Karin Nielsen
Aukje AJM van Tilborg
Hester J Scheffer
Martijn R Meijerink
Elly SM de Lange-de Klerk
Sybren Meijer
Emile FI Comans
M Petrousjka van den Tol
PET-CT AFTER RADIOFREQUENCY ABLATION OF COLORECTAL LIVER METASTASES; SUGGESTIONS FOR TIMING AND IMAGE INTERPRETATION

Eur J Radiol. 2013 Dec;82(12):2169-75
Abstract

Introduction
The main area of concern regarding radiofrequency ablation (RFA) of colorectal liver metastases is the risk of developing a local site recurrence (LSR). Reported accuracy of PET-CT in detecting LSR is high compared to morphological imaging alone, but no internationally accepted criteria for image interpretation have been defined. Our aim was to assess criteria for FDG PET-CT image interpretation following RFA, and to define a timetable for follow-up detection of LSR.

Methods
Patients who underwent RFA for colorectal liver metastases between 2005-2011, with FDG-PET follow-up within one year after treatment were included. Results of repeat FDG-PET scans were evaluated until a LSR was diagnosed.

Results
Hundred-seventy scans were obtained for 79 patients (179 lesions), 57 scans (72%) were obtained within 6 months of treatment. Thirty patients developed local recurrence; 29 (97%) within 1 year. Only 2% of lesions of <1cm and 4% of <2cm showed a LSR.

Conclusion
The majority of local site recurrences are diagnosed within one year after RFA. Regular follow-up using FDG PET-CT within this period is advised, so repeated treatment can be initiated. Rim-shaped uptake may be present until 4-6 months, complicating evaluation. The benefit in the follow-up of lesions <2cm may be limited.
Introduction

Colorectal cancer is the second most common malignancy in the Western world. At diagnosis of the primary tumor, metastases are already present in 20-25% of patients and another 20-25% of patients will develop metachronous metastases. Of these, 90% will become apparent within 3 years (1).

Although surgical resection of colorectal liver metastases remains the treatment of choice with a 5-year survival of up to 50% with additional chemotherapy, the majority of patients are ineligible for surgery due to location, size or number of metastases, or due to co-morbidity (2;3).

For patients with irresectable colorectal liver metastases, several alternative treatment options that can achieve complete local tumor control have emerged, of which radiofrequency ablation (RFA) is the most extensively studied and most widely available. RFA can result in complete tumor clearance and recent literature suggests that 5-year survival rates following RFA have increased from 18% in early data (4) to 36% in recent years (5), with rates as high as 48% in patients treated for a solitary lesion (6).

The main area of concern following RFA treatment is the risk of developing a local site recurrence (LSR), which occurs in 3.6-27% of cases mostly depending on the size of the treated lesion (5;7). Prompt diagnosis of a local site recurrence is important because repeated treatment can lead to complete tumor clearance, especially when recurrences are still of limited size(8). Currently, computed tomography (CT) and magnetic resonance imaging (MRI) are the most commonly used imaging methods to monitor post-ablative lesions for remnant or recurrent disease. One shortcoming of follow-up using these imaging modalities is the presence of post-ablation effects; for instance, in contrast enhanced computed tomography (ceCT), reactive tissue can present as a hypodense area around the ablated lesion. This can often be indistinguishable from viable tumor tissue, without proof of lesion growth on consecutive scans (9).

Recent literature suggests that fluorine-18 deoxyglucose positron emission tomography (FDG-PET) could play an important role in assessing the presence of residual tumor following RFA (9-13). Unlike traditional anatomic imaging, FDG-PET visualizes glucose metabolism. Because glucose uptake is enhanced in tumor cells, FDG-PET has proven to be able to largely overcome the drawback of post ablation effect (14;15). Using PET-CT, PET images are combined with CT data to provide accurately fused functional and morphological data sets in a single session (16). Several studies have shown the superiority of PET-CT over morphologic
imaging alone in the follow-up after ablation of colorectal liver metastases with a sensitivity and specificity of PET-CT (92% and 100%) compared to ceCT (83% and 100%) regarding the detection of local tumor progression (9-12).

Despite of these good results, no standardized PET-CT regime has yet been proposed in the literature and diagnostic criteria with respect to PET-CT image interpretation are lacking. Both qualitative and semi-quantitative criteria have been used in image interpretation (9;10;12;17-19) and there is a growing need for standardization (11). In the present study, we analyzed PET data in order to assess the time-point at which a local site recurrence is visible on PET-CT. We also intended to explore the normal post-ablation effects in the FDG uptake in treated lesions with the aim to describe image interpretation criteria for local failure.

**Material and Methods**

**Patients**

This observational study was conducted with the approval of the institutional Science Commission and following the Code of Ethics of the World Medical Association (Declaration of Helsinki). All included patients were treated between January 2005 and January 2011 for colorectal liver metastases with RFA alone or in combination with resection, and they all underwent at least one PET (or PET-CT) and ceCT in the first year after treatment. Patients who received their first PET scan beyond the initial 12-month period were excluded. All patients were included in our database and analyzed.

The decision to treat was based on pre-operative PET-CT and ceCT images and was made by a multidisciplinary liver tumor board consisting of an oncological surgeon, an interventional and a diagnostic radiologist, a medical oncologist, a hepatologist, a radiation oncologist, a pathologist and a nuclear medicine physician. RFA treatment was indicated when colorectal liver metastases were ineligible for surgical resection due to site, size or location of the tumor or because a patient’s impaired general condition prevented major surgery.

Primary RFA treatment of metastases was performed during a laparotomy. The definite decision to perform RFA was based on intra-operative ultrasound. Recurrent hepatic tumors after previous local treatment were treated percutaneously with CT-guidance, when possible. We defined three separate groups of patients: patients primarily treated with RFA, a group that developed isolated new intrahepatic lesions after first RFA treatment and a group of patients that developed a LSR.
PET-CT AFTER RFA OF COLORECTAL LIVER METASTASES

FDG-PET
A baseline FDG-PET was done within the six weeks before the intervention to exclude extrahepatic disease, in addition to a contrast enhanced (ce)CT. A follow-up scan was obtained for all patients included in the study, ideally within 3-6 months of treatment, but within a maximum of twelve months. All patients were instructed to fast for at least 6 hours prior to FDG injection. The FDG dose and the acquisition time of the PET study were calculated based on the patient’s weight and height. Until January 2007, FDG-PET acquisition was performed using a stand-alone PET scanner (ECAT EXACT HR+, Siemens, Germany), and PET images were visually correlated to the ceCT, made before the PET scan. From January 2007, scanning was performed using an integrated PET-CT scanner (Philips Gemini TOF, Eindhoven, The Netherlands). A low dose CT was made to allow for attenuation correction and anatomical localization of areas with increased FDG uptake. The scan trajectory covered mid-thigh to skull vertex, taking 2-5 minutes per bed position. The outcome of the PET-CT was correlated to follow-up data or to histopathological results when available.

Data analysis
All PET and CT images were independently reviewed by both an experienced nuclear medicine physician (> 8 yr, EFIC) and radiologist (> 6 yr, MRM), using consensus analysis for any discrepancies.

A PET scan was considered positive for local site recurrence in cases showing an area of focally increased FDG uptake that was incompatible with normal post-treatment inflammation and located within the vicinity of the outer boundary of the RFA treated lesion (as seen on the ceCT scan) (figure 1). As the resolution of FDG-PET is known to be approximately 7 mm, new small, hypodense lesions on ceCT but negative on PET were considered as positive for a LSR. Minimal, rim-shaped FDG uptake in the periphery of the entire RFA-treated lesion was considered to be a physiological inflammatory reaction following RFA and this diagnosis was confirmed if no focally-increased uptake was visible on follow-up scans (figure 2). Evaluation of local hepatic recurrence could not be histologically confirmed as standard.

Statistical analyses
Clinicopathologic variables, post-operative imaging, recurrence patterns and repeated treatments were analyzed. Continuous variables were compared using Student’s t-test and categorical variables were compared by cross table analysis using the Fisher exact test and Chi² test of and linear-to-linear association. A significance level of 0.05 was used. A ROC-curve with an area under the curve (AUC) was used to demonstrate association between lesion size and LSR. Follow-up was calculated from time of primary RFA treatment until
death or last follow-up. All calculations were performed using SPSS version 20 (SPSS Inc., Chicago, IL, USA).

Figure 1 Local site recurrence on A: ceCT, B: PET, C: PET-CT. It is seen as a hypodense lesion (A) and focal FDG uptake at the border of the ablation zone after 4 months (B, C).
Results

Between January 2005 and January 2011, 79 consecutive patients with 246 lesions underwent RFA therapy or RFA combined with resection, and were screened within one year after treatment using at least one PET. A total of 179 lesions were ablated and 67 lesions were resected. The majority of the patients had 1-3 lesions treated with RFA (68), but this could increase up to 9 lesions. Baseline characteristics are summarized in table 1. Twelve patients were referred to a medical oncologist following local RFA treatment, and received chemotherapy. Median follow-up was 32.4 months (range 5-85). Twenty-one patients were treated with RFA for colorectal liver metastases in that period, but did not undergo PET-CT within the first year (n = 1) or only underwent ceCT (n=20) and were not included in the study. Three patients in this group developed a local site recurrence (14%).

Figure 2 Rim-shaped inflammatory FDG uptake around a RFA treated lesion after 4 months on A: PET, B: PET-CT and C: ceCT. After 7 months this disappeared without additional treatment on follow-up scan after 7 months D: PET, E: PET-CT and F: ceCT.
### Table 1. General characteristics associated with local site recurrences (LSR)

<table>
<thead>
<tr>
<th></th>
<th>LSR +</th>
<th>LSR -</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex ratio (M/F)</td>
<td>1.6</td>
<td>2.3</td>
<td>0.316</td>
</tr>
<tr>
<td>Mean age, yr (SD)</td>
<td>63.9 (8.3)</td>
<td>61.7 (11.5)</td>
<td>0.322</td>
</tr>
<tr>
<td>Primary site</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colon</td>
<td>17</td>
<td>31</td>
<td>0.475</td>
</tr>
<tr>
<td>Rectum</td>
<td>12</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>Number of lesions (mean, SD)</td>
<td>2.79 (2)</td>
<td>2.56 (1.7)</td>
<td>0.585</td>
</tr>
<tr>
<td>Extrahepatic disease at time of RFA</td>
<td></td>
<td></td>
<td>1.000</td>
</tr>
<tr>
<td>Yes</td>
<td>3</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>27</td>
<td>43</td>
<td></td>
</tr>
<tr>
<td>Chemotherapy after RFA</td>
<td></td>
<td></td>
<td>0.064</td>
</tr>
<tr>
<td>Yes</td>
<td>2</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>28</td>
<td>35</td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>0</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Lesion size</td>
<td></td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>1cm</td>
<td>1</td>
<td>46</td>
<td></td>
</tr>
<tr>
<td>2cm</td>
<td>2</td>
<td>46</td>
<td></td>
</tr>
<tr>
<td>3cm</td>
<td>14</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>4 cm</td>
<td>7</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>≥5 cm</td>
<td>9</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>0</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

**PET-CT after primary RFA treatment**

All patients underwent pre-operative staging with PET and CT or PET-CT, and all underwent at least one PET within one year of RFA-treatment. A total of 170 scans were carried out during follow-up of primary RFA treatment of colorectal liver metastases. In 57 patients, the first scan was made within 6 months (72%), according to protocol, and in 22 (28%) between 6-12 months following treatment. No adverse events were reported.

Thirty of the 79 patients (38%) developed LSR, following the primary treatment of 33/179 (18%) lesions. This percentage did not differ significantly from the patients that did not undergo PET-CT (p = 0.069). Local site recurrences were detected on the first post-operative scan in 26 patients, on the second in 2 patients and on the third scan in the last 2 patients. All LSR were visible on PET. In 23 patients, the local site recurrence was diagnosed on both PET and CT, in 3 patients the local site recurrence was not seen on CT and in 4 patients PET and CT images were reviewed simultaneously. Both reviewers agreed independently in all cases.
Of the 30 patients who developed a LSR, 17/30 showed lesions that became visible within 6 months. In 10 of the remaining 13 patients, the first scan was not made within 6 months. In 1 patient, the initial scan showed rim-like uptake and only later showed focal uptake, in 1 patient the local site recurrence became visible on the second PET at 8 months and 1 patient showed a local site recurrence only on the third PET at 15 months, without any FDG enhancement on earlier scans. In 27 of the 30 patients (90%) a local site recurrence became apparent within 9 months after treatment and 29/30 (97%) became visible within 1 year. The median interval between ablation and the visibility of a local site recurrence was 6.1 months (range 2-15). In 19/30 patients (63%) the local site recurrence was amenable for renewed treatment.

Of the 4 patients in whom it was unclear whether the enhanced FDG uptake around the ablated area was physiological or due to recurrent disease, one scan showed clear focal uptake in the rim of a treated liver lesion on a consecutive scan, confirming a local site recurrence. FDG uptake normalized in one patient within 6 months, and two patients were treated for a local site recurrence despite an unclear diagnosis (no histology available). One of these patients suffered from a liver abscess as a complication after RFA, thus explaining the increased rim-shaped uptake. The other patient remained tumor-free following re-treatment (follow-up of 9 months) and one developed extrahepatic disease and was referred for chemotherapy.

Factors that may be associated with development of local recurrence in our patient group are summarized in table 1. Size is correlated with the development of local site recurrence with an AUC of 0.793 (figure 3), lesions < 1cm (2%) and < 2 cm (4%) rarely develop this type of recurrent disease.

**Treatment of new, recurrent intrahepatic disease**
Following initial RFA of colorectal liver metastases, 8/79 patients (10%) developed 20 isolated, new intrahepatic lesions. Seven patients were candidates for repeated treatment: 1 patient underwent resection, 2 patients underwent RFA in combination with resection, 2 patients received RFA during laparotomy and 2 patients underwent percutaneous RFA. After repeated treatment, 6 patients underwent a total of 13 PET-CT scans, all first scans within 6 months. One patient developed a local site recurrence after 4 months and this was repeatedly treated.

**Treatment of local site recurrences**
Of the patients that developed a LSR, 20/31 (65%) (30 after primary RFA and 1 after treatment of a recurrent new intrahepatic lesion) were eligible for repeated local treatment,
and follow-up in 18 (61%) involved the use of PET. The first scan after repeated treatment was conducted within six months in 16/18 patients (89%), and between 6-12 months in 2/18 patients (11%). In 3/18 patients, increased FDG uptake was seen in the rim of the lesion on the first scan, after three months. One patient developed true focal uptake suggestive of a local site recurrence after 7 months, and in the other two patients, the increased FDG uptake disappeared without treatment on follow-up scans within 5 months after the first scan. Nine patients had developed a local site recurrence by the first scan, after a median of 4 months, and two patients had developed a local site recurrence by the second scan, after 7 and 13 months.

Figure 3 ROC curve: Association between lesion size and local site recurrence (AUC 0.793)

Discussion

The majority of the PET-CT scans described in this study were obtained within the first six months after RFA. Over 95% of all local site recurrences became apparent within one year of RFA treatment, and only one patient was diagnosed on the third scan after fifteen months. No local site recurrence was detected during follow-up after 15 months. Local site
recurrence are rare in treated lesions <2 cm. Our results show that an initial negative PET-CT does not rule out a local site recurrence and a second or even third PET may be necessary, as demonstrated by six of our patients. Rim-shaped uptake in the first 4-6 months after ablation is not an indicator for outcome after RFA; follow-up scans may show either a local site recurrence or normalized FDG distribution. Our study shows a relatively high rate of local site recurrence. This result was biased by patient selection; some patients only received a FDG-PET scan after a local site recurrence was suspected following diagnostic CT. If no indications for a local site recurrence were present on ceCT, a patient never underwent a PET-CT. Local site recurrence rates between the two groups didn’t differ significantly.

Timing of PET imaging
Early diagnosis of local recurrence and small volume metastases are the primary goals of early and intense surveillance strategies. Consequently, surveillance should enhance the proportion of treatable cases of recurrent disease and lead to increased survival (although the optimal timing of re-treatment of liver disease has yet to be determined). So far, consensus is lacking on both follow-up imaging after resection of the primary colorectal carcinoma and follow-up imaging after local treatment of liver metastases (20). Numerous studies have attempted to define an optimal algorithm but none have succeeded (21-23), and the frequency, duration and benefit of surveillance have not been formally tested (24). In a recent systematic review by Jones et al. (23) follow-up after resection of hepatic metastases was assessed, and besides confirming the weakness of the evidence, the authors were not able to identify a significant survival benefit attributable to intensive follow-up (25). To the best of our knowledge no prospective studies comparing follow-up schemes after RFA have yet been published.

Renewed treatment of recurrent disease following previous local treatment potentially enables to reset the oncological clock. This provides a solid rationale for intensive follow-up after treatment, with the aim of detecting recurrent disease in an early stage (despite the unsatisfactory survival benefits of regular follow-up after resection of colorectal liver metastases). These factors have led to increased interest in post-ablation staging. PET-CT has proven to outperform ceCT in early detection of local site recurrences (9;11).

Timing of the PET-CT after RFA is essential for adequate image interpretation and our results show that imaging before 4-5 months will be challenging, as a rim shaped uptake may still be present. In addition, the spatial resolution of FDG-PET implies that lesions smaller than approximately 7 mm may produce a false negative result due to partial volume effects. Results of Liu et al. suggest that PET-CT imaging within 24 hours after RFA provide a good indication for development of a local site recurrence in a small number of patients (12) (26).
Further evaluation is needed if smaller residual tumor can be objectivised that soon after treatment.

The majority of patients receive chemotherapy either before or after RFA treatment. It has been suggested that chemotherapy within a month before PET imaging can decrease the sensitivity of PET for detecting tumors, through a lowering of the FDG uptake. This could make diagnosing a local site recurrence more challenging (19;27). Our data do not reinforce this hypothesis, since 12 patients received chemotherapy after RFA treatment and all local site recurrence were diagnosed within 1 year.

**PET image interpretation**

Pre-operative PET-CT is utilized due to its ability to detect extrahepatic disease, while PET-CT after ablation is primarily used to determine local progressive disease at the ablated site.

A post-RFA lesion is difficult to distinguish from an local site recurrence on CT, and diagnostic criteria are still lacking. Following RFA, a post-treatment CT shows a hypodense area that could mask viable tumor cells as they cannot be distinguished from necrotic areas. This post-treatment effect makes it virtually impossible to diagnose a local site recurrence on a single scan and a definitive diagnosis is often based on lesion growth on a subsequent follow-up scan. This may lead to a delay in the decision to retreat.

On MRI, a post-ablation area is characterized by a rim surrounding the ablated area, with a low signal intensity on T1 and a high signal intensity on T2. This rim is usually regular and thin. When residual tumor is still present, in some but not all cases, the rim appears thicker and more irregular. These subtleties mean that extensive experience with post-RFA findings is crucial for accurate interpretation. The results of comparisons of the sensitivity of MRI and PET-CT in detecting local site recurrence are inconsistent; the results of PET-CT may be superior or equivalent to the results of MRI (9;13;28).

No internationally accepted guidelines are currently available for the diagnosis of a local site recurrence on PET-CT and a whole variety of qualitative and semi-quantitative criteria have been used (9;10;12;17-19). A rim-like FDG-enhanced aspect is sometimes present following RFA, but our results show that about 50% of this post-treatment effect will disappear spontaneously on follow-up scans without any additional treatment within 5-6 months. For the patients that develop a true LSR, however, differentiation between this post-ablation effect and a local site recurrence is difficult. While homogenous enhancement of FDG is likely to be a post-treatment effect and focal uptake more likely to be viable tumor, the difference is not always clear and extensive experience is essential. Future studies, in which histology is obtained from all PET-CT suspected sites of recurrent disease, should provide more information in this respect. Some studies have suggested that a local site recurrence...
Our study has shown that almost all LSR are detectable within one year. Increased FDG uptake in PET may be related to a local site recurrence. Until the outcomes of more detailed studies become available, our present results indicate that some local site recurrences will become visible on the second or even third scan, without a previous increase in FDG uptake.

Semi-quantification of the results of FDG-PET, using the standard uptake value (SUV), has been used to differentiate between benign and malignant hepatic lesions, and to diagnose a local site recurrence (9). However, SUV can vary considerably and it is often unclear which SUV measurement has been used (SUV mean, SUV max, SUVlbm, tec.). Because the values that correspond to a definite local site recurrence and to physiologic inflammation have not yet been established, the upper limit of 3.5 used in certain studies is somewhat dubious. SUV cannot reliably quantify uptake at the ablation site because most recurrences are believed to be in the sub-centimetre range; underestimation is an evident risk due to the partial volume effect.

An additional limitation is that SUV is highly dependent on the time between administration of FDG and the start of acquisition. Therefore, the consistency of SUV measurements depends on the precise application of a standardized interval schedule, recommended to be 60 minutes (29). This time interval is rarely mentioned in most literature on PET-CT and it is therefore impossible to compare different outcomes even within a single patient, let alone between different study groups. Historical study results can therefore not be applied directly in other studies (29). It is also impossible to reliably measure SUV on fused PET and CT images. It is clear that many issues related to semi quantitative FDG uptake measurements remain to be resolved. It is therefore too soon to rely on SUV alone.

There is limited information on the cost-effectiveness of FDG-PET in the diagnostic work-up for treatment of metachronous colorectal liver metastases. The available literature suggests a moderate benefit for PET and CT over CT alone (30). These studies did not include integrated PET-CT. To the best of our knowledge, only one study discussed the cost-effectiveness of the use of FDG-PET and PET-CT after RFA of hepatic malignancies (13). This study shows the PET-CT being more cost-effective than CT and MRI. However, long term cost effectiveness needs to be assessed by including results and costs of future treatment with clinically relevant endpoints.

It is well-established that PET-CT shows a high sensitivity and specificity in the detection of a LSR after RFA of colorectal liver metastases. Focal FDG uptake at the ablation zone is clinically considered prove in this regard. However, in literature there is little attention for timing and image interpretation of the PET-CT.

Our study has shown that almost all LSR are detectable within one year. Increased FDG
uptake around the rim of an ablated area can disappear spontaneously within 5 months and therefore is not pathognomonic for a LSR. We propose that a 3-6 monthly PET-CT should be performed within the first year after RFA, bearing in mind that rim-shaped FDG uptake up to 5 months can still be physiological. This regime may increase the detection of smaller recurrent lesions and therefore improve the efficacy of repeated (minimally invasive) local treatment. Lesions < 2cm rarely develop a LSR, so the yield of PET-CT in the follow-up of these lesions may be minimal. These suggestions only apply to lesions primarily treated with RFA.

Future studies on follow-up after RFA of colorectal liver metastases should include the use of new imaging modalities, such as PET-MRI. Future large prospective trials are necessary to establish a survival benefit of an intensive follow-up regime after ablative treatment.
PET-CT AFTER RFA OF COLORECTAL LIVER METASTASES

uptake around the rim of an ablated area can disappear spontaneously within 5 months and therefore is not pathognomonic for a LSR. We propose that a 3-6 monthly PET-CT should be performed within the first year after RFA, bearing in mind that rim-shaped FDG uptake up to 5 months can still be physiological. This regime may increase the detection of smaller recurrent lesions and therefore improve the efficacy of repeated (minimally invasive) local treatment. Lesions < 2cm rarely develop a LSR, so the yield of PET-CT in the follow-up of these lesions may be minimal. These suggestions only apply to lesions primarily treated with RFA.

Future studies on follow-up after RFA of colorectal liver metastases should include the use of new imaging modalities, such as PET-MRI. Future large prospective trials are necessary to establish a survival benefit of an intensive follow-up regime after ablative treatment.

Reference List


