Review Article
The role of ^{18}F-FDG positron emission tomography in the follow-up of liver tumors treated with [90]Yttrium radioembolization

Oreste Bagni[1*], Luca Filippi[1*], Orazio Schillaci[2]

[1]Department of Nuclear Medicine, Santa Maria Goretti Hospital, Via Canova 3, 04100 Latina, Italy; [2]Department of Biomedicine and Prevention, University Tor Vergata, Viale Oxford 81, 00133, Rome, Italy. *Equal contributors.

Abstract: In the last years, radioembolization (RE) has emerged as a novel technique for the treatment of malignant hepatic lesions using ^{90}Y embedded in spheres, which are infused directly into the hepatic arterial circulation. ^{90}Y-spheres, once implanted in liver, can release a significant radiation burden to neoplastic cells with a relative low dose to normal parenchyma. [90]Y RE results as a combination of embolization and radiation therapy, thus the standard radiologic follow up modalities may be not sufficiently accurate to assess tumor response to treatment. [18]Fluoro-deoxyglucose Positron Emission Tomography (^{18}F-FDG PET) detects glucose uptake and metabolic activity in tumor cells. ^{18}F-FDG PET has become a well established diagnostic tool in many oncological scenarios. Furthermore, PET response criteria (PERCIST) have been recently introduced to categorize the metabolic response to therapy of cancer patients. Several semiquantitative parameters, such as SUVmax and its changes, the Functional Tumor Volume and the Total Lesion Glycolysis can be useful to accurately assess tumor changes after therapy. The purpose of this article is to present the literature on the role of ^{18}F-FDG PET in the evaluation of patients with primary and secondary liver tumors treated with ^{90}Y RE.

Keywords: Liver tumors, ^{90}Y radioembolization, PET-CT, PERCIST, total lesion glycolysis, function tumor volume

Introduction

Liver represents a site of metastatic involvement in many oncological scenarios. Post mortem examination demonstrated hepatic involvement in 50-70% of metastases from melanoma, lymphoma, breast, lung and colon cancer [1]. Unfortunately, despite of many advances in diagnosis and therapy, the prognosis of both primary and secondary hepatic tumors remains poor. Surgery is often the most effective approach, but it is not always practicable due to the anatomic location of lesions or the massive involvement at presentation. Several treatments modalities both systemic and loco-regional (ethanol injection, radiofrequency ablation, cryoablation, transarterial chemoembolization) have been evaluated [2-5].

In the last years, radioembolization (RE) has emerged as new a technique for treatment of malignant hepatic lesions using ^{90}Y embedded

in microspheres, which are infused directly into the hepatic arterial circulation [6-8]. ^{90}Y-spheres, once implanted in liver, can release a significant radiation burden to neoplastic cells with a relative low dose to normal parenchyma due to the different vascularization pattern. In this regard, a recently published report indicates that the mean dose to viable tumors results of 183.6 ± 156.5 Gy, with a mean dose to the parenchyma of 97.1 ± 22.1 Gy [9].

[90]Y RE can be considered a combination of embolization and radiation therapy, thus the standard radiologic follow up modalities may be not sufficiently accurate to assess tumor response to treatment. In particular, morphologic response criteria are based on size changes or on the degree of tumor arterial enhancement after treatments. While widely used for assessing response to conventional chemotherapy, this approach may be not suitable for evaluating hepatic malignancies after ^{90}Y RE. The lack

Table 1. Summary of the main manuscripts on the use of FDG PET/CT in patients submitted to ^{90}Y radioembolization

References	Year of publication	Tumor	Spheres	Time point of FDG PET post procedure evaluation	Endpoint
PET as baseline scan before the procedure					
Deneecke et al.	2008	CRLM	NS	Not performed	Define an algorithm pre RE
Wong et al.	2010	CRLM	NS	Not performed	Identify a parameter predictive of extrahepatic disease
Zalom et al	2012	Mixed tumors	Resin	3 mo	Define if ^{18}F-FDG PET/CT provides important information on clinical outcomes after RE
Hepatocellular carcinoma					
Kokcuk et al.	2013	HCC	Resin	Not performed	Assess the prognostic role of ^{18}F-FDG PET in HCC undergoing RE.
Sabet et al.	2014	HCC	Resin & Glass	4 weeks	Define the role of ^{18}F-FDG in monitoring HCC response to RE
Colorectal liver metastases					
Wong et al.	2002	CRLM	Glass	3 mo	Assess the role of ^{18}F-FDG PET in CRLM undergoing RE
Cianni et al.	2009	CRLM	Resin	3 mo	Assess response though RECIST and ^{18}F-FDG PET
Zerizer et al.	2012	CRLM	Resin	6-8 weeks	Compare PET derived parameters, RECIST and tumor density criteria
Tochetto et al.	2012	CRLM	NS	3 mo	Correlation between MDCT attenuation and SUV changes after RE
Gulec et al.	2011	CRLM	NS	4 weeks	Assess the role of TLG and FTV as prognostic indicator after RE
Fendler et al.	2013	CRLM	Resin	3 mo	Validation of PET derived parameters after RE
Breast cancer liver metastases					
Coldwell et al.	2007	BCLM	Resin	3 mo	Assess efficacy, safety and response to RE
Cianni et al.	2013	BCLM	Resin	3 mo	Assess efficacy, safety and response to RE
Haug et al.	2012	BCLM	Resin	3 mo	Assess if PET and SUV changes are predictive of response to RE
Intrahepatic cholangiocarcinoma					
Haug et al.	2011	ICC	Resin	3 mo	Assess if PET and SUV changes are predictive of response to RE
Mouli et al.	2'13	ICC	Glass	Not performed	Assess efficacy, safety and response to RE
Filippi et al.	2014	ICC	Resin	6 weeks	Define if changes in TLG correlate with patients' final outcome
Other tumors					
Klingenstein et al.	2013	Uveal Melanoma	Resin	2-3 mo	Evaluate safety, efficacy of RE by using ^{18}F-FDG PET

Abbreviations: CRLM, colorectal liver metastases; NS, not specified; HCC, hepatocellular carcinoma; BCLM, breast cancer liver metastases.

of accuracy of standard radiology, in fact, may be explained by the development of necrotic, oedematous or hemorrhagic changes after 90Y RE, causing paradoxal increase of the dimensions in responding lesions.

18Fluoro-deoxyglucose Positron Emission Tomography (18F-FDG PET) detects glucose uptake and metabolic activity in tumor cells. 18F-FDG PET has become a well established diagnostic tool in many oncological scenarios [10]. Several semiquantitative parameters, such as Standardized Uptake Value (SUV) and its changes, can be useful to more accurately assess tumor changes after therapy. Furthermore, PET response criteria (PERCIST) have been recently introduced to categorize the metabolic response to therapy of cancer patients [11].

The purpose of this review is to present the existing literature on the role of 18F-FDG PET in the evaluation of patients with primary and secondary liver tumors treated with 90Y RE (**Table 1**).

Radioembolization

90Y RE is a loco-regional treatment using 90Y-spheres which are conveyed to the liver through the arteries. The rationale of this therapeutic approach is based on the characteristic dual blood supply of liver (i.e. from the hepatic artery and the portal vein). Portal vein supplies blood to the normal hepatocytes. On the contrary, tumoral cells receive blood mainly from the hepatic artery [12, 13]. Therefore, the injection of tumoricidal agents in the hepatic artery through an angiographic catheter should allow the preferential release of therapeutic material to the neoplasia. The principle of 90Y RE is, in fact, to selectively deliver high radiation burden to hepatic tumors, with low dose delivered to the surrounding normal parenchyma.

Indications and contraindications

The typical indications of 90Y RE are represented by unresectable and chemotherapy-refractory primary or secondary hepatic tumors. The absolute contraindications are: 1) pregnancy; 2) hepato-pulmonary shunt leading to excessive lung irradiation; 3) demonstrable gastrointestinal deposition of 90Y-spheres. It can be reasonable excluding patients with a life expectancy < 3 months [14].

Other criteria of inclusion-exclusion are: liver-only or liver-predominant disease; age ≥ 18 years; ability and willingness to provide written informed consent; Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2; bilirubin < 2.0 mg/dl, albumin >2.0 g/dl, international normalized ratio (INR) < 1.5; creatinine < 2.0 mg/dl; platelets ≥ 100,000/µl, Hb ≥ 9.0 g/dl, and WBC ≥ 1,500/µl. Patients with predominant extrahepatic disease, active CNS metastases, or diffuse peritoneal metastases should be excluded.

The procedure

Pre-treatment angiography with selective visceral catheterization is performed in order to evaluate the vascular and tumor anatomy and blood-flow dynamics, enabling a determination of the optimal placement of the catheter for selective treatment. 99mTc-macroaggregated albumin scan is mandatory to test gastrointestinal flow and estimate the percent of injected activity shunted to the lungs. After 7-10 days the patients returns for the treatment session performed by selective catheterization of the main hepatic artery by transfemoral approach, embolization of gastroduodenal and gastric artery. The infusion of 90Y microspheres is usually performed under fluoroscopic guidance via a microcatheter place in the right/left hepatic artery [15].

Radiopharmaceuticals

Yttrium-90 is the most routinely used radioisotope for RE. It is a pure beta emitter with a half-life of 64.2 hours. It is produced by neutron bombardment of Yttrium-89 in the nuclear reactor. It decays into the stable element Zirconium-90. The range of tissue penetration of the emissions is 2.5 to 11 mm. There are two commercially available 90Y microspheres.

TheraSphere® (MDS Nordion, Ottawa, Canada) consists of nonbiodegradable glass microspheres, with yttrium in matrix, and have a diameter of 32 ± 10 µm. Six activity vials are available differing from each other only in the number of spheres per vial e.g. 1.2 million microspheres are present in a vial with an activity of 3 Gigabecquerel (GBq). Each microsphere has an activity of 2500 Becquerel at the time of calibration [16].

SIR-Spheres® (Sirtex, Lane Cove, Australia) consist of biodegradable resin microspheres,

labeled with yttrium. The spheres have a diameter of 22 ± 10 μm and hence are associated with more embolic effect. One vial of SIR-Spheres® of 3 GBq is available and contains 40-80 million microspheres ranging from 20 to 60 microns. SIR-Spheres® was approved by the FDA for metastatic colorectal cancer. Each microsphere has a specific activity of 50 Bq at the time of calibration [17].

Radiologic parameters for assessment of the response to radioembolization

There is limited information about the relation between changes in CT characteristics and progression-free and overall survival after RE. Furthermore, it is not well studied whether CT scans can provide clinically useful objective parameters before or after RE and whether the availability of these parameters may improve patients' selection and treatment outcome after RE.

Local response to treatment is usually defined following the World Health Organization (WHO) criteria [18] as follows: 1) complete response (CR), complete disappearance of all known disease and no new lesions; 2) partial response (PR), 50% reduction in total tumor load of all measurable lesions; 3) stable disease (SD), does not qualify for CR/PR; 4) progressive disease (PD), 25% increase in size of one or more measurable lesions or the appearance of new lesions. In this scenario, Response Evaluation Criteria in Solid Tumor (RECIST) have been introduced in 2000 [19, 20]. Key points of RECIST are the definition of minimum size of measurable lesions and the number of lesions to be considered in follow up [20]. Four categories of response are registered: 1) CR: disappearance of all target lesions; 2) PR: 30% decrease in the sum of the greatest dimension of target lesions; 3) PD: 20% increase in the sum of the longest diameter of target lesions; 4) SD: small changes that do not meet above criteria. However, many antitumoral therapies may result in changes in tumor vascularization, cavitation, and necrosis that do not substantially modify tumor size. Consequently using RECIST criteria to evaluate tumor response after treatments might be not sufficiently accurate to predict patients' outcome [21].

Other methods of evaluations are available. The European Association for the Study of the Liver (EASL) criteria recommended that assessment of tumor response should be performed taking into account the reduction in viable tumor burden as recognized by non-enhancing areas demonstrated on dynamic CT or magnetic resonance imaging studies [22]. This criterion is widely used by the majority of groups studying HCC and a proposal to formally amend RECIST was published in 2010. The Modified RECIST criteria (mRECIST) include evaluation of the arterial enhancement of target lesions [23].

Salem et al. recently characterized the features of hepatocellular tumors in 23 patients on CT scans before and after RE, assessing the radiographic tumor response by morphology, attenuation, size, and structure (MASS) criteria, and determined CT features that were associated with better progression-free and overall survival [24]. The authors found decreased size in the 68% of tumors, decreased attenuation in 64% and demonstrated increased tumor necrosis in 48%. RECIST-defined PR was seen in 10% patients, SD in 80%, and PD in 10%. The authors concluded that imaging response criteria that account for changes in tumor morphology, percentage of tumor necrosis, attenuation, and size may be accurate to evaluate tumor response after 90Y RE.

Role of 18F-FDG PET as baseline scan before the procedure

It is well known that 18F-FDG PET is used as a staging procedure in many oncological conditions [25]. However, there are still few data addressing the potential utility of this imaging modality in therapy planning of patients affected by hepatic tumors treated with 90Y spheres.

Denecke et al. evaluated 22 patients who sequentially underwent contrast enhanced CT, MRI with hepatocyte-specific contrast, angiography with 99mTc-MAA perfusion scintigraphy and 18F-FDG PET [26]. The impact of each test on the therapy decision and 90Y RE management was recorded. Patient evaluation using CT revealed contraindications for 90Y RE in 4/22 patients (18%), while 2 were excluded and 3 were assigned to locally ablative treatment based on MRI and PET results (28%). The remaining 13 patients were finally administered with 90Y spheres, after an accurate study of vascularization and hepato-pulmunary shunt with 99mTc-MAA. Therefore, a sequential diagnostic
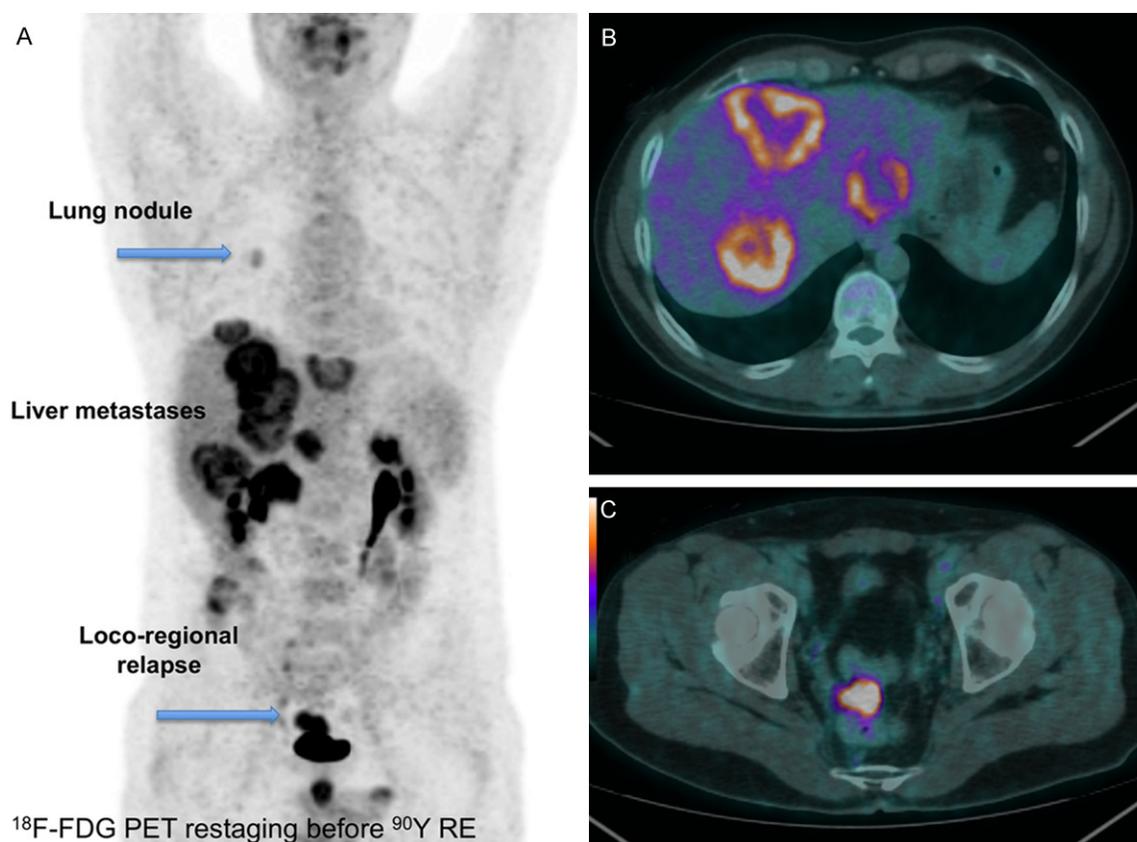
Figure 1. ^{18}F-FDG PET performed before ^{90}Y radioembolization in a 39 year-old-male patient with colorectal liver metastases. Maximum Intensity Projection (MIP) thick slab (A) showed intense tracer uptake in liver (right and left lobe) associate with ^{18}F-FDG accumulation in rectum and lung (arrows). Fused axial images well demonstrated hepatic lesions (B) and loco-regional relapse. Patient was considered ineligible to the procedure due to the extensive extra-hepatic disease.

algorithm with all these imaging procedures should be performed for an accurate patients' selection before ^{90}Y RE.

Wong and colleagues found a strong correlation between a semiquantitave parameter (tumor metabolic load index - TMLI) and the presence of extrahepatic disease in 48 patients affected by colorectal liver metastases before ^{90}Y RE [27]. The authors indentified a TMLI threshold, below which extrahepatic metastases are unlikely and thus may provide guidance for patients' selection and stratification after therapy.

A recent study evaluated whether the ^{18}F-FDG PET can provide important information on clinical outcomes in patients having undergone ^{90}Y RE [28]. In a cohort of 31 patients affected by liver metastases from different histologies, PET was performed 3 months before and after the procedure. The authors found that patients

with new lesions outside the liver had a significantly shorter survival than cases without extrahepatic localizations. These findings are in agreement with the clinical experience that extrahepatic metastases of colorectal cancer can lead to an adverse outcome (**Figure 1**). The same authors did not find any association between the decrease of ^{18}F-FDG uptake in lesions after ^{90}Y RE and survival.

^{18}F-FDG PET-based parameters for assessment of the response to radiembolization

In routine clinical practice, PET images are qualitatively interpreted for tumors' staging and follow up by comparing the intensity and the pattern of ^{18}F-FDG uptake in potential tumor sites with the physiological distribution of the tracer [29]. Of course, qualitative interpretation of PET images is strictly dependent from operator's experience.

When small changes in tumors after treatment should be assessed, semiquantitative methods are mandatory. In particular, Standardized Uptake Value (SUV) and its modifications are widely used for the diagnosis and follow up in many oncological scenarios [30]. As soon as in 1993 Whal et al. evaluated the response to chemotherapy in breast cancer by using quantitative ^{18}F-FDG PET [31]. Regarding the prognostic value of PET scan, Reidl et colleagues assessed the correlation between SUVmax, some cellular characteristics and the clinical behaviour of tumors: SUV max significantly correlated with GLUT-1, Ki-67 and p53, with a longer survival for patients with a low SUV versus those with a high SUV [32]. Therefore, SUV is routinely used to assess tumor response to therapy.

Whal and colleagues have recently proposed PET-based criteria to define the metabolic response to treatment [11]. According to PET Response Criteria in Solid Tumors (PERCIST), patients'response is categorized as follows: 1) complete metabolic response (CMR), complete resolution of ^{18}F-FDG uptake within the target lesion so that it is less than the mean liver activity and indistinguishable from the blood pool; 2) partial metabolic response (PMR), reduction of a minimum of 30% in the target lesions' SUL (SUV corrected per lean body mass) peak; 3) Progressive Disease (PD), more than 30% increase in the target lesions' SUL; 4) Stable Metabolic Disease (SMD), no CMR, no PMR or PD. These criteria have been applied, although partially modified, in the evaluation of metabolic response after ^{90}Y RE in intrahepatic cholangiocarcinoma and breast cancer liver metastases [33, 34].

However, PERCIST criteria are quite time-consuming and require proper workstation for calculation and comparing the scans acquired in different times [35]. New criteria for metabolic response have been introduced by Rubello's group: PET Residual Disease in Solid Tumor (PREDIST) [36]. According to PREDIST, complete metabolic response to therapy (CMRt) is discriminated from residual disease by comparing post-therapy ^{18}F-FDG uptake of lesions to liver. To our knowledge, the PREDIST criteria have not been applied to assess response to treatment after ^{90}Y RE. Finally, it is becoming more and more important in oncology to identify as early as possible patients with poor clinical outcome in order to timely start adjuvant or palliative treatments. Total Lesion Glycolysis (TLG) and Functional or Metabolic Tumor Volume (FTV or MTV) are potentially important parameters for studying the behavior of tumor [37].

Clinical applications in liver malignancies

Hepatocellular carcinoma

It is well known that there is no primary role for ^{18}F-FDG PET in hepatocellular carcinoma (HCC), due to its low sensitivity in the overall HCC population [38]. Well-differentiated HCC, in fact, does not present significant ^{18}F-FDG uptake, while variable ^{18}F-FDG -uptake can be observed in poorly-differentiated HCC [39, 40]. The largest series regarding the potential usefulness of ^{18}F-FDG PET in HCC patients's selection before ^{90}Y RE was reported by Kucuk et al [41]. Nineteen patients who received RE treatment for HCC were included in the study and underwent ^{18}F-FDG PET/CT before ^{90}Y RE for evaluation of disease stage and metabolic activity of liver lesions. The authors found that higher SUVmax lesions unexpectedly had better progression free survival rates after ^{90}Y RE, suggesting ^{90}Y RE has a treatment advantage over other therapeutic options in these patients.

Sabet et al. recently assessed the feasibility of using ^{18}F-FDG PET in 33 patients affected by HCC and treated with ^{90}Y RE [42]. Patients were submitted to PET at baseline and 4 weeks after the procedure. According to the baseline metabolic status of the HCC lesions, patients were divided into 2 groups: ^{18}F-FDG -negative (n = 12) and ^{18}F-FDG -positive (n = 21) HCC. ^{18}F-FDG -positive patients were further divided in early metabolic responders and non-responders in relationship with the SUVmax changes of the treated lesions. ^{18}F-FDG -negative patients had a significantly longer OS than ^{18}F-FDG -positive patients. Among ^{18}F-FDG -positive patients, metabolic responders survived significantly longer than metabolic non-responders. Therefore, the authors suggested that quantitative ^{18}F-FDG PET can be useful to predict survival after ^{90}Y RE in HCC patients. Worthy of note, the assessment of the metabolic response resulted feasible as early as 4 weeks post treatment. The results of the reported studies suggest that ^{18}F-FDG might play an important role both to stratify patients before therapy and to predict final outcome after ^{90}Y RE.

Colon rectal cancer

There is a relatively consistent amount of papers addressing the role of 18F-FDG for the monitoring of patients affected by colorectal liver metastases submitted to 90Y RE. In a recent review by Annunziata S. and colleagues, the authors searched in Pubmed/Medline using a combination of the terms: "SIRT" or "radioembolization" or "yttrium" and "positron emission tomography" or "PET" [43]. An overall number of 268 papers was found. Among these articles, nineteen were specifically focused on the role of 18F-FDG in the monitoring of colorectal liver metastases after 90Y RE.

As soon as in 2002, Wong et al. reported on 8 patients with unresectable colorectal liver metastases treated with 90Y-glass spheres [44]. At 3 months post-treatment, the follow up imaging demonstrated metabolic response in 12 treated lobes, compared with CT/MRI, which showed an anatomic response in only 2 lobes. Serum CEA levels decreased, correlating with PET findings. The authors concluded that PET can be an accurate indicator of treatment response.

Cianni and co-workers assessed the response to 90Y RE in 41 patients with colorectal liver metastases by following RECIST criteria and 18F-FDG PET examinations [45]. They found CR in 2 patients, PR in 17, SD in 14 patients and PD in 8 subjects. However, PET parameters, such decrease in SUVmax, were not taken into account nor correlated with the overall survival.

As regards the role of 18F-FDG respect to the RECIST criteria, Zerizer et al. evaluated 25 patients (for a total of 121 liver lesions from colorectal cancer) by 18F-FDG PET and contrast-enhanced CT before and 6-8 weeks after 90Y RE [46]. According to PET, 15 patients had PR and 10 SD, while following RECIST only 2 PR were found and the remaining 23 showed SD. Furthermore, 18F-FDG decrease in hepatic lesions correlated with the decrease in tumor markers and significantly predicted progression free survival. The authors suggested 18F-FDG PET as mandatory imaging modality in the follow up of liver tumors after 90Y RE, further demonstrating that an assessment of metabolic tumor response can be feasible at 6 weeks post procedure.

In 2012, Tochetto's group investigated the relationship between several contrast ehanced CT-based parameters, such as tumor attenuation and tumor size, and the volume-weighted SUV at 18F-FDG PET [47]. Patients with colorectal liver metastases were evaluated at baseline and 3 months after 90Y RE. In agreement with previously cited papers, 18F-FDG PET identified a greater percentage of response when compared to CT and RECIST criteria. Furthermore, a strict correlation was found between 18F-FDG uptake in lesions and the response based on CT-attenuation criteria, thus suggesting that early changes in the attenuation of colorectal liver metastases after 90Y RE may be predictive of future response at 18F-FDG PET.

Novel PET-derived parameters have emerged as powerful prognostic tool in cancer patients' follow up. In particular, the assessment using 18F-FDG PET of the so-called Metabolic Tumor Volume (MTV) or Functional Tumor Volume (FTV) proved of interest for both target volume definition in radiotherapy and monitoring response to therapy [48, 49]. Beside FVT, another metabolic-volumetric parameter has been introduced: Total Lesion Glycolysis (TLG), combining SUV (mean) and metabolic tumor volume, which resulted of utmost value as prognostic indicator in many oncological settings [50, 51]. Gulec et al. evaluated these two metabolic parameters in 20 patients with colorectal cancer liver metastases: 18 with bilobar multiple metastases and 2 with unilobar lesions, all treated with a combination of chemotherapy and 90Y RE [52]. A decrease in TLG and FTV was observed in all but one patient, in particular subjects receiving chemo+ 90Y RE had a greater reduction respect those receiving chemo-only. Most interestingly, median survival for patients with 4-week post-treatment FTV value above and below 30 cc were 10.9 and 26.9 months, respectively. The authors concluded that pre-treatment and post-treatment TLG and FTV present a strong correlation with survival.

In a large series of 80 patients with colorectal liver metastases, Fendler and co-workers recently tested the validity of several parameters derived from PET for predicting survival after 90Y RE [53]. 18F-FDG PET was performed at baseline and 3 months after the procedure and TLG, FTV and changes in SUV were calculated. Moreover, response to treatment was evaluated both according to PERCIST and RECIST. The authors found that decrease in FTV and TLG
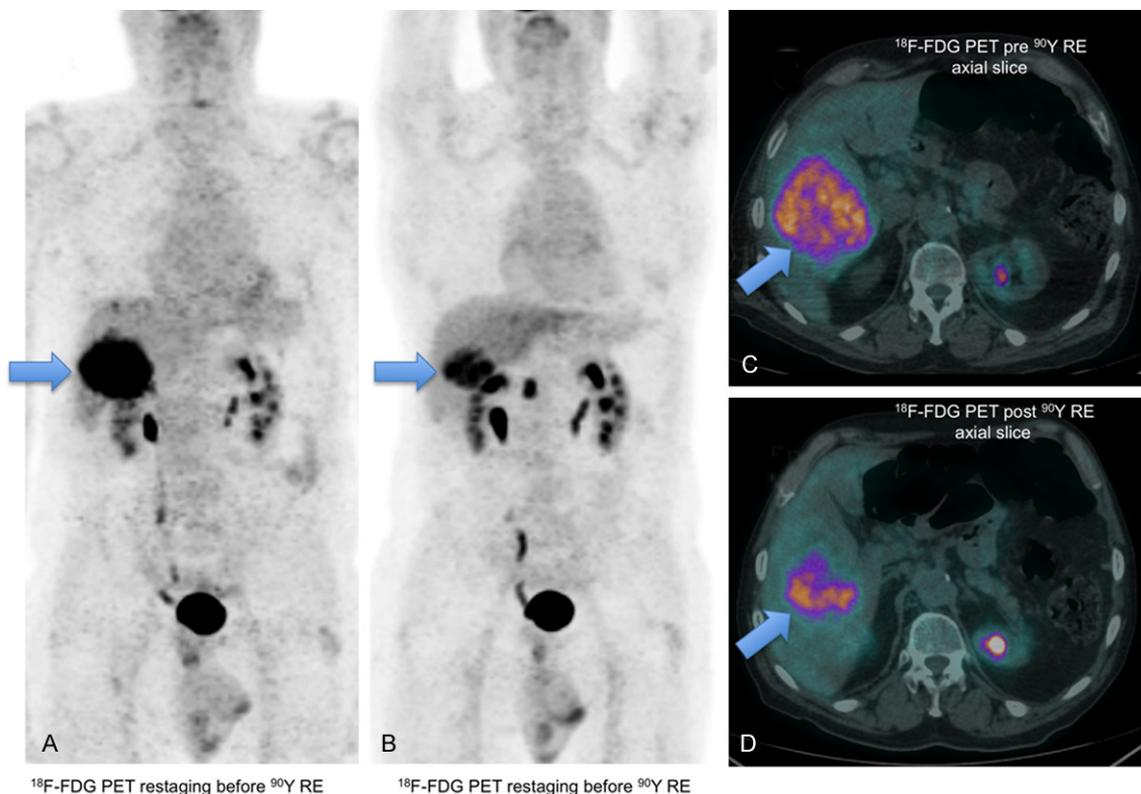
Figure 2. A 67 year-old-male patient with colorectal liver metastases. 18F-FDG PET MIP before radioembolization (A) showed intense tracer uptake in a gross tumor in the right hepatic lobe (arrow), while no other areas of abnormal tracer accumulation were evident. MIP acquired 6 weeks after 90Y spheres administration (B) revealed a significant reduction of the liver mass (arrow). The significant metabolic response is well evident in the axial images acquired before (C) and after (D) the procedure.

predicts survival, while no correlation was found for changes in SUV and RECIST criteria. In summary, many papers support the evidence that 18F-FDG PET can be useful to assess metabolic response in colorectal liver metastases after 90Y RE (**Figure 2**).

Breast cancer

In liver metastases from breast cancer, 90Y RE proved useful as palliative therapy with response rates ranging from 39% to 61% with mean survival of 2-14 months [54, 55].

In 2007, Coldwell and Kennedy reported good results of 90Y RE in 44 patients with hepatic lesions from breast cancer [56]. They found the following response rate according to RECIST: 41% PR, 47% SD and 5% PD. When the response to 90Y RE was analyzed by 18F-FDG PET, 95% of patients resulted in PR and only 5% was in SD.

In a recent report, Cianni et al. evaluated the response to 90Y RE in 52 patients with liver

metastases from breast cancer both according to RECIST and 18F-FDG PET [57]. At first follow up performed at 8 weeks post procedure, the majority of subjects (81%) showed a reduction of hepatic lesions' metabolism consistent with PR, among them 2 subjects showed complete disappearance of 18F-FDG uptake and were considered in CR. These results are in agreement with those of Colwell's group, indicating a higher percentage of metabolic response by using 18F-FDG PET.

Another group published a research on the role of 18F-FDG PET in predicting survival after 90Y RE in a cohort of 58 patients with hepatic metastases from breast cancer [33]. 18F-FDG PET was performed at baseline and 3 months after the procedure. To evaluate response of the disease to treatment, the authors used modified PET Response Criteria in Solid Tumors (PERCIST). According to the unmodified PERCIT, in fact, the change of SUVmax in the 2 hottest lesions per organ is considered. On the contra-
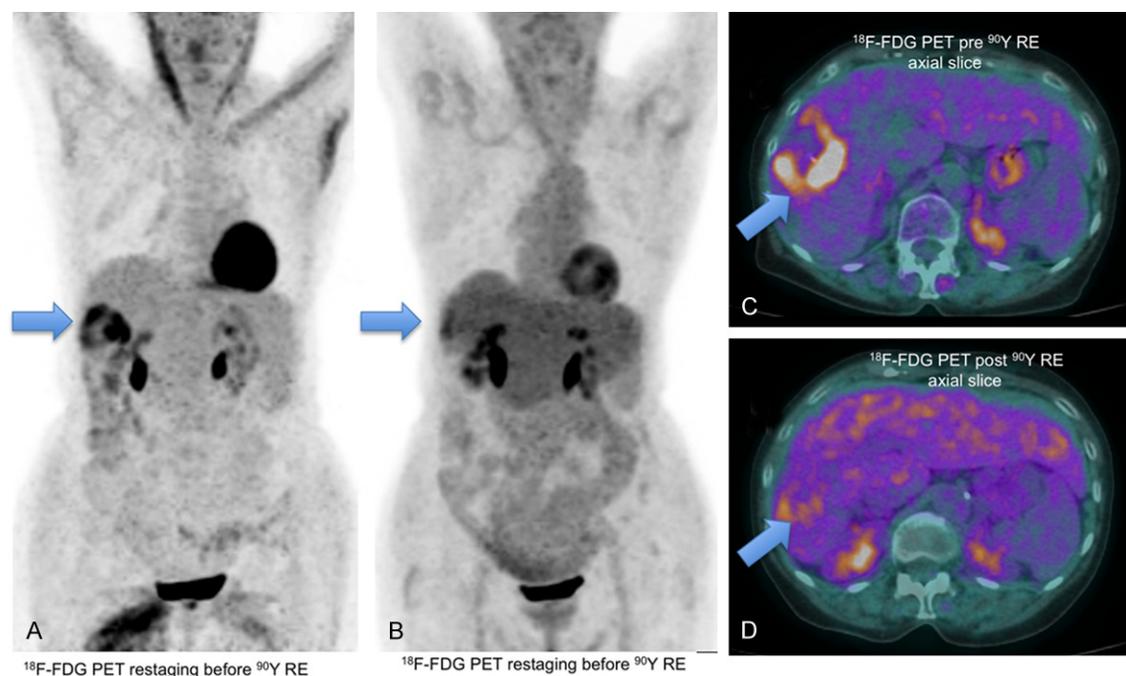
Figure 3. A 72 year-old-female patient with chemo-resistant intrahepatic colangiocarcinoma, which had previously undergone surgery and then relapsed. 18F-FDG MIP (A) acquired before the radioembolization revealed 18F-FDG uptake in the right hepatic lobe (arrow). 18F-FDG MIP 6 weeks after therapy (B) depicted an almost complete metabolic response of the hepatic lesion. The significant metabolic response is well evident in the axial images acquired before (C, arrow) and after (D, arrow) the procedure.

ry, Haug et al. based their definition of the response on the summed percentage change in the SUVmax in up to 5 of the most prominent hepatic lesions. Response as assessed with SUVmax correlated significantly with survival after 90Y RE. Furthermore, a high pre-embolization SUVmax (i.e. > 20) resulted strongly predictive of survival. Further studies are needed to assess the role of 18F-FDG PET in the assessment of the response to 90Y RE in patients with breast cancer liver metastases.

Intrahepatic cholangiocarcinoma

There are relatively few data addressing the utility of 90Y RE in unresectable and chemotherapy-resistant intrahepatic cholangiocarcinoma (ICC). One reason is due to the rarity of the neoplasm. Moreover, 90Y RE has emerged as a relatively novel treatment for otherwise untreatable tumor or metastases of the liver, with a growing body of evidence reporting very encouraging results (**Figure 3**).

The largest series of ICC patients treated with 90Y RE was published by Mouli et al [58]. The authors retrospectively evaluated the utility of

the procedure in 46 patients at a single institution during an 8-year period. Survival varied based on presence of multifocal, infiltrative and bilobar disease. However, 18F-FDG was not used to evaluate the response to treatment and patients were assessed by CT or MRI.

Haug et al. investigated the role of 18F-FDG PET in predicting survival in 26 consecutive ICC patients treated with 90Y RE [34]. Among 23 patients in whom follow-up was available, 5 (22%) showed a PR, 15 (65%) SD and 3 (13%) PD. The change in all 18F-FDG values significantly predicted survival after radioembolization; in particular, ΔSUV (max) and ΔSUV (mean) responders had a median survival of 114 weeks (responders) versus 19 weeks (non-responders).

Filippi and colleagues have recently investigated the relationship between changes in TLG, assessed by means 18F-FDG PET at 6 weeks after 90Y RE, and final outcome in 17 patients affected by ICC [59]. Subjects were divided in 2 groups (group 1: 6 weeks ΔTLG > 50%, group 2: ΔTLG < 50%). Patients with a ΔTLG > 50% and ΔTLG < 50% had a mean OS of 79.6 + 3.6 and

43.1 + 2.0 weeks, respectively (p < 0.001). Furthermore, patients with ΔTLG > 50% had a significantly longer TTP than those with ΔTLG < 50%. Hence, the authors concluded that ΔTLG calculated on post-treatment ^{18}F-FDG PET agrees with patients' final outcome.

Other tumors

Although relatively rare, uveal melanoma spreads beyond the eye in about the 50% of cases with the liver being involved in the 80-90% of cases [60, 61]. Only a small percentage of patients can be effectively treated with surgery. In the remaining patients, ^{90}Y RE can represent an intriguing therapeutic option. In a recent report, Klingenstein et al. evaluated 13 patients with melanoma liver metastases submitted to ^{90}Y RE by performing ^{18}F-FDG PET at baseline and 2-3 months after treatment [62]. PR was observed in 8 (62%), SD in 2 (15%), and PD in 3 (23%) patients under terms of standard criteria, and PR in 3 (23%), SD in 3 (23%), and PD in 7 (54%) patients according to PET criteria. Neither RECIST nor PET criteria showed a significant difference in predicting overall survival (P = 0.12 and 0.11, respectively).

Neuroendocrine tumors are highly vascularized malignancies, thus several published papers reported that ^{90}Y radioembolization can be effective and safe in hepatic NET [63, 64]. However, it is well known that ^{18}F-FDG PET has a relatively low sensitivity in neuroendocrine tumors and other tracers like ^{68}Ga-DOTATOC re more suitable for the imaging of these tumors [65]. Moreover, recent published papers suggest that good results in hepatic NET might be achieved by combining peptide-receptor radionuclide therapy (PRRT) and ^{90}Y RE [66-68].

Conclusions

[90]Y RE has emerged as a safe and effective treatment in primary and secondary liver tumors. ^{18}F-FDG PET-CT can play a fundamental role either as baseline scan before the procedure or as follow up imaging modality after treatment. Several semiquantitative parameters such as FTV and TLG have been proved to have powerful prognostic value in predicting survival after ^{90}Y RE. The optimal time point for assessing metabolic response after ^{90}Y RE has not been established yet. Identifying patients with poor clinical outcome can be of utmost importance in order to timely start as early as possible adjuvant or palliative treatments. The most of the previous cited papers have assessed the response to ^{90}Y RE at 3 months. There are few reports of early metabolic assessment at 4 and 6-8 weeks. Finally, the solidest evidences on the role of metabolic imaging in monitoring the response to ^{90}Y RE come from clinical experiences in patients affected by colorectal liver metastases. However, there is a growing literature concerning the possible role of ^{18}F-FDG PET in monitoring the response to ^{90}Y RE also for patients affected by other tumors, like breast cancer metastases and intrahepatic cholangiocarcinoma. Further studies are needed to better evaluate the impact of ^{18}F-FDG PET in these oncological settings.

Disclosure of conflict of interest

None.

Address correspondence to: Oreste Bagni, via Canova 3, 04100 Latina. Tel: 0039-0773-6553591, Fax: 0039-0773-6553593, E-mail: obagni1@virgilio.it

References

[1] Bengmark S, Hafstrom L. The natural history of primary and secondary malignant tumors of the live. The prognosis for patients with hepatic metastases from colonic and rectal carcinoma by laparatomy. Cancer 1969; 23: 198-202.

[2] Mulcahy MF, Benson AB 3rd. Bevacizumab in the treatment of colorectal cancer. Expert Opin Biol Ther 2005; 7: 997-1005.

[3] Blum HE. Hepatocellular carcinoma: therapy and prevention. World J Gastroenterol 2005; 47: 7391-7400.

[4] Ramsey DE, Kernagis LY, Soulen MC, Geschwind JF. Chemoembolization of hepatocellular carcinoma. J Vasc Interv Radiol 2002; 13: S211-S22

[5] Cianni R, Urigo C, Notarianni E, Saltarelli A, D'Agostini A, Iozzino M, Dornbusch T, Cortesi E. Radioembolisation using yttrium 90 (Y-90) in patients affected by unresectable hepatic metastases. Radiol Med 2010; 115: 619-633.

[6] Stubbs RS, Cannan RJ, Mitchell AW. Selective internal radiation therapy (SIRT) with 90Yttrium microspheres for extensive colorectal liver metastases. Hepatogastroenterology 2001; 38: 333-337.

[7] Goin JE, Salem R, Carr BI, Dancey JE, Soulen MC, Geschwind JF, Goin K, Van Buskirk M, Thurston K. Treatment of unresectable hepatocellular carcinoma with intrahepatic yttrium 90

microspheres: factors associated with liver toxicities. J Vasc Interv Radiol 2005; 16: 205-213.

[8] Andrews JC, Walker SC, Ackermann RJ, Cotton LA, Ensminger WD, Shapiro B. Hepatic radioembolization with yttrium-90 containing glass microspheres: preliminary results and clinical follow-up. J Nucl Med 1994; 35: 1637-1644.

[9] Tapp KN, Lea WB, Johnson MS, Tann M, Fletcher JW, Hutchins GD. The impact of image reconstruction bias on PET/CT 90Y dosimetry after radioembolization. J Nucl Med 2014; 55: 1452-8.

[10] Kluetz PG, Meltzer CC, Villemagne VL, Kinahan PE, Chander S, Martinelli MA, Townsend DW. Combined PET/CT Imaging in Oncology. Impact on Patient Management. Clin Positron Imaging 2000; 6: 223-230.

[11] Wahl RL, Jacene H, Kasamon Y, Lodge MA. From RECIST to PERCIST: Evolving Considerations for PET response criteria in solid tumors. J Nucl Med 2009; 50: 122S-150S.

[12] Ackerman NB, Lien WM, Kondi ES, Silverman NA. The blood supply of experimental liver metastases. I. The distribution of hepatic artery and portal vein blood to "small" and "large" tumors. Surgery 1969; 66: 1067-72.

[13] Lien WM, Ackerman NB. The blood supply of experimental liver metastases. II. A microcirculatory study of the normal and tumor vessels of the liver with the use of perfused silicone rubber. Surgery 1970; 68: 334-40.

[14] Kennedy A, Nag S. Recommendations for radioembolization of hepatic malignancy using yttrium-90 microspheres brachytherapy: a consensus panel report from the radioembolization brachytherapy oncology consortium. Int J Radiat Oncol Biol Phy 2007; 68: 13-23.

[15] Cristina V, Pracht M, Lachenal Y, Adib S, Boubaker A, Prior J, Senys A, Wagner AD, Bize P. Interventional radiology procedures for malignancies of the liver treatment: Intraarterial procedures. Rev Med Suisse 2014; 431: 1130-2.

[16] MDS Nordion Inc (2014) Publications (international). Available via http://www.nordion.com/404.asp?404;http://www.nordion.com/therasphere/physicians-publications-eu.asp

[17] SIRTeX Medical Ltd (2014) Publications (international). Available via http://www.sirtex.com/eu/clinicians/publications/.

[18] World Health Organization. WHO Handbook for Reporting Results of Cancer Treatment. Offset Publication 48. Geneva Switzerland: World Health Organization; 1979.

[19] Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, Verweij J, Van Glabbeke M, van Oosterom AT, Christian MC, Gwyther SG. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 2000; 92: 205-216.

[20] Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009; 45: 228-247.

[21] Barnacle AM, McHugh K. Limitations with the Response Evaluation Criteria in Solid Tumors (RECIST) guidance in disseminated pediatric malignancy. Pediatr Blood Cancer 2006; 46: 127-134.

[22] European Association For The Study Of The Liver. European Organisation For Research And Treatment Of Cancer. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol 2012; 56: 908-943.

[23] Moschouris H, Malagari K, Papadaki MG, Kornezos I, Stamatiou K, Anagnostopoulos A, Chatzimichael K, Kelekis N. mRECIST criteria and contrast-enhanced US for the assessment of the response of hepatocellular carcinoma to transarterial chemoembolization. Diagn Interv Radiol 2014; 20: 136-142.

[24] Salem M, Jain N, Taylor S, Dyson G, Beebe-Dimmer J, Choi M, Shields AF, Critchfield JJ, Philip PA. Radiographic Parameters in Predicting Outcome of Patients with Hepatocellular Carcinoma Treated with Yttrium-90 Microsphere Radioembolization. ISRN Oncology 2013; 2013: 538376.

[25] Ben-Haim S, Ell P. 18F-FDG and PET/CT in the evaluation of cancer treatment response. J Nucl Med 2009; 50: 88-99.

[26] Denecke T, Rühl R, Hildebrandt B, Stelter L, Grieser C, Stiepani H, Werk M, Podrabsky P, Plotkin M, Amthauer H, Ricke J, Lopez Hänninen E. Planning transarterial radioembolization of colorectal liver metastases with Yttrium 90 microspheres: evaluation of a sequential diagnostic approach using radiologic and nuclear medicine imaging techniques. Eur Radiol 2008; 18: 892-902.

[27] Wong CY, Gates VL, Tang B, Campbell J, Qing F, Lewandowski RJ, Thie J, Ho CL, Savin M, Salem R. Fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography predicts extrahepatic metastatic potential of colorectal metastasis: a practical guide for yttrium-90 microsphere liver-directed therapy. Cancer Biother Radiopharm 2010; 25: 233-6.

[28] Zalom M, Yu R, Friedman M, Bresee C, Waxman A. FDG PET/CT as a prognostic test after 90Y

radioembolization in patients with metastatic hepatic disease. Clin Nucl Med 2012; 37: 862-865.

[29] Gámez-Cenzano C, Pino-Sorroche F. Standardization and Quantification in FDG-PET/CT Imaging for Staging and Restaging of Malignant Disease. PET Clin 2014; 9: 117-127.

[30] Filippi L, D'Arienzo M, Scopinaro F, Salvatori R, Bagni O. Usefulness of dual-time point imaging after carbonated water for the fluorodeoxyglucose positron emission imaging of peritoneal carcinomatosis in colon cancer. Cancer Biother Radiopharm 2013; 28: 29-33.

[31] Wahl RL, Zasadny K, Helvie M, Hutchins GD, Weber B, Cody R. Metabolic monitoring of breast cancer chemohormonotherapy using positron emission tomography: initial evaluation. J Clin Oncol 1993; 11: 2101-2111.

[32] Riedl CC, Akhurst T, Larson S, Stanziale SF, Tuorto S, Bhargava A, Hricak H, Klimstra D, Fong Y. 18F-FDG PET scanning correlates with tissue markers of poor prognosis and predicts mortality for patients after liver resection for colorectal metastases. J Nucl Med 2007; 48: 771-775.

[33] Haug AR, Tiega Donfack BP, Trumm C, Zech CJ, Michl M, Laubender RP, Uebleis C, Bartenstein P, Heinemann V, Hacker M. 18F-FDG PET/CT predicts survival after radioembolization of hepatic metastases from breast cancer. J Nucl Med 2012; 53: 371-377.

[34] Haug AR, Heinemann V, Bruns CJ, Hoffmann R, Jakobs T, Bartenstein P, Hacker M. 18F-FDG PET independently predicts survival in patients with cholangiocellular carcinoma treated with 90Y microspheres. Eur J Nucl Med Mol Imaging 2011; 38: 1037-1045.

[35] Maffione AM, Ferretti A, Vinjamuri S, Rubello D. The PERCIST criteria: an insightful appraisal. Nucl Med Commun 2013; 34: 619-20.

[36] Maffione AM, Ferretti A, Chondrogiannis S, Rampin L, Marzola MC, Grassetto G, Capirci C, Colletti PM, Rubello D. Proposal of a new 18F-FDG PET/CT predictor of response in rectal cancer treated by neoadjuvant chemoradiation therapy and comparison with PERCIST criteria. Clin Nucl Med 2013; 38: 795-797.

[37] Romesser PB, Lim R, Spratt DE, Setton J, Riaz N, Lok B, Rao S, Sherman EJ, Schöder H, Lee NY. The relative prognostic utility of standardized uptake value, gross tumor volume, and metabolic tumor volume in oropharyngeal cancer patients treated with platinum based concurrent chemoradiation with a pre-treatment [18F] fluorodeoxyglucose positron emission tomography scan. Oral Oncol 2014; 50: 802-808.

[38] Izuishi K, Yamamoto Y, Mori H, Kameyama R, Fujihara S, Masaki T, Suzuki Y. Molecular mechanisms of [18F]fluorodeoxyglucose accumulation in liver cancer. Oncol Rep 2014; 31: 701-706.

[39] Pant V, Sen IB, Soin AS. Role of 18F-FDG PET CT as an independent prognostic indicator in patients with hepatocellular carcinoma. Nucl Med Commun 2013; 34: 749-757.

[40] He YX, Guo QY. Clinical applications and advances of positron emission tomography with fluorine-18-fluorodeoxyglucose (18F-FDG) in the diagnosis of liver neoplasms. Postgrad Med J 2008; 991: 246-251.

[41] Kucuk ON, Soydal C, Araz M, Bilgic S, Ibis E. Prognostic importance of 18F-FDG uptake pattern of hepatocellular cancer patients who received SIRT. Clin Nucl Med 2013; 38: e283-239.

[42] Sabet A, Ahmadzadehfar H, Bruhman J, Sabet A, Meyer C, Wasmuth JC, Pieper CC, Biersack HJ, Ezziddin S. Survival in patients with hepatocellular carcinoma treated with 90Y-microsphere radioembolization. Prediction by 18F-FDG PET. Nuklearmedizin 2014; 53: 39-45.

[43] Annunziata S, Treglia G, Caldarella C, Galiandro F. The role of 18F-FDG-PET and PET/CT in patients with colorectal liver metastases undergoing selective internal radiation therapy with yttrium-90: a first evidence-based review. Scientific World Journal 2014; 2014: 879469.

[44] Wong CY, Salem R, Raman S, Gates VL, Dworkin HJ. Evaluating 90Y-glass microsphere treatment response of unresectable colorectal liver metastases by [18F]FDG PET: a comparison with CT or MRI. Eur J Nucl Med Mol Imaging 2002; 29: 815-820.

[45] Cianni R, Urigo C, Notarianni E, Saltarelli A, Salvatori R, Pasqualini V, Dornbusch T, Cortesi E Selective internal radiation therapy with SIR-spheres for the treatment of unresectable colorectal hepatic metastases. Cardiovasc Intervent Radiol 2009; 32: 1179-1186.

[46] Zerizer I, Al-Nahhas A, Towey D, Tait P, Ariff B, Wasan H, Hatice G, Habib N, Barwick T. The role of early 18F-FDG PET/CT in prediction of progression-free survival after 90Y radioembolization: comparison with RECIST and tumour density criteria. Eur J Nucl Med Mol Imaging 2012; 39: 1391-1399.

[47] Tochetto SM, Töre HG, Chalian H, Yaghmai V. Colorectal liver metastasis after 90Y radioembolization therapy: pilot study of change in MDCT attenuation as a surrogate marker for future FDG PET response. AJR Am J Roentgenol 2012; 198: 1093-1099.

[48] Park GC, Kim JS, Roh JL, Choi SH, Nam SY, Kim SY. Prognostic value of metabolic tumor volume measured by 18F-FDG PET/CT in advanced-stage squamous cell carcinoma of the larynx and hypopharynx. Ann Oncol 2013; 24: 208-214.

[49] Liao S, Penney BC, Wroblewski K, Zhang H, Simon CA, Kampalath R, Shih MC, Shimada N, Chen S, Salgia R, Appelbaum DE, Suzuki K, Chen CT, Pu Y. Prognostic value of metabolic tumor burden on 18F-FDG PET in nonsurgical patients with non-small cell lung cancer. Eur J Nucl Med Mol Imaging 2012; 39: 27-38.

[50] Roh JL, Kim JS, Kang BC, Cho KJ, Lee SW, Kim SB, Choi SH, Nam SY, Kim SY. Clinical significance of pretreatment metabolic tumor volume and total lesion glycolysis in hypopharyngeal squamous cell carcinomas. J Surg Oncol 2014; 110: 869-75.

[51] Lee SM, Bae SK, Kim TH, Yoon HK, Jung SJ, Park JS, Kim CK. Value of 18F-FDG PET/CT for Early Prediction of Pathologic Response (by Residual Cancer Burden Criteria) of Locally Advanced Breast Cancer to Neoadjuvant Chemotherapy. Clin Nucl Med 2014; 39: 882-6.

[52] Gulec SA, Suthar RR, Barot TC, Pennington K. The prognostic value of functional tumor volume and total lesion glycolysis in patients with colorectal cancer liver metastases undergoing 90Y selective internal radiation therapy plus chemotherapy. Eur J Nucl Med Mol Imaging 2011; 38: 1289-1295.

[53] Fendler WP, Philippe Tiega DB, Ilhan H, Paprottka PM, Heinemann V, Jakobs TF, Bartenstein P, Hacker M, Haug AR. Validation of several SUV-based parameters derived from 18F-FDG PET for prediction of survival after SIRT of hepatic metastases from colorectal cancer. J Nucl Med 2013; 54: 1202-1208.

[54] Bangash AK, Atassi B, Kaklamani V, Rhee TK, Yu M, Lewandowski RJ, Sato KT, Ryu RK, Gates VL, Newman S, Mandal R, Gradishar W, Omary RA, Salem R. 90Y radioembolization of metastatic breast cancer to the liver: toxicity, imaging response, survival. J Vasc Interv Radiol 2007; 18: 621-8.

[55] Jakobs TF, Hoffmann RT, Fischer T, Stemmler HJ, Tatsch K, La Fougere C, Murthy R, Reiser MF, Helmberger TK. Radioembolization in patients with hepatic metastases from breast cancer. J Vasc Interv Radiol 2008; 19: 683-90.

[56] Coldwell DM, Kennedy AS. Use of yttrium-90 microspheres in the treatment of unresectable hepatic metastases from breast cancer. Int J Radiation Oncol 2007; 69: 800-804.

[57] Cianni R, Pelle G, Notarianni E, Saltarelli A, Rabuffi P, Bagni O, Filippi L, Cortesi E. Radioembolisation with (90)Y-labelled resin microspheres in the treatment of liver metastasis from breast cancer. Eur Radiol 2013; 23: 182-189.

[58] Mouli S, Memon K, Baker T, Benson AB 3rd, Mulcahy MF, Gupta R, Ryu RK, Salem R, Lewandowski RJ. Yttrium-90 radioembolization for intrahepatic cholangiocarcinoma: safety, response, and survival analysis. J Vasc Interv Radiol 2013; 24: 1227-1234.

[59] Filippi L, Pelle G, Cianni R, Scopinaro F, Bagni O. Change in total lesion glycolysis and clinical outcome after 90Y radioembolization in intrahepatic cholangiocarcinoma. Nucl Med Biol 2014; 42: 59-64.

[60] Singh AD, Turell ME, Topham AK. Uveal melanoma: trends in incidence, treatment, and survival. Ophthalmology 2011; 118: 1881-1885.

[61] Sato T. Locoregional management of hepatic metastasis from primary uveal melanoma. Semin Oncol 2010; 37: 127-138.

[62] Klingenstein A, Haug AR, Zech CJ, Schaller UC. Radioembolization as locoregional therapy of hepatic metastases in uveal melanoma patients. Cardiovasc Intervent Radiol 2013; 36: 158-165.

[63] Rajekar H, Bogammana K, Stubbs RS. Selective internal radiation therapy for gastrointestinal neuroendocrine tumour liver metastases: a new and effective modality for treatment. Int J Hepatol 2011; 2011: 404916.

[64] King J, Quinn R, Glenn DM, Janssen J, Tong D, Liaw W, Morris DL. Radioembolization with selective internal radiation microspheres for neuroendocrine liver metastases. Cancer 2008; 113: 921-929.

[65] Kumar R, Sharma P, Garg P, Karunanithi S, Naswa N, Sharma R, Thulkar S, Lata S, Malhotra A. Role of (68)Ga-DOTATOC PET-CT in the diagnosis and staging of pancreatic neuroendocrine tumours. Eur Radiol 2011; 21: 2408-2416.

[66] Vasamiliette J, Hohenberger P, Schoenberg S, Diehl S, Dinter DJ, Marx A, Stroebel P, Strauss LG, Dimitrakopoulou-Strauss A. Treatment monitoring with 18F-FDG PET in metastatic thymoma after ⁹⁰Y-DOTATOC and selective internal radiation treatment (SIRT). Hell J Nucl Med 2009; 12: 271-273.

[67] Ezziddin S, Meyer C, Kahancova S, Haslerud T, Willinek W, Wilhelm K, Biersack HJ, Ahmadzadehfar H. ⁹⁰Y Radioembolization after radiation exposure from peptide receptor radionuclide therapy. J Nucl Med 2012; 53: 1663-1669.

[68] Filippi L, Ciorra A, Sardella B, Schillaci O, Bagni O. Sequential use of 90Y microspheres radioembolization and 177Lu-Dotatate in pluri-metastatic neuroendocrine tumors: a case report. Nucl Med Mol Imaging 2014; 48: 321-325.