13 solid tumors were examined. Besides a preclinical PERCIST paradigm, 43 imaging metrics were evaluated, both in the whole tumor and in a single highest-intensity tumor slice. These metrics included SUV_{mean} obtained from various fixed percentages of the SUV_{max} thresholds (SUV_{Th}) and SUV_{mean} obtained from the voxels involved in a sphere centered at the SUV_{max} voxel (SUV_{peak}). Spheric volumes of 4, 14, and 33 mm^3 (radius of 1, 2, and 3 voxels, respectively) were considered, leading to SUV_{P4}, SUV_{P14}, and SUV_{P33}, respectively. In particular, Bland–Altman plots of test–retest data allowed us to estimate an SUV_{25} (i.e., using a 25% of the SUV_{max} threshold) reproducibility percentage (R; 95% level of confidence) of about 20% and 25% for solid and necrotic tumors, respectively (from Figs. 3C and 3G, respectively, in Savaikar et al.). Finally, a coined quantitative response assessment score favored SUV_{25} followed by SUV_{P14} as optimal metrics of response to therapy in patient-derived tumor xenograft models.

We would like to stress the central role of R in assessing treatment response for any investigated SUV metrics, that is, the minimal relative change between 2 SUVs assessed from 2 successive examinations that is required to be considered a significant difference (*2*). In this connection, we suggest that a further SUV metric, that is, the $SUV_{max\text{-}V}$ (defined as an average SUV computed from an arbitrary total hottest volume, regardless of the location of the hottest voxels included within the ^{18}F-FDG–positive lesion), might be particularly suitable in the current context involving 21 tumors with a necrotic-core phenotype (and with varying tumor dimensions), thus exhibiting a low ^{18}F-FDG uptake at the core and well-separated ^{18}F-FDG–positive areas (Fig. 2 in Savaikar et al.). Indeed, it has been previously shown, in lung cancer patients, that the R of $SUV_{max\text{-}N}$, which is an average SUV computed from the N hottest voxels (N denotes the number of pooled voxels) regardless of their location within an ^{18}F-FDG–positive lesion, was significantly lower for an N of 30 than is the R of SUV_{peak} obtained from SUV_{max} and its 26 neighboring voxels (*3*). In a subsequent study, $SUV_{max\text{-}40}$ was found to more likely represent the most metabolically active portions of tumors than was SUV_{peak}, which was obtained from the voxels involved in a 1-mL sphere centered at the SUV_{max} voxel, with close R performance (*4*). Finally, the $SUV_{max\text{-}N}$ procedure for treatment-response assessment has been described in a Takayasu-arteritis patient, emphasizing that the greater the N value, the lower the $SUV_{max\text{-}N}$ R and, hence, the more efficient the metrics (Table 1 in Caubet et al. (*5*)). Since the voxel volume may depend on the PET system, it is noteworthy that instead of $SUV_{max\text{-}N}$, one could alternatively use $SUV_{max\text{-}V}$. When comparing baseline scans with posttreatment scans, volume should be set in the scan showing the lowest total ^{18}F-FDG–positive volume but at the greatest possible value, since the greater the volume value, the lower the $SUV_{max\text{-}V}$ R.

To conclude, Savaikar et al. addressed the important issue of reaching a consensus on the reproducibility of imaging metrics for assessing response to therapy in oncology animal models (*1*). We suggest that the $SUV_{max\text{-}V}$ metrics may have a place in this toolbox, with volume set at the greatest possible value in the scan showing the lowest tumor uptake (which is expected to be the posttreatment one). Finally, in the current series, whether R of $SUV_{max\text{-}V}$ for V = 14 and 33 mm^3 might be lower than R of SUV_{25}, SUV_{P14}, and SUV_{P33} remains to be assessed.

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Lesion Detection and Administered Activity

TO THE EDITOR: There is a preoccupation in nuclear medicine imaging with the risks posed by the use of radionuclides and with reduction of administered activities (*1*). Nearly all nuclear medicine presentations include information on the absorbed or effective doses from the radiopharmaceutical under discussion. The tiny carcinogenic risk, an extra 1 in 1,000 risk from a typical diagnostic administered activity, is minimal (*2*) when the lifetime risk of cancer is up to 1 in 2 (*3*). The debatable risk (*4*) of induced cancer from the absorbed dose must be balanced against the risks of misdiagnosis and the consequent effect on potential lifesaving treatment, especially in patients with cancer. Of course, pediatric and benign disease investigation may require a more conservative approach.

Confirmation of the detrimental effects of reducing the administered activity on lesion detection can be seen in a recent paper in *The Journal of Nuclear Medicine* by Rauscher et al. (*5*). Their study, on the effect of reducing the administered activity on the sensitivity of ^{68}Ga PSMA-11 PET/CT imaging, shows that, as would be expected, the lower the simulated administered activity, the fewer the number of lesions detected. Three readers identified 21 lesions at a rate of 100%, 100%, and 90% with a baseline administered activity of 120–192 MBq and 85%, 81%, and 90% with two thirds of the baseline tracer activity.

The standard recommended activity of ^{68}Ga PSMA-11 of approximately 1.8–2.2 MBq/kg of body weight is still under debate (*6*). If between 10% and 19% of lesions are missed by a reduction of one third of an administered activity of 120–192 MBq (*5*), this may imply that potentially up to one fifth of lesions are being missed by the standard administered activity compared with increasing the administered activity by one third.

Recommended standard administered activities should be optimized using clinical and phantom studies defining the required lesion size as seen on the image, the lesion-to-background ratio, and the administered activity required to achieve this in a time during which the patient can be expected to be motionless. There is the

complication that the fraction of the injected activity that is captured by the lesion will depend on the biodistribution and metabolism of the disease being imaged. There is also the additional complication of the varying sensitivity and resolution of different types of imaging equipment marketed by different manufacturers.

It is time to move on from the situation in which recommended activities are derived from the average of activities that produce an acceptable image to a more scientific approach to ensure that small but clinically important lesions that may change patients' management are not missed.

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