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EDITORIAL COMMENTARY

^{18}F-FDG PET-derived parameters as prognostic indices in hepatic malignancies after ^{90}Y radioembolization: is there a role?

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The liver is a site of prominent metastasization for many tumours, especially breast and colorectal cancers [1]. Unfortunately, despite many advances in diagnosis and therapy, the prognosis of both primary and secondary hepatic tumours remains poor. Surgery is the most effective approach, but it can often be impracticable due to the anatomic location of the lesions or the massive involvement at presentation. Several treatment modalities both systemic and loco-regional (ethanol injection, radiofrequency ablation, cryoablation, transarterial chemoembolization) have been evaluated [2, 3].

In recent years, ^{90}Y radioembolization (RE) has emerged as a novel procedure used for the treatment of primary or secondary hepatic lesions. ^{90}Y, embedded in resin or glass microspheres, is infused directly into the circulation through angiographic catheters placed in the hepatic arteries [4]. ^{90}Y spheres, once implanted in the liver, can release a significant radiation burden to the neoplastic cells with a relatively low dose to the normal parenchyma due to the different vascularization pattern.

To assess tumour response to ^{90}Y RE, Response Evaluation Criteria In Solid Tumours (RECIST) has been largely used [5], but it can present some limitations, since various peri- and endotumoural processes can occur after the procedure, including oedema, haemorrhage and ring enhancement, which can confound interpretation of response. Besides RECIST, other morphological criteria have been proposed [6]. On the other hand, 2-[^{18}F]fluorodeoxyglucose (FDG) PET/CT is a well-established diagnostic tool in many oncological scenarios [7]. Although it plays a limited role in the case of non-FDG-avid lesions such as some neuroendocrine tumours and well-differentiated hepatocellular carcinoma, FDG PET appeared to be useful in detecting metabolic response to ^{90}Y RE, especially in cases of colorectal and breast cancer metastases to the liver [8, 9].

Regarding the prognostic value of a PET scan, a strict relationship between FDG uptake as measured by the maximum standardized uptake value (SUV_{max}) and some cellular characteristics of tumours has been reported [10]. Therefore, SUV_{max} and its changes have been traditionally taken into account as prognostic indicators of tumour response after treatment. Furthermore, PET Response Criteria in Solid Tumors (PERCIST) criteria have been recently introduced to more accurately define the metabolic response of tumours to the therapies [11]. Haug and colleagues published research on the role of FDG PET in predicting survival after ^{90}Y RE in a cohort of 58 patients with hepatic metastases from breast cancer [12]. FDG PET was performed at baseline and 3 months after the procedure. To evaluate the response of the disease to treatment, the authors applied modified PERCIST criteria. According to the unmodified PERCIST, the change of SUV_{max} in the two hottest lesions per organ is considered. On the contrary, Haug et al. based their definition of the response on the summed percentage change in the SUV_{max} in up to five of the most prominent hepatic lesions, demonstrating that response assessed with this approach correlated significantly with survival after ^{90}Y RE. More recently, Camacho et al. confirmed a significant correlation between overall survival and metabolic response assessed 3 months post procedure by PERCIST criteria in patients with cholangiocarcinoma [13].

It is well known that SUV measurements can be affected by many issues, such as the reconstruction algorithm, the scanner

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used, the interval between tracer injection and the acquisition, the partial volume effect and so on [14]. Furthermore, SUV concerns information only on tumour metabolic activity and does not consider the overall tumoural volume. Therefore, several PET-derived volumetric parameters have been introduced to overcome these drawbacks. In particular, the metabolic tumour volume (MTV), assessed by FDG PET, defines metabolic tumour burden and proved to be of interest for the prediction of disease prognosis [15]. Further information on tumour behaviour before and after treatments can be achieved by using total lesion glycolysis (TLG), a PET-derived parameter combining SUV(mean) and MTV [16]. In a large series of 80 patients with colorectal liver metastases, Fendler and coworkers recently tested the validity of these PET-derived parameters for predicting survival of patients with colorectal liver metastases after ^{90}Y RE [17]. FDG PET was performed at baseline and 3 months after the procedure and TLG, MTV and changes in SUV were calculated. The authors found that a decrease in MTV and TLG predicted survival, while no correlation was found for changes in SUV and RECIST criteria.

The optimal time point to assess metabolic response after the ^{90}Y spheres' administration is a widely discussed argument. The previously cited reports [12, 13, 18] assessed metabolic response after 3 months. It might be reasonably hypothesized that this time point might represent a good compromise to assess tumour response and avoid confounding factors due to eventual transient radiation-induced liver inflammation. Nevertheless, recently published papers suggest that an early assessment of metabolic changes after ^{90}Y RE may be feasible. Zerizer et al. evaluated the role of the early assessment of metabolic response in 25 patients with hepatic metastases from colorectal cancer treated with ^{90}Y RE by performing FDG PET 6–8 weeks after the procedure [17]. A significant correlation was found between the decrease of SUV_{max} and patients' progression-free survival.

In the current issue of the *European Journal of Nuclear Medicine and Molecular Imaging*, Sabet et al. add further evidence on this topic [19]. The authors analysed the prognostic impact of the tumour to liver ratio (TLR), a SUV-derived index, in patients with colorectal liver metastases treated with ^{90}Y RE. The three liver lesions with the highest SUV_{max} were selected as targets and the normal parenchyma was considered as the background. The TLR was calculated before the procedure and 4 weeks after the treatment. A decrease>50 % of TLR was chosen as the threshold to discriminate between responders and non-responders. Sabet el al. found that responders (TLR >50 %) had a median overall survival significantly longer than non-responders (TLR< 50 %). Early metabolic response and low hepatic tumour burden emerged as independent predictors of improved survival after ^{90}Y RE. This study is an interesting attempt to identify as early as possible patients with poor clinical outcome in order to timely start adjuvant or palliative treatments. Nevertheless, it should be noted that the authors used the liver as normal background for normalization, but the liver itself is the target of RE. An increased FDG uptake in the normal liver can be evident at the 4-week examination due to transient inflammation after RE. This issue may be a confounding factor when the TLR is calculated.

On the other hand, PET-derived volumetric parameters (i.e. MTV and TLG) are achieving a more and more important role as early prognostic indicators after ^{90}Y RE. In a phase II study, Gulec et al. found a very strong association between survival and TLG values in patients with colorectal liver metastases treated with ^{90}Y spheres [20]. The median survival for patients with 4-week post-treatment TLG values of above and below 100 g were 10.9 and 26.9 months, respectively. These results have been recently confirmed: the decrease in TLG (ΔTLG), measured 6 weeks after ^{90}Y RE, has been demonstrated to strictly agree with clinical outcome of patients affected by intrahepatic cholangiocarcinoma [21].

In conclusion, the above-mentioned scientific reports suggest that PET-derived indices may have a role in predicting outcome after ^{90}Y RE. Nevertheless, much work has to be done in this field. The volumetric indices, in fact, have been proved to be reliable and accurate, but they are quite time-consuming and need dedicated software. Undoubtedly, the TLR has practical advantages, being easy to calculate without the necessity of dedicated workstations. However, this SUV-based parameter provides limited information on tumour behaviour, since it does not take into account the volumetric data.

It is worthy of note that most of the published papers come from single-centre studies with a relatively small cohort of patients. In addition, there is a heavy heterogeneity in histology of tumours treated with ^{90}Y spheres. Of course, every malignancy presents specific treatment history and biology, which might result in different susceptibility to the procedure. A well-designed multicentre study with larger and more homogeneous cohorts of patients is needed for a standardization, particularly for determining wherein patients' treatment management can be influenced by the early metabolic assessment.

Conflicts of interest None.

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