The Potential Value of Functional Adrenal Imaging in Primary Aldosterone

TO THE EDITOR: We read with interest the article "Clinical Value of ^{68}Ga-Pentixafor PET/CT in Subtype Diagnosis of Primary Aldosteronism Patients with Adrenal Micronodules," by Ding et al. (*1*). The article tested the utility of C-X-C motif chemokine receptor 4 imaging with ^{68}Ga-pentixafor for identification of adrenal microadenomas and differentiating unilateral from bilateral adrenal disease. The authors comment correctly that "existing methods such as ^{131}I-NP-59 and ^{11}C-metomidate have significant shortcomings, including time-consuming acquisition protocols, low specificity, and the need for pretreatment dexamethasone." Like pentixafor, metomidate is not a functional agent and as a ligand binds to an expressed protein and serves as a measure of expression; metomidate additionally faces challenges given the half-life constraints imposed by the use of ^{11}C as the PET radionuclide. NP-59, developed at our institution, does require dexamethasone suppression of normal cortisol production to unmask abnormal aldosterone.

Additionally, NP-59 is labeled with the isotope ^{131}I, with unfavorable imaging characteristics and dosimetry. However, NP-59 is a functional imaging agent, with its uptake based on steroid production, and has been shown to correlate with adrenal venous sampling in primary aldosterone by Gross et al. (*2*). Although others have improved the imaging quality of NP-59 through the use ^{123}I or ^{124}I, the longer imaging protocol and dosimetry characteristics limit its utility for routine screening (*3*).

Ding et al., however, failed to mention that Brooks et al. recently demonstrated an improved ^{18}F version of NP-59, FNP-59, published in *The Journal of Nuclear Medicine* in 2022 (*3*). FNP-59 uptake was based on hormone synthesis within the adrenal gland, serving as a true functional imaging agent of cholesterol use by the adrenal gland (*3*). Although we demonstrated uptake based on hormone synthesis, there were challenges based on biologic uptake in relation to the ^{18}F decay rate. To this end, improvements using an acetyl ester version of FNP-59 have shown significantly improved uptake in the adrenal gland (*4*) and applications in other pathologies in which altered cholesterol metabolism is present (*5*). Thus, the ester version of FNP-59 could solve many of the challenges of NP-59, especially in combination with the new total-body PET scanners on the market (*6*,*7*), by overcoming the limitations of tracer decay versus biologic uptake. Although pentixafor has a definite place in evaluating adrenal lesions such as nodules, as shown by Ding et al. (*1*), or adrenocortical carcinoma (*8*), it has limitations as a nonfunctional agent in trying to quantify where in the adrenal gland hormone dysfunction and autonomy is occurring in situations in which multinodular disease or hyperplasia is present.

DISCLOSURE

No potential conflict of interest relevant to this article was reported.

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REPLY: We are grateful for the interest in our article and the insightful comments received. We recognize the complexity of imaging in primary aldosteronism and acknowledge the continuous advancements in this field.

In agreement with the authors of the letter to the editor regarding our article, "Clinical Value of ^{68}Ga-Pentixafor PET/CT in Subtype Diagnosis of Primary Aldosteronism Patients with Adrenal Micronodules," we highlighted that existing methods such as ^{131}I-NP-59 and ^{11}C-metomidate have notable limitations (*1*). The utility of ^{11}C-metomidate is constrained by the short half-life of ^{11}C, making it less practical for routine clinical use. Similarly, ^{131}I-NP-59, despite being a functional imaging agent based on steroid production, has unfavorable imaging characteristics and requires dexamethasone suppression, making it cumbersome for routine screening.

As mentioned in the letter to the editor, recent developments in NP-59 imaging, particularly the improved ^{18}F-labeled version (FNP-59), are noteworthy. Brooks et al. demonstrated that FNP-59 can serve as a true functional imaging agent, reflecting hormone synthesis within the adrenal gland (*2*). This advancement addresses some of the limitations of ^{131}I-NP-59, particularly its imaging characteristics and dosimetry. The ester version of FNP-59, which shows significantly improved uptake in the adrenal gland, represents a promising improvement. We acknowledge the value of such functional imaging agents in providing crucial insights into hormone synthesis and adrenal gland function. However, our study focused on the utility of ^{68}Ga-pentixafor PET/CT as a nonfunctional imaging agent for identifying adrenal microadenomas and differentiating unilateral from bilateral