^{18}F-FDG PET/CT in Local Ablative Therapies: A Systematic Review

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Driven by the continuous improvement in the accuracy of cross-sectional imaging, image-guided minimally invasive local ablative therapies have received incremental interest over the past few years. In this article, we systematically review the currently available literature on ^{18}F-FDG PET/CT to monitor the efficacy of these local ablative therapies. By including all local ablative treatment modalities, tumor types, and organ sites, we provide a comprehensive overview of the current status, identify general patterns across studies, and provide recommendations for future studies and clinical practice. The Quality Assessment of Diagnostic Accuracy Studies (QUADAS) criteria were used to assess the quality of the reported diagnostic accuracy of the retrieved studies. Data in the literature suggest that ^{18}F-FDG PET/CT is a highly accurate tool to assess the technical success of local treatment, to identify residual or recurrent tumor early after intervention, and to provide prognostic and predictive information. However, prospective interventional studies based on ^{18}F-FDG PET/CT findings of disease activity are mandatory to develop uniform and quantitative criteria for PET evaluation. Moreover, the optimal timing of ^{18}F-FDG PET/CT after treatment may vary according to the location of the disease, with very early imaging being possible in solid organs such as the liver but post-treatment imaging being challenging for 3 mo in a location such as the lung parenchyma.

Key Words: local ablative therapy; ^{18}F-FDG PET/CT; response monitoring; radiofrequency ablation; radioembolization

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Driven by the continuous improvement in the accuracy of cross-sectional imaging for oncologic applications, image-guided minimally invasive local ablative therapies have received incremental interest for several reasons. More sensitive screening techniques have resulted in the detection of smaller tumors in earlier stages of disease (*1,2*), when they are more amenable to local therapy. This advantage is of special importance in the aging population of cancer patients, in whom comorbidity and reduced tolerance of treatment-related adverse effects often limit the application of major surgery or systemic therapy (*3,4*). Additionally, the concept of achieving long-term tumor control favors local ablative therapy of selected lesions to postpone or complement systemic therapy.

Local ablative therapies aim to induce cell death within a limited and confined range from application (*5*), either with a curative intent or to create a margin for improved local tumor control. These modalities exploit thermal energy–based cell death (radiofrequency ablation [RFA], microwave ablation, high-intensity focused ultrasound, and cryoablation), electric energy–based cell death (irreversible electroporation), radiation energy–based cell death (glass or resin microspheres filled with β-emitting radioisotopes [^{90}Y] or [^{166}Ho]), or chemical-induced cell death (transarterial chemoembolization or percutaneous ethanol injection therapy). Recent well-designed randomized controlled trials demonstrate that local ablative therapy has come of age. For example, the CLOCC study demonstrated that curative RFA can provide an alternative treatment option to resection for small-sized colorectal liver metastases (*6*). The SIRFLOX study showed that the addition of ^{90}Y radioembolization to chemotherapy in liver-dominant metastatic colorectal cancer delayed disease progression in the liver (*7*).

For various tumor types, these local ablative therapies have become part of clinical practice; for example, RFA for liver and lung metastases, ^{90}Y radioembolization for primary hepatocellular carcinoma and colorectal liver metastases, and cryoablation in non–small cell lung cancer or renal cancer (*8,9*). However, to establish local ablative therapy in current clinical practice, accurate tools to exactly measure the effectiveness of local ablative therapy on tumor viability are mandatory.

Anatomic imaging techniques, such as contrast-enhanced CT or dynamic contrast-enhanced or diffusion-weighted MRI, assess changes in tumor size, perfusion, permeability, and tissue composition. Most guideline-supported response criteria are based on changes in lesion size, with or without evaluation of lesion density or enhancement characteristics, and the appearance of new lesions (*10–16*). However, many studies have adapted these criteria or empirically established new criteria, with the intent of increasing their accuracy in evaluating responses to local ablative therapy. Importantly, the effect of ablative therapy is not selective to tumor cells but affects stromal and local healthy cells to a similar extent. Consequently, local ablative therapy may in most cases induce necrosis, cystic degeneration, and hemorrhagic or edematous changes in the tissue (*17–20*), which might initially result in enlargement of the lesion, whereas the final change in volume takes weeks or month to occur. Moreover, previous local and systemic therapies in cancer patients can affect the appearance of normal parenchyma (*21,22*). For these reasons, anatomic criteria have consistently been shown to underestimate the antitumor effect of local ablative therapies. In addition, changes in lesion enhancement, density, or diffusion might

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in most cases not reflect actual pathologic tumor responses, especially at early stages (*23–25*).

On the other hand, metabolic changes at the cellular level have been demonstrated to precede changes in tumor size or tissue parameters; for example, in RFA the earliest cellular events are loss of mitochondrial enzymes and lactate dehydrogenase activity (*17*). A sharp decrease in glycolytic activity can thus be expected. Within the first few days, this event is followed by coagulation necrosis, tissue dehydration, and recruitment of a variety of inflammatory immune cells (*5*). Accurate information on the efficacy of local ablative therapy early after application is of paramount importance for treatment planning and implementation of systemic therapy. Studies on the role of ^{18}F-FDG PET/CT in monitoring the effect of local ablative therapies are increasing but vary widely in design, number of patients, time point of imaging, criteria for response, and choice of comparator modality.

This article systematically reviews the currently available literature on the use of ^{18}F-FDG PET/CT to monitor the efficacy of local ablative therapies. By including all local ablative treatment modalities, tumor types, and organ sites, we aim to provide a comprehensive overview of the current status, identify general patterns across studies, and provide recommendations for future studies and clinical practice.

MATERIALS AND METHODS

Search Strategy

To identify all relevant publications, we performed systematic searches of PubMed and the Cochrane Library, using the following search terms ("Ablation Techniques"[Mesh] OR radioembolization OR radioembolisation OR Y90 OR Y-90 OR 90Y OR 166Ho OR Ho-166 or Ho166 OR chemoembolization OR chemoembolisation OR radiofrequency ablation OR RFA OR radio frequency ablation OR cryoablation OR microwave ablation OR HIFU OR high intensity focused ultrasound OR high-intensity focused ultrasound) AND ("Positron-Emission Tomography"[Mesh] OR PET OR PET/CT OR fluorodeoxyglucose OR fluorine-18-deoxyglucose OR fluoro-deoxyglucose OR 18F-FDG OR F-18-FDG OR FDG). The references of the identified articles were searched for relevant publications. The Cochrane Library search yielded no relevant additional results. Approval of the institutional review board for this literature review was waived.

Selection Process

Two reviewers independently screened for eligibility all potentially relevant abstracts obtained from the database search. Studies were not restricted to anatomic sites or tumor types. A study was included if it investigated the performance of ^{18}F-FDG PET/CT or ^{18}F-FDG PET for treatment monitoring, if it involved human subjects and local ablative therapies, if it reported clinical outcomes, and if an English version of the article was available. The local ablative therapies could include RFA, cryoablation, microwave ablation, high-intensity focused ultrasound, ^{90}Y radioembolization, ^{166}Ho radioembolization, or chemoembolization.

Full-text articles on these studies were obtained and reviewed. A study was excluded if it used investigational drugs or techniques, did not include original data (e.g., reviews, editorials, letters, legal cases, interviews, case reports, comments, and follow-up reports from previous cohorts), reported on fewer than 15 patients evaluable with ^{18}F-FDG PET/CT, or had a wide spread in imaging time points.

Differences in judgment were resolved by a consensus procedure, and all articles were scored using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) system.

NOTEWORTHY

- ^{18}F-FDG PET/CT is a highly accurate tool to identify residual or recurrent tumor immediately after local ablative therapy.
- An increase or inadequate decrease, per PERCIST, of ^{18}F-FDG uptake in the lesion after ablation, as well as focal or multifocal ^{18}F-FDG uptake in the margins of the ablation zone, is highly indicative of residual or recurrent disease.
- The optimal timing of ^{18}F-FDG PET/CT after treatment may vary according to the location of the disease, with very early imaging being possible in solid organs such as the liver but posttreatment imaging being challenging for 3 mo in a location such as the lung parenchyma.

RESULTS

Search Results

The literature search, performed in September 2017, generated 727 records, of which 559 were excluded upon screening of the abstract. The main reasons for exclusion were the use of PET imaging for dosimetry, no use of local ablative therapy, use of ^{18}F-FDG not for monitoring but for diagnosis, or a combination of these reasons. The full text of the remaining 168 records was screened for eligibility, and 52 of these were included in this review. The main reasons for exclusion were no full text, no data on clinical outcome, use of an investigational drug or procedure, no original data, fewer than 15 patients, or varying time points for imaging.

Five studies reported ^{18}F-FDG PET/CT results to evaluate technical treatment success, and 47 studies reported the results of early time points to evaluate treatment efficacy. Supplemental Tables 1–4 (available at http://jnm.snmjournals.org) summarize the data from the selected reports (Supplemental Tables 1 and 2, immediate time points; Supplemental Tables 3 and 4, later time points). Most studies involved only limited numbers of patients and were retrospective. Moreover, imaging time points and image evaluation criteria were highly variable across studies. Supplemental Table 5 summarizes the studies according to the QUADAS criteria: studies with no or one minor comment are discussed in the text; studies with 2 or more minor comments or one major comment are not discussed but their results are included in Supplemental Tables 1–4.

Immediate ^{18}F-FDG PET/CT Imaging to Evaluate Technical Treatment Success

Similar to surgical resection with curative intent, the cornerstone of successful local ablative therapy is to achieve complete tumor destruction with oncologically clear margins, particularly in RFA, microwave ablation, and cryoablation. Anatomic imaging modalities have so far not been adequate for assessing vital tumor residue (*18–20*); intraoperative biopsies are highly informative but not feasible in most settings (*26*). The shutdown of pathways involved in glucose metabolism can serve as an early measure of therapy-induced cell death (*17,27*). For tumors that appear as ^{18}F-FDG–avid on preoperative imaging, functional imaging with ^{18}F-FDG during or immediately after the procedure has been investigated as a tool to measure technical treatment success. To this end, the standard ^{18}F-FDG dose can be split into 2 doses, with the first being given just before the procedure for treatment planning and the second being given to identify residual viable tumor before inflammatory

changes occur (e.g., split-dose protocol). Such an approach facilitates additional treatment in the same session and potentially increases treatment efficacy (*28*).

Five studies (*28–32*) (in total, 145 patients) evaluated the prospective value of ^{18}F-FDG PET/CT less than 24 h after treatment with thermal ablation (4× RFA and 1× RFA/microwave ablation) in liver metastases (Supplemental Tables 1 and 2). All 5 reported visual interpretation of the ^{18}F-FDG PET/CT, and 3 studies also reported quantitative analyses (SUV_{max} or tissue radioactivity concentration). All found good accuracy for ^{18}F-FDG PET/CT in predicting local tumor residue or local tumor progression. Ryan et al. exploited a split-dose approach and identified focal uptake immediately after RFA in 1 of 23 patients. The uptake was confirmed to be viable tumor tissue, and the patient received additional treatment. In 2 of 22 patients with a negative ^{18}F-FDG PET/CT result, follow-up imaging detected local recurrence (*28*). The lowest reported sensitivity for immediate ^{18}F-FDG PET/CT, 63%, was in a study by Vandenbroucke et al. (combining nodular and rimlike uptake to detect viable tumor localization) (*30*). Two other studies reported an accuracy above 90% and superiority over contrast-enhanced CT (*31,32*). One study found no significant difference from the sensitivity and specificity of MRI (*31*).

Response Monitoring to Evaluate Treatment Efficacy

Correct assessment of the response to local ablative therapy early after the procedure is vital for early response-adapted treatment strategies, especially if local ablative therapy is used in addition to other treatments (*33*).

However, the necrotic, cystic, and hemorrhagic changes induced by local ablative therapies evoke inflammatory responses in the lesion and surrounding healthy tissue in the days to weeks after the procedure. Histologic changes include a central zone of necrosis surrounded by a zone of inflammation caused by the recruitment of neutrophils, lymphocytes, and macrophages (*17,18,34*). Although contrast-enhanced CT and diffusion-weighted MRI are hindered by abnormal enhanced patterns, ^{18}F-FDG PET/CT may also be confounded by these inflammatory changes during the postablation healing process.

Response monitoring for up to several months after intervention might be influenced by inflammation; however, ^{18}F-FDG PET/CT still seems more sensitive for determining the treatment effect and detecting local recurrence.

RFA and Cryoablation in Liver Metastases

Four studies (in total, 111 patients) evaluated ^{18}F-FDG PET/CT less than 1 mo after RFA or cryoablation in liver metastases (Supplemental Tables 3 and 4) (*35–38*). All 4 studies showed ^{18}F-FDG PET/CT to be more sensitive than CT or MRI in detecting local recurrence. False-positive findings can be due to inflammation or abscess formation, though the reported specificity was high: 80%–100%. The study of Joosten et al. showed that ^{18}F-FDG PET/CT within 3 wk of treatment correctly predicted 6 of 7 recurrences (*35*).

RFA and Cryoablation for Lung Lesions

In the setting of RFA for lung metastases or primary lung cancer, the clinical utility might be different from that for liver lesions (Supplemental Tables 3 and 4), as reported in 8 studies (in total, 402 patients). Four other studies did not meet the QUADAS criteria. Deandreis et al. observed a poor specificity: ^{18}F-FDG PET/CT was true-positive in 3 of 7 patients, particularly those with a nodular pattern, and false-positive in 4 of 7 (*39*). Higuchi et al. (*40*) and Higaki et al. (*41*), in studying similarly sized prospective series, reported that imaging less than 1 mo after RFA did not correlate with local tumor progression at later time points. In a study by Yoo et al., on 26 patients with irresectable primary non–small cell lung cancer who underwent RFA, imaging with ^{18}F-FDG PET/CT within 4 d was not predictive of 1-y events, but imaging at 6 mo corresponded better with outcome at 1 y (*42*). Multiple studies confirm the higher diagnostic accuracy of ^{18}F-FDG PET/CT than of CT from 3 mo after intervention (*43–45*). A continuous decrease in SUV_{max} from intervention to 3 mo and then 6 mo was identified as a physiologic pattern, with a high negative predictive value. An increase in ^{18}F-FDG uptake, or an absolute ^{18}F-FDG uptake having an SUV_{max} of more than 2.5, has been suggested to be predictive of recurrence (*45*).

Regional Ablative Therapy in Hepatocellular Carcinoma

Five studies (in total, 142 patients) reported on the role of ^{18}F-FDG PET/CT in regional ablative therapy for hepatocellular carcinoma; 4 other studies regarding hepatocellular carcinoma did not meet the QUADAS criteria. In a retrospective study on 33 patients with hepatocellular carcinoma treated with ^{90}Y-microspheres, Sabet et al. found that patients with a response on ^{18}F-FDG PET/CT had a significantly better overall survival than metabolic nonresponders, 10 mo versus 5 mo (*46*). Similar observations stem from the retrospective analyses of 27 patients by Ma et al.; the use of ^{18}F-FDG PET/CT 4–6 wk after treatment to identify responders according to a 90% decrease in tumor SUV_{max}, compared with baseline, resulted in a sensitivity of 100% and specificity of 92.5% (*47*). Responders according to this criterion had a longer time to progression, 18.3 mo versus 7.1 mo. ^{18}F-FDG PET/CT responses correlate with responses assessed by modified RECIST but tend to occur earlier. Paudyal et al. investigated the use of ^{18}F-FDG PET/CT during follow-up and showed that recurrence was also detected earlier on PET/CT than on contrast-enhanced CT (*48*). Li et al. showed, in 22 patients, that a negative ^{18}F-FDG PET/CT result after transarterial chemoembolization with or without bevacizumab correlated with overall survival, whereas imaging with ^{11}C-acetate PET performed slightly worse (*49*).

Radioembolization in Liver Metastases

The role of ^{18}F-FDG PET/CT after radioembolization for liver metastases has been studied the most: 3 studies reported the results of imaging less than 1 mo after treatment (*50–52*), and 12 studies reported on imaging at more than 1 mo after treatment (*53–62*) (in total, 563 patients; Supplemental Tables 3 and 4). Four other studies did not meet the QUADAS criteria. All studies with ^{18}F-FDG PET/CT within 1 mo showed a strong correlation between metabolic response and outcome. One study showed that PET was able to detect more responses than CT, but the study did not analyze the correlation between PET response and survival (*50*). A study by Michl et al., imaging at 3 mo, reported a high correlation between ^{18}F-FDG PET/CT response and survival but no correlation between CT response and survival (*55*). In line with this study, the other studies imaging more than 1 mo after radioembolization found a high correlation between metabolic response and survival (*53,54,63–66*), and metabolic response cannot be identified on anatomic imaging using RECIST (*66*).

For example, Fendler et al. prospectively studied ^{18}F-FDG PET/CT in 80 patients with liver metastases from colorectal cancer at 3 mo after ^{90}Y-microsphere treatment (*53*). As opposed to RECIST version 1.1 and SUV, the PET measures of metabolic tumor volume and total lesion glycolysis were predictive of overall survival. In patients with a decrease of more than 30% in metabolic tumor

volume (27/80 patients), overall survival was 92 wk, significantly better than in nonresponders (49 wk). Slightly less predictive was a more than 30% decrease in total lesion glycolysis; in 30 of 80 responding patients, overall survival was 91 wk, versus 48 wk in nonresponders. Similar findings by Shady et al. support this notion that volume-based parameters have a better prognostic impact than single-voxel measures (*65*). A retrospective analysis of 17 patients with liver metastases from pancreatic cancer who underwent ^{90}Y radioembolization reported that more than a 30% decrease in either SUV_{peak} or total lesion glycolysis (according to PERCIST) identified the same patients as complete or partial responders (*55*).

Radioembolization in Cholangiocarcinoma

In a study to predict survival in intrahepatic cholangiocarcinoma patients after ^{90}Y-microsphere treatment, Haug et al. compared ^{18}F-FDG PET/CT response at 3 mo with MRI-based responses (*67*). They showed in 26 patients that, in contrast to changes in SUV, a decrease in metabolic tumor volume was an independent predictor of overall survival (hazard ratio, 0.20). Along this line, a prospective study on 17 patients with intrahepatic cholangiocarcinoma by Filippi et al. demonstrated that a decrease in total lesion glycolysis of more than 50% within 6 wk after treatment was significantly associated with both longer time to progression (36.9 vs. 13.7 wk) and improved overall survival (79.6 vs. 43.1 wk) (*68*).

DISCUSSION

In general, studies suggest that ^{18}F-FDG PET/CT can show local posttreatment tumor progression earlier than other imaging modalities. In solid organs, absence of or markedly decreased ^{18}F-FDG uptake in the lesion after local ablative treatment as measured by SUV_{max} indicates successful ablation. Moderate uptake in a homogeneous rimlike pattern is accepted as physiologic and caused by tissue remodeling and scar formation. An inadequate decrease in ^{18}F-FDG uptake in the lesion after ablation, as well as focal or multifocal ^{18}F-FDG uptake in the margins of the ablation zone, marks residual vital tumor. Similarly, an increase in ^{18}F-FDG uptake, whether immediate or after an initial decrease, always indicates residual or recurrent disease. The PERCIST criterion of at least a 30% decrease in SUV_{max} appears to be a safe cutoff for response. Parameters that incorporate tumor volume as well (metabolic tumor volume and total lesion glycolysis) do not prevail over SUV_{max} but might reflect that larger tumors are prone to incomplete ablation. These response characteristics are valid for the included local ablative modalities and different tumor types, provided that the lesions are more ^{18}F-FDG–avid than the surrounding tissue at baseline. For solid organs, these criteria apply to early first-imaging time points, within 1 mo after therapy. To avoid false-positive results, we would suggest 2–4 wk. If false-positive findings are encountered, they can be caused by abscesses (in the appropriate clinical context), which typically present with a rimlike markedly increased ^{18}F-FDG uptake pattern.

Treatment of lung lesions is assessed differently from treatment of solid organs. From an imaging perspective, lung parenchyma has different characteristics that affect the assessment of reactive changes in normal tissue adjacent to locally destroyed tumor. The target lesions, metastases, and primary lung cancers are solid and most likely respond similarly to lesions located in solid organs. Surrounding normal lung parenchyma contains far fewer cells, reflected by a low physiologic rate of glycolysis (normal SUV_{max}, 0.6–0.7) (*69*) and a very low density (Hounsfield units, ~ -800). Furthermore, the composition of lung parenchyma is different from that of solid organs, consisting mostly of endothelial cells and immune cells, with fewer stromal cells and less extracellular matrix. Thus, early responses to local ablative treatment—coagulation of proteins, formation of interstitial edema, and an influx of immune cells—rapidly result in profound increases in ^{18}F-FDG uptake and appear as increased density in normal lung parenchyma. Bearing this in mind, the findings not associated with recurrence include not only the absence of ^{18}F-FDG uptake but also the presence of high uptake at the pleural border of a treated lesion and intense focal uptake at the site of the lesion—findings that usually reflect a profound inflammatory response and formation of organizing pneumonia or granuloma, respectively. However, moderate uptake and rimlike uptake with intense focal uptake indicate incomplete tumor ablation or recurrence.

For lesions in the lung parenchyma, the PERCIST criterion of a more than 30% decrease in SUV_{max} appears reasonable for defining response, and an SUV_{max} of more than 3 is highly suggestive of residual or recurrent tumor. These criteria apply regardless of histologic subtype or primary tumor. Most studies demonstrated that, unlike solid-organ lesions, imaging of lung parenchyma lesions within the first 3 mo after local ablation yielded unspecific findings that had no predictive impact. Therefore, a first-imaging time point of more than 3 mo is suggested.

As exemplified by our tabulated data, the heterogeneity of the studies that evaluated ^{18}F-FDG PET/CT monitoring of response to local ablative therapy was a limitation in extracting evidence-based data that underpin the wide application of ^{18}F-FDG PET/CT for these indications. Most studies had a relatively small sample size and were retrospective, affecting the power of the data. Furthermore, in the absence of a generally accepted noninvasive gold standard, the studies differed greatly with respect to the comparator, and histopathologic confirmation of imaging results was included in only a small minority of studies. Given the heterogeneity of the protocols that generated the available data, we chose to accept all tumor types, local ablative modalities and techniques, and disease locations in order to identify general patterns for the optimal use of ^{18}F-FDG PET/CT for monitoring local ablative therapies.

Another limitation is the extrapolation of data from earlier studies using equipment that in current clinical practice has been replaced by more advanced technology. A striking example is the replacement of stand-alone PET devices by integrated high-resolution PET/CT scanners, which revolutionized the impact of molecular imaging. The same holds true for modern CT and MRI. For example, apparent-diffusion-coefficient mapping and whole-body MRI have found their way into clinical practice. Additionally, new software tools for analyzing data, such as texture analysis, allow characterization of lesions beyond anatomic changes. Further developments such as integrated PET/MRI may again increase the potential for optimal, early assessment of treatment response.

It is well appreciated that ^{18}F-FDG is the radiopharmaceutical of choice for a wide variety of indications. Nevertheless, being a rather nonspecific agent, targeting not only tumor cells but also therapy-induced inflammation, the development of tumor-specific radiopharmaceuticals such as radiolabeled peptides and antibodies may further increase the accuracy by selectively depicting residual or recurrent tumor.

CONCLUSION

Data in the literature suggest that ^{18}F-FDG PET/CT is a highly accurate tool for determining the success of minimally invasive

local treatment, for identifying residual or recurrent tumor early, and for providing prognostic and predictive information. However, prospective interventional studies based on ^{18}F-FDG PET/CT findings of disease activity are still scarce. Furthermore, the optimal timing of ^{18}F-FDG PET/CT after treatment varies according to the location of the disease, with very early imaging being possible in solid organs such as the liver but posttreatment imaging being challenging for 3 mo in a location such as the lung parenchyma. Uniform, quantitative criteria, such as PERCIST, for the assessment of PET images are needed to allow more accurate comparison of data in the literature.

DISCLOSURE

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

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