TITLE: [^{18}F]FDG PET/CT in local ablative therapies: a systematic review

RUNNING TITLE: ^{18}F-FDG PET/CT in local ablative therapies

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ABSTRACT:

Driven by the continuous improvement of the accuracy of cross-sectional imaging, image-guided minimally invasive local ablative therapies have received incremental interest over the past years. This study systematically reviews 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 current status, identify general patterns across studies and provide recommendations for future studies and clinical practice. The QUADAS criteria are used to assess the quality of reported diagnostic accuracy of the retrieved studies.

Data in literature suggest that [^{18}F]FDG PET/CT is a highly accurate tool to assess 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 on the localization of disease, allowing (very) early imaging in solid organs as the liver, while post-treatment inflammation is a challenge in the first 3 months after therapy in the lung parenchyma.

KEY WORDS:

local ablative therapy, [^{18}F]FDG PET/CT, response monitoring, radiofrequency ablation, radioembolisation

INTRODUCTION:

Driven by the continuous improvement of the accuracy of cross-sectional imaging for oncological applications, image-guided minimally invasive local ablative therapies have received incremental interest for several reasons. More sensitive screening techniques resulted in the detection of smaller tumors in earlier stages of disease [1, 2], which are more amendable to local therapy. This is of special importance in the aging population of cancer patients, in which 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 favours local ablative therapy of selected lesions in order 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 an 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 (MWA), high-intensity focused ultrasound (HIFU) and cryo-ablation), electric energy-based cell death (irreversible electroporation (IRE), radiation energy-based cell death (e.g. glass or resin microspheres filled with beta-emitting radioisotopes [^{90}Y] or [^{166}Ho]) or chemical induced cell-death (trans-arterial chemoembolisation (TACE) or percutaneous ethanol injection therapy (PEIT)). Recent well-designed randomized controlled trials demonstrate that local ablative therapy comes 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 addition of ^{90}Y-radioembolisation 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; e.g. RFA for liver and lung metastases, [^{90}Y]-radioembolisation for primary hepatocellular carcinoma and colorectal liver metastases or 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 the tumor viability are mandatory.

Anatomical imaging techniques, such as contrast-enhanced computed tomography (ceCT) or dynamic contrast enhanced (DCE) or diffusion-weighted (DW) magnetic resonance imaging (MRI), respectively assess changes in tumor size, perfusion and permeability and tissue composition. Most guideline supported response criteria are based on changes of 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 to increase 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 similar extent. Consequently, local ablative therapy may in most cases induce necrosis, cystic degeneration, haemorrhagic and/or oedematous changes in the tissue [17-20], which might initially result in enlargement of the lesion, while 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, anatomical criteria have consistently shown to underestimate the anti-tumor effect of local ablative therapies. In addition, changes in lesion enhancement, density or diffusion characteristics might in most cases not reflect actual pathological tumor responses especially at early stages [23-25].

On the other hand, metabolic changes at the cellular level have demonstrated to precede changes in tumor size or tissue parameter; e.g. 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 days, it 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 to monitor the effect of local ablative therapies are increasing, but

vary largely in study design, number of patients, time point of imaging, criteria for response and choice of comparator modality.

This study systematically reviews the currently available literature on [^{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 current status, identify general patterns across studies and provide recommendations for future studies and clinical practice.

METHODS:

Search strategy

To identify all relevant publications, we performed systematic searches in PubMed and in 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 Cochrany Library search yielded no relevant additional results. Approval of the institutional review board for this literature review was waived.

Selection process

Two reviewers (EA and LH) independently screened all potentially relevant abstracts for eligibility obtained from the database search. Studies were not restricted to anatomical sites or tumor type and were included if:

a. the study investigated the performance of [^{18}F]FDG PET/CT or [^{18}F]FDG PET for treatment monitoring
b. the study involved human subjects
c. the study involved local ablative therapies, including;
    (i) radiofrequency ablation
    (ii) cryoablation
    (iii) microwave ablation
    (iv) high intensity focussed ultrasound
    (v) [^{90}Y]-radioembolisation, [^{166}Ho]-radioembolisation

(vi) chemoembolisation

d. the study reports clinical outcome

e. English version of the manuscript was available

Full-text articles of these selected records were obtained and excluded from this study when: investigational drugs or techniques are exploited, when publication type did not include original data (e.g. reviews, editorials, letters, legal cases, interviews, case reports, comments and follow-up reports from previous cohorts), when <15 evaluable patients with [^{18}F]FDG PET/CT were reported and when there was a wide spread in imaging time-points.

Differences in judgment were resolved by consensus procedure.

All articles were scored using the QUADAS system (supplementary table 5).

RESULTS:

Search results

The literature search performed in September 2017 generated a total of 727 records, of which 559 studies were excluded based on screening of the abstract. Main reasons for exclusion were a) PET imaging was used for dosimetry, b) study did not involve local ablative therapy or c) [^{18}F]FDG was not used for monitoring but for diagnostic purposes, or a combination of these criteria. The full text of the remaining 168 records was screened for eligibility, of which 52 studies were included in this review. Main reasons for exclusion were a) no full text available, b) no data on clinical outcome was reported, c) study involved investigational drug or procedure, d) publication type, e) study involved <15 patients or f) varying time points of imaging.

Five studies report [^{18}F]FDG PET/CT results to evaluate technical treatment success; 47 studies report results of early time points to evaluate treatment efficacy. In the supplementary data, tables 1-4 summarize the data from the selected reports (table 1 and 2 immediate time points and table 3 and 4 later time points). Most studies involve only limited numbers of patients and are retrospective in design. Moreover, imaging time points and imaging evaluation criteria are highly variable across studies. Table 5 summarizes the studies according to the QUADAS criteria, studies with no or one minor comment (indicated in orange) are discussed in the text, studies with two or more minor comments or one major comment are not discussed but their results are included in Table 1-4.

Immediate [^{18}F]FDG PET/CT imaging to evaluate technical treatment success

Similar to surgical resection with curative intent, cornerstone of successful local ablative therapy is to achieve complete tumor destruction with oncological clear margins, particularly in RFA, microwave and cryoablation. Anatomical imaging modalities have so far not been adequate to assess of vital tumor residue [18-20]; intra-operative 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 in two doses, the first dose just prior to procedure for treatment planning and a second dose to identify residual viable tumor before inflammatory changes occur (e.g. split-dose protocol). Such 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 <24 hours after treatment with thermal ablation (4x RFA, and 1x RFA/MWA) in liver metastases (tables 1 and 2). All five reported visual interpretation of the [^{18}F]FDG PET/CT and three studies also reported quantitative analyses (SUV_{max} or tissue radioactivity concentration (TRG)). All found a good accuracy of [^{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 one (out of 23) patient, which was confirmed to be viable tumor tissue, and this patient received additional treatment. In 2/22 patients with a negative [^{18}F]FDG PET/CT follow-up, imaging detected local recurrence [28]. The lowest reported sensitivity of immediate [^{18}F]FDG PET/CT was in the study of Vandenbroucke et al.: 63% (combining nodular and rim like uptake to detect viable tumor localisation) [30]. Two other studies reported an accuracy above 90% and superiority compared to ceCT [31, 32]. One study found no significant difference compared to the sensitivity and specificity of MRI [31].

Response monitoring to evaluate treatment efficacy

Correct assessment of responses to local ablative therapy at early time points after the procedure is vital for early response adapted treatment strategies, especially if local ablative therapy is used in addition to other treatment modalities [33].

However, the necrotic, cystic and haemorrhagic changes induced by local ablative therapies evoke inflammatory responses in the lesion and surrounding healthy tissue in the days to

weeks following 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]. Whereas ceCT and DWI-MRI techniques are hindered by abnormal enhanced patterns, [^{18}F]FDG PET/CT may also be confounded by these inflammatory changes during the post-ablation healing process.

Response monitoring up to several months after intervention might be influenced by inflammation, however [^{18}F]FDG PET/CT still seems more sensitive for treatment effect and detection of local recurrence.

RFA and cryoablation in liver metastases

Four studies (total 111 patients) evaluated [^{18}F]FDG PET/CT <1 month after RFA/cryoablation in liver metastases (tables 3 and 4) [35-38]. All four studies showed a higher sensitivity of [^{18}F]FDG PET/CT to detected local recurrence compared to CT and/or MRI. False positive findings can be due to inflammation or abscess formation, though reported specificity was high: 80%-100%. The study of Joosten et al. showed that [^{18}F]FDG PET/CT within 3 weeks of treatment, correctly predicted 6/7 recurrences [35].

RFA and cryoablation for lung lesions

In settings of RFA for lung metastases or primary lung cancer, the clinical utility might be different than for liver lesions (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 3/7 patients, particularly with nodular pattern, and 4/7 were false positive [39]. Higuchi et al. [40] and Higaki et al. [41] report in similar sized prospective series that imaging <1 month after RFA did not correlate with local tumor progression at later time points. The study by Yoo et al. in 26 patients with irresectable primary non-small cell lung cancer who underwent RFA [42], [^{18}F]FDG PET/CT performed within 4 days was not predictive of 1-year event. But [^{18}F]FDG PET/CT at 6 months corresponded better with outcome 1 year after intervention [42]. Multiple studies confirm the

higher diagnostic accuracy for [^{18}F]FDG PET/CT from 3 months after intervention, as compared to CT [43-45]. A continuous decrease in SUV_{max} from intervention to 3 months and 6 months was identified as physiological pattern, with high negative predictive value. An increase in [^{18}F]FDG uptake or absolute [^{18}F]FDG uptake of SUV_{max} >2.5 has been suggested to predict recurrence [45].

Regional ablative therapy in hepatocellular carcinoma

Five studies (in total 142 patients) report on the role of [^{18}F]FDG PET/CT in regional ablative therapy for hepatocellular carcinoma, four other studies did not meet the QUADAS criteria. In a retrospective study on 33 patients with hepatocellular carcinoma treated with ^{90}Y-microspheres, Habet et al. found that patients with a response on [^{18}F]FDG PET/CT had a significantly better overall survival than metabolic non-responders, 10 months versus 5 months [46]. Similar observations stem from the retrospective analyses of 27 patients by Ma et al.; [^{18}F]FDG PET/CT 4-6 weeks after treatment decrease of 90% in tumor SUV_{max} as compared to baseline, resulted in a sensitivity of 100% and specificity of 92,5% [47]. Responders according to this criterion had longer time-to-progression, 18.3 months versus 7.1 months. ^{18}F-FDG-PET/CT responses correlate to 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 ceCT [48]. Li et al. showed in 22 patients that a negative [^{18}F]FDG PET/CT after TACE with or w/o bevacizumab correlated with overall survival, whereas imaging with [^{11}C]acetate PET performed slightly worse [49].

Radioembolisation in liver metastases

The role of [^{18}F]FDG PET/CT after radioembolisation for liver metastases is mostly studied: 3 studies report results of imaging <1 month after treatment [50-52] and 12 studies report on imaging at >1 month after treatment [53-62] (in total 563 patients, table 3 and 4). Four other studies did not meet the QUADAS criteria. All studies with [^{18}F]FDG PET/CT within 1 month,

showed a strong correlation between metabolic response and outcome. One study showed that PET was able to detect more responses than CT, but did not analyse the correlation between of PET-response and survival [50]. The study of Michl et al., imaging at 3 months reported a high correlation of [^{18}F]FDG PET/CT findings with survival and observed no correlation between CT response and survival [55]. In line with this study, the other studies imaging >1 month after radioembolisation found a high correlation between metabolic response and survival [53, 54, 63-66], which are not identified by anatomical 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 months after [^{90}Y]-microspheres treatment [53]. As opposed to RECIST1.1 criteria or SUV, the PET measures metabolic tumor volume and total lesion glycolysis were predictive of overall survival. In patients with a decrease of >30% in metabolic tumor volume (MTV) (27/80 patients) overall survival was 92 weeks, significantly better than in non-responders (49 weeks). Slightly less predictive was a >30% decrease in total lesion glycolysis (TLG); in 30/80 responding patients, overall survival was 91 weeks versus 48 weeks in non-responders. Similar findings by Shady et al. support this notion that volume-based parameters have better prognostic impact over single-voxel measures [65]. A retrospective analysis of 17 patients with liver metastases from pancreatic cancer who underwent [^{90}Y]-radioembolisation report that >30% decrease in either SUV_{peak} or the TLG (according to PERCIST criteria) identified the same patients as complete or partial responders [55].

Radioembolisation in cholangio carcinoma

Haug et al. used [^{18}F]FDG PET/CT at 3 months after [^{90}Y]-microspheres for intra-hepatic cholangio carcinoma to predict survival, in comparison to MR based responses [67]. They show in 26 patients that, in contrast to changes in SUV, a decrease in MTV is an independent predictor of overall survival (hazard ratio 0.20). Along this line, the prospective study in 17 patients with intra-hepatic cholangio carcinoma by Filippi et al. demonstrates that

a decrease in TLG of >50% within 6 weeks after treatment is significantly associated with both longer time-to-progression (36.9 versus 13.7 weeks) as well as improved overall survival (79.6 versus 43.1 weeks) [68].

DISCUSSION:

In general, studies suggest that [^{18}F]FDG PET/CT indicates local tumor progression at an earlier time point after treatment as compared to other imaging modalities. In solid organs, absent or a 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 rim like pattern is accepted as physiological and caused by tissue remodelling and scar formation. Inadequate decrease of [^{18}F]FDG uptake in the lesion after ablation marks residual vital tumor, as well as focal or multifocal [^{18}F]FDG uptake in the margins of the ablation zone. Similarly, an increase in [^{18}F]FDG uptake, whether immediate or after an initial decrease, always indicates residual or recurrent disease. PERCIST criteria of at least 30% decrease in SUV_{max} appears to be a safe cut-off for response. Parameters that incorporate tumor volume as well (MTV and TLG) do not prevail over SUV_{max}, but might reflect that larger tumor lesions 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 one month after therapy. To avoid false positive results, we would suggest 2-4 weeks. If false positive findings are encountered, can be caused by abscesses in the appropriate clinical context, which typically present with a rim like markedly increased [^{18}F]FDG uptake pattern.

Assessment of treatment of lung lesions differs from evaluation of treatment in solid organs. From an imaging perspective, lung parenchyma has different characteristics that impact the assessment of reactive changes in adjacent normal tissue to local tumor destruction. The target lesions, metastases and primary lung cancers, are solid and most likely respond similar to lesions located in solid organs. Surrounding normal lung parenchyma contains

much less numbers of cells, reflected by a low physiologic rate of glycolysis (normal SUV_{max} 0.6-0.7) [69] and a very low density (Hounsfield units approx. -800). Furthermore, the composition of lung parenchyma is different from solid organs; mostly endothelial cells and immune cells, less stromal cells and extracellular matrix. Thus early responses to local ablative treatment, with coagulation of proteins, interstitial oedema and influx of immune cells, rapidly results in profound increases in [^{18}F]FDG uptake and appear as increased density in normal lung parenchyma. Bearing this in mind, not only the absence of [^{18}F]FDG uptake, but also high uptake at the pleural border of a treated lesion and intense focal uptake located at the site of the lesion was not associated with recurrence, in most cases resemble profound inflammatory responses and organizing pneumonia or granuloma formation, respectively. However, moderate uptake and rim like uptake with intense focal uptake are indicative of incomplete tumor ablation or recurrence.

Also for lesions located in the lung parenchyma, the PERCIST criterion >30% decrease in SUV_{max} appears reasonable to define response and SUV_{max} >3 is highly suggestive of residual or recurrent tumor. No differences were observed with regard to the histological subtype or primary tumor. Opposite to lesions treated in solid organs, most studies demonstrate that imaging within the first 3 months after local ablation yields unspecific findings that have no predictive impact. Therefore, first imaging time point >3 months is suggested.

As exemplified by our tabulated data, the heterogeneity of the studies that evaluate [^{18}F]FDG-PET/CT to monitor responses to local ablative therapy is a limitation to extract evidence-based data that underpin the wide scale application of [^{18}F]FDG PET/CT for these indications. Most studies have a relatively small sample size and are retrospective in nature, impacting on the power of the data. Furthermore, in absence of a generally accepted non-invasive gold standard, studies differ greatly with respect to the comparator, while histopathological 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 and local ablative modalities and techniques, as well as disease

localisation, in order to identify general patterns for optimally use of [^{18}F]FDG PET/CT as imaging modality for monitoring local ablative therapies.

Another limitation is the extrapolation of data from earlier studies using equipment which 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, ADC-mapping and whole body MRI have found their way into clinical practice. Additionally, new software tools for analysing data such as texture analysis allow characterization of lesions beyond anatomical 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 non-specific 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.

In conclusion, data in literature suggest that [^{18}F]FDG PET/CT is a highly accurate tool to identify successful minimal invasive local treatment, to identify residual or recurrent tumor early and to provide 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 may vary on the localization of disease, allowing (very) early imaging in solid organs as the liver, while post-treatment inflammation in the lung parenchyma is a challenge in the first 3 months after therapy. Uniform, quantitative criteria for the assessment PET such as PERCIST are needed to allow more accurate comparison of literature data.

NOTEWORTHY:

1. [^{18}F]FDG PET/CT is a highly accurate tool to identify residual or recurrent tumor immediately after local ablative therapy.

2. Increase or inadequate decrease, as 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 are highly indicative of residual or recurrent disease.

3. The optimal timing of [^{18}F]FDG PET/CT after treatment may vary on the localization of disease, allowing (very) early imaging in solid organs as the liver, while post-treatment inflammation is a challenge in the first 3 months after therapy in the lung parenchyma.

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TABLES:

TABLE 1. Summary of studies with imaging <24 hours to evaluate technical treatment success														
author	local therapy	tumor type	nr of pts	study design	baseline imaging	post-therapy timepoint 1	post-therapy timepoint 2	post-therapy timepoint 3	post-therapy timepoint +	comparator imaging (criterion)	criteria for PET evaluation	clinical endpoint	clinical outcome measure	QUADAS criteria met
Cornelis et al. J Nucl Med 2016	thermal ablation (RFA or microwave)	liver metastases from different primary tumors	n=21	retro-spective	no	immediate	-	-	no	ceCT	visual, tissue radioactivity concentration (TRC)	1-year tumor response	follow-up, ceCT	yes
Vandenbroucke et al. J Vasc Interv Radiol 2014	RFA	liver metastases	n=20	n/a	no	24 hours	-	-	-	ceCT	visual, predefined patterns	tumor response	follow-up, PET/CT	yes
Kuehl et al. Clin Oncol 2008	RFA	liver metastases colorectal and hepatocellular carcinoma	n=55	retro-spective	yes	<24 hours	1 month	3 months	yes	ceCT	SUVmax, visual	local tumor progression	histology, or ceCT and follow-up	yes
Kuehl et al. Eur J Radiol 2008	RFA	liver metastases from colorectal cancer	n=16	pro-spective	yes	<24 hours	4 weeks	3 months	-	PET alone, MR	SUVmax, visual	local tumor progression	histology, or ceCT and follow-up	yes
Ryan et al. Radiology 2013	RFA	liver metastases from different primary tumors	n=23	retro-spective	yes	immediate	-	-	-	no	visual	local tumor progression	most recently available follow-up CT, MR, or PET	yes

TABLE 2. Main results of studies with imaging <48 hours to evaluate technical treatment success					
author	local therapy	tumor type	nr of pts	main results/conclusion	QUADAS criteria met
Cornelis et al. J Nucl Med 2016	thermal ablation (RFA or microwave)	liver metastases from different primary tumors	n=21	11 of the 25 tumors recurred within 1 year. The accuracy of the qualitative analysis of FDG PET was 92% (23/25) (P < 0.001), and the area under the ROC curve was 0.929 (95% CI, 0.740-0.990). Immediate PET/CT accurately predicts the success of liver metastasis ablation at 1 year and is superior to immediate contrast enhanced CT.	yes
Vandenbroucke et al. J Vasc Interv Radiol 2014	RFA	liver metastases	n=20	Nodular enhancement and rim-like enhancement together had the highest sensitivity to detect viable tumor localisation (63% and 48% respectively). Nodular enhancement had the highest specificity.	yes
Kuehl et al. Clin Oncol 2008	RFA	liver metastases colorectal and hepatocellular carcinoma	n=55	35/78 tumors showed local tumor progression (LTP) There was no significant difference in the mean time until the detection of local tumor progression: 4.1 ± 3 months when PET/CT was used and 5.85 ± 4.6 months when using contrast-enhanced computed tomography (P > 0.11). PET/CT supports RFA by early identification of residual tumor or LTP.	yes
Kuehl et al. Eur J Radiol 2008	RFA	liver metastases from colorectal cancer	n=16	The accuracy and sensitivity for tumor detection was 86% and 76% for PET alone, 91% and 83% for PET/CT and 92% and 75% for MRI, respectively. In comparison to PET alone, PET/CT was significantly better for detecting LTP after RFA. There were no significant differences between MRI and PET/CT, but these preliminary results need further verification.	yes
Ryan et al.	RFA	Liver metastases from different primary tumors	n=23	28 (97%) of the ablated lesions showed no residual FDG activity directly after RFA. One patient with residual activity underwent immediate biopsy that revealed residual viable tumor and was immediately re-treated. Follow-up imaging showed local recurrences in two (7%) lesions that were negative at PET immediately after ablation.	yes

TABLE 3. Summary of studies with imaging to evaluate treatment efficacy														
author	local therapy	tumor type	nr of pts	study design	baseline imaging	post-therapy timepoint 1	post-therapy timepoint 2	post-therapy timepoint 3	post-therapy timepoint +	comparator imaging (criterion)	criteria for PET evaluation	clinical endpoint	clinical outcome measure	QUADAS criteria met
indication: RFA and cryoablation in liver metastases														
Joosten et al. Eur J Surg Oncol 2005	RFA and cryo-ablation w/ or w/o resection	liver metastases from colorectal cancer	n=43	retro-spective		<3 weeks	6 weeks	3 months	yes	ceCT	visual		follow-up	yes
Langenhoff et al. J Clin Oncol 2002	RFA and cryo-ablation w/ or w/o resection	liver metastases from colorectal cancer	n=23	pro-spective	yes	<3 weeks	6 weeks	3 months	6 months	ceCT	visual	local recurrence	follow-up and tumor marker	yes
Donckier et al. J Surg Oncol 2003	RFA	liver metastases	n=17	pro-spective	yes	1 week	1 month	3 months	yes	ceCT	visual	local recurrence	follow-up and/or histology	yes
Chen et al. Ann Nucl Med 2013	RFA	primary liver tumor or metastases	n=28	retro-spective	no	<8 weeks	-	-	-	ceCT, MR	visual	local recurrence	follow-up, ceCT, PET, MR	yes
Nielsen et al Eur J Radiol 2013	RFA	liver metastases from colorectal cancer	n=79	retro-spective	Yes	<1 year	-	-	-	ceCT	Visual	local recurrence	ceCT	no
Sahin et al. Ann Surg Oncol 2012	RFA	liver metastases from	n=104	retro-spective	yes	variable (median 12	-	-	-	ceCT	not specified	local recurrence, overall survival	ceCT, follow-up	no

		colorectal cancer				months)								
indication: RFA and cryoablation for lung lesions														
Yoo et al. Am J Roentgenol 2011	RFA	irresectable primary non-small cell lung cancer	n=30		yes	4 days (n=26)	6 months (n=23)	-	no	no	SUVmax	1-year clinical event	follow-up, ceCT	Yes
Lafuente et al. Rev Esp Med Nucl Imagen Mol 2016	RFA	lung metastases colorectal cancer	n=18	pro-spective	yes	1 month	3 months	-	-	no	SUVmax and retention index	local recurrence	histology	No
Deandreis et al. Radiology 2011	RFA	lung carcinoma or lung metastases	n=34	pro-spective	yes	(24 hrs)	1 month	3 months	yes	ceCT	SUVmax, visual	local recurrence	follow-up	Yes
Higuchi et al. J Cancer Res Clin Oncol 2014	RFA	lung carcinoma or lung metastases	n=20	pro-spective	yes	7-14 days	3-6 months	-	-	ceCT (RECIST)	visual	local recurrence, 2-yr OS		Yes
Higaki et al. Ann Nucl Med 2008	RFA	lung carcinoma or lung metastases	n=15	pro-spective	yes	0-3 months	3-6 months	6-9 months	-	ceCT	SUVmax		follow-up	Yes
Alafate et al. Acta Med Okayama 2013	RFA	lung cancer or lung metastases	n=25	retro-spective	Yes	3 months	6 months	-	-	ceCT	SUVmax	tumor response	follow-up	No
Wang et al. Int J Clin Exp Med 2015	RFA	lung metastases from - lung carcinoma	58	pro-spective	Yes	3 months	9 months	12 months	yes	ceCT	SUVmax	local recurrence	follow-up	Yes
Bonichon et al. Eur J Nucl Med Mol	RFA	lung metastases	n=89	pro-spective	Yes	3 months	-	-	-	ceCT	SUVmax	local recurrence	ceCT	yes

Imaging 2013														
Singnurkar et al. J Nucl Med 2010	RFA	lung carcinoma or lung metastases	n=68 (56 adequate imaging)	retro-spective	Yes	1-4 months	6-12 months	-	-	ceCT	SUVmax, visual	local recurrence	follow-up	No
Suzawa et al. Clin Nucl Med 2013	RFA	lung carcinoma or lung metastases	n=143	retro-spective	No	3 months	6 months	9 months	yes	ceCT	SUVmax	local recurrence	follow-up, histology	Yes
LoGiurato et al. Nucl Med Commun 2015	cryoablation	non-small cell lung cancer	n=28	retro-spective	yes (n=19 lesions)	6 months (n=23) or 12 months (n=4)	12 months	18 months	24 months	CT	SUVmax	local recurrence	PET/CT and CT	Yes
indication: regional ablative therapy in hepatocellular carcinoma														
Higashi et al. Eur J Nucl Med Mol Imaging 2010	TACE, TAC, RFA or systemic chemo-therapy	hepato-cellular carcinoma	n=60 -	retro-spective	yes	<1 month	-	-	-	no	SUVmax, visual		follow-up, tumor markers	No
Sabet et al. Nuklearmedizin 2014	Y-90 microspheres	hepato-cellular carcinoma	n=33	retro-spective	yes	4 weeks	-	-	-	no	SUVmax	overall survival	follow-up	Yes
Ma et al. Theranostics 2014	TACE	hepato-cellular carcinoma	n=27	retro-spective	Yes	4-6 weeks	-	-	-	ceCT (mRECIST)	SUVmax	overall survival , time to progression	follow-up, ceCT	Yes
Kim et al. Nucl Med Mol Imaging 2012	RFA, TACE or ethanol injection	hepato-cellular carcinoma	n=31	retro-spective	no	<1 month	-	-	-	no	SUVmax, visual	local recurrence	follow-up with ceCT and tumor marker	No
Paudyal et al.	RFA	hepato-	n=24	pro-	yes	3 months	6	9 months	yes	ceCT	SUVm	local	follow-	yes

Oncol Rep 2007		cellular carcinoma		spective			months				ax	recurrence	up	
Li et al. Eur J Nucl Med Mol Imaging 2017	TACE (+/- bevacizumab)	hepato-cellular carcinoma	n=22	pro-spective	yes	10 weeks				11C-Acetate PET, CT (RECIST)	Metabolic response	overall survival	follow-up	Yes
Cascales-Campo et al. Transplant Proc 2015	TACE	hepato-cellular carcinoma undergoing orthotopic liver transplantation	n=20	retro-spective	yes	Variable interval after TACE (<8 weeks before liver transplant)	-	-	-	No	SUVmax	tumor response, survival rate 1-year and 3-year	histology, follow-up	No
Song et al. Clin Radiol 2015	TACE	hepato-cellular carcinoma	n=73	retro-spective	no	variable (mean 41 days)	-	-	-	ceCT	ratio SUVmax tumor to SUVmean liver	treatment success, overall survival	follow-up, ceCT, tumor marker	No
Wang et al. J Dig Dis 2013	status after surgery and/or RFA	recurrence of hepato-cellular carcinoma	n=36	pro-spective	no	varying <2-3 months	-	-	-	ceUS	visual	local recurrence	biomarker, histology, follow-up	Yes
indication: radioembolisation in liver metastases														
Miller et al. Am J Roentgenol 2007	Y-90 microspheres	liver metastases from different primary tumors	n=23	retro-spective	yes	<30 days	60 days	90 days	yes	CT (WHO, RECIST, necrosis)	visual	tumor respons	follow-up	Yes

Gulec et al. Eur J Nucl Med Mol Imaging 2011	Y-90 resin microspheres	liver metastases from colorectal cancer	n=20	pro-spective	yes	4 weeks	-	-	-	no	functional tumor volume, TLG	overall survival	follow-up	Yes
Sabet et al. Eur J Nucl Med Mol Imaging 2015	Y-90 microspheres	liver dominant metastatic colorectal cancer	n=51	retro-spective	yes	4 weeks	-	-	-	no	SUVmax, ratio SUVmax to liver (>50% decrease)	overall survival	follow-up	Yes
Kalva et al. Am J Clin Oncol 2017	Y-90 micro-spheres	liver metastases from colorectal cancer	n=45	retro-spective	yes	45 days (n=35)	6 months	9 months	yes	ceCT and/or MR (RECIST)	PERCIST	overall survival	follow-up	No
Fendler et al. J Nucl Med 2013	Y-90 micro-spheres	liver metastases from colorectal cancer	n=80	pro-spective	yes	3 months	-	-	-	ceCT (RECIST 1.1)	MTV, TLG, SUVmax, SUVpeak	overall survival	follow-up	Yes
Fendler et al. J Nucl Med 2016	Y-90 micro-pheres	liver metastases from breast cancer	n=81	retro-spective	yes	3 months	6 months (n=30)	9 months (n=30)	yes	no	SUVmax (>30% decrease)	treatment response, overall survival	follow-up, tumor marker	Yes
Haug et al. J Nucl Med 2012	Y-90 micro-spheres	liver metastases from breast cancer	n=58		yes	3 months	-	-	-	ceCT and MR (RECIST)	SUVmax (PERCIST)	overall survival	follow-up	No
Michl et al. J Nucl Med 2016	Y-90 micro-spheres	liver metastases from	n=17	retro-spective	yes	3 months	-	-	-	ceCT (RECIST)	SUVpeak, TLG	overall survival, progression	follow-up, ceCT/M	yes

		pancreatic cancer									(PERCIST)	free survival, intrahepatic progression	R, tumor markers	
Sofocleous et al. Clin Colorectal Cancer 2014	Y-90 micro-spheres	liver metastases from colorectal cancer	n=19	pro-spective	yes, in 15/19 patients	4-8 weeks	3-4 months	5-6 months	yes	ceCT (RECIST)	PERCIST	liver-PFS, PFS, OS	follow-up, ceCT or MR, and tumor markers	Yes
Sofocleous et al. Clin Colorectal Cancer 2015	Y-90 micro-spheres	liver metastases from colorectal cancer	n=53	retro-spective	yes	4-8 weeks	12-16 weeks	-	-	ceCT (RECIST)	SUVmax (PERCIST)	tumor response	follow-up	No
Szyszko et al. Nucl Med Commun 2007	Y-90 micro-spheres	liver metastases different primary tumors	n=21	pro-spective	yes	6 weeks	6 months	12 months	-	ceCT (RECIST)	SUVmax	tumor response	follow-up, ceCT	Yes
Zerizer et al. Eur J Nucl Med Mol Imaging 2012	Y-90 micro-spheres	liver metastases from colorectal cancer	n=25	pro-spective	yes	6-8 weeks	-	-	-	ceCT (RECIST, Choi)	EORTC criteria	2-year PFS (excluding extrahepatic progression)	follow-up, tumor markers	Yes
Bagni et al. Cancer Biother Radiopharm 2015	Y-90 micro-spheres	liver metastases from breast cancer	n=17	pro-spective	yes	6 weeks	-	-	no	no	TLG (>50% decrease)	overall survival	follow-up	Yes
Barabasch et al. Invest Radiol 2015	Y-90 microspheres	liver metastases from different primary tumors	n=35	pro-spective	yes	6 weeks (n=31)	-	-	-	MRI (ADCmin)	SUVmax (>30% decrease)	tumor response	follow-up, MRI	Yes
Kucuk et al. Worl J Surg	Y-90 micro-spheres	liver metastases	n=78	retro-spective	yes	6 weeks	12 week	18 weeks	yes	no	SUVmax	treatment response	follow-up	yes

Oncol 2011		from different primary tumors					s				(>20% decrease)			
Willowson et al. EJNMMI res 2017	Y-90 micro-spheres	liver metastases from colorectal cancer	n=22	retrospective	yes	<8 weeks	-	-	-	no	delta-TLG (50% decrease) SUVpeak	overall survival	follow-up	Yes
Edalat et al. Clin Nucl Med 2016	Y-90 micro-spheres	liver metastases colorectal cancer	n=16	retro-spective	yes	0.9-5.7 months	n/a	n/a	n/a	ceCT and/or MR	PERCIST, TLG, SUVpeak, SAM	overall survival	follow-up	No
Shady et al. Eur J Rad 2016	Y-90 microspheres	liver metastases from colorectal cancer	n=49	retro-spective	yes	3-11 weeks (median 6 weeks)					SUVmax, SUVpeak, MTP and TLG	overall survival	follow-up	yes
Shady et al. AJR 2016	Y-90 microspheres	liver metastases from colorectal cancer	n=25	retro-spective	yes	4-8 weeks	every 2 months until progression			ceCT (RECIST, Choi)	EORTC criteria	liver progression free survival	follow-up	yes
indication: radioembolisation for cholangiocellular carcinoma														
Haug et al. Eur J Nucl Med Mol Imaging 2011	Y-90 micro-spheres	intrahepatic cholangio-cellular carcinoma	n=26	pro-spective	Yes	3 months	-	-	-	no	delta-SUVmax, delta-	overall survival	follow-up	Yes

											SUVmean, deltaMTV			
Filippi et al. Nucl Med Biol 2015	Y-90 micro-spheres	intrahepatic cholangio-cellular carcinoma	n=17	pro-spective	Yes	6 weeks	3 months	6 months	9 months	no	detla-TLG (PERCIST)		follow-up	Yes

TABLE 4. Main results of studies with imaging at early and late time points to evaluate treatment efficacy					
Author	local therapy	tumor type	nr of pts	Main results/ conclusion	QUADAS criteria met
indication: RFA and cryoablation in liver metastases					
Joosten et al. Eur J Surg Oncol 2005	RFA and cryo-ablation w/ or w/o resection	liver metastases from colorectal cancer	n=43	In a subgroup analysis on 43 patients with 104 ablated lesions, CT scan immediate after treatment was not able to predict local treatment failure, whereas FDG-PET scan within 3 weeks after local ablative treatment predicted 6/7 local recurrences.	yes
Langenhoff et al. J Clin Oncol 2002	RFA and cryo-ablation w/ or w/o resection	liver metastases from colorectal cancer	n=23	51 lesions became photopenic on FDG-PET, while 5 lesions showed persistent activity on FDG-PET. In 4/5 FDG-PET-positive lesions, a local recurrence developed during follow-up; one FDG-PET-positive lesion turned out to be an abscess. None of the FDG-PET-negative lesions developed a local recurrence during follow-up. FDG-PET showed all 9 cases with extra-hepatic recurrence. Detection of recurrence by FDG-PET was considerably earlier than the detection by CT.	yes
Donckier et al. J Surg Oncol 2003	RFA	liver metastases	n=17	In four patients, FDG-PET at 1 week and 1 month showed peripheral hypermetabolic residue after RFA, whereas CT did not revealed residual tumor. In three patients, local persistence of viable tumor cells was biopsy-proven at reintervention. In the fourth, follow-up CT showed subsequent development of a local recurrence. FDG-PET accurately monitors the local efficacy of RFA for treatment of liver metastases, as it early recognizes incomplete tumor ablation, not detectable on CT	yes
Chen et al. Ann Nucl Med 2013	RFA	primary liver tumor or metastases	n=28	PET identified 16 out of 17 recurrent/residual tumors with a sensitivity of 94.1 %, specificity 81.3%. Sensitivity of CT and MRI 66.7%, specificity 62,5 and 87,5% respectively. The study suggests that FDG-PET is superior to MRI and/or CT and is more cost-effective in post RFA hepatic tumor assessment.	yes
Nielsen et al Eur J Radiol 2013	RFA	liver metastases from colorectal cancer	n=79	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 <2 cm may be limited.	no
Sahin et al. Ann Surg Oncol 2012	RFA	liver metastases from colorectal cancer	n=104	PET/CT findings were equivalent to ce CT in 55 patients (67%), superior in 22 (27%), and inferior in 5 (6%). Pre-RFA or post-RFA PET imaging did not affect overall survival. PET/CT was superior to ce CT in demonstrating recurrence after RFA in about a quarter of the patients with CLM.	no

indication: RFA and cryoablation for lung lesions					
Yoo et al. Am J Roentgenol 2011	RFA	irresectable primary non-small cell lung cancer	n=30	Patients with a complete metabolic response at early PET/CT had a 1-year event rate of 43%, whereas those with partial or no response or disease progression had a 1-year event rate of 67% (p = 0.27). Patients with a complete metabolic response at 6-month PET/CT had a 1-year event rate of 0%. Those with a partial response and those with disease progression had an overall event rate of 75% (p = 0.001) Early post-RFA PET/CT is not necessary and 6-month post-RFA PET/CT findings correlate better with clinical outcome at 1 year.	yes
Lafuente et al. Rev Esp Med Nucl Imagen Mol 2016	RFA	lung metastases colorectal cancer	n=18	The retention index (dual time point PET) at 1 month after RFA showed a sensitivity and specificity of 83% and 92%, respectively. Dual time point PET/CT can predict the outcome at one month after RFA in lung metastases from digestive tract cancers. The retention index can be used to indicate the need for further procedures to rule out persistent tumor due to incomplete RFA.	no
Deandreis et al. Radiology 2011	RFA	lung carcinoma or lung metastases	n=34	Within 3 months after RF ablation, incomplete treatment was diagnosed in four of 28 patients (14%, three at 1 month and one at 3 months). Findings of FDG PET/CT were true positive in four, false positive in one, and true negative in 23 patients. Findings of chest CT were true positive in one, false positive in one, false negative in three, and true negative in 23 patients.	yes
Higuchi et al. J Cancer Res Clin Oncol 2014	RFA	lung carcinoma or lung metastases	n=20	The FDG-PET results 7-14 days after RFA did not predict recurrence, whereas positive findings 3-6 months after RFA significantly correlated with local recurrence (p = 0.0016) We confirmed the effectiveness of RFA for unresectable primary and secondary thoracic malignancies. FDG-PET analysis 3-6 months after ablation is a useful tool to assess local control.	yes
Higaki et al. Ann Nucl Med 2008	RFA	lung carcinoma or lung metastases	n=15	Of 60 tumors, 10 showed local progression. The area under the ROC curve (AUC) for the 6-9 months (P = 0.044) was the largest and almost equal to that of the 3-6 months (P = 0.024). AUC for the 0-3 months was the smallest and statistically insignificant (P = 0.705). The cutoff value of 1.5 of SUVmax at 3-9 months after RFA showed 77.8% sensitivity and 85.7-90.5% specificity. The appropriate follow-up initiation time point is at least 3 months following RFA.	yes
Alafate et al. Acta Med Okayama 2013	RFA	lung cancer or lung metastases	n=25	SUVmax was more reliable than the size measurements by CT in the first 6 months after RFA, and PET/CT at 6 months post-RFA may be more appropriate for the assessment of FDG accumulation than that at 3 months post-RFA.	no
Wang et al. Int J Clin Exp Med 2015	RFA	lung metastases from - lung carcinoma	n=58	Increased metabolic activity, new uptake of FDG, and irregular or nodular high uptake of FDG (maximum standard uptake value (SUVmax) ≥3) of the ablated zone after 3 months were all findings concerning recurrence or residual.	yes
Bonichon et al. Eur J Nucl	RFA	lung metastases	n=89	PET/CT at 3 months and the reference standard were available in 77 patients and 100 lesions. Accuracy was 66.00% (95% CI 55.85-75.18%), sensitivity 90.91% (95 % CI 58.72-99.77 %),	yes

Med Mol Imaging 2013				specificity 62.92% (95% CI 52.03-72.93%), PPV 23.26% (95% CI 11.76-38.63%), and NPV 98.25% (95% CI 90.61-99.96%). The specificity of PET/CT at 3 months is low. It is useful for its negative predictive value, but positive findings need to be confirmed.	
Singnurkar et al. J Nucl Med 2010	RFA	lung carcinoma or lung metastases	n=68 (56 adequate imaging)	Post-RFA factors that related to reduced recurrence-free survival included an unfavorable uptake pattern (P < 0.01), post-RFA SUV (P < 0.01), and an increase in SUV over time after ablation (P = 0.05).	no
Suzawa et al. Clin Nucl Med 2013	RFA	lung carcinoma or lung metastases	n=143	The area under the ROC curve of PET was higher than that of CT at all 4 time points (0.71 vs 0.55 at 3 months, 0.82 vs 0.60 at 6 months, 0.84 vs 0.66 at 9 months, and 0.92 vs 0.68 at 12 months), and its diagnostic performance was significant at each time point (P = 0.0010 at 3 months and P < 0.001 at 6, 9, and 12 months). FDG PET/CT is better able to assess local tumor progression at 3 and 6 months after lung RFA than CT alone.	yes
LoGiurato et al. Nucl Med Commun 2015	cryoablation	non-small cell lung cancer	n=28	FDG PET-CT is a valuable tool for determining treatment response and for distinguishing benign from malignant lesions after cryoablation. The CT area was most predictive of future recurrence at baseline, whereas SUVmax more than or equal to 2.5 was most predictive of future recurrence at first follow-up.	yes
indication: regional ablative therapy in hepatocellular carcinoma					
Higashi et al. Eur J Nucl Med Mol Imaging 2010	TACE, TAC, RFA or systemic chemo-therapy	hepato-cellular carcinoma	n=60	Visual PET diagnosis of post-therapeutic lesions was a good predictor of overall survival of unresectable HCC patients. The low FDG group showed significantly longer survival (average: 608 days) than that (average: 328 days) of the high FDG group (p < 0.0001).	no
Sabet et al. Nuklearmedizin 2014	Y-90 microspheres	hepato-cellular carcinoma	n=33	FDG-negative patients had a significantly longer OS (13 months, 95%CI 7-19) than FDG-positive patients (9 months, 95%CI 7-11; p = 0.010). Among FDG-positive patients, metabolic responders survived significantly longer than metabolic non-responders (10 months, 95%CI 8-12 vs. 5 months, 95%CI 4-6; p = 0.003). Pre- and post-therapeutic FDG PET independently predicts overall survival in patients with HCC undergoing radioembolization.	yes
Ma et al. Theranostics 2014	TACE	hepato-cellular carcinoma	n=27	The ΔTSUVmax%, based on the VOI, had the highest discriminative prognostic value.The OS was significantly better in the PET/CT response group than in the PET/CT non-response group (p=0.025).	yes
Kim et al. Nucl Med	RFA, TACE or ethanol injection	hepato-cellular	n=31	By visual analysis, the respective values for sensitivity, specificity, positive predictive value, negative predictive value, and accuracy were 87.5, 71.4, 77.8, 83.3, and 80.0 %. However, there	no

Mol Imaging 2012		carcinoma		were no significant differences in the SUVmax and TNR between the two groups.	
Paudyal et al. Oncol Rep 2007	RFA	hepato-cellular carcinoma	n=24	FDG PET detected recurrence earlier than CT between 4-6 months in 2 patients and between 7-9 months in 6 patients whereas CT was positive in 4 patients. Overall detection rate of recurrence with FDG PET was 92% which was higher than that of CT (75%).	yes
Li et al. Eur J Nucl Med Mol Imaging 2017	TACE (+/- bevacizumab)	hepato-cellular carcinoma	n=22	In patients treated with TACE and placebo, there was a significant difference in mean OS in patients with positive FDG PET as compared with that in patients with negative FDG PET (p = 0.048). Although the OS days in patients with positive acetate PET were shorter as compared with those in patients with negative acetate PET, there was no statistically significant difference (p = 0.063).	yes
Cascales-Campo et al. Transplant Proc 2015	TACE	hepato-cellular carcinoma undergoing orthotopic liver transplantation	n=20	Among patients whose post-TACE SUV decreased to <3, >70% necrosis was observed upon study of a hepatectomy sample, with a survival rate of 100% and 80% at 1 and 3 years, respectively.	no
Song et al. Clin Radiol 2015	TACE	hepato-cellular carcinoma	n=73	Comparing the receiver-operating characteristic area, (18)F-FDG-PET/CT was found to be superior to CECT for the detection of viable tumour in patients with HCC after TACE (p = 0.04). The overall survival rate was significantly higher in the low SUV ratio (TSUVmax/LSUVmean<1.65) group (p = 0.024).	no
Wang et al. J Dig Dis 2013	status after surgery and/or RFA	recurrence of hepato-cellular carcinoma	n=36	The sensitivity, specificity of (18) F-FDG-PET/CT for intrahepatic HCC recurrence were 96.7% and 83.3%, respectively. The corresponding values of CEUS were 56.7% and 100%, respectively. The sensitivity and accuracy of (18) F-FDG-PET/CT for the diagnosis of HCC recurrence were significantly higher than those of CEUS (P < 0.01).	yes
indication: radioembolisation in liver metastases					
Miller et al. Am J Roentgenol 2007	Y-90 micro-spheres	liver metastases from different primary tumors	n=23	PET detected significantly more responses to treatment (21/33, 63%) than CT using RECIST (2/33, 6%) or combined criteria (8/33, 24%) (p < 0.05, McNemar test). The use of necrosis and size criteria on CT and corrlation with PET may improve the accuracy of assessment of response to 90Y treatment in patients with liver metastases and detect response earlier than standard size criteria.	yes
Gulec et al. Eur J Nucl Med Mol	Y-90 resin microspheres	liver metastases from	n=20	Pretreatment and posttreatment FTV and TLG showed very strong association with survival. These values can be useful quantitative criteria for patient selection and disease prognostication when (90)Y SIRT is contemplated in patients with CRCLM.	yes

Imaging 2011		colorectal cancer			
Sabet et al. Eur J Nucl Med Mol Imaging 2015	Y-90 micro-spheres	liver dominant metastatic colorectal cancer	n=51	The median OS after RE was 7 months [95 % confidence interval (CI) 5-8]; early metabolic responders (n = 33) survived longer than non-responders (p < 0.001) with a median OS of 10 months (95 % CI 3-16) versus 4 months (95 % CI 2-6). Molecular response assessment in CRC using (18)F-FDG PET/CT appears feasible as early as 4 weeks post-RE.	yes
Kalva et al. Am J Clin Oncol 2017	Y-90 micro-spheres	liver metastases from colorectal cancer	n=45	Per RECIST, 1 patient (2%) had partial response, 34 (71%) had stable disease, and 6 (13%) had progressive disease. PET response was seen in 46% of patients with 2 patients (4%) demonstrating complete and 22 (42%) demonstrating partial metabolic response. The median survival was 186 days (95% CI, 149-277 d). Response on PET was the only independent predictor of superior overall survival.	no
Fendler et al. J Nucl Med 2013	Y-90 micro-spheres	liver metastases from colorectal cancer	n=80	Responders who had a change in metabolic volume or total lesion glycolysis had significantly longer survival (92 vs. 49 wk [P = 0.006] and 91 vs. 48 wk [P = 0.025], respectively). However, neither RECIST 1.1 criteria nor changes in SUV(peak) or SUV(max) after treatment predicted outcome (P = 0.086 for RECIST; P = 0.310 for change in SUV(peak); P = 0.155 for change in SUV(max)).	yes
Fendler et al. J Nucl Med 2016	Y-90 micro-spheres	liver metastases from breast cancer	n=81	Twenty-nine of 56 (52%) patients responded to radioembolization based on FDG PET criteria.	yes
Haug et al. J Nucl Med 2012	Y-90 micro-spheres	liver metastases from breast cancer	n=58	Response as assessed with SUV(max) correlated significantly with survival after radioembolization, with responders having significantly longer survival (65 wk) than nonresponders (43 wk; P < 0.05' The change in SUV(max) as assessed by (18)F-FDG PET/CT before and 3 mo after SIRT was identified as the only independent predictor of survival in patients with hepatic metastases of breast cancer.	no
Michl et al. J Nucl Med 2016	Y-90 micro-spheres	liver metastases from pancreatic cancer	n=17	Metabolic response by change in SUVpeak (7/17) and change in total-lesion glycolysis (7/17) was a predictor for overall survival (P = 0.039; hazard ratio [HR], 0.24; 95% confidence interval [CI], 0.06-0.93), progression-free survival (P = 0.016; HR, 0.15; 95% CI, 0.03-0.69), and time to intrahepatic progression (P = 0.010; HR, 0.16; 95% CI, 0.04-0.65). Summed CT diameter did not predict overall or progression free survival.	yes
Sofocleous et al. Clin Colorectal Cancer 2014	Y-90 micro-spheres	liver metastases from colorectal cancer	n=19	Responses by RECIST, PERCIST, and CEA were, respectively, 0%, 20%, and 32% at 4 to 8 weeks and 5%, 33%, and 21% at 3 to 4 months post SIRT; 53% of patients had stable disease (by RECIST) at 3 to 4 months.	yes

Sofocleous et al. Clin Colorectal Cancer 2015	Y-90 micro-spheres	liver metastases from colorectal cancer	n=53	Evaluation using PERCIST was more likely than RECIST to document response or progression compared with the baseline assessment before RE.	no
Szyszko et al. Nucl Med Commun 2007	Y-90 micro-spheres	liver metastases different primary tumors	n=21	FDG PET imaging is more sensitive than CT in the assessment of early response to SIR spheres, allowing clinicians to proceed with further therapeutic options.	yes
Zerizer et al. Eur J Nucl Med Mol Imaging 2012	Y-90 micro-spheres	liver metastases from colorectal cancer	n=25	The responses on the FDG PET/CT studies were highly correlated with the responses of tumor markers. The responses on (18)F-FDG PET/CT studies also significantly predicted PFS, while RECIST and tumor density did not.	yes
Bagni et al. Cancer Biother Radiopharm 2015	Y-90 micro-spheres	liver metastases from breast cancer	n=17	Subjects with a ΔTLG >50% and ΔTLG <50% had a mean OS of 16.4□±□0.6 and 10.3□±□0.4 months, respectively (p□<□0.001). Cox regression analysis demonstrated hepatic tumor load (p□=□0.048) and ΔTLG as the only significant (p□=□0.005) predictors of survival.	yes
Barabasch et al. Invest Radiol 2015	Y-90 micro-spheres	liver metastases from different primary tumors	n=35	Diffusion-weighted magnetic resonance imaging appears superior to PET/CT for early response assessment in patients with hepatic metastases of common solid tumors.	yes
Kucuk et al. Worl J Surg Oncol 2011	Y-90 micro-spheres	liver metastases from different primary tumors	n=78	In the evaluation of treatment response; 43(55%) patients were responder (R) and 35 (45%) patients were non-responder (NR) in the sixth week F18-FDG PET/CT. FDG PET/CT is seen to be a successful imaging method in evaluating treatment response for predicting survival times in this patient group.	yes
Willowson et al. EJNMMI res 2017	Y-90 micro-spheres	Liver metastases from colorectal cancer	n=22	Early reduction in TLG at follow-up may be prognostic for overall survival.	yes

Edalat et al. Clin Nucl Med 2016	Y-90 micro-spheres	liver metastases colorectal cancer	n=16	After Y-90 microspheres, ΔSAM showed an objective response rate of 40%. Median overall survival (OS) of the cohort after Y was 9.2 months (CI 95% 2.2-16.2). Patients demonstrating objective response based on ΔSAM had a median OS of 22.7 months (CI 95% 12.4-33.0) vs. 6.7 (CI 95% 4.2-9.2) in non-responders (P = 0.007).	no
Shady et al. Eur J Rad 2016	Y-90 micro-spheres	Liver metastases from colorectal cancer	n=49	Metabolic response based on changes in MTV and TLG can predict OS post-radioembolisation of colorectal liver metastases.	yes
Shady et al. AJR 2016	Y-90 micro-spheres	Liver metastases from colorectal cancer	n=25	EORTC PET criteria, Choi criteria, and tumor attenuation criteria appear to be equally reliable surrogate imaging biomarkers of liver PFS after radioembolisation in patients with liver metastases from colorectal cancer.	yes
indication: radioembolisation in cholangiocellular carcinoma					
Haug et al. Eur J Nucl Med Mol Imaging 2011	Y-90 micro-spheres	intrahepatic cholangio-cellular carcinoma	n=26	The change in all FDG values significantly predicted survival by Kaplan-Meier analysis after radioembolisation.	yes
Filippi et al. Nucl Med Biol 2015	Y-90 micro-sheres	intrahepatic cholangio-cellular carcinoma	n=17	A decrease in total lesion glycolysis (TLG) of >50% within 6 weeks after treatment is significantly associated with both longer time-to-progression (36.9 versus 13.7 weeks) as well as improved overall survival (79.6 versus 43.1 weeks)	yes

TABLE 7. Evaluation of included studies according to QUADAS criteria								
	Risk of bias				**Applicability concerns**			
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard	criteria met
studies with imaging <48 hours to evaluate technical treatment success								
Cornelis et al. J Nucl Med 2016					<25 patients, different primary tumors			yes
VandenBroucke et al. J Vasc Interv Radiol 2014				Short follow-up (8-10 weeks)	<25 patients			yes
Kuehl et al. Clin Oncol 2008				Not all patients received a PET-CT shortly after treatment				yes
Kuehl et al. Eur J Radiol 2008					<25 patients			yes
Ryan et al. Radiology 2013					<25 patients, different primary tumors			yes
indication: RFA and cryoablation in liver metastases								
Joosten et al. Eur J Surg Oncol 2005	43/58 of patients had a PET							yes
Langenhoff et al. J Clin Oncol 2002					<25 patients			yes
Donckier et al. J Surg Oncol 2003					<25 patients			yes
Chen et al. Ann Nucl Med 2013				Wide range of imaging time points (<8 weeks)				yes
Nielsen et al. Eur J Radiol 2013			Follow-up not specified	Wide range of imaging time points				no
Sahin et al.					compares			no

Ann Surg Oncol 2012					survival with and without PET			
indication: RFA for lung lesions								
Yoo et al. Am J Roentgenol 2011				Long interval (6 months) after intervention				yes
LaFuente et al. Rev Esp Med Nucl Imagen Mol 2016			Unclear how local recurrence was objected		<25 patients			no
Deandreis et al. Radiology 2011								yes
Higuchi et al. J Cancer Res Clin Oncol 2014					<25 patients			yes
Higaki et al. Ann Nucl Med 2008				Wide range of imaging time points (1-3 months, 3-6 months and 6-9 months)	<25 patients			yes
Alafate et al. Acta Med Okayama 2013					<25 patients, exclusion of patients with local recurrence or adjuvant chemotherapy			no
Wang et al. Int J Clin Exp Med 2015								yes
Bonichon et al. Eur J Nucl Med Mol Imaging 2013								yes
Singnurkar et al. J Nucl Med 2010	12/68 patients inadequate follow-up			Wide range of imaging time points (1-4 months)				no

Suzawa et al. Clin Nucl Med 2013		Unclear if reviewers were blinded for outcome						yes
LoGiurato et al. 2015		Cut-off value was not predefined						yes
indication: regional ablative therapy in hepatocellular carcinoma								
Higashi et al. Eur J Nucl Med Mol Imaging 2010					Various interventions and some patients received systemic treatment			no
Sabet et al. Nuklearmedizin 2014								
Ma et al. 2014		Many parameters tested in a small sample size						yes
Kim et al. Nucl Med Mol Imaging 2012				Short follow-up (6 months)	Small population with various interventions			no
Paudyal et al. Oncol Rep 2007					<25 patients			yes
Li et al. Eur J Nucl Med Mol Imaging 2017					<25 patients			yes
Cascales-Campos et al. Transplant Proc 2015				Time point after intervention not specified. <8 weeks before liver transplantation	<25 patients			no
Song et al. Clin Radiol 2015		Cut-off value was not predefined		Wide range of imaging time points				no
Wang et al. J Dig Dis 2013					Follow-up with PET on			yes

					indication			
indication: radioembolisation in liver metastases								
Miller et al. 2007				Short follow-up (mean 101 days)				yes
Gulec et al. Eur J Nucl Med Mol Imaging 2011					<25 patients, Response evaluation not primary research goal			yes
Sabet et al. Eur J Nucl Med Mol Imaging 2015								yes
Kalva et al. Am J Clin		Cut-off value was not predefined			Response evaluation not primary research goal			no
Fendler et al. J Nucl Med 2013								yes
Fendler et al. J Nucl Med 2016								yes
Michl et al. J Nucl Med 2016					<25 patients			
Haug et al. J Nucl Med 2012	43/58 of patients had a PET-CT			Long (3 months) interval between intervention and imaging				no
Sofocleous et al. Clin colorectal cancer 2014	Small group of patients, divided in 3 cohorts				<25 patients			yes
Sofocleous et al. Clin colorectal cancer 2015				64% had additional therapies during follow-up/response evaluation				no
Szysko et al. Nuc Med Comm 2007				Only 14/21 patients had a PET-CT after 6 weeks	<25 patients			yes
Zerizer et al.								yes

Eur J Nucl Med Mol Imaging 2012								
Bagni et al. Cancer Biother Radiopharm 2015				Range of imaging time points < 6 weeks	<25 patients			yes
Barabasch et al. Invest Radiol 2015								yes
Kucuk et al. World J Surg Oncol 2011				Different primary tumors				yes
Willowson et al. EJNMMI res 2017					<25 patients			yes
Edalat et al. Clin Nucl Med 2016				Interval between intervention and PET not specified	<25 patients			no
Shady et al. AJR 2016					<25 patients, different primary tumors			yes
Shady et al. Eur J Rad 2016				Wide range of imaging time point (between 3-11 weeks)				yes
indication: radioembolisation in cholangiocellular carcinoma								
Haug et al. Eur J Nucl Med Mol Imaging 2011								yes
Filippi et al. Nuc Med Biol 2015					<25 patients			yes