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LETTER TO THE EDITOR

Imaging Neuroendocrine Hepatic Metastases Following ^{90}Y-Radioembolization: Is It Time to Implement Routine Use of PET Molecular/Metabolic Probes?

Luca Filippi[1] · Orazio Schillaci[2,3] · Roberto Cianni[4] · Oreste Bagni[1]

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Dear Sir,

We have read with great interest the paper by Braat and colleagues [1] concerning the use of radioembolization (RE) with ^{90}Y-resin microspheres in a large cohort of 244 patients affected by hepatic metastases from neuroendocrine tumours (NET). We would like to thank the authors for this insightful research, collecting the data from eight participating hospitals and demonstrating the clinical usefulness of ^{90}Y-RE for treating NET hepatic metastases with a disease control rate of $> 90\%$. As regards the aforementioned paper, we have the following observations.

The authors evaluated hepatic NET response to ^{90}Y-RE according to response evaluation criteria in solid tumours (RECIST) and modified RECIST (mRECIST) at 3 months after the procedure. However, even though they are currently used in clinical practice, both RECIST and mRECIST present several limitations for the assessment of hepatic lesions after locoregional therapy, especially in discriminating between residual tumour and treatment-induced changes such as haemorrhage, oedema and necrosis [2]. Such limitations emphasize the need for alternative imaging tools. In this respect, for many years somatostatin receptor scintigraphy (SRS) with ^{111}In-pentetreotide has been used for NET diagnosis, evaluation of the response to treatment and selecting patients to be submitted to targeted radionuclide therapy. However, the sensitivity of SRS is strictly dependent on NET size and dramatically drops down for lesion of less than < 1 cm. To overcome this limitation, three compounds binding to somatostatin receptors have been recently introduced for the imaging of NET with PET technology: ^{68}Ga-DOTA-Phe1-Tyr3-octreotide (DOTATOC), ^{68}Ga-DOTA-NaI3-octreotide (DOTANOC) and ^{68}Ga-DOTA-Tyr3-octreotate (DOTATATE) [3]. PET with ^{68}Ga-DOTA compounds has high spatial resolution also allowing the calculation of several quantitative parameters. A first preliminary report suggests that PET with ^{68}Ga-DOTANOC may be useful to assess the response of well differentiated (G1-G2) hepatic NET submitted to ^{90}Y-RE. In particular, molecular response, defined as a reduction superior to 50% in tumour-to-spleen (T/S) uptake ratio, resulted correlated with patients' overall survival at multivariate analysis [4]. Furthermore, it has to be pointed out that PET imaging allowed an assessment of the response at 6 week after therapy, significantly earlier than the time point of evaluation reported by Braat et al. [1]. The early identification of non-responders to ^{90}Y-RE may be of value for readily submitting these patients to other effective treatments.

It has to be underlined that the over-expression of somatostatin receptors may be reduced or completely absent in the more biologically aggressive NET. It has been reported that these more aggressive forms are often negative at PET scan with ^{68}Ga-DOTA compounds, while they usually present highly increased incorporation of ^{18}fluorine-deoxyglucose (FDG). There is a growing amount of scientific literature suggesting the clinical usefulness of dual-tracer PET with FDG/^{68}Ga-DOTA peptides in

✉ Luca Filippi
l.filippi@ausl.latina.it

[1] Nuclear Medicine Unit, "Santa Maria Goretti" Hospital, via Canova, Latina, Italy

[2] Department of Biomedicine and Prevention, University Tor Vergata, Rome, Italy

[3] IRCCS Neuromed, Pozzilli, Italy

[4] Department of Interventional Radiology, S. Camillo Hospital, Rome, Italy

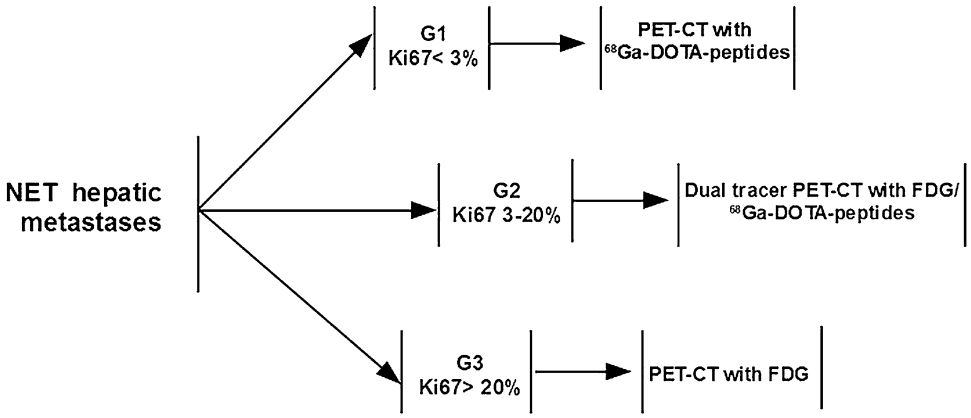

Fig. 1 Schematic representation of the possible complementary/combined use of molecular/metabolic PET probes for hepatic NET imaging according to their grade of differentiation and ki67 value

patients affected by primary or recurrent NET [5]. However, it has to be kept in mind that the two tracers are not interchangeable since the former (FDG) reflects the glycometabolic activity of the lesion, while the latter concerns its receptorial status. Both these data have significant impact on NET patients' therapeutic management. Of note, the dual-tracer approach provides additional dosimetric burden as compared to the traditional single-tracer modality and thus should be subject to a strict medical justification.

Taking into account that hybrid PET-CT technology allows simultaneously performing multi-slice CT and PET scan, it is time to implement this imaging modality for the routine evaluation of hepatic NET after ^{90}Y-RE. Since NET are a very heterogeneous group of tumours, it might be reasonable envisaging the combined use of molecular and metabolic PET probes according to NET grade of differentiation and Ki-67 value (Fig. 1).

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflicts of interest.

Ethical Approval This article does not contain any studies with human participants or animals performed by any of the authors.

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