Comment on: "Tumor Aggressiveness and Patient Outcome in Cancer of the Pancreas Assessed by Dynamic ^{18}F-FDG PET/CT"

TO THE EDITOR: We read with great interest the article by Ron Epelbaum et al. (*1*) on the use of dynamic ^{18}F-FDG PET/CT to assess tumor aggressiveness and overall outcome in patients with pancreatic cancer. The authors have successfully shown how quantitative parameters of tracer kinetics can add value to ^{18}F-FDG PET imaging. They also sensibly speculate about the potential capabilities of dynamic ^{18}F-FDG PET as an evolving strategy that may, in the future, enhance the accuracy of pretreatment risk stratification and become integrated into prognostic scores for individualized treatment tailoring. On the other hand, as mentioned by the authors, quantitative dynamic PET analysis is currently considered a cumbersome technique with value demonstrated mainly in research settings. Although it is expected that the modeling component of this approach will be simplified for future clinical use, the nature of extensive data acquisition by this technique seems not to be altered significantly, since it is determined mostly by ^{18}F-FDG kinetics and tumor biology. For this reason, the protracted acquisition time will still limit widespread application of this valuable method in routine practice outside major academic centers. As mentioned by the authors, several studies have found that standardized uptake value (SUV) measured by static ^{18}F-FDG PET scans was an independent predictive factor for overall survival in the multivariate analysis (*2*). Similarly, in this study SUV_1 (early) and SUV_2 (late) were predictors of overall survival in the univariate model; however, as was predictable, these factors were not significant predictors of survival in the multivariate model, which included ^{18}F-FDG kinetic parameters.

The first of 3 comments on this article is about the correlations between SUV and ^{18}F-FDG kinetic parameters. Previous studies have shown correlations between early and late SUVs of ^{18}F-FDG PET imaging and transmembrane glucose transporters and hexokinase expression in pancreatic (*3*) and other tumor cells (*4*). Likewise, ^{18}F-FDG kinetic parameters including K_1 and k_2 are indicators of transmembrane transport of ^{18}F-FDG, and k_3 and k_4 are indicators of intracellular ^{18}F-FDG phosphorylation and dephosphorylation, respectively. Therefore, SUVs and kinetic parameters and their derivatives, such as global influx of ^{18}F-FDG and retention index ($[(SUV_2 - SUV_1)/SUV_1]$), have intrinsic correlations, which raise concerns about the potential multicollinearity between them when they are applied as independent explanatory variables in regression models (*5*). In the current study, as was briefly noted by the authors, the highly predictive significance of kinetic parameters covered the role of SUV_1 and SUV_2 in the multivariate survival analysis. Early and late SUVs and ^{18}F-FDG kinetic parameters are indicators of glucose metabolism—the actual biologic explanatory cause; therefore, it seems statistically reasonable to choose ^{18}F-FDG kinetic parameters since these values have a smaller degree of random error (*6*). However, it is not cost-effective for most imaging centers to assign their PET facilities to time-consuming dynamic PET imaging. In addition, a significant proportion of patients cannot tolerate remaining motionless while in the gantry of PET/CT scanners for an extended time (more than 60 min in this study). Considering these facts, we believe a piece of clinically important data was not reported in this article and that it would be valuable for the authors to conduct a multivariate survival analysis after excluding kinetic parameters to clarify the value of SUVs in this group of patients. This new analysis may hopefully develop clear cutoffs for early and late SUV measurements, which can be applied as practical predictive factors of overall survival in the clinical setting.

The second comment is related to parameters that can be retrieved from dual- or multiple-time-point PET studies. In some studies on dual-time-point imaging, it has been speculated that measuring retention indices of SUVmax could overcome many factors that limit the value of SUVmax measurements, including blood glucose levels and body weight (*7,8*). These studies also demonstrated the added value of calculating the retention index in prognostic models. Although SUV_1 and SUV_2 could not significantly predict long-term survival, retention indexes were independent predictive factors on the Cox regression model (*7,8*). Therefore, we believe it would be productive for the authors to calculate the retention index of SUVmax and use it in univariate and multivariate analysis. However, involving retention index in the multivariate analysis requires that the possibility of multicollinearity between variables be considered again.

The third comment is related to ^{18}F-FDG PET parameters that can be used for predicting progression-free and overall survival. Some studies performed on patients with various types of cancer suggested that volume-based PET parameters such as metabolic tumor volume (MTV) and total lesion glycolysis (TLG = SUVmean × MTV) may predict overall survival whereas SUVmax alone is not an optimal predictive factor (*9,10*). Hence, measuring and incorporating MTV and TLG in the survival models may add more remarkable aspects to this study. However, in addition to multicollinearity issues in the statistical analysis, partial-volume correction methods should be considered to measure these parameters precisely (*11*).

In conclusion, we believe that calculation and head-to-head comparison of all prospective imaging biomarkers in dynamic PET studies, including estimated SUV thresholds, retention indices, TLG, MTV, and kinetic parameters, would better elucidate the correlation among these factors and may provide further valuable strategies for future investigations and routine practice.

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REPLY: We would like to thank Dr. Salavati and his coauthors for the interesting comment on our study (*1*). As they mentioned, dynamic PET and PET/CT are more time-consuming and at the moment are therefore confined to research projects for scientific purposes. Furthermore, dynamic PET/CT requires dedicated evaluation software. However, the introduction of new-generation PET/CT scanners has reduced the total acquisition time because of, for example, new detector materials such as lutetium oxyorthosilicate, which improves the counting rate performance, as well as 3-dimensional acquisition protocols. Moreover, new-generation PET/CT scanners also allow dynamic (list-mode) multibed acquisitions. In the future, this technologic improvement will allow for dynamic partial-body PET/CT studies without the need for additional bed positions in static mode, with a shorter acquisition than in our study (*2*). We agree that an additional limitation hampering the use of dynamic protocols in a clinical environment is the lack of operator-friendly and robust evaluation software—an omission that will hopefully be addressed by manufacturers. The existing software for calculation of transport rates is based on a 2-tissue-compartment model for oncologic studies. This software is not robust enough because it is based on an iterative fitting, like the Levenberg–Marquardt algorithm. We presented a solution that is based on the use of an oncologic reference database and a support vector machine algorithm (*3*). Routine use of dynamic PET/CT requires that the calculated rates be reproducible—a problem that should be solved in the future.

Ludwig Strauss proposed at the end of the 1980s the use of the standardized uptake value (SUV) as a robust value that can easily be calculated for the evaluation of PET data (*4*). SUVs are widely used and lead to good results, provided that the values are acquired under standardized conditions, such as at a defined time point after tracer injection, with glucose levels within the normal range, and with the same reconstruction algorithms. John W. Keyes, Jr., wrote an interesting paper in *The Journal of Nuclear Medicine* in 1995 titled "SUV: Standard Uptake or Silly Useless Value?" In this paper he doubted the usefulness of SUV and discussed the limitations of this semiquantitative approach in detail (*5*). Nineteen years later, everybody uses the SUV or its derivatives (such as SUVmax, SUVlean, or even total lesion glycolysis) as a first quantitative approach. It remains to be seen how silly or useless dynamic multibed PET/CT (including parametric imaging) in oncology will be in the future.

Dynamic imaging allows the registration of tracer kinetics over time instead of at only one time point after the tracer injection as static images do. Pharmacokinetic studies are helpful not only for the evaluation of new tracers but also for the evaluation of small therapeutic effects, such as the use of ^{18}F-FDG early after the onset of chemotherapy. Furthermore, the use of kinetic parameters may help to differentiate between benign and less aggressive tumors (e.g., lipomas from low-grade liposarcomas) (*6*). In a recent paper, we demonstrated a correlation between k_1 and angiogenesis-related genes (*7*). Based on dynamic datasets, parametric imaging can be applied using different algorithms. Parametric images allow the visualization of dedicated parameters of radiopharmaceutical kinetics, such as perfusion, transport, or phosphorylation in the case of ^{18}F-FDG. Karakatsanis et al. recently presented some aspects of the use of whole-body PET parametric imaging and, for example, Patlak analysis in addition to SUVs for tumor diagnosis and therapy response monitoring (*8*).

We agree that several approaches available today may be used for the evaluation of oncologic ^{18}F-FDG imaging, including metabolic tumor volume and total lesion glycolysis. We decided to use an analysis based primarily on the pharmacokinetic data, and this proved to be successful. We hope our colleagues will succeed as well in future using any other approach they may wish to choose.

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