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REPLY: We have read with great interest the comments of Hofman et al. regarding our recently published study (*1*) about the high prognostic value of ^{18}F-FDG PET for metastatic neuroendocrine tumors (NETs). In that prospective study, patients with ^{18}F-FDG–avid NETs, defined by a standardized uptake value (SUV) exceeding 4.5 or a tumor-to-nontumor SUV ratio (T/NT ratio) exceeding 2.5, had dramatically decreased overall survival (OS) in comparison with patients with ^{18}F-FDG–negative NETs. Median OS was only 15 mo (95% confidence interval, 4–27) for ^{18}F-FDG–avid NETs versus 119.5 mo (95% confidence interval, 72–∞) for ^{18}F-FDG–negative NETs ($P < 10^{-3}$). This difference was still significant for patients with positive somatostatin receptor scintigraphy (SRS) results, usually considered a good prognostic indicator (*2,3*).

This point underlines the better prognostic value of ^{18}F-FDG than of SRS, with a survival rate of 0% at 4 y in cases of ^{18}F-FDG positivity, regardless of the SRS results, and 70% for patients with positive SRS results and negative ^{18}F-FDG results (*1*).

Similar results evidencing this great prognostic value have been published by Binderup et al. in another prospective study (*4*), reporting SUV_{max} to be the only predictor of progression-free survival in multivariate analysis (hazard ratio, 8.4; $P < 0.001$).

There is also well-documented evidence that ^{18}F-FDG PET is a better prognostic indicator than Ki-67 evaluation, as several patients with low (<2%) or intermediate (2%–20%) Ki-67 may exhibit ^{18}F-FDG avidity and poor prognosis (*1,4*).

In a cohort of 52 such patients, namely with ^{18}F-FDG–avid NETs and positive SRS results, treated with peptide receptor radionuclide chemotherapy (PRCRT) using ^{177}Lu-DOTATATE combined with 5-fluouracil, Kashyap et al. (*5*) reported a progression-free survival of 48 mo; OS was not reached. The difference in OS between these studies (*1,5*) may probably be accounted for by the fact that patients with ^{18}F-FDG–avid NETs did not receive PRCRT in our study, as this approach is not available in our country (France) and only chemotherapy was therefore administered. This difference can also be at least partially explained by the contrasting positivity criteria used: we considered patients with a T/NT SUV ratio of more than 2.5% as exhibiting a positive prognostic evaluation, whereas the other study used a T/NT SUV ratio of 1 (*5*). To minimize this bias, the authors completed their analysis using our cutoff value for ^{18}F-FDG prognostic evaluation (SUV $\geq$ 4.5 or T/NT ratio $\geq$ 2.5) and found no statistical difference in survival, indicating that PRCRT has the ability to restore the prognosis of patients with ^{18}F-FDG–avid NETs.

Another parameter that may have had an impact on the observed differences is the fact that Kashyap et al. (*5*) included only patients with concordant PET and SRS positivity for all tumoral foci, which was not necessarily the case in our study. Nevertheless, their results underlined the great interest in using an aggressive therapy such as PRCRT in cases of ^{18}F-FDG avidity.

Conversely, patients with no ^{18}F-FDG avidity in our study did not receive specific therapy and exhibited a long median OS, suggesting that the use of aggressive therapy in this group of patients is of questionable value.

On the basis of our results and those of Binderup et al. (*4*) and Kashyap et al. (*5*), ^{18}F-FDG PET should be recommended for the prognostic evaluation of NETs and for deciding on a treatment course. The following recommendations can be proposed, irrespective of Ki-67 evaluation. If the patient is a potential candidate for surgery, SRS and ^{18}F-FDG PET should be performed to achieve the most accurate staging and prognostic work-up. If the patient is not a candidate for surgery, ^{18}F-FDG PET should be performed first to evaluate disease aggressiveness. Then, if ^{18}F-FDG PET is positive regarding prognosis (SUV $\geq$ 4.5 or T/NT ratio $\geq$ 2.5), aggressive therapy is required, and SRS can be performed if PRCRT is discussed. However, if ^{18}F-FDG PET is negative regarding prognosis, no aggressive therapy is required, and SRS can be performed if cold somatostatin analog is discussed.

Finally, we agree with Hofman et al. that, for metastatic NETs, therapeutic trials should now be conducted to define the best treatment course and confirm the highly interesting results reported in their study (*5*). In this setting, it would be intriguing to propose ^{18}F-FDG PET as an inclusion criterion, with the objective of including only patients with aggressive disease, assessed on the basis of ^{18}F-FDG avidity. In cases of indolent disease, such as tumors that are not ^{18}F-FDG–avid, it is more than likely that the differences between the therapeutic arms would not be evidenced.

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