^{18}F-FDG PET After Radiofrequency Ablation: Is Timing Everything?

Monitoring response to cancer treatment by exploiting changes in tumor glucose metabolism has evolved as a promising application of ^{18}F-FDG PET. Conventional anatomic imaging, such as CT and MRI, often provides equivocal results when used for assessment of treatment response. It is particularly difficult with these methods to identify whether residual masses consist of viable tumor tissue or represent posttreatment changes. Anatomic imaging used to define treatment response faces an even more difficult challenge as new treatment approaches are being evaluated. Generally, new biologic

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therapies are cytostatic rather than cytotoxic, with tumor shrinkage not being the primary treatment effect. In addition, localized tumor therapies such as microembolization or thermal ablation often result in persistent radiologic abnormalities.

In this issue of *The Journal of Nuclear Medicine*, Okuma et al. (*1*) have revealed important information regarding temporal changes in tissue ^{18}F-FDG uptake after radiofrequency ablation using an experimental animal model. Increased ^{18}F-FDG uptake in tumor tissue decreased to background levels at 1 d and 1 wk after treatment.

However, a ring-shaped increase in ^{18}F-FDG uptake was observed around the coagulative necrosis induced by radiofrequency ablation. The tracer uptake in surrounding lung tissue reached a peak between the first and second weeks after treatment, with the peak uptake being 4.1 times higher than uptake in muscle tissue. The ring-shaped increase in ^{18}F-FDG accumulation around the area of radiofrequency ablation continuously decreased during follow-up. By comparing the ^{18}F-FDG PET findings with histopathologic findings, this study provides important insights into the underlying biologic changes in ablated tumor and surrounding tissue that could guide the timing of ^{18}F-FDG PET after radiofrequency ablation.

Radiofrequency ablation is increasingly being considered as an alternative therapy for localized treatment of solid tumors. The use of this technique has rapidly evolved over the past few years, and the technique is being applied to tumors in different locations, including liver, kidney, breast, and lung (*2*). Radiofrequency ablation systems comprise a radiofrequency generator, an active electrode, and dispersive electrodes. The radiofrequency energy is introduced into the tissue via the active electrode, and the ions within the tissue oscillate in an attempt to follow the change in the direction of the alternating current. This movement results in frictional heating of the tissue at temperatures beyond 60°C, which causes coagulative necrosis surrounding the electrode. The advantage of such a thermal intervention system is the capacity to heat tissue to a lethal temperature in a specific anatomic location with reduced surgical trauma, a shorter procedure time, a shorter hospitalization, and a faster recovery. In the treatment of

lung nodules, radiofrequency ablation allows for destruction of lung tumors with minimal damage to surrounding normal lung tissue (*2*).

Determining whether the treatment was successful is crucial because incomplete ablation or early recurrences could potentially be considered for repeated ablation. In a small initial series of 8 patients with primary non–small cell lung cancer who underwent radiofrequency ablation followed by surgery, only 3 patients (37.5%) had complete ablation (*3*). In the remaining 5 patients, up to 20% of the treated areas still contained viable tumor cells. Most of the incomplete ablations occurred in tumors larger than 2 cm. However, in another study, residual tumor cells were found in the periphery and, in particular, surrounding bronchovascular areas of even smaller tumors (*4*). In 31 patients, complete necrosis after initial radiofrequency ablation was achieved in only 32 (59%) of 54 lung neoplasm (*5*).

These results clearly indicate the need for accurate noninvasive imaging techniques to evaluate treatment success. Cross-sectional imaging modalities have difficulty distinguishing residual or recurrent tumor from changes after radiofrequency ablation. In an experimental animal swine model with a total of 72 treated lung regions, the inner zone was hypointense on T2-weighted MR images in the acute phase and showed no contrast enhancement (*6*). In contrast, the outer zone was hyperintense on T2-weighted images and showed ringlike contrast enhancement on T1-weighted images. Although the lesions became smaller in the chronic phase, the MRI signal pattern did not change. Typical features seen on CT include ground-glass shadows around

the tumor lesions immediately after radiofrequency ablation and homogeneous opacity with no contrast enhancement in the early phase (4). After 2 mo, most lesions demonstrate decreased tissue density and cystic changes, some with central cavitations. However, tissue alterations and areas of obstructive pneumonitis often result in discordance between the lesion diameter on CT and histopathology (7). Therefore, these CT findings do not provide well-defined criteria as to the success of treatment. Often, follow-up imaging is necessary to identify residual or recurrent disease by an increase in tumor size or changes in contrast enhancement characteristics and may significantly delay subsequent therapy.

Metabolic ^{18}F-FDG PET is hampered by the considerable inflammatory changes induced by radiofrequency ablation. Histopathologic specimens obtained in the early phase in porcine lung demonstrated a 3-layered composition of posttreatment changes (7). The inner layer consisted of coagulative necrosis and was surrounded by a layer with hyaline membrane formation in the inner surfaces of the alveolar walls as well as alveolar fluid collection and vascular congestion. The outer layer exhibited strong vascular congestion accompanied by hemorrhage, fibrin deposition, and neutrophilic infiltration. Three days after radiofrequency ablation, the inflammatory cell infiltration enhanced, and a further increase was seen 10 d after treatment. In addition, granulation tissue rich in collagen fibers was observed (7). Okuma et al. (1) found that the neutrophilic infiltration in the alveoli corresponded to a ring-shaped increase in ^{18}F-FDG uptake around the treated area. At 4 wk after treatment, prominent granulation tissue dominated the outer layer, with necrosis seen in the inner layer. Subsequently, the granulation tissue transformed to fibrous granulomatous tissue, and a fibrovascular rim developed around the treated area. These changes corresponded to a continuous normalization in ^{18}F-FDG uptake. The ablated lesions demonstrated gradual resorption in the chronic phase, and a cavity formed.

As one would expect, the study by Okuma et al. showed that coagulative necrosis did not exhibit increased ^{18}F-FDG uptake (1). The challenge for imaging modalities is to identify areas of incomplete ablation and early recurrences from repopulation of residual microscopic disease. In a small series, neither ^{18}F-FDG PET nor CT or MRI was able to identify residual microscopic disease 2 wk after treatment (4). Given the limitations of metabolic ^{18}F-FDG PET, including the limited spatial resolution, partial-volume effects for small-volume disease, and false-positive ^{18}F-FDG uptake in inflammatory changes, what does PET have to offer?

Although some studies indicated that the full extent of lethal injury after radiofrequency ablation occurs within 24–72 h after treatment (8,9), Okuma et al. (1) have shown a decrease in tumor ^{18}F-FDG uptake to the background level at 1 d after treatment. Inflammatory changes, including the migration of inflammatory cells in tissue surrounding the ablation zone, is a process that takes several hours. Therefore, a potential time for ^{18}F-FDG PET to assess treatment response might be the same day as the procedure or within the first 12 h. Of note, emission data from 1 or 2 bed positions would be sufficient to reduce any potential inconvenience to the patient. Similar conclusions were derived from radiofrequency ablation of liver tumors (10). Otherwise, a waiting time of 6–8 wk might be necessary before ^{18}F-FDG PET can be used to reliably assess for residual or recurrent disease. Coregistered ^{18}F-FDG PET/CT might have additional benefits for treatment monitoring after radiofrequency ablation by allowing detailed comparison of morphologic posttreatment changes with metabolic activity, particularly when residual contrast enhancement is present on CT. However, respiratory gating might be necessary to fully exploit the use of ^{18}F-FDG PET/CT (11).

Dual-time-point ^{18}F-FDG PET has been suggested to allow for better differentiation between cancer and inflammatory changes (12,13). Dual-time-point imaging refers to 2 PET scans obtained in the same session, the first at approximately 1 h and the second at 2 h after ^{18}F-FDG injection. The underlying hypothesis is that cancer tissue is characterized by an increase in ^{18}F-FDG uptake, whereas inflammatory cells either show no significant change or some tracer washout between the first and second scans. However, Okuma et al. (1) found an increase in ^{18}F-FDG uptake in inflammatory changes at all PET-imaging times, a characteristic that would not be of help in distinguishing residual cancer tissue from inflammatory changes after radiofrequency ablation.

With the success of metabolic ^{18}F-FDG PET, one should not disregard the large array of molecular imaging tools that have been developed for oncology applications over the past few years. The intracellular accumulation of ^{18}F-fluorothymidine reflects cell proliferation, and ^{18}F-fluorothymidine might be better suited for early detection of persistent or recurrent disease than is ^{18}F-FDG. Encouraging results in experimental animal models showed no relevant ^{18}F-fluorothymidine uptake in inflammatory lesions (14), but these findings need to be confirmed clinically. PET tracers targeting angiogenesis (15) might also be suitable to differentiate between residual tumor and treatment-induced inflammation.

What did we learn from Okuma et al. (1)? Assessment of treatment response with ^{18}F-FDG PET is likely to be more difficult after radiofrequency ablation than in other settings because of a distinct and prolonged inflammatory response after treatment. Very early ^{18}F-FDG PET, within the first 12–24 h or 6–8 wk after radiofrequency ablation, might be the best timing. However, it is important to remember previous experience in which sufficient evidence from preclinical studies guided decisions in the clinical setting and yet the results in humans were different. We are looking forward to the clinical validation of ^{18}F-FDG PET after radiofrequency ablation. Careful follow-up imaging of

tumors treated with radiofrequency ablation and, potentially, comparison with pretreatment imaging are likely necessary to differentiate recurrence from microscopic residual tumor deposits, and PET/CT might be the method of choice for comparing anatomic and metabolic changes.

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