^{18}F-FLT PET Evaluation of Radiation Response

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Over the past 2 decades, the limitations of anatomic imaging in assessing the response to photon radiation therapy have led many to explore the use of PET. In the setting of rectal cancer, for which neoadjuvant chemoradiation before surgery is the standard of care for many patients, several trials have attempted to correlate changes in tumor uptake of ^{18}F-labeled FDG after radiation therapy with pathologic complete response. Using a threshold change of 40% for maximum standardized uptake value (SUV_{max}), in a study of 22 patients one group found that ^{18}F-FDG PET correctly identified all patients who were later found to have a pathologic complete response (1). Others have reported that a greater decrease in SUV was found to be predictive of pathologic complete response, though the chosen threshold for change in SUV_{max} varied from 46% to 76%, indicating a need for further investigation (2).

^{18}F-3′-deoxy-3′-fluorothymidine (FLT) was developed for the noninvasive monitoring of cellular proliferation in cancer (3). With respect to radiation therapy, ^{18}F-FLT has 2 potential advantages over ^{18}F-FDG: first, ^{18}F-FDG uptake reflects glucose metabolism, which is elevated in cancers but also in sites of radiation-induced

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inflammation; second, although ^{18}F-FLT is not trapped in DNA, it is retained in cells via phosphorylation by thymidine kinase 1, a process that is more directly associated with proliferation and impacted by radiation than glycolysis (4). Several publications have indicated the utility of ^{18}F-FLT PET in detecting early responses to radiation therapy (5,6), principally in patients with head and neck malignancies. In a study of 20 rectal cancer patients receiving chemoradiation, negative ^{18}F-FLT findings were more predictive of a pathologic complete response than negative ^{18}F-FDG findings (negative predictive value, 75% for ^{18}F-FLT vs. 38% for ^{18}F-FDG), and posttreatment inflammation was found to be related to SUV_{max} in ^{18}F-FDG images but not in ^{18}F-FLT images (7). Despite some data showing its prognostic value in radiation therapy, the larger goal of using PET to optimize and individualize patient therapy remains elusive. As of now, additional studies are required before PET during the course of radiation therapy can be used to modify therapy and improve outcome.

In this issue of *The Journal of Nuclear Medicine,* the study by Lin et al. sought to examine early changes in ^{18}F-FLT retention after x-irradiation and charged particle irradiation with protons or carbon ions in vitro and in mice with xenografts (8). Their data indicate that ^{18}F-FLT uptake correlates with response to radiation therapy. Interestingly, the authors show that decreased ^{18}F-FLT uptake is detectable as early as 24 h after radiation therapy. Previous studies in humans have generally used ^{18}F-FLT PET 2–3 wk after the initiation of radiation therapy. It is therefore encouraging that changes in ^{18}F-FLT can be detected so soon after therapy and that changes in tracer retention after charged particle therapy are consistent with those demonstrated in response to conventional photon radiation therapy.

Although this study had some encouraging results, there are several issues to be addressed before it can be translated to patient studies. As the authors acknowledge, they used only the colon 26, mouse colon carcinoma, cell line for their experiments. It remains unclear if their findings apply to different cell models or tumor types. In addition, radiation therapy has a limited role in colorectal cancer; imaging of response would be used primarily in those patients receiving neoadjuvant treatment of rectal cancer and is clearly not useful in most other treatment scenarios. Studies focusing on the early response to radiation therapy would be particularly applicable in patients with head and neck or localized prostate cancer, in whom radiation therapy is often used with curative intent and proton treatment is being studied.

Another issue is that the irradiation regimen used by the authors is not representative of that used in humans. To limit toxicity and prevent the accelerated repopulation of tumor cells, radiation is typically administered to patients in multiple fractions (9) rather than a single 5-Gy fraction of x-ray, proton, or carbon ion irradiation. Although the optimal fractionation system for charged particle irradiation has not been characterized, proton therapy tends to be given with extended fractionation (10), whereas in limited studies with carbon ions patients have received an average of 12.5 fractions (11). It would be interesting to conduct a study that examines how different fractionation schemes affect tumor growth and ^{18}F-FLT uptake.

On the other hand, the ^{18}F-FLT uptake schema used by the authors may merit further investigation. First, the authors chose to measure uptake 24 h after radiation therapy. As mentioned, studies of PET after radiation therapy have typically been conducted weeks after therapy, but the timing of scans still needs to be optimized to maximize their predictive value. Although very early changes were interesting, 24 h may be too soon to demonstrate a change that is useful in the clinical setting. Indeed, although the results were statistically significant, the decreases in ^{18}F-FLT may not be meaningful. Reproducibility studies of PET imaging in patients have indicated that changes in tumor SUV of at least 20% are needed to distinguish significant differences in metabolism from scan-to-scan variations in tracer retention (12,13). The approximately 30% decrease in ^{18}F-FLT uptake after radiation

therapy in xenografts, though above this threshold, may not translate to patients' tumors, which are likely far more heterogeneous in ^{18}F-FLT uptake. Increasing the time between administration of radiation therapy and PET imaging may allow for larger observed changes in ^{18}F-FLT uptake and more robust predictions of response using standard treatment schedules.

At present, ^{18}F-FDG PET has a limited role in the routine assessment of the response of cancer to treatment: it is primarily used in patients with lymphoma, and primarily to escalate therapy in nonresponders (14). For such imaging approaches to be used they must be very predictive of failure before oncologists will alter treatment, given the limited other treatment options that are usually available. Hence, a lynchpin for using imaging to predict the response to therapy is the existence of a successful alternative to the treatment being administered. In the MUNICON II trial, patient therapy for esophagogastric cancer was modified on the basis of ^{18}F-FDG PET scans conducted 14 d after the start of chemotherapy, and nonresponders were provided additional radiochemotherapy before surgery. Despite this intervention, the prognosis of nonresponders did not improve significantly (15). Without a viable secondary course of action, the predictive value of imaging becomes moot.

The data presented in this new study are a welcome sign that ^{18}F-FLT PET can provide an early indication of the effectiveness of multiple radiation modalities in vitro and in vivo. However, issues regarding the cell model, radiation regimen, and timing of PET imaging require further research before this information can be applied to clinical oncology.

DISCLOSURE

No potential conflict of interest relevant to this article was reported.

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