Letters to the Editor

Response to Letter to Editor re: "Combined Quantification of 18F-FDG and 68Ga-DOTATATE PET/CT for Prognosis in High-Grade Gastroenteropancreatic Neuroendocrine Neoplasms"

From:

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Dear Dr. Dunnick, We appreciate the thoughtful comments by Chan and colleagues regarding the methodology of our recently published paper on the combined use of ^{18}F-FDG and ^{68}Ga-DOTATATE PET/CT for prognostication in G3 GEP-NENs [1]. We believe that clarification of the methodological issues raised will facilitate adoption of the FDZ score into the clinical setting.

First, we agree that the application of many radiological biomarkers is not generalizable beyond specific scanner configurations. We believe it is a strength of our work that our results were reproducible in an external patient cohort without image harmonization, suggesting potential for clinical adoption across diverse sites. The impact of possible variation in scanner performance can be minimized with "determination of the SUV_{max} distribution at each medical center for calculation of the FDZ score" [1]. Second, the short-term reproducibility of SUV_{max} on ^{68}Ga-SSTR2 PET within a given patient was previously demonstrated [2], without being affected by administration of a long-acting somatostatin analog [3]. However, it is important to keep in mind that the biological characteristics of G3 GEP-NENs may change, decreasing the predictive value of a given FDZ score over time. Overall, we do not expect the variability in SUV_{max} to be a major barrier to implementation of the FDZ score, especially in light of the known variability of the Ki-67 index [4].

Regarding the third and fourth points, the lack of information on tumor heterogeneity is a drawback of our SUV_{max}-based model. Incorporation of additional variables of prognostic significance such as the presence of metabolically discordant lesions [5], lowest tumor SUV [6], and total tumor volume [6] would add value to our model, at the expense of a larger required sample size due to the increased number of predictor variables. Finally, our decision to use SUV_{max} was inspired by previously published studies on the prognostic significance of SUV_{max} in GEP-NEN patients [7]. SUV_{max} is highly correlated with SUV_{peak} while being much easier to measure, and the observed reduction in relative noise by using SUV_{peak}-type measurements in lieu of SUV_{max} is much less than theoretically predicted due to noise correlations [8].

On the whole, our study illustrates the principle that G3 GEP-NENs with higher somatostatin receptor expression and lower metabolic activity have relatively favorable prognosis. The comments we received provide potential methodological improvements we can consider in larger patient cohorts for a more refined application of this general principle. Our next goal is to verify the reproducibility of our results in a prospective cohort of G3 GEP-NEN patients, followed by inclusion of other NEN patients with possible methodological improvements.

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