Modifying the Poor Prognosis Associated with ^{18}F-FDG–Avid NET with Peptide Receptor Chemo-Radionuclide Therapy (PRCRT)

TO THE EDITOR: Applying conventional diagnostic imaging paradigms, a negative ^{18}F-FDG PET/CT study in a patient with biopsy-proven metastatic neuroendocrine tumor (NET) would be considered false-negative. With molecular imaging, however, we have emerged from using imaging merely to detect and measure lesion size to increasingly using it to characterize disease phenotype, which was formerly the domain of pathology. We therefore read with interest the recent publication by Bahri et al. (*1*) confirming that in patients with metastatic NET, ^{18}F-FDG PET/CT has powerful prognostic utility superior even to conventional pathologic factors such as histologic grade or Ki-67. These data substantiate earlier data by Binderup et al. (*2*) and Garin et al. (*3*). These findings highlight the ability of PET/CT to reproducibly characterize all sites of disease in a given patient, minimizing the sampling error inherent with histopathologic sampling of a random site of disease (*4*).

In their prospective study, Bahri et al. (*1*) demonstrated a median overall survival of 15 mo for ^{18}F-FDG–positive NET compared with 119.5 mo for ^{18}F-FDG–negative NET. The authors also explored the additional value of somatostatin receptor imaging. In keeping with the concept that patient outcomes are related to the degree of tumor differentiation, patients with positive somatostatin receptor imaging results had a better prognosis than those without, but even so, ^{18}F-FDG also retained its prognostic utility within this group.

The adverse prognosis associated with ^{18}F-FDG avidity need not necessarily be the fate of such patients. We have recently published data regarding the efficacy of peptide receptor chemo-radionuclide chemoradiotherapy (PRCRT) with ^{177}Lu-DOTATATE combined with 5-fluorouracil in a cohort of 52 patients with ^{18}F-FDG-avid NET (*5*). Despite the anticipated poor prognosis of this cohort, we demonstrated an unexpectedly long progression-free survival of 48 mo, whereas median overall survival had not been reached at the time of publication. We have since updated the overall survival data of this cohort after a median follow-up of 58 mo, still with no patients lost to follow-up. Median overall survival from the commencement of PRCRT was 55 mo (Kaplan–Meier survival analysis based on log-rank testing). In response to the data presented by Bahri et al., we have further performed subanalysis in patients with a maximum standardized uptake value of at least 4.5 ($n = 44$) or a tumor- to normal-tissue ratio of at least 2.5 ($n = 23$), groups defined to have a relative risk for death of 6.2 and 23, respectively. Median survival for these subgroups in our cohort was the same as for our overall group.

These remarkable results attest to the superior efficacy of PRCRT compared with conventional therapeutic strategies, since we can assume that most patients in the study by Bahri et al. did not have access to this therapeutic modality because of lack of regulatory approval for PRRT in France, where the study was undertaken. Additionally, our results have a lead-time bias that is disadvantageous to our analysis, as survival in our study was not measured from diagnosis but rather from the time of PRCRT in a population that was previously treated with conventional therapeutic regimens, including at least one line of chemotherapy in 67%. Thus, our median survival of 55 mo is remarkable in comparison to the 15 mo defined by Bahri et al., suggesting that PRCRT prolongs survival by years in many patients with ^{18}F-FDG–avid metastatic NET.

In addition to the encouraging results for the cohort, 4 patients have no evidence of disease after a follow-up of 30–97 mo, indicating that a small proportion of patients can be cured. Two achieved a complete response with PRCRT alone, whereas the other two were rendered disease-free after surgery; one to excise the primary site after complete regression of metastatic disease, and another in whom an R0 resection of residual primary and metastatic disease was achieved after major disease regression (*6*). Importantly, the resected residual disease in both patients was of significantly lower grade than that documented before treatment. Furthermore, 27% of patients in our cohort ultimately achieved a complete metabolic response on ^{18}F-FDG PET/CT despite the presence of residual disease on somatostatin receptor PET/CT. In these patients, it appears PRCRT is able to convert the disease from an aggressive to an indolent phenotype. PRCRT is remarkably well tolerated, as we and others have previously described (*5,7,8*). However, there is a risk of long-term toxicity. With longer follow-up in our cohort, there have been 2 cases of myelodysplasia, although both patients remain alive after 44 and 79 mo of follow-up. This risk must be weighed against the risk of death from the underlying NET and suggests that the risk–benefit ratio is likely to be highest for patients with higher grades of NET. Although the optimal sequences for available therapies remain uncertain, we believe that the most sensible approach is to use the most efficacious and least toxic therapy upfront. For metastatic ^{18}F-FDG–avid ENETS (European Endocrine Tumor Society) grade 2 NET, our results recommend that PRCRT be the first-line therapeutic modality of choice, and we have recently changed our multidisciplinary neuroendocrine service guidelines to reflect this recommendation.

There is further room to optimize delivery of PRCRT by refinement in patient selection and delivery of therapy (*9*), including the use of ^{90}Y in patients with larger-volume disease and the use of newer chemotherapeutic combinations such as capecitabine and temozolomide for pancreatic NET (*10*). We are hopeful that these refinements will further improve patient outcomes.

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Michael S. Hofman*
Michael Michael
Raghava Kashyap
Rodney J. Hicks
**Peter MacCallum Cancer Centre*
St. Andrews Place
East Melbourne 3002, Australia
E-mail: michael.hofman@petermac.org

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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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Etienne Garin*
Julien Edeline
**University of Rennes, CS 44229*
Rennes F-35042, France
E-mail: e.garin@rennes.unicancer.fr.

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