

Neuroendocrine Liver Metastases

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We read with interest the papers of Braat et al. [1] and Zener et al. [2] regarding the results of transarterial treatments in patients with Neuroendocrine Neoplasms (NEN) liver metastases.

Available guidelines in NEN liver metastases acknowledge the role of loco-regional therapies in NENs with liver-predominant disease not responding to systemic therapy, to control tumor growth and symptoms [3]. However, there is a substantial lack of large-scale prospective studies and randomized clinical trials in the setting of loco-regional therapies.

These two studies provide data on large series of patients with NEN of any origin and grade treated either with transarterial chemoembolization (TACE) [2] or with Y90-Radioembolization (RE) [1]. Both studies included a substantial number of patients with intrahepatic tumor load > 50%, extrahepatic disease, functioning lesions and heavily pretreated disease. Despite these unfavorable (and heterogeneous) baseline characteristics, both RE and TACE proved to be safe in NEN patients, with acceptable periprocedural toxicities. While TACE may induce biliary complications, partly related to particles sizes, concerns have been raised on the incidence of long-term complications after RE, such as late onset of cirrhosis, especially in patients undergoing also peptide receptor radionuclide therapy. Analyzing these studies,

periprocedural major complications appear to be slightly more frequent after TACE than after RE; however, as the authors pointed out, some data could have been missed in the multicentre retrospective registry, and long-term results on liver function are not available [1].

Though it is difficult to draw definitive considerations about overall survival (OS) due to the heterogeneity of the enrolled patients and of the carried out treatments, reported outcomes are similar in these two studies, confirming previous analyses in which no significant difference in OS was observed comparing different embolotherapies [4]. A small proportion of patients in both studies had poorly differentiated tumors, and both studies confirmed tumor differentiation to affect survival (median overall survival in G3 NEN of 10.8 months after RE and 13 months after TACE). Thus, despite the reported feasibility of transarterial treatments in G3 NEN patients, the role of loco-regional therapies in this subgroup remains questionable. Moreover, in both studies high tumor load (> 50% after TACE or > 75% after RE) proved to be a poor prognostic factor for survival. Therefore, tumor extension should be taken into consideration when setting the indications for transarterial treatments.

The role of radiological tumor response to treatment in predicting survival remains a matter of debate. While Braat et al. [1] reported significantly higher survival rates in patients with disease control assessed according to RECIST (Response Evaluation Criteria for Solid Tumor) 1.1, the study by Zener et al. [2] seems to question the role of modified RECIST (mRECIST) in assessing tumor response to TACE. In fact, the authors reported better responses using smaller size particles (< 100 μm), yet no difference in survival was found when comparing the particles' sizes. Thus, the role of mRECIST has still to be defined in

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assessing response to loco-regional therapies in NEN liver metastases. Moreover, Zener et al. [2] speculated on the possible role of other factors besides tumor response affecting survival after TACE, such as treatment toxicity and systemic effects, and suggest the use of adjuvant medications after TACE to improve the results.

In summary, although both studies represent a major effort in the attempt to identify indications to transarterial treatments in NENs, the placement of loco-regional treatments in NENs' management still represents an unmet need. Further prospective randomized studies should investigate transarterial treatments alone or in combination with the most recently approved systemic therapies [5], as well as possible molecular or radiological biomarkers that could be used as selection criteria for different treatment options.

Compliance with Ethical Standards

Conflict of interest Irene Bargellini received honoraria for speaking at symposia from Bayer, Terumo Europe, Sirtex and BTG and a research grant from BTG. The other authors declare that they have no conflicts of interest.

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