Assessing Tumor Response to Therapy

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Most anticancer drugs are effective only in subgroups of patients, and our current understanding of tumor biology does not allow us to predict accurately which patient will benefit from a specific therapeutic regimen. Various techniques have, therefore, been developed for monitoring tumor response to therapy, but measuring tumor shrinkage on CT represents the current standard. Although response assessment on CT has been refined over many years, fundamental limitations remain. Interobserver variability in tumor size measurements is still high because of difficulties in delineating tumor tissue from secondary changes in the surrounding tissues. Furthermore, CT is inaccurate in differentiating viable tumor from necrotic or fibrotic tissue. Consequently, the degree of response may be underestimated on CT. Conversely, if tumor shrinkage is short lived and followed by rapid tumor regrowth, CT may overestimate the beneficial effects of a treatment. Finally, CT is limited in characterizing responses in tumors that do not change in size during therapy. Because the growth rate of untreated human tumors varies tremendously, an unchanged tumor size after some weeks of therapy may represent a drug effect but may also indicate a slowly growing tumor that was not affected by the applied therapy. Molecular imaging with PET and the glucose analogue ^{18}F-FDG PET has been shown to improve response assessment in several tumor types. In malignant lymphoma, international criteria for monitoring response to therapy have recently been revised, and the ^{18}F-FDG signal now plays a central role in defining tumor response. In a variety of solid tumors, single-center studies have indicated that ^{18}F-FDG PET may provide earlier or more accurate assessment of tumor response than CT, suggesting that ^{18}F-FDG PET could play a significant role in personalizing the treatment of malignant tumors. However, generally accepted criteria for response assessment in solid tumors are missing, which makes it frequently impossible to compare the results of different studies. International guidelines and criteria for response assessment by ^{18}F-FDG PET in solid tumors are, therefore, eagerly awaited.

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Tumor response is a fundamental concept in clinical oncology but perhaps the least understood. In fact, the need to classify tumors as responding or nonresponding can be seen as a direct consequence of our currently limited understanding of tumor biology. In essence, tumor response simply describes the phenomenon whereby some patients benefit from a particular therapy whereas others, despite apparently identical clinical and histopathologic characteristics, do not. Thus, between tumors there are significant and clinically relevant biologic differences that we currently do not understand and that become apparent only when specific treatments are administered. Monitoring tumor response to therapy is therefore a crucial part of clinical oncology.

The definitive proof of the effectiveness of a therapy is improvement in clinical symptoms and survival. However, imaging is generally used to assess therapeutic effects earlier and more objectively. Current response assessment is based primarily on changes in tumor size as measured by CT or other anatomic imaging modalities. Criteria for tumor response have been refined over more than 25 y (*1–3*), but fundamental limitations remain. Therefore, considerable effort has been expended to develop more accurate techniques for monitoring tumor response to therapy. Imaging of tumor metabolism with PET and the glucose analog ^{18}F-FDG represents an attractive approach for assessing the effects of therapy objectively and quantitatively. First reports using planar ^{18}F-FDG imaging for treatment monitoring were published more than 20 y ago (*4*), and subsequent studies in the early 1990s suggested that tumor response might be identified earlier through changes in the ^{18}F-FDG signal than through changes in measured size (*5,6*).

In the meantime, many studies on treatment monitoring with ^{18}F-FDG PET have been published. Furthermore, clinical ^{18}F-FDG PET has become widely available. Therefore, there is considerable interest in the use of response assessment by ^{18}F-FDG PET for patient management and in clinical trials. However, it is often difficult to compare the results of individual studies because of methodologic differences and varying clinical endpoints. In addition, the clinical usefulness of ^{18}F-FDG PET for treatment monitoring depends on a variety of factors including the baseline metabolic activity of the tumor tissue, the type of treatment administered, the effectiveness of therapy, and the presence or absence of alternative treatments.

The aims of this supplement are therefore to present a careful discussion of the available literature and to provide guidance for treatment monitoring with ^{18}F-FDG PET. To set the stage for the following papers, this introduction briefly discusses the importance of tumor response assessment in

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clinical practice and drug development. In addition, the strengths and limitations of various approaches for predicting or monitoring tumor response are summarized. Common methodologic differences between individual studies are described, and their effects on the reported diagnostic accuracy of ^{18}F-FDG PET are discussed. The introduction concludes with a brief overview of the scope of the other papers in the supplement.

PREDICTING TUMOR RESPONSE TO THERAPY

Examples of Molecular Markers for Prediction of Response

Because most cancer treatments are associated with significant side effects and costs, intense efforts have been made to understand the mechanisms underlying the responsiveness of an individual tumor or at least to identify parameters that correlate closely with tumor response. So far, this research has been successful only in some tumor types and some forms of therapy. In breast cancer, overexpression of the human epidermal growth factor receptor 2 (HER2) correlates with response to trastuzumab, an antibody targeting the HER2 protein (*7*). Breast cancer cells overexpressing HER2 are dependent on the growth stimulatory signals originating from HER2, and blocking of HER2 signaling by trastuzumab inhibits proliferation and causes apoptosis. In the absence of HER2 overexpression, trastuzumab is ineffective; testing of HER2 expression levels is therefore required before treatment with this drug (*8*). In colorectal cancer, mutations in codon 12 and 13 of the KRAS gene have recently been shown to induce resistance to the epidermal growth factor receptor 1 (EGFR) antibodies cetuximab and panitumumab (*9*). KRAS plays an important part in the EGFR signaling pathway and transmits signals downstream from EGFR. Mutations in codon 12 and 13 render KRAS constitutively active and therefore allow EGFR signaling to continue even when EGFR is blocked by cetuximab or panitumumab. The presence of KRAS mutations makes a response to anti-EGFR antibodies so unlikely that treatment with cetuximab or panitumumab is recommended only in the absence of these mutations (*9*).

Specific somatic mutations of the EGFR kinase domain greatly increase the sensitivity of non–small cell lung cancer (NSCLC) cells to EGFR kinase inhibitors such as gefitinib and erlotinib (*10*). These mutations appear to increase the binding affinity of the EGFR kinase domain for this class of drugs and may also lead to the activation of signaling pathways not activated by wild-type EGFR. In addition, point mutations of the EGFR kinase domain have been described that confer resistance to EGFR kinase inhibitors by markedly decreasing binding affinity (*10*).

Limitations of Response Prediction by Molecular Markers

Thus, for some drugs and tumor types, molecular characterization of the tumor tissue can help to guide treatment. However, these molecular predictors of tumor response are far from perfect. For example, only about 50% of HER2-overexpressing breast cancers do respond to trastuzumab (*7*); similar response rates have been observed in NSCLC with EGFR kinase mutations treated with erlotinib or gefitinib (*11,12*). Conversely, a sizable percentage of patients without EGFR kinase mutations do respond favorably to treatment with EGFR kinase inhibitors (*11,12*). In colorectal cancer, antibody monotherapy results in response rates of 10%–15% in patients without KRAS mutations, whereas virtually no responses are observed in patients with KRAS mutations. This indicates that other factors, currently not well understood, modulate the sensitivity of tumor cells to specific targeted drugs. These factors may include unfavorable intratumoral pharmacokinetics, overexpression of receptor ligands, and activation of other oncogenic signaling pathways. For example, resistance to gefitinib has been related to drug efflux mediated by multidrug transporters (*13*), overexpression of the EGFR ligand amphiregulin (*14*), and amplification of the MET oncogene (*15*).

These observations emphasize the need to take into account more than one molecular alteration to assess the responsiveness of tumor cells to therapy. Gene expression profiling using microarray technology now allows simultaneous measurements of the expression of thousands of genes at the RNA level. This technology has been extensively studied for assessment of prognosis and prediction of tumor response to therapy (*16,17*). In breast cancer, certain gene expression signatures have been shown to be associated with an increased responsiveness to chemotherapy. However, validation of these signatures has been challenging (*18,19*), as a large number of genes are analyzed in a comparatively small number of patients, resulting in a large fraction of chance correlations between gene expression and response (*19*). The biometric techniques to analyze gene expression techniques are still evolving (*18*).

With regard to gene expression profiles and other molecular markers, it is important to differentiate whether they represent prognostic or predictive markers for patient outcome. A prognostic marker is defined as a property of the tumor that correlates with patient outcome irrespective of the treatment used. An example of a prognostic marker is tumor stage, which in almost all malignant tumors correlates closely with patient outcome. In contrast, a predictive marker correlates with the effectiveness of a specific therapeutic intervention. This distinction is important because only predictive markers will aid in the selection of specific treatment regimens. Unfortunately, however, the relationships between prognostic and predictive can be complex. Mutations of the EGFR kinase domain increase the sensitivity of NSCLC cells to treatment with EGFR kinase inhibitors. Unexpectedly, however, EGFR kinase mutations have also been shown to correlate with higher response rates and longer time to progression in patients treated with standard platinum-based chemotherapy (*11,12*). Therefore, EGFR kinase mutations may be a prognostic marker in NSCLC,

thus confounding their use as predictive markers that can help to select patients for treatment with EGFR kinase inhibitors.

Another fundamental problem of using gene expression profiles or other molecular characteristics of tumor tissue to predict tumor response is the fact that malignant tumors are constantly evolving and adapting to their environment. As a consequence, most responses to chemotherapy or targeted drugs are relatively short lived and resistant cancer cells evolve quickly. For some protein kinase inhibitors, such as gefitinib or imatinib, specific secondary mutations of the kinase domain have been shown to cause resistance, but generally the mechanisms of resistance appear complex and are currently not well understood (*10*). In the clinical setting, only a small fraction of the tumor mass (e.g., a needle biopsy sample) is usually available for analysis by gene expression profiling or other molecular biology techniques. Considerable sampling error with respect to expression of molecular markers may result. More representative material can be obtained by surgery, but except for the adjuvant situation, months or even years will elapse between surgery and the start of systemic therapy for recurrent disease, and tumor cells may have changed their biologic characteristics in the meantime.

Because of these inherent limitations in the current approaches for response prediction, the need for techniques to monitor tumor response to therapy is apparent. The common goal of these techniques is to evaluate the effectiveness of therapy earlier than is feasible through symptoms or other clinical parameters. Furthermore, the techniques aim to measure tumor response more objectively. Monitoring tumor response to therapy is part of the clinical management of cancer patients, where the primary goal is to identify nonresponding tumors early, in order to stop ineffective therapies and avoid complications caused by tumor progression. In drug development, there is generally more interest in responding tumors because tumor response is considered an objective marker of drug activity. The ultimate goal in drug development is to use tumor response as a surrogate for clinical benefit, because response is generally faster to assess and also less confounded by covariates such as patient status at the start of the clinical trial or the effects of second-line therapy.

CURRENT APPROACHES FOR MONITORING RESPONSE

Serum Markers for Monitoring Response

In clinical practice and clinical trials, 2 approaches have been used to monitor tumor response to therapy. One is to measure markers specifically secreted by cancer cells into the blood; the other approach, which is much more common, uses changes in tumor size as a criterion for tumor response.

The use of changes in serum markers as a measure of tumor response to therapy is appealing because it is noninvasive, can be repeated frequently, and has a relatively low cost. Furthermore, it offers the opportunity to measure tumor response at multiple sites with a single parameter. In some malignant tumors, including prostate, ovarian, and thyroid cancer, tumor markers (prostate-specific antigen, CA125, and thyroglobulin) are frequently used to monitor tumor response for patient management and in clinical trials. In many other malignant diseases, however, only a fraction of the tumors express specific markers at sufficient levels to allow their use for treatment monitoring. In addition, tumor marker levels reflect not only the viable tumor mass but also the production and clearance rate of the respective marker. In thyroid cancer, for example, thyroid-stimulating hormone levels regulate production of thyroglobulin. Thyroid hormone withdrawal is therefore associated with a marked increase of thyroglobulin levels, even in the absence of tumor progression (*20*). Similarly, prostate-specific antigen production is regulated by androgen levels, confounding the use of prostate-specific antigen levels for monitoring antihormonal therapy of prostate cancer (*21*).

Tumor Shrinkage as a Criterion for Response

Because of these limitations of serum markers, changes in tumor size represent the mainstay of tumor response assessment. It appears intuitive that a reduction of tumor size after therapy indicates a better prognosis than does an unchanged or increasing tumor size. However, this assumption is not necessarily correct, as illustrated by Figure 1. This figure shows the diameters of 2 exponentially growing spherical tumors. Tumor A is growing with a volume doubling time of 90 d, whereas tumor B is growing more slowly, with a volume doubling time of 200 d. Such volume doubling times have been observed in several studies of patients with untreated NSCLC (*22*). Both tumors are assumed to be diagnosed at the same time, when the diameter has reached 3 cm. Then, a treatment is administered for 3 mo, and the diameter of tumor A decreases by one third whereas tumor B is unaffected by

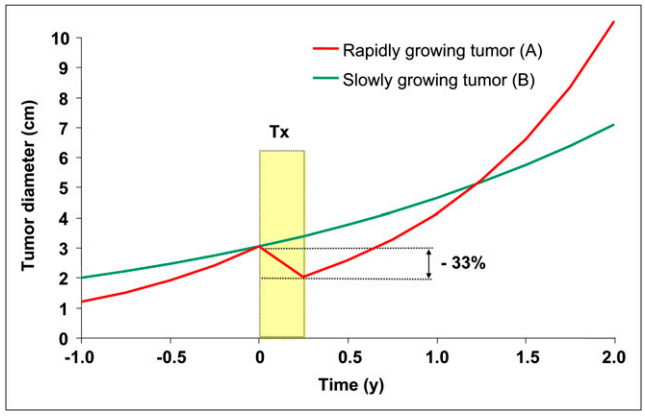

FIGURE 1. Hypothetical example of relationship between growth rates, tumor response to therapy, and outcome. Graph shows diameters of rapidly growing tumor (tumor A, red) and more slowly growing tumor (tumor B, green) over time. Both tumors are diagnosed when their diameter has reached 3 cm. Tumor A responds to 3-mo course of therapy (Tx), whereas growth of tumor B is unaffected. At 2 y, however, outcome is better for tumor B, because tumor A regrows quickly.

treatment. According to current response criteria, tumor A would be considered as responding and tumor B as nonresponding. Because the growth rates of tumors A and B before diagnosis are unknown, the treating physician would conclude that the prognosis is better for tumor A than for tumor B. However, Figure 1 shows that this conclusion is incorrect, as tumor A regrows quickly and exceeds tumor B in size within about a year. This simple example illustrates that tumor shrinkage after therapy may not predict a better prognosis when other tumor characteristics are unfavorable.

Recent publications indicate that this possibility is not only hypothetical. In the last year, 2 papers were published that evaluated the correlation between changes in tumor size after chemotherapy and patient survival. Both studies included patients with advanced NSCLC. Advanced NSCLC seems to be ideally suited for such an analysis because prognosis is poor and second-line treatments have only limited efficacy. Therefore, one would expect a strong correlation between response to chemotherapy and survival. Such a correlation was observed by Lara et al. (*23*), who reanalyzed data from 3 randomized trials including a total of 984 patients. A partial or complete response on CT after 8 wk of therapy correlated significantly with patient survival (hazard ratio, 0.61; $P < 0.01$). In contrast, Birchard et al. (*24*) found no correlation between changes in tumor size after 2–3 mo of chemotherapy and patient survival in a group of 99 NSCLC patients. These 2 studies indicate that even in a rapidly growing tumor such as NSCLC, the correlation between tumor response and outcome is far from perfect. This result is in line with previous observations by Sekine et al. (*25*) published 10 y earlier. This metaanalysis of more than 50 phase II trials in patients with advanced NSCLC found that the correlation coefficient between response rate and median patient survival was only 0.5 (*25*).

Methodologic Challenges in Measuring Tumor Size

In addition to the fact that tumor shrinkage after therapy is only one parameter affecting patient survival (Fig. 1), methodologic problems with size measurements and response classifications may explain the lack of a close correlation between tumor shrinkage and patient survival in clinical trials. As discussed in detail by Wahl et al. in this supplement to *The Journal of Nuclear Medicine* (*26*), the currently used criteria for response assessment by anatomic imaging modalities (World Health Organization [WHO], response evaluation criteria in solid tumors [RECIST]) were defined about 30 y ago, at a time when tumor response was determined on planar chest radiographs or by caliper measurements of palpable lymph node metastases (*1*). Despite enormous progress in medical imaging, the definition of tumor response has remained unchanged (*3*).

Furthermore, tumor responses as assessed by anatomic imaging modalities may be inaccurate because of errors in tumor measurements, errors in selection of measurable targets, and interobserver variability of measurements. Even in recent analyses, response rates as determined by local investigators and independent central review committees have been shown to vary by more than 100% in some studies (*27*). In a study evaluating CT measurements of 40 NSCLCs, the intraobserver rate for misclassification of unchanged lesions as progressive disease was 9.5% for unidimensional measurements (RECIST) and 20.5% for bidimensional (WHO) measurements. Interobserver misclassification rates were 29.8% and 42.5%, respectively (*28*). Misclassifications occurred predominantly in masses with irregular and spiculated borders (*28*). In patients with atelectasis, interobserver variability in defining tumor extension has been reported to be as high as 100% (*29*).

Anatomic imaging is also limited with regard to differentiating residual viable tumor tissue from treatment-induced fibrosis and scarring. After chemoradiotherapy, lack of tumor response on CT generally does not exclude a major histopathologic response. For example, in the Southwest Oncology Group 8805 trial (*30*) evaluating concurrent cisplatin/etoposide plus radiotherapy followed by surgical resection in patients with NSCLC, 46% of the patients with stable disease on CT demonstrated a significant histologic response (*30*). With chemotherapy alone, a closer correlation between tumor response on CT and histopathologic response has been observed in NSCLC in some (*31*) but not all studies (*32*). Furthermore, some studies have indicated that response to neoadjuvant chemotherapy as assessed by CT is either not a prognostic factor or only a weak prognostic factor (*32,33*). In other studies, a clear correlation between tumor response to neoadjuvant therapy and survival was observed, but this correlation may be biased because patients lacking a response on CT are less likely to undergo surgery. For example, Lorent et al. (*34*) found that tumor response was a strong prognostic factor in a group of 131 patients with stage III-N2 NSCLC treated by induction chemotherapy followed by surgical resection ($P < 0.0001$). However, in the subgroup of completely resected patients, tumor response on CT was no longer a prognostic factor.

Finally, drugs that stabilize disease without an objective response may slow tumor growth sufficiently to improve patient survival. This limitation of current techniques for assessment of response has frequently been discussed in the context of targeted cytostatic drugs. For example, in a phase III study evaluating the EGFR kinase inhibitor erlotinib for treatment of advanced, chemotherapy-refractory NSCLC, the response rate for the EGFR kinase inhibitor erlotinib was only 8.9%. Nevertheless, erlotinib improved median overall survival by 43% when compared with best supportive care. Thus, the beneficial effect of erlotinib was apparently not restricted to patients achieving an objective response (*35*). Such discrepant findings between response rates and survival are not unique for targeted agents but have previously been reported for classic cytotoxic chemotherapeutic agents as well. For example, in a randomized phase III study comparing single-agent carboplatin with combination chemotherapy including mitomycin, vinblastine, and cisplatin, carboplatin showed a significantly lower response rate but was associated

with a significantly longer progression-free and overall survival (*36*).

Disease Stabilization as a Criterion for a Favorable Response

In view of these well-recognized problems of using tumor shrinkage as a criterion for response, it has been proposed that disease stabilization may be a better parameter for monitoring tumor response to therapy. Lara et al. (*23*) recently demonstrated in an analysis of 3 large multicenter trials that disease control rates are a stronger predictor of survival than are objective response rates. However, growth rates of untreated NSCLCs are currently unpredictable, and reported tumor doubling times vary more than 10-fold (*22*). In nonrandomized studies, it is therefore challenging to differentiate between initially fast-growing tumors responding well to therapy and per se slowly growing tumors. The same holds true for evaluating the effectiveness of a specific treatment regimen in an individual patient. The problem is illustrated in Figure 2, which shows that stable disease can be the result of growth inhibition but may alternatively be due to slow tumor growth. The Iressa Survival Evaluation in Lung Cancer study (ISEL) shows that this concern is not only theoretic (*37*). This study randomized patients with advanced NSCLC to receive the EGFR kinase inhibitor gefitinib (Iressa; AstraZeneca) or placebo (*37*). At the conclusion of the study, 31% of the patients in the placebo arm were classified as having stable disease, indicating that a significant percentage of advanced NSCLCs is growing relatively slowly in the absence of specific therapy. Furthermore, the data of the ISEL study suggest that growth rates of NSCLC change unpredictably over time, as 91% of 563 patients in the placebo arm had been considered to have progressive disease before entry into the study. Therefore, disease stabilization after therapeutic interventions needs to be interpreted with caution, even in a generally rapidly growing tumor, such as NSCLC.

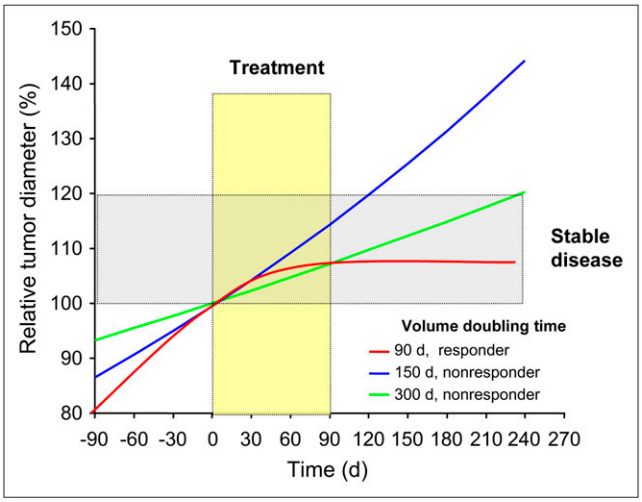

FIGURE 2. Hypothetical growth curves of 3 tumors with volume doubling times ranging from 90 to 300 d. In only one tumor does treatment delay growth. However, all tumors would be considered stable disease according to current response criteria, which define stable disease as increase in tumor size of less than 20%.

MONITORING RESPONSE BY MOLECULAR IMAGING

Because of these well-recognized limitations of current approaches for monitoring tumor response to therapy, there has been considerable interest in new functional or molecular imaging techniques. This interest has been further stimulated by a growing number of alternative treatment regimens. For many malignant diseases, several treatment regimens have become available, acting on different targets in the tumor tissue. For treatment of metastatic colon cancer, 10 chemotherapy combinations are listed in the Physician Data Query database of the National Institutes of Health, which summarizes evidence-based treatment options for all malignant diseases (*38*). Several of these regimens can be combined with the vascular endothelial growth factor antibody bevacizumab or the EGFR antibody cetuximab, which gives rise to an enormous number of clinically used drug combinations.

Effective use of these treatment options will require that nonresponding tumors be identified early in the course of therapy, as current techniques to predict the effectiveness of a particular regimen in an individual patient are limited. Early identification of nonresponding patients could also lead to considerable costs savings, since many new drugs are expensive. In the United States, for example, 1 mo of treatment with cetuximab costs more than $16,000 (*39*). The high costs for new cancer drugs are largely due to the failure of drug candidates in late phase III studies (*40*). New imaging biomarkers of tumor response that correlate better with patient outcome than do size measurements could thus significantly reduce the costs of drug development and thereby eventually decrease drug costs in clinical practice (*41*).

Among several pursued molecular imaging approaches for treatment monitoring, such as dynamic contrast-enhanced MRI, diffusion-weighted MRI, MR spectroscopy, optical imaging, and contrast-enhanced ultrasound (*41*), PET with the glucose analog ^{18}F-FDG is currently clinically most advanced. ^{18}F-FDG PET has been shown in numerous studies to be a robust imaging technique not requiring sophisticated protocols for data acquisition and analysis. Furthermore, within the last 5 y, PET has become clinically available at almost all major hospitals.

ASSESSMENT AND PREDICTION OF RESPONSE BY ^{18}F-FDG PET

A series of studies published in the last 20 y has evaluated the use of PET with the glucose analog ^{18}F-FDG for monitoring tumor response to therapy. A consistent observation of these studies has been that ^{18}F-FDG PET is more accurate than CT in differentiating residual viable tumor tissue from treatment-induced necrosis and fibrosis. Specifically, ^{18}F-FDG PET has been shown to be able to identify patients with

a good response to therapy despite the presence of residual masses on CT. In malignant lymphoma, but also several solid tumors, patients with negative PET results after completion of therapy have been found to have a favorable prognosis, even if CT suggested considerable residual tumor tissue.

Furthermore, ^{18}F-FDG PET has been shown to allow earlier treatment monitoring, thus offering the opportunity to predict patient outcome after the first or second cycle of chemotherapy. This advantage allows for studies in which therapy can be changed according to the individual chemosensitivity of the tumor tissue. For example, less toxic treatments may be used in patients with lymphoma demonstrating a good response on ^{18}F-FDG PET after 2 cycles of chemotherapy. Conversely, treatment can be intensified in patients with a poor response on ^{18}F-FDG PET. With solid tumors treated by preoperative chemotherapy, patients without a response on ^{18}F-FDG PET may thereby undergo tumor resection earlier and avoid the side effects of ineffective therapy. In short, treatment monitoring with ^{18}F-FDG PET may have a significant impact on patient management in several clinical situations. In fact, ^{18}F-FDG PET is already increasingly used to monitor tumor response clinically. According to a recent analysis of the National Oncologic PET Registry, 19% of the registered scans were performed for treatment monitoring (*42*).

Nevertheless, published data on the accuracy of ^{18}F-FDG PET in specific clinical situations often appear heterogeneous. Reported positive and negative predictive values of ^{18}F-FDG PET for response assessment vary widely, and some studies conclude that ^{18}F-FDG PET is a highly sensitive but not very specific test, whereas others consider ^{18}F-FDG PET as very sensitive but relatively unspecific. Some seemingly conflicting results can be explained by an inconsistent and partly confusing terminology. Because the term *response* indicates the absence of viable tumor or at least a reduction in viable tumor mass, the sensitivity of a test to detect response describes its ability to detect the absence and regression of disease. This definition is a reversal of that in common use for the term *sensitivity,* which otherwise describes the ability of a test to detect disease. Conversely, the specificity of a test to detect response is its ability to detect the presence of disease—again, a definition opposite to that in the general use for the term *specificity.* Unfortunately, some studies evaluating treatment monitoring by ^{18}F-FDG PET have used the terms *sensitivity* and *specificity* in the conventional sense, that is, sensitivity and specificity for detecting viable tumor after therapy, whereas others have used these terms for detection of response, that is, the absence of tumor. As a consequence, the sensitivities reported for the first group of studies correspond to the specificities reported for the second group of studies, and vice versa. For the same reasons, the positive and negative predictive values of ^{18}F-FDG PET have sometimes the opposite meaning in different clinical studies. For example, most studies in lymphoma provide the positive and negative predictive value of ^{18}F-FDG PET for prediction of disease progression or recurrence. In contrast, many studies on solid tumors report the positive and negative predictive value for ^{18}F-FDG PET for later response on anatomic imaging or histology, that is, the absence of tumor progression. When one is comparing the results of different studies, it is therefore highly important to ensure that the same definitions for sensitivity and specificity have been applied. Otherwise, data on sensitivity and specificity or positive predictive value and negative predictive value need to be converted appropriately before any comparisons are made.

Another source of confusion is the gold standard for tumor response to therapy. Table 1 lists some commonly used reference standards for tumor response to which findings on ^{18}F-FDG PET were compared. As the change in the number of viable tumor cells according to these different response definitions varies between 0% and 100%, it becomes obvious that the diagnostic performance of ^{18}F-FDG PET to detect these dissimilar types of tumor responses will be different. Sometimes, both the reference standard and the terminology with regard to sensitivity and specificity are different for 2 studies, leading to apparently contradictory results. For example, Brucher et al. found that the sensitivity and specificity of ^{18}F-FDG PET to detect histopathologic response to neoadjuvant chemoradiotherapy in esophageal cancer were 100% and 55%, respectively (*43*). In apparent contrast to these findings, Swisher et al. reported a sensitivity of 26% and a specificity of 95% in a similar clinical situation (*44*). However, Brucher et al. reported the sensitivity and specificity of ^{18}F-FDG PET to detect histopathologic response, whereas Swisher et al. reported the sensitivity and specificity of ^{18}F-FDG PET to detect viable tumor tissue. Consequently, the sensitivity in the study by Swisher et al. corresponds to the specificity in the study by Brucher et al. and vice versa. Thus, both studies actually found that ^{18}F-FDG PET is a highly specific test to detect viable tumor tissue, that is, lack of response to chemoradiotherapy. Still, the reported sensitivities of ^{18}F-FDG PET for detection of tumor tissue

TABLE 1. Common Response Definitions Used in Clinical Trials

Response criterion	Brief definition	Expected effect on viable tumor cell mass
Pathologic complete response (ypT0)	No viable residual tumor tissue on thorough histopathologic analysis	100%
Pathologic response	<10% viable tumor cells in residual tumor mass	<−90%
Objective response	>30% decrease in maximum diameter of tumor	<−65%
Stable disease	<30% decrease and <20% increase in maximum diameter of tumor	>−65% and <+20%
Biologic response	Inhibition of drug target as assessed by ex vivo analysis of tumor tissue	Undefined

(specificity for response) appear very different (26% vs. 55%). This discrepancy is explained by the different definitions of a histopathologic response. Brucher et al. considered tumors as histopathologically responding when there were less than 10% viable tumor cells. In contrast, Swisher et al. defined histopathologic response as the absence of viable tumor cells (ypT_0). Applying this stricter definition of tumor response to the data of Brucher et al. yields a sensitivity of 27%, which is almost identical to the sensitivity reported by Swisher et al.

The reported diagnostic performance of ^{18}F-FDG PET for treatment monitoring is also influenced by the varying effectiveness of therapy in different tumor types and in different stages of a disease. If treatment is highly effective, a large fraction of the treated patients will show a favorable response; that is, the pretest probability of a favorable response is high. In this context, ^{18}F-FDG PET will tend to show a high positive predictive value for response but a relatively low negative predictive value. Conversely, the negative predictive value of PET will be rather high when the treatment is ineffective and most of the patients are classified as nonresponders according to the reference standard. For example, in aggressive non-Hodgkin lymphoma, Haioun et al. (*45*) found that only 44% of patients with a positive mid-treatment ^{18}F-FDG PET scan (PET nonresponders) showed disease progression during follow-up. Consequently, the negative predictive value of positive PET results for a favorable progression-free survival (i.e., a favorable response to therapy) was only 44%. In contrast, Mikhaeel et al. (*46*) reported that the negative predictive value of mid-treatment ^{18}F-FDG PET for a favorable progression-free survival was 71%. Although this difference in the negative predictive value appears substantial, it does not, in fact, hint at a major difference in the diagnostic performance of ^{18}F-FDG PET. In the study by Haioun et al. the sensitivity and specificity of ^{18}F-FDG PET in identifying favorably responding tumors was 70% and 76%, respectively. According to the data by Mikhaeel et al., the sensitivity and specificity of ^{18}F-FDG PET is 79% and 77%, respectively. However, the prevalence of early disease progression (i.e., an unfavorable response) was much lower in the study by Haioun et al. In that study, 23% of the patients eventually experienced tumor progression, whereas the frequency of tumor progression was 40% in the study by Mikhaeel et al. Thus, the lower prevalence of an unfavorable response in the study by Haioun et al. appears to be the key factor for the observed lower negative predictive value of ^{18}F-FDG PET.

A further important aspect for comparison of clinical studies evaluating treatment monitoring with ^{18}F-FDG PET is the varying approaches for image analysis. For staging of malignant tumors, ^{18}F-FDG PET scans are assessed visually, and focally increased ^{18}F-FDG uptake not explained by the normal biodistribution of ^{18}F-FDG is considered to be suggestive of metastatic disease. In a similar way, PET scans may also be read after completion of chemo- or radiotherapy. However, mildly increased ^{18}F-FDG uptake (intensity $\leq$ mediastinal blood pool) can represent a problem, because it can also be observed with treatment-induced fibrosis. Studies frequently differ with respect to the interpretation of "mild ^{18}F-FDG uptake." Some authors considered mild ^{18}F-FDG uptake as positive in order to maximize the sensitivity of ^{18}F-FDG PET for detection of tumor tissues; others emphasized the specificity of ^{18}F-FDG PET and read these scans as negative. For malignant lymphomas, a consensus guideline on the interpretation of mild ^{18}F-FDG uptake has recently been published (*47*). For other malignant tumors, such guidelines are still lacking.

Quantitative analysis allows a less observer-dependant interpretation of ^{18}F-FDG PET scans. Furthermore, quantitative analysis is frequently necessary when ^{18}F-FDG PET is performed during treatment to predict subsequent tumor response. Standardized uptake values have been shown to provide the same accuracy for assessing tumor response as do more sophisticated approaches for quantitative data analysis (*48–50*). However, quantitative analysis of ^{18}F-FDG PET scans is feasible only when images are acquired according to a standardized protocol. Because tumor standardized uptake values increase with time, it is, for example, crucial for the baseline and follow-up studies to be acquired at the same time after injection of ^{18}F-FDG (*51*).

AIMS OF THIS SUPPLEMENT

Considering the significant number of studies on treatment monitoring with ^{18}F-FDG PET and the enormous potential of ^{18}F-FDG PET for personalizing cancer therapy, it appeared appropriate and timely to ask experts in the field to review the current literature on treatment monitoring with ^{18}F-FDG PET in this supplement of *The Journal of Nuclear Medicine*. The aim of this supplement is to explore the clinical impact of PET on individualizing treatment regimens in cancer patients and to describe the potential use of PET in personalized medicine. Each contribution is intended to be a resource of currently available data on therapy monitoring in various tumor types. In addition, the contributions describe the clinical need for treatment monitoring by ^{18}F-FDG PET in specific situations and provide guidance on practical issues, such as timing of the PET scans in relation to therapy.

The articles in the supplement also describe the limitations of current studies on treatment monitoring with ^{18}F-FDG PET. The fact that a variety of approaches has been used for the acquisition and analysis of ^{18}F-FDG PET studies likely has caused significant differences in the quantitative assessment of tumor ^{18}F-FDG uptake. The supplement therefore starts with a review of protocols for data acquisition and analysis by Dr. Boellaard (*52*). This paper describes in detail technical and biologic factors influencing standardized uptake value measurements in clinical ^{18}F-FDG PET studies. The list of potentially confounding variables is long, and some authors have therefore concluded that quantitative analysis of ^{18}F-FDG PET scans is too complex for clinical use. However, Dr. Boellaard's analysis shows that despite these challenges, standardization of image acquisition, reconstruction, and

analysis is clinically feasible and that an international consensus regarding these issues is currently evolving (*52*).

In the following paper, Drs. Hutchings and Barrington discuss the current literature on ^{18}F-FDG PET for monitoring the treatment of patients with malignant lymphoma (*53*). In Hodgkin disease and aggressive non-Hodgkin lymphoma, many studies have indicated that ^{18}F-FDG PET is more accurate than CT for predicting patient outcome after chemotherapy. On the basis of these data, the International Working Group response criteria in malignant lymphoma have recently been revised, and assessment of tumor response is now based mainly on the findings on ^{18}F-FDG PET (*54*). Several ongoing studies use response assessment by ^{18}F-FDG PET as a basis for decisions to intensify treatment in patients with poorly responding disease or to apply shorter and less toxic regimens for lymphomas that respond well to the first 2 cycles of chemotherapy (*53*). Such "response-adapted therapy" (*55*) has an enormous potential to decrease the long-term complications of chemotherapy in low-risk patients and to improve cure rates in patients at high risk for recurrence after conventional chemotherapy. Therefore, it is likely that malignant lymphoma will be the first disease in which ^{18}F-FDG PET is used to personalize chemotherapy.

The next 6 papers (*56–61*) summarize the clinical experience with ^{18}F-FDG PET for treatment monitoring in common solid tumors (lung cancer, colorectal cancer, breast cancer, cancer of the cervix and ovaries, head and neck cancers, and esophageal cancer). Because these tumors are more resistant to chemo- and radiotherapy than are malignant lymphomas, changes in tumor glucose metabolic activity are smaller and occur more slowly than in lymphomas. Therefore, quantitative analysis of the ^{18}F-FDG PET scan is much more frequently used in solid tumors, and response criteria are generally different from those in lymphomas. Furthermore, relatively few patients with solid tumors are cured by chemo- or radiotherapy. Even patients in whom ^{18}F-FDG PET shows a good response will frequently have microscopic residual disease remaining after completion of therapy, eventually leading to tumor recurrence. Therefore, studies on lung, colorectal, and breast cancer have focused on detecting nonresponding tumors early rather than on identifying patients who are cured by chemo- or radiotherapy (*56–58,61*). In this context, the goal of ^{18}F-FDG PET is to guide decisions in order to intensify or change treatment in nonresponding patients. In esophageal cancer, one recent study has used ^{18}F-FDG PET to personalize neoadjuvant therapy: patients without a metabolic response on PET after 2 wk of neoadjuvant chemotherapy underwent immediate tumor resection instead of continued chemotherapy. Survival data from this phase II study are encouraging, and prospective validation in a randomized phase III setting is planned (*61*). In head and neck cancer, a large percentage of patients can be cured by chemoradiotherapy (*60*). In contrast to lung, esophageal, and colorectal cancer, the focus of studies in head and neck cancer has therefore been to identify patients who do not need to undergo surgery after completion of chemoradiotherapy (*60*).

The overwhelming majority of clinical trials have studied ^{18}F-FDG PET for monitoring conventional chemotherapy and radiotherapy. For these 2 types of treatment, there is now considerable evidence that a decrease in ^{18}F-FDG signal during treatment reflects a loss of viable tumor cells (*56–61*). A modulation of tumor glucose metabolism in the absence of cell death (metabolic stunning) has been discussed by some authors, but the clinical and experimental evidence for this phenomenon is limited. As reviewed by Drs. Contractor and Aboagye (*62*), new targeted drugs, however, can exert a specific effect on cellular glucose metabolism. A series of recent studies has indicated that several oncogenes are closely involved in the regulation of glucose metabolism of cancer cells (*63*). Because the function of these oncogenes is specifically inhibited by targeted drugs, tumor glucose metabolism may be more directly and rapidly affected by them than by cytotoxic agents. Conversely, inhibition of glucose metabolism by these drugs may not necessarily lead to cell death. In experimental studies, several targeted drugs have within hours markedly reduced ^{18}F-FDG uptake by cancer cells (*62*). However, with the exception of imatinib for treatment of gastrointestinal stromal tumors, clinical experience in monitoring treatment with targeted agents by ^{18}F-FDG PET is limited. If validated in clinical trials, ^{18}F-FDG PET could become an important tool for monitoring the biologic activity of drug candidates in phase I/II studies.

The articles in this supplement focus on ^{18}F-FDG because it represents the only PET probe clinically approved so far and because only relatively few studies have evaluated treatment monitoring with other imaging probes. Nevertheless, several imaging probes targeting DNA synthesis, hypoxia, and amino acid metabolism are in the early stages of clinical development for monitoring tumor response to therapy. Drs. Dunphy and Lewis review the preclinical and initial clinical data obtained with these imaging agents. Another class of agents reviewed by these authors is ligands with specific binding to receptors expressed on malignant tumors, such as the estrogen and androgen receptors. These new imaging agents are expected to complement ^{18}F-FDG in treatment monitoring by providing more specific information on the biologic effects of therapeutic agents. In addition, new agents may be useful for tumors with low ^{18}F-FDG uptake, such as prostate cancer (*64*).

The supplement concludes with a proposal for PET Response Criteria in Solid Tumors (PERCIST) by Dr. Wahl and colleagues (*26*). The urgent need for generally accepted criteria for response assessment by ^{18}F-FDG PET is emphasized by all other reviews in this supplement. Standardization of response criteria is a prerequisite for the further validation of ^{18}F-FDG PET by multicenter studies and metaanalyses. One may argue that optimal criteria for assessing tumor response and predicting patient outcome will be dependent on the tumor type studied and the specific treatment used. Therefore, the value of general response criteria can be questioned. However, as outlined by Dr. Wahl and colleagues, the results of ^{18}F-FDG PET for monitoring tumor

response in different tumor types have been fairly consistent and justify the definition of common response criteria. Of course, such general criteria will not be as accurate as response criteria defined for specific clinical situations. However, the ability to pool data in metaanalyses and to compare response rates across different studies will almost certainly outweigh this limitation. Disease- or treatment-specific definitions of a response are not part of the current standards for response assessment (WHO, RECIST, and RECIST 1.1) either.

One may also argue that more clinical data are needed to make sound definitions of a metabolic response on ^{18}F-FDG PET. However, it appears unlikely that response criteria can be significantly improved by single-center studies. Various degrees of metabolic changes during treatment have been shown to correlate with patient survival, and it is unlikely that single-center studies will have sufficient statistical power to identify significant differences between the accuracies of different definitions of a metabolic response. For multicenter studies, however, generally accepted guidelines for response assessment are a prerequisite. Therefore, the refinement of response criteria will have to be an iterative process. In this context, the aim of the proposed PERCIST 1.0 is to serve as a starting point for use in clinical trials and in standardized clinical reporting. As for the WHO and RECIST criteria, subsequent refinements and additions will likely be necessary as more data on the use of ^{18}F-FDG PET in different clinical situations emerge. When the WHO criteria were defined about 30 y ago, data on the accuracy of size changes for assessing tumor response were limited. Still, these criteria have proven useful for standardizing response assessment in research and clinical practice. Compared with the situation 30 y ago, many more data are now available for assessment of tumor response by ^{18}F-FDG PET than were then available for assessing tumor response by size changes. Considering the limitations of current approaches for treatment monitoring and the enormous potential of ^{18}F-FDG PET for personalizing cancer therapy, it is high time to come to a consensus on response criteria for assessment of tumor response by ^{18}F-FDG PET. It is hoped that this supplement will stimulate this process and thereby facilitate the use of ^{18}F-FDG PET in clinical practice and drug development.

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