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## Detection of residual tumor after radiofrequency ablation of liver metastasis with dual-modality PET/CT: initial results

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**Abstract** The aim of this study was to determine the accuracy of dual-modality positron emission tomography (PET)/computed tomography (CT) in the detection of residual tumor after radiofrequency ablation (RFA) of liver metastasis of colorectal cancer. Eleven patients with 16 hepatic metastases (mean size 2.9 cm) from colorectal cancer were enrolled in this study, and 19 RFA procedures and 32 PET/CT examinations were performed. The patients had PET/CT before and after RFA using [<sup>18</sup>F]-2-fluoro-2-deoxy-D-glucose. CT images alone were read by two radiologists, PET images alone were evaluated by two nuclear physicians. Fused images were read by one physician of each speciality in consensus. The accuracy for detection of residual tumor by the different imaging modalities following RFA was

assessed. Eleven patients with a mean age of 63 (range 55–71) years were evaluated. The mean follow-up period was 393 days. The overall procedure-based sensitivity for detection of residual tumor was 65% for PET and PET/CT and 44% for CT alone. The accuracies were 68% and 47%, respectively. Four patients had residual tumor after RFA, six patients total developed local recurrence. PET/CT therefore possibly proved superior to CT alone when assessing the liver for residual tumor after RFA.

**Keywords** Positron emission tomography/computed tomography · Radiofrequency ablation · Postinterventional surveillance · Metastases · Residual tumor

### Introduction

In patients with liver metastases from colorectal cancer surgery is the reference method; however, only a small number (10–15%) qualify for the surgical approach [1, 2]. The main limiting factors for resection of hepatic metastases are unfavorable distribution of tumor sites, impaired liver function, or other co-morbidities. Interventional therapy has been shown to provide a promising alternative in these patients [3–12]. While different procedures, such as laser-induced thermotherapy or chemoembolization are available, radiofrequency ablation (RFA) has emerged as the most commonly used and promising treatment option [12, 13]. Several studies have demonstrated good results for RFA for both a palliative and a curative approach [14]. How-

ever, local recurrence rates at the ablative site following RFA have been found to be as high as 47% [15]. Thus, close radiological follow-up is required for early detection of local tumor recurrence. Radiological imaging procedures based on tumor morphology alone have been hampered by problems to differentiate residual tumor from tumor necrosis and adjacent liver tissue. The overall sensitivity to detect residual tumor when assessed with ultrasound, computed tomography (CT) or magnetic resonance imaging (MRI) ranges between 44% and 89% [16–18]. However, early detection of residual tumor allows initiation of additional treatment with potential benefits for patient survival [8, 9]. Recently, Langenhoff et al. [14] reported very promising results when assessing patients after local ablative therapy with positron emission tomography

(PET) and [ $^{18}\text{F}$ ]-2-fluoro-2-deoxy-D-glucose (FDG) as a radioactive tracer. Additional studies showed results which were partly lower in terms of local tumor recurrence, but found similar results for FDG-PET as an adequate tool for follow-up of RFA interventions [19, 20].

Recently available combined PET/CT systems provide accurately fused functional and morphologic data sets in a single session. The potential advantage of PET/CT compared with PET alone is based on lesion detection and localization as demonstrated in initial evaluations [21]. The current analysis is aimed (1) to assess the accuracy of PET/CT imaging for detection of residual tumor following RFA, (2) to evaluate a potential benefit of dual-modality PET/CT images over PET alone and CT alone for the detection of residual tumor, and (3) to determine the value of PET/CT for planning and performing further interventional action.

## Materials and methods

### Patients

Thirteen patients with histologically proven colorectal cancer and liver metastases were enrolled, 11 male and two female with a mean age of 63 (range 55–71) years. Histopathological findings were available from biopsies or resection samples of prior surgery. Two patients with one RFA and one metastases each were excluded, because of a lack of PET/CT follow-up. All patients were not eligible for surgery for the following reasons: (1) patients with recurrence of liver metastases following hemihepatectomy, (2) patients who did not qualify for an operation because of cardiac conditions, (3) patients who did not qualify for an operation owing to poor liver conditions (insufficiency of gall secretion, metastases in unresectable localization due to vessel proximity). All enrolled patients had PET/CT imaging before and after the intervention.

The PET/CT examination prior to RFA was performed with a whole-body field of view for pre-interventional staging 1 day before RFA in every case. After 15 RFA procedures, PET/CT was carried out within 2 days and focused on the liver; after four interventions (altogether 19 RFA procedures) the patients were not able to attend the control scan owing to medical conditions, or refused survey at this time. Data analysis was performed retrospectively. Informed consent for PET/CT was available from all patients. The study was performed in full accordance with guidelines for retrospective analysis of the institutional review board of the university hospital.

### Radiofrequency ablation

RFA was performed percutaneously in all 11 patients. The patients were treated with either one of two radiofrequency

systems: an internally cooled electrode system (Radionics, Burlington, MA, USA), using a 480-kHz CC1 generator which automatically adjusts energy output on the basis of tissue impedance; alternatively a system with expandable electrodes (RITA Medical Systems, Mountain View, CA, USA) was used. The choice of system depended on the access path to the intrahepatic lesion and lesion size [22]. All procedures were performed under CT guidance with sterile conditions, local anaesthesia and an intravenous anaesthesia pump. Additionally heart rate, arterial oxygen saturation, blood pressure and ECG were monitored in every RFA session. Access to the lesion was chosen on the basis of the intrahepatic position of the tumor. In all cases it was either a transhepatic or an intercostal access. In most patients, the needle had to be repositioned after initial ablation to ensure complete tumor coverage [22, 23]. The mean RFA time for the internally cooled system was 21 min per needle position ( $\pm 6$  min) to ensure coverage and tumor necrosis. In RFA procedures using the expandable system the mean RFA time after achievement of the target temperature was 7 min ( $\pm 3$  min).

Directly after termination of the RFA session, contrast-enhanced CT (Somatom Sensation 16, 140 mA s, 120 kV, 5-mm slice thickness, 1.25 incremental reconstruction) focused on the ablative area was performed for surveillance of procedure success. In cases of nodular or irregular-shaped appearance of the lesions' margin with synchronous contrast enhancement, the intervention was considered incomplete. In that case, the patients were retreated immediately in the same session. The lesion size of all lesions was measured and a mean value of the extent of the lesions was calculated.

### PET/CT imaging

Dual-modality PET/CT was performed before and after RFA with a biograph system (Siemens Medical Solutions, Hoffman Estates, IL, USA). The system is composed of two components: a dual-slice CT scanner with a minimum gantry rotation time of 800 ms and a maximal scan time of 100 s and a full ring PET tomograph [24]. The PET system has an axial field of view of 15.5 cm per bed position and an in-plane spatial resolution of 4.6 mm. The system acquires the computed tomography first, followed by the positron emission tomography. After the examination CT and PET data sets can be viewed separately or in fused mode on a special computer workstation. Whole-body PET/CT was performed for all 11 patients prior to the intervention for tumor staging. Follow-up examinations after RFA were limited to cover the liver when patients were able to attend the postinterventional survey in proper time, i.e., within 2 days. The other patients were examined according to the whole-body protocol.

Whole-body CT covered a field of view from the skull to the upper thighs (130 mA s, 130 kV, 5-mm sections with a

2.4 incremental reconstruction, 8-mm table feed). During the whole-body CT examination, 140 ml of iodinated contrast agent (Xenetix 300, Guerbet, Sulzbach, Germany) was administered according to a standardized protocol and a delay of 50 s for the first 90 ml with a flow rate of 3 ml/s. After that, the last 50 ml was then administered with a flow of 1.5 ml/s. Intravenous contrast media were applied in every PET/CT examination. [25]. Additionally 1,500 ml of a negative oral contrast agent containing 0.2% of locust bean gum and 2.5% of mannitol dissolved in water was administered in all whole-body examinations for small bowel distension [26]. When PET/CT was focused on the liver area after the RFA, the same technical parameters were used, but with 100 ml of iodinated contrast agent with a delay of 60 s. PET images were acquired 60 min after administration of 350 MBq FDG with a limited breath-hold protocol, to reduce motion artifacts mainly in the diaphragm area [27]. PET images covered the same field of view as whole-body CT. Blood glucose levels were measured before administration of FDG to ensure a maximum range up to 130 mg/dl. The acquisition time of PET was adapted according to the weight of the patient, using 3 min per bed position for patients up to 65 kg, 4 min per bed position for patients up to 85 kg, and 5 min per bed position for patients over 85 kg. CT data were used for attenuation correction of the PET images. Scatter correction and iterative reconstruction was performed [28].

#### Image evaluation

CT images alone, PET images alone, and fused PET/CT data sets were assessed separately. CT images were read by two radiologists in consensus, while PET images were evaluated by two nuclear physicians in consensus. Both reader groups had the same clinical information about the patients and were unaware of the results from the other imaging modality. The radiologist who performed the RFA was not involved in image evaluation. Afterwards, two different readers (one radiologist, one nuclear physician) evaluated the fused PET/CT images in consensus. All images were assessed for regions of residual tumor by comparing the images before and after RFA for each imaging procedure. Irregular peripheral contrast enhancement and a multilobular shape at the ablative margin were considered as a criterion for residual tumor in CT [12]. Glucose uptake was considered to be malignant, if areas of focally increased glucose metabolism were detected adjacent to the RFA necrosis. A standardized uptake value (SUV) of more than 2.5 in extrahepatic lesions and of 3.5 in intrahepatic lesions, as well as a SUV above the surrounding tissue level on quantitative analysis supported the diagnosis [29–31]. Thus, PET and PET/CT data sets were evaluated both qualitatively and quantitatively for areas of increased glucose metabolism.

#### Data analysis

Each imaging technique was assessed separately. Concordance between CT, PET and PET/CT images was verified. All findings were compared with the available clinical data during follow-up and were classified into true positive for residual tumor, false positive, true negative, or false negative. Additionally the sensitivity and the accuracy were determined.

#### Follow-up and treatment efficacy

The standard of reference was based on the available clinical and radiological follow-up. The follow-up period included all clinical data, such as histopathology, radiological procedures (CT, PET/CT, MRI), as well as laboratory tests and physical examinations. Imaging procedures which included the liver served as the standard of reference in all patients as well as additional biopsy samples in two cases and additional elevated tumor markers in six patients. The mean follow-up time for all patients was 393 (range 205–720) days. In case of tumor recurrence during the follow-up period, CT-guided re-RFA was performed by the same physician to the area of residual tumor based on the imaging findings and the histopathology biopsy samples mentioned.

## Results

Thirteen patients underwent RFA for liver metastases of colorectal tumors. Eleven patients had PET/CT before and after the RFA procedure within the time interval mentioned. Thus, two patients only had CT and MRI for follow-up, leaving 11 patients for data analysis. Nineteen RFA sessions were performed with these 11 patients with 16 metastases including re-RFA. Fifteen PET/CT examinations were performed within 2 days after RFA for detection of residual tumor; the other four were done after a median time of 58 days for the nearest surveillance of success of the intervention. Altogether 32 PET/CT examinations were performed for follow-up including the 19 PET/CT examinations mentioned (excluding pre-RFA).

The mean general follow-up including all other available imaging modalities as well as clinical follow-up after RFA was 393 (range 205–720) days.

The mean lesion size was 2.9 cm (range 2.0–3.8). Four patients showed residual viable tumor at the ablative margin after RFA with a mean SUV of 8.7 (range 7.7–10.5), based on the criteria mentioned. According to the standard of reference, six patients showed local tumor recurrence in different liver localizations. The accuracy for detection of residual tumor was 68% for PET and PET/CT and 47% for CT. There were no false-positive findings within any of the three imaging procedures. The sensitivity of CT for

detection of residual tumor after RFA was 44%; 65% sensitivity was found for PET alone and PET/CT. The residual tumors which were found with PET/CT had a mean diameter of 0.8 cm (0.7–1.0 cm). After five RFA sessions (in four patients), a homogeneous, rim-like area of increased glucose metabolism at the ablative margin was noted on PET and PET/CT (all within 2 days) data sets. The mean SUV in these cases was 3.7 (range 3.5–4.8). Local recurrence occurred in all of these four patients after a mean time of 111 (range 85–133 days) days. However, on the basis of the rim-like tracer distribution at the ablative margin without an area of focally increased glucose metabolism, this was attributed to tissue regeneration in the periphery of the necrosis rather than residual tumor. In cases of tumor recurrence, this presented as an area of focally increased glucose metabolism rather than rim-like FDG uptake on further follow-up.

In four patient (five metastases), partly the same as with the rimlike area of elevated glucose metabolism mentioned, PET and PET/CT demonstrated residual local tumor in the area of the ablation site on further follow-up, while the corresponding CT alone was found to be negative. This diagnosis led to earlier reintervention in these patients on the basis of PET and PET/CT data as compared with CT alone with the potential benefit of extended disease-free survival in these patients.

## Discussion

PET/CT imaging possibly proved more accurate when evaluating the ablative zone for residual tumor than image analysis based on morphologic data alone. The advantages of fused PET/CT data sets over PET alone and CT alone are related to accurate localization of focally increased glucose metabolism in terms of therapeutic planning in an area of residual tumor, offering guidance of subsequent interventional procedures to these areas of viable tumor cells. PET/CT therefore may be expected to play a distinctive role in follow-up of patients undergoing RFA of liver lesions for the detection of residual tumor and local tumor recurrence.

Monitoring of therapy effectiveness is deemed to be a major issue in interventional liver therapy. CT and MRI are, although widely used, of limited sensitivity, specificity and accuracy when assessing the liver for residual tumor following RFA [14, 16, 17, 19, 32]. This limitation relates to their strictly morphologic character which can only partly be compensated by administration of contrast agents. The sensitivity and specificity of the CT component of PET/CT imaging demonstrated only moderate values in our study. The limitations were related mainly to difficulties when differentiating viable tumor tissue from adjacent necrosis or therapy-induced hyperperfusion in the periphery of the necrosis.

Several studies reported promising results when assessing follow-up surveillance and detection of residual tumor

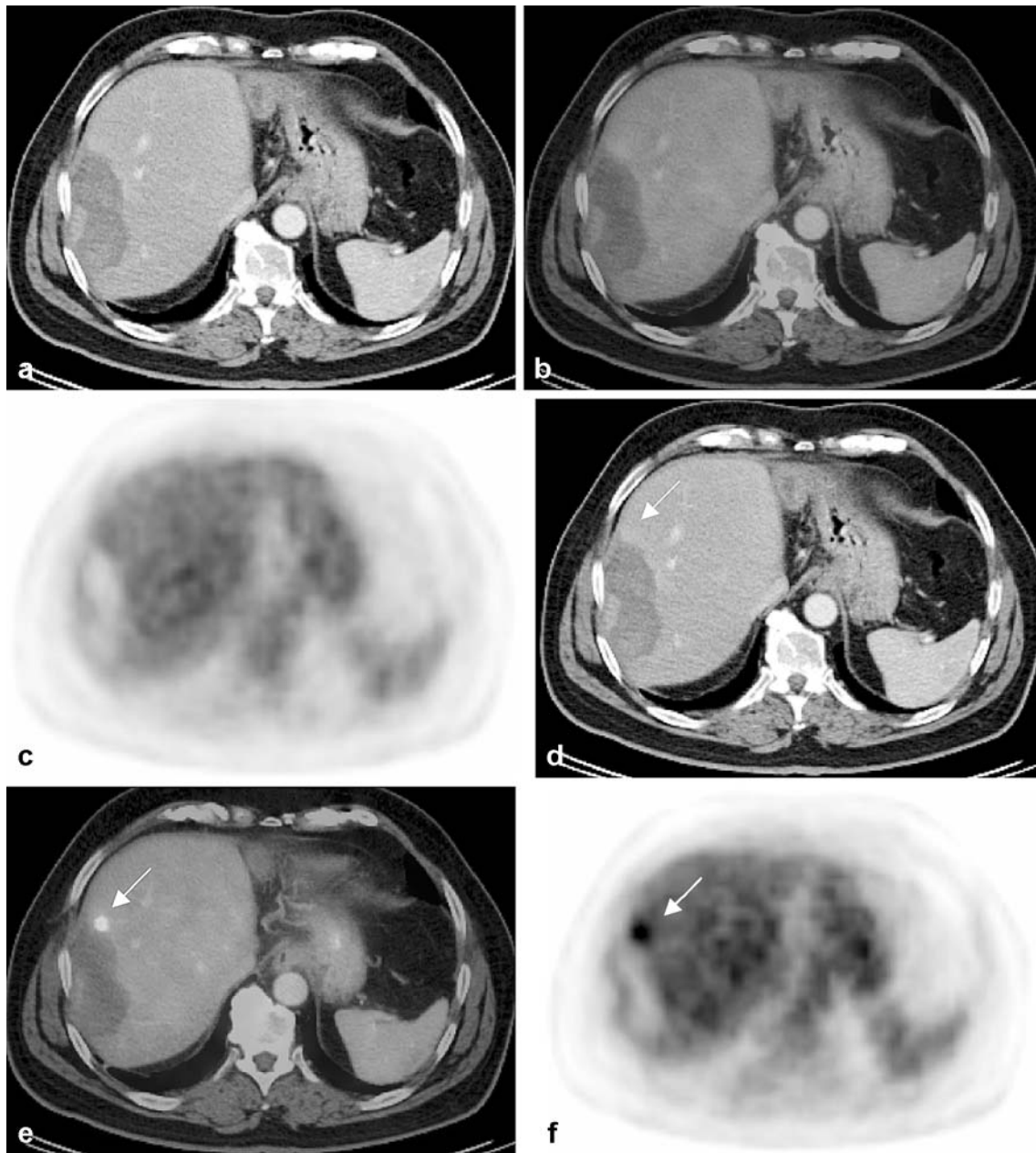
with PET imaging [14, 19, 20]. Langenhoff et al. found no local recurrence in 51 PET-negative liver lesions after ablative procedures (total number of lesions 96). The positive predictive value for the detection of local recurrence in lesions with a positive FDG-PET after treatment was 80%; the negative predictive value was 100%. In two of six patients treated with RFA FDG-PET remained positive after RFA. Local tumor recurrence was detected within 6 months of follow-up. PET imaging was performed within 3 weeks of RFA in their study. Anderson et al. detected local tumor recurrence at the ablation site in eight of 11 FDG-PET scans. The PET control scans in this study were performed later (9±5 months). RFA was performed percutaneously or intra-operatively. Thus, functional imaging was not performed directly after thermal ablation in two studies.

Donckier et al. showed in a well-defined follow-up interval an advantage of FDG-PET over CT in the detection of residual tumor after RFA. The findings concerning the residual tumor after RFA were in good concordance with our results. Although several sites require different follow-up intervals [9], follow-up scans directly after the RFA would be ideal (1) to shorten the period to a possible reintervention and (2) to generate a logistical advantage in terms of hospital stay for the patient.

Comparing the results from our analysis with data from the available literature, we find some discrepancies. While Langenhoff et al. found only very few cases of residual tumor and local tumor recurrence, we reported a sensitivity of 65% and an accuracy of 68% for the detection of residual tumor with PET/CT. Six patients developed local tumor recurrence despite negative initial PET/CT findings (Fig. 1). Some of these discrepancies may be attributed to differences in the referred patient population, the population size and the fact that RFA and cryoablation were used in the previous study.

However, the previously reported PET imaging results have raised high expectations. Considering a spatial resolution of approximately 4–6 mm with currently available PET systems as well as usage of FDG as an unspecific radioactive tracer, it must be assumed that small areas of residual tumor will not be detected by FDG-PET. In addition, the liver represents an organ which moves because of respiratory motion. PET data are acquired during shallow breathing and PET has been shown to miss small areas of tumor owing to respiratory motion with smearing of FDG uptake [27]. Furthermore, it has been reported that the sensitivity of FDG-PET may decrease dramatically in lesions of less than 1 cm (as low as 21%) [33].

Four patients (five RFA procedures) in our study showed a rimlike area of increased glucose metabolism surrounding the ablative necrosis (Fig. 2d–f). It is important to state, that these patients had local tumor recurrence, but only in a focal manner (Fig. 2g–i). Thus, this homogeneous rim-like area of elevated glucose utilization cannot be attributed to residual tumor. However, detection of residual tumor in this area remains challenging, as increased glucose metabolism

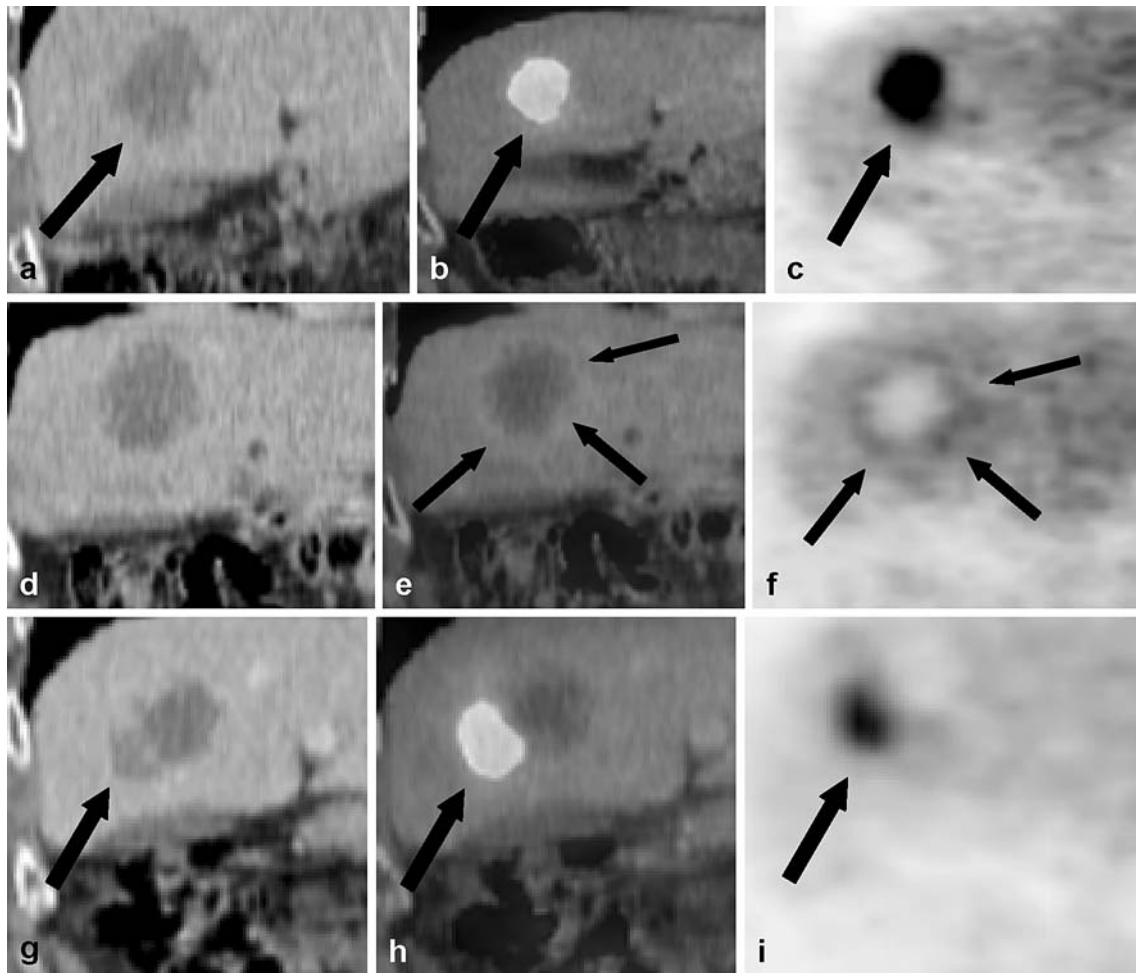


**Fig. 1** **a** Axial contrast-enhanced computed tomography (CT) image 90 days after a radiofrequency ablation (RFA) procedure in the right liver lobe: no evidence of local tumor recurrence. **b** Corresponding axial positron emission tomography PET/CT image (red scale): no evidence of local tumor recurrence. **c** Corresponding axial PET image (red scale): no evidence of local tumor recurrence. **d** Axial contrast-enhanced CT image 230 days after the RFA procedure in the right

liver lobe: no evidence of local tumor recurrence (*arrow*). **e** Corresponding PET/CT image (red scale) showed local tumor recurrence with increased glucose metabolism at the ventral pole of the ablative area (*arrow*). **f** Corresponding PET image (inverted gray scale) showing local tumor recurrence with increased glucose metabolism at the ventral pole of the ablative area (*arrow*) as well

due to tissue regeneration may superimpose on small areas of residual tumor, resulting in false-negative PET and PET/CT results. A similar phenomenon can frequently be found on contrast-enhanced morphologic data sets after RFA, representing heat-induced hyperperfusion and tissue regeneration. [9, 16, 17, 19, 32]. To date, there is only limited information on this rimlike area of increased glucose me-

tabolism on FDG-PET and PET/CT [34]. However, this rim-like tracer distribution was found in PET/CT examinations performed later within this 2-day time range rather than on the first day after RFA. Therefore, it might be necessary to perform follow-up PET/CT directly after RFA or at least within 24 h. Thus, tissue regeneration might not produce an increased rimlike glucose metabolism during



**Fig. 2** **a** Coronal contrast-enhanced CT image with one metastasis of colorectal cancer in the right liver lobe (*arrow*). **b** Corresponding coronal PET/CT (red scale) image with one metastases of colorectal cancer with increased glucose metabolism (*arrow*). **c** Corresponding PET image (inverted gray scale) with one metastasis of colorectal cancer with increased glucose metabolism (*arrow*). **d** Coronal contrast-enhanced CT image 2 days after RFA covering the same area showing the hypodense ablative area. **e** Corresponding PET/CT image (red scale) showing a rim-like increased glucose metabolism owing to tissue regeneration after RFA (*arrows*). **f** Corresponding

PET image (inverted gray scale) showing a rim-like increased glucose metabolism owing to tissue regeneration after RFA (*arrows*). **g** Coronal contrast-enhanced CT image showing 133 days after RFA local tumor recurrence at the right laterocaudal rim of the ablative area (*arrow*). **h** Corresponding PET/CT image (red scale) showing 133 days after RFA local tumor recurrence with increased glucose metabolism at the right laterocaudal rim of the ablative area (*arrow*). **i** Corresponding PET image (inverted gray scale) showing 133 days after RFA local tumor recurrence with increased glucose metabolism at the right laterocaudal rim of the ablative area (*arrow*)

this time. Further studies addressing this issue are required to define the time frame in which such areas of tissue regeneration must be dealt with.

PET/CT has already shown an outstanding ability of more exact FDG-avid tumor detection than PET and morphological imaging alone [35, 36]. While this ability can be considered as an advanced fundament in the determination and localization of residual tumor, further therapeutic action can be taken to ensure treatment of the remaining viable tumor cells. This is frequently being done by additional RFA, where exact anatomical localization of the residual mass is needed [3–9, 37].

When introducing the electrode into the tumor, accurate anatomical localization of the area of increased glucose

metabolism was found to help the positioning of the ablative device in all cases. While these numbers of patients are too small to draw a definite conclusion as to the value of dual-modality PET/CT for guidance of reinterventions, they, however, may point to an advantage of PET/CT over PET or CT alone, even if the results presented for the detection of residual tumor by PET are the same as with PET/CT. However, since PET alone is significantly hampered by only limited anatomical information, it cannot be used as a guiding tool for interventional procedures.

The study has several limitations. The patient population is quiet small, so a definitive conclusion about the rim-like elevated glucose metabolism on PET and PET/CT and the impact on the detection of residual tumor needs larger

patient cohorts. Furthermore, the CT portion of the PET/CT examination represents an adapted, combined imaging protocol, which may deviate from CT examinations of different sites where RFA is performed. Therefore, there might still be room for improvement of the CT and corresponding contrast injection protocol, especially concerning small, low-contrast lesions [38]. Since these are initial results, the next patient studies addressing this issue will have to be investigated in a prospective manner.

This initial study possibly points out an advantage of FDG-PET and FDG-PET/CT over CT alone when assessing

the liver for residual tumor after RFA. However, FDG-PET and PET/CT are maybe not as accurate and sensitive as suggested by the available data. Larger patient cohorts are required to define their accuracy in the assessment of ablation areas after RFA and to characterize the ideal time to perform PET or PET/CT after thermoablative procedures.

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