen for all serial scanning of an individual patient throughout the clinical trial. The use of CT in combined PET/CT scanners is strongly encouraged to provide anatomic registration for PET data.

The whole-body acquisition should sample from the angle of the jaw to the level of the mid thigh. Because several target lesions may be identified on the initial 18F-FDG PET study or on anatomic imaging studies, it is critical for a given patient, all subsequent 18F-FDG PET studies be performed identically to the first to ensure the quantitative integrity of the data and the validity of comparisons. For example, if the patient is scanned from the head to the thighs in the baseline scan, subsequent scans should also be started at the head and extend to the thighs. The parameters for the timing of both emission and transmission acquisitions vary from one patient to another depending on the size of the patient, the PET camera used, and the amount of 18F-FDG injected. Therefore, the timing of the acquisitions cannot be standardized. However, the times at which target lesions are imaged after 18F-FDG injection should be as close as possible to those used on the baseline or previous study. It is strongly encouraged that serial studies to evaluate therapeutic response be done in exactly the same way, at the same institution, on the same type of camera, and using the same dose, imaging times, acquisition parameters, and reconstruction parameters.

PET Timing Relative to Prior Therapy

Insufficient data are available on the optimal interval from completion of therapy to imaging with 18F-FDG PET. Nevertheless, the working group recommends that the complete treatment history of the patient be documented, particularly the use of supportive therapies such as bone marrow expansion drugs and the recent use of corticosteroids. Pretreatment scanning is generally critical to assess subsequent response. The timing of posttreatment scanning depends on numerous variables, including correlative studies, whether a complete clinical response variable is under consideration, the expected responsiveness of the tumor type to the therapy being used, and the endpoints of the study.

Currently available information supports the recommendation that posttreatment imaging be performed 2 wk after the end of a specific chemotherapy cycle. The exact timing may depend on the frequency and duration of therapy. It is
postulated that the transient and nondurable alterations in 18F-FDG uptake that may occur in tumors during the immediate-posttreatment period will be minimized using this approach. A specific understanding of the basic biology of the tumor from previous clinical and preclinical studies may help one determine the optimal posttreatment time point.

Data on the treatment interval after the completion of radiotherapy are less clear. Acute inflammatory changes with subsequent alterations in 18F-FDG uptake in both tumor and surrounding tissue have been documented (31). Newer radiation therapies such as γ-knife and focal high-dose radiation appear to enhance inflammatory reactions, and thus confound the interpretation of 18F-FDG PET scans, in patients studied within a short period after completing these therapies (32). Many investigators recommend a delay of 6–8 wk or longer after radiation therapy before performing the posttreatment 18F-FDG PET study (33). Although further study may be required to arrive at an appropriate interval for scanning after completion of radiation therapy, a longer wait clearly helps in distinguishing inflammatory response from viable residual tumor.

Image Analysis

The working group agreed that there is no single optimal method for analysis of 18F-FDG PET whole-body images in oncology but that there can be standardized protocols for use in a particular clinical trial. The working group recommended that phase 1 trials use either full or partial kinetic analysis, such as Patlak analysis, if deemed necessary, along with semiquantitative SUV analysis based on lean body mass and body surface area. The reason for recommending that SUVs be calculated on the basis of both lean body mass and body surface area is to develop a body of data to determine whether they are equivalent or whether one is better than the other. It is also critical that before a particular clinical trial begins, the method of ROI determination be agreed on and specified in the protocol.

Of obvious importance is that whole-body 18F-FDG PET provides information additional to that obtained from standard anatomic imaging studies such as CT or MRI. Therefore, it is also critical that the whole-body 18F-FDG PET study be interpreted carefully and reported as a clinical study would be reported to ensure that new lesions are identified. This care will be critical in the development of subsequent response criteria. SUV should be determined in order to assess the 18F-FDG uptake and define the response in target lesions of interest. Image reconstruction parameters depend on the PET scanner and other variables. Filters, image reconstruction techniques and parameters, and application of the attenuation map must be consistent across all scanning of a given patient. The exact timing of image acquisition for each target lesion is critical and must be kept constant on all subsequent studies of a given patient.

SUV should be determined for all target lesions and should be calculated consistently on the basis of either lean body mass or body surface area. No data indicate that one is superior to the other. Each clinical trial should set a protocol calling for all SUV calculations to be done the same way.

In addition, the SUV of a reference organ or tissue not involved in the neoplastic process should be measured after each scan to help ensure that SUV changes in tumors are related either to treatment response or to disease progression.

ROI Determination

Tumors can be of various sizes and of various heterogeneities. Accurate and reproducible determination of the ROI will be critical for determining SUV. With therapy, alterations in the pattern of heterogeneity and in 18F-FDG uptake may occur and must be considered when one is drawing or determining the ROI. On the pretreatment scan, the identified target lesion should be the most visible and easily defined lesion. The mean SUV of the region and the maximum pixel SUV should be determined and recorded.

No prescribed methodologies for determining regions of interest have been validated. Thresholding techniques or freehand drawing are typically used. No specific recommendations on either of these approaches can be made. The choice of method will depend on the technical support staff, expertise, and image-processing capabilities of an individual PET center. However, in each clinical trial, the same ROI technique should be specified (e.g., whether to include necrotic areas) and used in subsequent 18F-FDG PET studies to ensure quantitative consistency. Quantitative measurements of mean and maximum tumor ROI counts per pixel, calibrated as mBq/L (μCi/L), should be obtained with the scanner. The consensus of the working group was that maximum or “peak” approaches are the most robust and reproducible and that the maximum SUV and mean SUV of each tumor should be recorded. The panel strongly encouraged further cooperative studies, including work with camera manufacturers, to improve reproducibility and standardization between centers by developing more standard and automated methods of defining regions.

During the course of treatment, the extent and shape of an imaged tumor might change. Documentation of either an increase or a decrease in dimensions or a change in shape is recommended.

As discussed, partial-volume effects on determinations of 18F-FDG uptake may be significant. If a significant decrease in tumor size is evident from anatomic imaging studies (which are typically available throughout therapy), this information should be documented because subsequent analysis may require partial-volume corrections of the 18F-FDG PET data. Further data analysis and research are required to better define how the assessment of response can be adjusted to account for partial-volume effects, tumor heterogeneity, and other confounding variables.

CONCLUSION

18F-FDG PET has gained acceptance as a valuable clinical tool for detecting, staging, and managing disease. It is now...
clear that 18F-FDG PET can also be an important tool for assessing therapeutic efficacy in large, multicenter clinical trials, but only with the application of standard protocols. Currently, there is no one best methodology for obtaining or analyzing 18F-FDG PET scans, nor is there one agreed-on standard for judging the significance of a response seen on 18F-FDG PET. Enacting these recommendations to develop standard protocols for NCI-sponsored clinical trials should go a long way toward determining when and for what indications 18F-FDG PET can serve as a surrogate measure of therapeutic efficacy. The result should be shorter clinical trials and improved therapy for patients with cancer.

REFERENCES


