Biomarkers, 2012; 17(6): 532–538

ISSN 1354-750X print/ISSN 1366-5804 online
DOI: 10.3109/1354750X.2012.699553

informa
healthcare

RESEARCH ARTICLE

FDG-PET for detecting local tumor recurrence of ablated liver metastases: a diagnostic meta-analysis

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Abstract

Context: Scanty reports have focused on FDG-PET after radiofrequency ablation (RFA), for recurrence of hepatic metastases. *Objective:* To assess FDG-PET diagnostic accuracy on detection of recurrent hepatic lesions. *Methods:* After a comprehensive search of PubMed and EMBASE, we performed a patient-based diagnostic meta-analysis of post-RFA FDG-PET. *Results:* Across nine included articles, independent, random-effects sensitivity and specificity were 0.73(0.50–0.88) and 0.85(0.72–0.93), respectively. A symmetrical SROC curve was produced with no significant heterogeneity. Specificity was optimal for surgical RFA and colorectal origin of metastases. *Conclusion:* Synthesis of published evidence suggests PET/CT as an appropriate tool for optimizing post-ablation follow-up.

Keywords: Radiofrequency ablation, positron emission tomography, metastasis, meta-analysis

Introduction

Interventional therapy of hepatic metastases by radiofrequency ablation (RFA) has been developed as an alternative palliative and potentially curative approach (Langenhoff et al. 2002). However, local tumor recurrence may be as high as 55% (Rossi et al. 1996, 1998), making close follow-up mandatory for early detection of progression and additional treatment (Curley 2001, McGhana & Dodd, 2001). Contrast-enhanced computed tomography (CT) and magnetic resonance imaging (MRI), especially with the use of liver-specific contrast agents remain the backbone of staging of malignant liver involvement (Bipat et al. 2005, Schima et al. 2005). Contrast-enhanced ultrasound may compete with CT in the diagnosis of hepatic metastases (Selzner M et al. 2004). The sensitivity to detect residual tumor may be as high as 89% using the above-mentioned imaging techniques (Lencioni et al. 2001, Lim et al. 2001, Dromain et al. 2002).

Functional imaging with 18-Fluoro-deoxy-glucose (^{18}FDG-PET) may play a crucial role in the post-ablation setting, given its high sensitivity for metastatic liver disease (Abdel-Nabi et al. 1998, Ruers et al. 2002), particularly in cases with primary colorectal cancer (CRC) (Delbeke et al. 1997, Meta et al. 2001).

Post-RFA imaging procedures lack the verification of residual disease, which is feasible only with surgical approaches that provide histologic proof of the tumor margins after radical excision (Solbiati et al. 2001). This is the Achilles heel of contrast-enhanced imaging modalities, namely their inability to differentiate residual tumor from reactive peri-ablational process, a confounding effect lasting from weeks to months after RFA. Therefore, CT and MRI are usually performed no sooner than 1 month after RFA (McGhana & Dodd 2001). As a functional imaging approach, FDG-PET may overcome this obstacle and correctly classify residual tumor and local recurrence.

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(Received 28 March 2012; revised 23 May 2012; accepted 30 May 2012)

In the present study, we retrieved all published studies on post-ablation FDG-PET and synthesized the available data using meta-analytic techniques in order to assess the diagnostic performance of FDG-PET to detect local recurrence of liver metastases.

Methods

We searched PubMed and EMBASE (final update: February 10, 2012) using as criterion-term "PET, FDG-PET, positron emission tomography, RFA, radiofrequency ablation, liver, hepatic, metastasis" both as text and MeSH term. No language restrictions were imposed. A complementary search included the references of all eligible studies.

After abstract recovery, all published relevant to the topic articles were identified by two authors (LSP and DCZ), in a blinded evaluation. Eligible studies were those (a) that included FDG-PET (the index test), after RFA of hepatic metastases; and (b) that presented extractable data on local recurrence, documented during clinical follow-up by imaging modalities and/or histology and/or tumor markers (the reference standard). Studies on primary tumors including hepatocellular carcinoma (HCC) were excluded due to low sensitivity of detection and variability of FDG uptake on tumor differentiation (Sacks et al. 2011b). Review articles, unpublished data, letters, comments and editorials were also excluded.

The revised QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies) was the reference tool for assessment of quality, which is regarded as suitable for studies when the reference outcome involves follow-up (Whiting et al. 2011). Demographics data, test results and reference outcome, were extracted and recorded in a blinded fashion. In case of discrepancy, decision was made upon consensus after un-blinded data screening.

Contingency tables (2×2) were constructed by patient-based data to calculate the sensitivity (Se) and specificity (Sp) for each study. True positive (tp), false positive (fp), true negative (tn), false negative (fn) observations were extracted, based on FDG-PET results and whether or not patients had local recurrence (of the ablated lesions) at end of the reference follow-up. Therefore, for consistency in the analysis, a positive PET that identified new metastasis as tumor recurrence was counted as false positive. In articles where only lesion-based data were reported, additional patient-based contingency tables were designed and patient-based data were calculated using sensitivity, specificity, negative predictive value, positive predictive value and the total number of patients, as provided by the text or the incorporated tables.

Initially, independent pooled sensitivity and specificity were estimated, using random-effects (RE) and fixed-effects (FE) models (Sotiriadis et al. 2003). Then, the Summary Receiver Operating Characteristic Curve (SROC) was calculated to deal with the problem of variable thresholds across studies, representing the tradeoff between sensitivity and specificity. The SROC curve was fitted as the linear regression of the logits of sensitivity and specificity in the form of $D = a + b \times S$ as previously described, where $D = \text{logit}(Se) - \text{logit}(1 - Sp)$ and $S = \text{logit}(Se) + \text{logit}(1-Sp)$. In the present analysis, we did not fit the SROC curve using the inverse of the variance of the logarithm of the ORs of the individual studies (weighted SROC) because the weighted analysis may produce biased estimates and no proper weighting method has been identified yet (Irwig et al.1994). Based on the produced SROC curve, Area Under the Curve (AUC) and Q* metric (the point where sensitivity equals specificity) were also estimated (Moses et al. 1993, Walter 2002). By fixing the specificity, the corresponding value on the SROC curve provided an estimate of the pooled sensitivity (pSe). Typically, the independent pooled RE specificity is used as the fixed value of specificity (Owens et al. 1996, Battaglia et al. 2002, Zintzaras and Germenis 2006). Taking into account the independent RE specificities in the main and subgroup analyses, we chose a value of 90% as fixed specificity for the present study. The independent estimates of sensitivity and specificity are usually reliable when they are close to the SROC curve (Owens et al. 1996).

Finally, we calculated the coefficient (slope) b of the unweighted SROC. If b does not significantly deviate from 0, a lack of significant heterogeneity is suggested, and a symmetric SROC curve is produced (Irwig et al. 1994; Zintzaras & Germenis 2006). If b deviates from zero ($b \neq 0$) the SROC becomes asymmetrical, suggesting variability beyond the threshold effect and within-study variation, implying statistical heterogeneity (Moses et al. 1993, Irwig et al. 1995, Walter 2002). In that case, to account for within and between study variability, a diagnostic meta-analysis using a bivariate, mixed-effects binomial regression model is more appropriate (Reitsma et al. 2005, Ziakas et al. 2012).

The Stata v11 software package (Stata Corporation, College Station, TX) and Meta-Analyst software, version beta 3.13 (Tufts Medical Center, MA), were used for data analysis.

Results

After the initial search, 507 potentially relevant citations were identified. A total of 479 were excluded on the basis of relevance by abstract selection and 28 were eligible for detailed full-text review. Eleven duplicate publications (presenting in both EMBASE and PubMed) and two citations published only in abstract form were further excluded. Of the remaining 15 publications, six were not eligible for analysis (three studies on hepatocellular carcinoma, one on PET before RFA, one study without RFA, and one study with mixed data on cryosurgery and RFA). A total of nine studies (Anderson et al. 2003, Donckier et al. 2003, Blokhuis et al. 2004, Veit et al. 2006, Khandani et al. 2007, Kuehl et al. 2008, Travaini et al. 2008, Liu

et al. 2010, Sahin et al. 2011) were finally included in our analysis and relevant data were extracted. Figure 1 presents the search strategy and the numbers of studies retrieved and excluded, with specification of reasons, in a flow diagram. The characteristics of included studies and the assessment of their quality are presented in Table 1. A major concern was the presumable inadequacy of PET in the absence of a dedicated CT scanner (and a fused image) to provide spatial visualization of the ablated area (new metastasis could be viewed as local recurrence) (Anderson et al. 2003, Donckier et al. 2003, Blokhuis et al. 2004). Another concern was that some studies described lesions with mixed histology, interfering with both the reference outcome (different risk of local recurrence for different histology) as well as the index test (different FDG fixation) (Anderson et al. 2003, Donckier et al. 2003, Blokhuis et al. 2004, Khandani et al. 2007, Travaini et al. 2008). However, the latter problem was solved in the majority of the studies, with FDG-PET being uniformly requested prior to RFA as a reference standard baseline (Table 1).

Individual studies' diagnostic data are shown in Table 2. Main and subgroup analyses results are presented in Table 3. In SROC analysis, the sensitivity and specificity were examined simultaneously (Figure 2).

Across all included studies, the independent pooled RE sensitivity (95% CI) was 0.73 (0.50–0.88) and the independent pooled RE specificity was 0.85 (0.72–0.93). If a threshold was chosen that the pooled RE specificity was 90%, then the pSe sensitivity was estimated at 78% (0.78). The area under the SROC curve (AUC) was 0.92 and the Q* point at which sensitivity equals specificity had a value of 88% (0.88). The slope b of the unweighted SROC was 0.20, ranging from –0.64 to 1.05.

Four included studies had investigated metastatic liver lesions with colorectal cancer (CRC) histological origin. By analyzing this subgroup, we recognized that the diagnostic accuracy of FDG-PET in metastatic recurrence of primary CRC was slightly improved compared to the total diagnostic estimates. More specifically, the independent pooled RE sensitivity (95% CI) was 0.85 (0.72–0.92) and the independent pooled RE specificity was 0.92 (0.79–0.98). The AUC, the

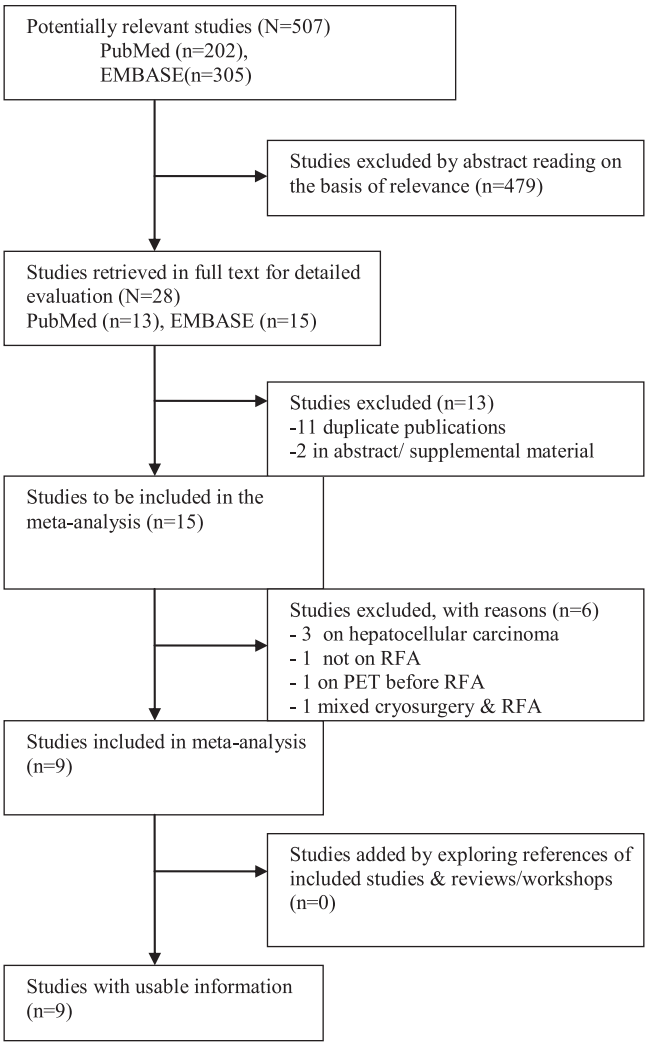

Figure 1. Flow diagram of included studies and search strategy.

Table 1. Summary and quality assessment of included studies.

		Risk of bias								Applicability	
ID	Study, year	Test	RFA access	Early PET (<72 h)	Pre-RFA PET	Histologies	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test
1	Shahin, 2011	PET/CT	Surg	No	One third	CRC only	☺	☺	☺	☺	☺	☺
2	Liu, 2010	PET/CT	Perc	Yes	All	CRC only	☺	☺	☺	☺	☺	☺
3	Travaini, 2008	PET/CT	Perc	No	All	CRC (83%)+	?	☺	☺	☺	☺	☺
4	Kuehl, 2007	PET/CT	Perc	Yes	All	CRC only	☺	☺	☺	☺	☺	☺
5	Khandani, 2007	PET/CT	Perc/surg	Yes	All	CRC (63%)+	?	☺	☺	☺	☺	☺
6	Veit, 2006	PET/CT	Perc	Yes	All	CRC only	☺	☺	☺	☺	☺	☺
7	Blockhius, 2004	PET	Surg	NR	Half	CRC (73%)+	?	☺	☺	☺	☺	?
8	Donckier, 2003	PET	Surg	No	All	CRC (65%)+	?	☺	☺	☺	☺	?
9	Anderson, 2003	PET	Perc/surg	No	NR	CRC (57%)+	?	☺	☺	☺	☺	?

☺, low risk; ☹, high risk; ?, Unclear risk; surg, surgical; perc, percutaneous; CRC, colorectal cancer; +, and other histologies; NR, not reported.

Table 2. Individual study diagnostic data, patient-based analysis.

ID	Study, year	n	tp	tn	fp	fn	Sensitivity (95%CI)	Specificity (95%CI)
1	Shahin, 2011	82	51	26	0	5	0.91 (0.80–0.97)	1.00 (0.87–1.00)
2	Liu, 2010	12	2	9	1	0	1.00 (0.16–1.00)	0.90 (0.55–1.00)
3	Travaini, 2008	9	1	4	0	4	0.20 (0.01–0.72)	1.00 (0.40–1.00)
4	Kuehl, 2007	16	7	8	0	1	0.88 (0.47–1.00)	1.00 (0.63–1.00)
5	Khandani, 2007	8	2	4	1	1	0.67 (0.09–0.99)	0.80 (0.28–0.99)
6	Veit, 2006	11	4	5	0	2	0.67 (0.22–0.96)	1.00 (0.48–1.00)
7	Blockhius, 2004	11	4	7	0	0	1.00 (0.40–1.00)	1.00 (0.59–1.00)
8	Donckier, 2003	17	3	7	1	6	0.33 (0.07–0.70)	0.88 (0.47–1.00)
9	Anderson, 2003	14	8	3	3	0	1.00 (0.63–1.00)	0.50 (0.12–0.88)

Abbreviations: tp, true positive; fp, false positive; tn, true negative; fn, false negative.

Table 3. Main and subgroup analysis results based on the CRC histological origin of liver metastases, on the combined use of PET/CT, on the surgical access and on early (within 2 days) PET scanning.

Studies	No (n)	Se (95%CI)	Sp (95%CI)	b (95%CI)	AUC	pSe	Q*
All	9 (180)	0.73 (0.50–0.88) (RE)	0.85 (0.72–0.93) (RE)	0.20 (–0.64 to 1.05)	0.92	0.78	0.88
		0.76 (0.65–0.85) (FE)	0.84 (0.72–0.92) (FE)				
CRC histological origin	4 (121)	0.85 (0.72-0.92) (RE)	0.92 (0.79-0.98) (RE)	–0.66 (–6.29 to 4.98)	0.92	0.78	0.90
		0.86 (0.75–0.92) (FE)	0.92 (0.79–0.98) (FE)				
Combined PET/CT	6 (138)	0.73 (0.48–0.89) (RE)	0.90 (0.78–0.96) (RE)	0.51 (–1.72 to 2.74)	0.95	0.87	0.90
		0.80 (0.68–0.88) (FE)	0.90 (0.78–0.96) (FE)				
Surgical Access of RFA	3 (110)	0.76 (0.26–0.96) (RE)	0.94 (0.77–0.98) (RE)	1.56 (–21.7 to 24.8)	0.99	0.99	0.98
		0.81 (0.67–0.89) (FE)	0.94 (0.77–0.98) (FE)				
Early PET scanning (within 2 days after RFA)	4 (47)	0.74 (0.51–0.88) (RE)	0.88 (0.69–0.96) (RE)	–0.18 (–4.55 to 4.18)	0.89	0.70	0.85
		0.74 (0.51–0.88) (FE)	0.88 (0.69–0.96) (FE)				

CRC, colorectal cancer; RFA, radiofrequency ablation; RE, random-effects; FE, fixed-effects; AUC, area under curve. The independent pooled sensitivity (Se) and pooled specificity (Sp) using RE and FE models, the slope b of the unweighted SROC curve, the AUC of the SROC curve, the pSe derived from SROC using a fixed Sp of 0.90, and the Q* point where sensitivity and specificity are equal are shown.

Q* point and the pSe (after fixing of specificity to 0.90) were almost similar 0.92, 90% (0.90) and 78% (0.78), respectively. The estimated slope b was –0.66, ranging from –6.29 to 4.98.

Across six studies using the combination PET and CT scanning after RFA of recurrent liver metastases, the RE sensitivity and the RE specificity were 0.73 (0.48–0.89) and 0.90 (0.78–0.96), respectively; the pSe was 87% (0.87), as the pooled specificity was chosen to 0.90. The AUC and the Q* were estimated at 0.95 and 90% (0.90), respectively. In addition, the slope b was calculated at 0.51(–1.72 to 2.74).

Moreover, the diagnostic performance of post-ablation FDG-PET was better across the three studies investigating surgical RFA. The RE specificity were 0.94 (0.77–0.98); AUC and Q* metric were estimated at 0.99 and 0.98, respectively while the RE sensitivity was 0.76 (0.26–0.96) and the pooled sensitivity (pSe) was 0.99

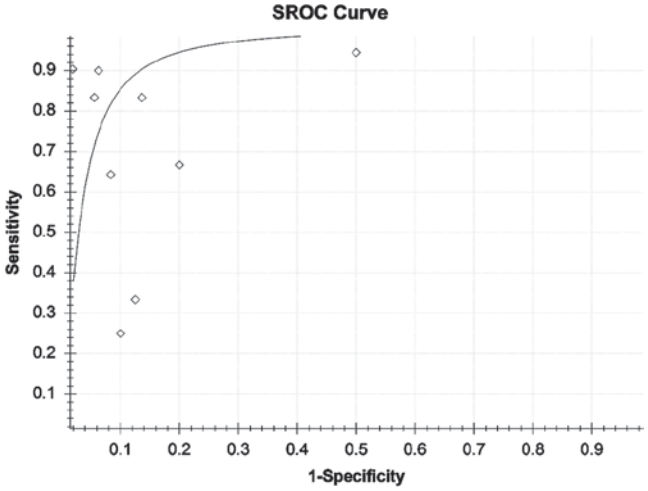

Figure 2. Summary receiver operating characteristics (SROC) curve analysis.

after fixing pooled specificity to 0.90. In this subgroup of studies, b was calculated at 1.56 (ranging from –21.7 to 24.8).

After the synthesis of diagnostic metrics in 4 studies where scanning has been performed within 2 days after RFA, the independent pooled RE sensitivity and specificity with 95% CI were estimated at 0.74 (0.51–0.88) and 0.88 (0.69–0.96), respectively. The AUC was 0.89, the Q* point was 0.85, the pSe was 0.70 (choosing as a threshold the pooled RE specificity to 0.90). The slope b of the unweighted SROC was –0.18 (–4.55 to 4.18).

The summary and subgroup diagnostic estimates for Se and Sp, using fixed-effects (FE) model, are also shown in Table 3.

Discussion

Our analysis summarized the use of FDG-PET as a diagnostic tool in the post-RFA setting for liver metastatic recurrence. Up to now, published data were insufficient for direct comparison of FDG-PET with other imaging methods, even though the combination of PET and CT scanning (PET/CT) was described as equal to MRI in one study (Kuehl et al. 2008) and as superior to CT in two studies (Veit et al. 2006, Sahin et al. 2011). Combined PET with CT scanning allows spatial localization and recognizes more clearly functional lesions than PET-alone (Veit et al. 2006, Kuehl et al. 2008). Recently, the use of FDG-PET/CT in radio-ablated liver metastases was found to be associated with earlier detection of local recurrence (Blokhuis et al. 2004, Travaini et al. 2008) and timely scheduling of subsequent interventions (Veit et al. 2006, Liu et al. 2010). After a literature overview of FDG-PET imaging of post-RFA liver metastases, we catalogued all identified parameters (colorectal histology of metastases, surgical access of RFA, imaging test and time of scanning) that may influence the diagnostic performance of FDG-PET and synthesized the diagnostic metrics of FDG-PET as provided by the individual studies.

Specificity of FDG-PET for detecting metastatic recurrence was almost excellent in surgical RFA [0.94(0.77–0.98)] and in cases with primary CRC [0.92(0.79–0.98)]. This effect is expected, as surgical access permits direct visualization of the tumor margins, with lower risk of incomplete ablation (translated in lower risk of local tumor recurrence) (Kuvshinoff & Ota 2002, Eisele et al. 2009, Ayav et al. 2010). Recurrence rate of post-RFA hepatic tumors in the periphery of the ablation site is high enough (21%) (Thanos et al. 2008) and in general, rates of recurrent liver metastasis by primary colorectal cancer vary in the literature from 3 to 60% (Lubezky et al. 2007, Wong et al. 2010). FDG/PET can accurately detect metabolic change in tumors prior to morphologic change (Langenhoff et al. 2002, Anderson et al. 2003). In this context, despite the undoubting difficulties, we could suggest the eventual use of FDG-PET in the detection of liver involvement in additional types of cancers. However, studies on primary hepatic tumors including hepatocellular carcinoma (HCC) described low sensitivity of detection and variability of FDG uptake upon tumor differentiation (Sacks et al. 2011b).

Inflammation, which is mainly confined to the periphery of ablation sites, may also be interpreted as residual tumour. The difficulty of FDG/PET to differentiate inflammatory changes from tumor growth may occasionally lead to false-positive results inflicting specificity in favor of increased sensitivity. The peripheral ablated zone does not exhibit metabolic activity for up to three days, as seen in experimental models. Thus, early scanning is a preferable approach to overcome the problem of inflammatory response, occurring days to months after RFA. (Tsuda et al. 2003, Antoch et al. 2005, Vogt et al. 2007). Although the basis of timely FDG-PET performance was not explored by our study, focusing further on the subgroup of studies investigating early FDG-PET scanning (within 2 days after RFA), we rationally found a small improvement of specificity, comparing to the pooled specificity across all included studies [0.88(0.69–0.96) vs. 0.85(0.72–0.93)]. In this context, we could propose the performance of early post-RFA FDG-PET to monitor effectively whether residual liver tumor exists in the periphery of the necrosis that results from RFA, to identify the completeness of ablation scope, to improve the efficacy of RFA and to formulate further future treatment.

Finally, we should notice that the slope b of the unweighted SROC curve in the main analysis of all included studies, as well as in all subgroup analyses (as seen in Table 3) include 0 in their 95% confidence intervals, indicating a lack of significant statistical heterogeneity, thereby producing symmetric SROC curves for the main and subgroup analyses.

There are several limitations in our analysis: First, we did not address the issue of disease progression outside the setting of local recurrence. Second, the paucity of relevant studies, the small number of patients included and the absence of direct comparisons of FDG-PET with the standard imaging modalities should

prompt us to be cautious with estimated results. Another issue is the absence of a validated protocol of follow-up after RFA that incorporates all the diagnostic modalities. That is to determine, how frequent and which method should be preferred. Various factors should be evaluated, including the risk of local tumour recurrence and disease progression, and effort should be made to minimize radiation exposure and maximize the diagnostic yield. It should be also noted that FDG-PET should not be preferred in cases of concurrent chemotherapy as it decreases FDG uptake (Lubezky et al. 2007, Sacks et al. 2011a). A combination of PET/CT and MRI could be an appropriate scheme, with early post-ablation PET/CT being mandatory, as already suggested (Kuehl et al. 2008).

Despite the limitations of our analysis, the synthesis of published evidence strengthens our knowledge on the diagnostic performance of FDG-PET/CT on liver metastasis and suggests FDG-PET/CT as an appropriate imaging tool for optimizing post-ablation follow-up.

Declaration of interest

The authors declare no conflicts of interest.

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