INVITED COMMENTARY

^{18}F-FDG PET in Candidates for Radiation Therapy: Is It Important and How Do We Validate Its Impact?

In the last decade there have been important advances in the potentially curative treatment of locoregionally advanced solid tumors with radiotherapy. The increasing trend toward administration of platinum-based chemotherapy with radiation has led to significant improvements in survival for patients with unresectable non–small cell lung cancer (NSCLC) (*1*,*2*), small cell lung cancer (*3*), advanced head and neck cancer (*4*), cervix cancer (*5*), esophageal cancer (*6*), and other common tumors. These benefits have been achieved principally because chemoradiation achieves greater tumor cell killing for the same level of toxicity compared with radiation therapy alone, resulting in an improvement in the therapeutic ratio (*7*). Dramatic advances in the delivery of radiotherapy have also been made possible by the integration of powerful computer planning and control systems with advances in linear accelerator design such as multileaf beam collimators and on-line portal imaging systems (*8*,*9*). These technical improvements allow more accurate placement of high radiation doses in the target volume while at the same time permitting relative sparing of normal tissues. Methods such as 3-dimensional conformal radiotherapy (*10*) and intensity-modulated radiotherapy (*11*) can therefore achieve further enhancements in the therapeutic ratio for commonly treated disease sites.

Although these advances are significant in terms of survival, they come at substantially higher cost and often with greater local toxicity. Additionally, they can only benefit those patients with disease extent that can be included entirely within the high-dose-radiation target volume. Attempted curative treatment in the presence of distant metastasis or unsuspected locoregional disease extension will degrade the recipient's quality of life without significant hope of its prolongation. It is all too common for patients to develop symptomatic distant metastasis or locoregional disease progression outside the radiation field soon after therapy, an indication that the true extent of disease was not appreciated when treatment was planned. This distressing occurrence is in part a reflection of the shortcomings of conventional noninvasive methods for structural imaging of malignant disease. Patients who are treated with radical irradiation rather than surgery generally do not undergo invasive surgical staging and, therefore, accurate imaging is central to their treatment planning.

It is fortuitous that the rapidly widening availability of PET, primarily using ^{18}F-FDG as the radiopharmaceutical, has coincided with increasing demand for more sensitive noninvasive staging and more accurate 3-dimensional determination of the extent of solid tumors. Clinical PET has repeatedly been shown in clinical trials to greatly enhance the accuracy of staging of many of the common solid tumors in patients who are candidates for surgical treatment and in whom the validity of imaging results can be established by pathologic examination. There are, however, still relatively few reports of the use of PET in patients who are candidates for radiotherapy, and the article by Dizendorf et al. (*12*) in this issue of *The Journal of Nuclear Medicin*e is a valuable addition to the literature. Their findings suggest that PET has the potential to significantly improve the results of aggressive radical radiation or chemoradiation therapy by preventing futile treatment of patients with gross distant metastasis or excessively advanced locoregional disease and by enhancement of the delivery of locoregional therapy for those patients who remain candidates for radical irradiation. This is particularly important clinically because, for many types of solid tumor, the number of potential radical radiotherapy candidates greatly exceeds the number of patients with resectable disease. In their study, radiotherapy was cancelled or treatment intent changed in 19% of the cases, whereas radiotherapy delivery was altered in 18%.

One of the particular problems relating to the reporting of this type of patient population is the difficulty in verifying discordant imaging results and determining the appropriateness of management changes that arise as a consequence of these. Although in surgical series the validity of staging investigations can often be established by pathologic examination, in many cases being evaluated for curative radiotherapy, the same factors that mitigated against surgical therapy also limit the ability to obtain pathologic confirmation. Whereas histologic verification may be a desirable reference standard for oncologic imaging, mate-

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rial is not always available because of technical and safety issues, and it may not be ethically justified to biopsy every lesion even if the patient's consent could be obtained. Histopathology is also clearly a tarnished gold standard because of sampling errors. This is evidenced by the fact that many patients with clear surgical margins still die of cancer. Although further imaging studies may clarify discordant results in the absence of tissue diagnosis, relying on investigations that have been shown in many studies to be less accurate than PET is also fraught with difficulty. Furthermore, because of the variable success of therapies, progression of disease or lack thereof on serial imaging may limit verification of baseline imaging findings.

In the study by Dizendorf et al. (*12*), 26 patients had their management altered without further confirmation by histopathology or imaging follow-up, presumably because the PET results were believed to be compelling. As the authors acknowledge, there is clearly the potential for false positive PET results (*13*) that might deny patients potentially curative treatment. Despite this potential, in the vast majority of cases that could be validated in this and other similar patient series, PET has been shown to be correct. It also needs to be recognized that current oncologic management often relies on pathologically unsubstantiated imaging results. For example, many patients are denied curative treatment on the basis of multifocal bone scan or CT abnormalities without sampling all, or indeed any, of the lesions detected. Nevertheless, without this form of validation, the scientific rigor of studies such as this can be open to question, potentially limiting clinical acceptance of the technique and decreasing the likelihood of publication of such results. How do we verify that clinicians who accept and act on information provided by PET without resorting to biopsy confirmation are acting appropriately? This is not an insignificant issue given global trends in health policy.

In an era of cost containment, there is increasing pressure not only to demonstrate the accuracy of new diagnostic techniques but also to show that they positively impact outcomes (clinical efficacy) and that these can be achieved at a cost that is acceptable to the community purchasing these services (cost-effectiveness). The evaluation of scientific evidence now goes under the banner of evidence-based medicine (EBM).

There are now established guidelines (*14*) for the evaluation of evidence regarding new diagnostic and therapeutic technologies. These guidelines rank well-designed randomized controlled trials (RCTs) as the best available evidence. However, the ability to generalize from the findings of RCTs to routine clinical practice, particularly evaluation of imaging techniques, has been questioned (*15*). Further, to avoid potential bias, it is widely held that comparison of diagnostic tests ought to involve independent, blinded reporting of the new test and a comparator with the accuracy of each assessed against a gold standard that is performed irrespective of the result of either test. Although this methodology has been used, for example to assess the accuracy of PET for staging the mediastinum in patients with NSCLC (*16,17*), it presupposes that diagnostic imaging tests are competing rather than complementary tests. This is not the case in many potential applications. For example, complementary use of CT and PET has been shown to provide higher accuracy than that of either test alone (*18,19*) for staging of NSCLC involvement of the mediastinum. Accordingly, we support the approach of Dizendorf et al. (*12*) in reporting PET results with all available clinical information because this reflects the best clinical imaging practice even though at odds with conventional EBM methodology. Our own data have demonstrated that adding PET to the staging algorithm of newly diagnosed NCSLC provides markedly improved prognostic stratification compared with conventional staging (*20*), particularly in patients being considered for radical radiotherapy (*21*). Although this may not directly effect health outcomes, accurate prognostic stratification is clearly important for patients and for clinicians attempting to evaluate a raft of competing, increasingly complex, and often expensive therapeutic interventions. Additionally, there is accumulating evidence that more accurate staging can improve treatment planning and ought logically to improve the likelihood of cure. In support of this contention, we have recently shown that survival rates in patients planned for radical radiotherapy using PET are superior to those in a group receiving the same type of treatment but staged without PET and substantially superior to survival rates reported in comparable series (*22*). These results likely reflect a combination of better patient selection and improved radiotherapy delivery as a consequence of more accurate staging.

The high impact of PET in the series reported by Dizendorf et al. (*12*) is not at all unexpected because patients being evaluated for radiotherapy tend to have more locoregionally advanced disease than patients being considered for surgery; therefore, their likelihood of having occult systemic metastasis is also increased in keeping with bayesian principles (*23*).

The multifactorial nature of clinical diagnosis, therapeutic planning and delivery, combined with individual patient responses determined by comorbidities and genetic determinants renders robust evaluation of the unique contribution of any one factor to outcome difficult, if not impossible. Nevertheless, the high impact reported by Dizendorf et al. (*12*) across a diverse range of malignancies evaluated for radiotherapy should encourage further studies in more tightly defined patient groups with outcome measures appropriate to the clinical setting being evaluated. With the limitations of pathologic evaluation discussed above and given that the primary aim of oncology management is to maximize disease-free survival, it seems reasonable to use this parameter as the reference standard for evaluating the diagnostic accuracy and clinical efficacy of oncol-

ogy imaging, because the true disease status will become apparent with time in the absence of effective treatment. This is the reference standard for therapeutic interventions that rely on diagnostic imaging staging, so it seems logical that this endpoint can also be applied to assess the veracity of diagnostic imaging evaluation. Various methods such as imaging, clinical examination, or pathologic evaluation can then be used to confirm disease recurrence, as dictated by the clinical situation and consistent with methodology used to validate disease progression in therapeutic trials. This imposes the requirement for a follow-up period commensurate with the natural history of the malignancy under evaluation and should sensibly also be required when pathology of the primary surgical intervention is used as a reference for evaluation of diagnostic tests. We also need to consider quality-of-life issues, including measures of the benefits of avoiding futile therapies when survival is unlikely to be altered.

The experience reported by Dizendorf et al. (*12*) is certainly in keeping with our own that PET is invaluable in patients planned for curative radiotherapy. These patients represent a group in whom pathologic staging is often not available, and current diagnostic imaging techniques consistently fail to provide sufficient accuracy to appropriately guide management. Given the cost and toxicity of many combined chemoradiation protocols, better patient selection and enhanced treatment delivery made possible by PET may reduce health expenditure at the same time as improving outcomes. That equals cost-effectiveness!

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